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(71) Applicant: PTC THERAPEUTICS INC. [US/US]; 100 Corporate Court, South Plainfield, New Jersey 07080 (US).

(72) Inventors: **LI, Wencheng**; 1684 Brookdale Drive, Martinsville, New Jersey 08836 (US). **EFFENBERGER, Kerstin Annemarie**; 406 Copperfield Lane, Metuchen, New Jersey 08840 (US). **CHILICKI, Justin**; 45 Vine Way, Bordentown, New Jersey 08505 (US). **GRACI, Jason**; 26 Conforti Avenue, West Orange, New Jersey 07052 (US). **TROTTA, Christopher Robert**; 9 Renoir Way, Somerset, New Jersey 08873 (US). **WELCH, Ellen M.**; 112 Bonaire Lane, Bonita Springs, Florida 34134 (US). **WU, Zhijian**; 9 Bell Drive, Westfield, New Jersey 07090 (US). **KIM, Min**

Jung; 111 North Scotch Plainfield Avenue, Westfield, New Jersey 07090 (US). **CAO, Liangxian**; 17 Winesap Drive, East Brunswick, New Jersey 08816 (US). **KUMAR, Binit**; 100 Corporate Court, South Plainfield, New Jersey 07080 (US).

(74) Agent: **SOUTHGATE, Christopher** et al.; 100 Corporate Court, South Plainfield, New Jersey 07080 (US).

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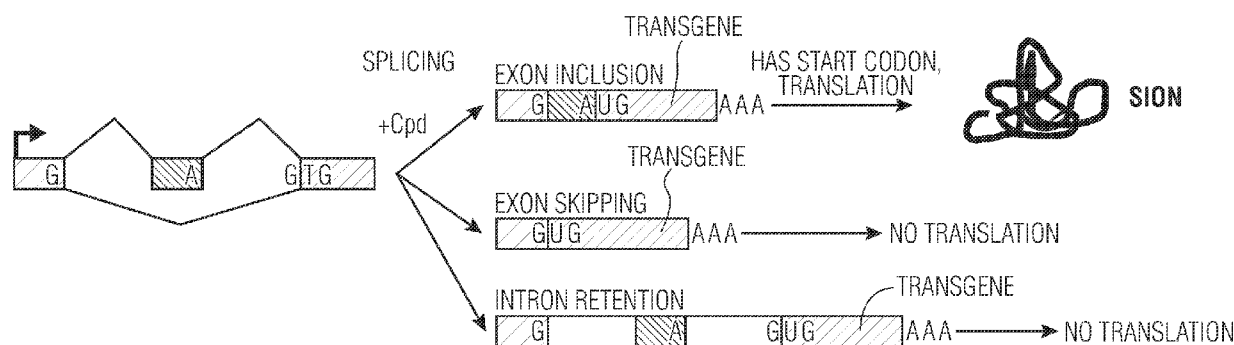


FIG. 1Ci

(57) Abstract: Described herein is a recombinant minigene cassette for controlling the expression of an operably linked transgene using a small molecule splicing modifier (SMSM) compound. In one example, the minigene cassette comprises three exons, exons 1, 2 and 3, each separated by an intron. A cis-acting regulatory element required for transgene expression within the minigene is split, for example, between the 3' end of the second exon with a small molecule inducible non-canonical splice site and the 5' end of the third exon with a 3' splice acceptor site. Accordingly, functionality of the regulatory element, and consequently transgene expression, is made contingent on small molecule inducible splicing between exons 2 and 3. Insertion of a splicing inducible minigene cassette into viral expression vectors will have broad therapeutic applicability especially for gene therapy applications where the small molecule inducer can provide systemic and temporal control of transgene expression.

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**REGULATION OF TRANSGENE EXPRESSION USING
A SMALL MOLECULE INDUCIBLE SPLICING SWITCH**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, pending U.S. Provisional Patent Application Serial No. 63/166,495 filed March 26, 2021, the content of which is hereby expressly incorporated by reference into the present application in its entirety.

FIELD OF THE DISCLOSURE

[0002] The disclosure relates generally to the field of gene regulation using a small molecule splicing modifier (SMSM) compound to modulate the functionality of a regulatory element that is required for transgene expression.

BACKGROUND

[0003] The recent FDA approval of the first recombinant adeno-associated virus (AAV) gene therapy products (GlyberaTM, LuxturnaTM and ZolgensmaTM) heralds the advent of recombinant AAV vector technology as the predominant tool for gene therapy of human genetic disease.

[0004] GlyberaTM (alipogene tiparvovec) is an adeno-associated virus serotype 1 (AAV1) vector administered intramuscularly for the treatment for hereditary lipoprotein lipase deficiency (LPLD) containing a cytomegalovirus (CMV) promoter driving the expression of human lipoprotein lipase (LPL) gene variant LPLS447X.

[0005] LuxturnaTM (voretigene neparvovec-rzyl) is a subretinally administered recombinant adeno-associated virus serotype 2 (AAV2) vector comprising a cytomegalovirus (CMV) enhancer and chicken beta actin (CBA) promoter driving expression of the gene for human retinal pigment epithelium 65 kDa protein (hRPE65), for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy.

[0006] ZolgensmaTM (onasemnogene abeparvovec-xioi) is a recombinant self-complementary adeno-associated virus serotype 9 (AAV9) that is administered by intravenous infusion for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1). The AAV vector contains a transgene encoding the human survival motor neuron (SMN) protein, under the control of a cytomegalovirus enhancer/chicken- β -actin (CBA) hybrid promoter.

[0007] For each of these approved AAV gene therapy products and a growing number of AAV therapies currently in clinical trials, transgene expression is typically driven by a constitutive promoter. Depending on the transgene being expressed and the mode of administration, long term expression, while desirable in certain circumstances, can lead to toxicity resulting from transgene overexpression, non-targeted transgene expression in tissues where the transgene is not normally expressed or from immune reactions caused by inadvertent transgene expression in antigen-presenting cells (APCs). Thus, the precise, temporal control of transgene expression that accounts for the natural variability in patients' disease biology and therapeutic response would be a particularly desirable feature of future gene therapy vectors. However, many of the known inducible gene expression systems rely on the co-expression of exogenous proteins, such as repressors in the inducible tetracycline and cumate systems or the rapamycin inducible FK506 binding protein 12. For a variety of reasons, these systems are ill-suited for AAV gene therapy applications. For example, the AAV capsid constrains the size of the viral vector to no more than ~4.7kb. The expression of the exogenous protein *in vivo* also runs the significant risk of inducing an adverse immune reaction *in vivo* or having potential off target effects on endogenous gene expression. Hormone- or stress-responsive promoters, while not needing an exogenous protein, either lack sufficient specificity under physiological conditions or are simply not compatible with therapeutic applications. Ligand-dependent riboswitches, in contrast, are small and their activity is also independent on co-expressed exogenous protein. However, most RNA-based switches suffer from a narrow regulatory range and leaky expression, which can preclude their use *in vivo*.

[0008] Hence, there is a need in the art for improved methods of regulating transgene expression that are tailored to gene therapy applications.

SUMMARY

[0009] This disclosure describes a splicing-induced-on-system (SION) and a splicing-induced-off-system (SIOFF), in which a small molecule induced splicing compound modulates the functionality of a minigene cassette's regulatory element required for transgene expression.

[0010] In a first aspect, a recombinant RNA sequence for controlling the activity of a regulatory element is disclosed comprising in 5' to 3' order: a first exon, a second exon comprising a 3' terminal inactive first portion of a RNA regulatory element, and a third exon comprising a 5' terminal inactive second portion of the RNA regulatory element, wherein inducible splicing of

the recombinant RNA between the second exon and the third exon restores the activity of the RNA regulatory element.

[0011] In one aspect, splicing between the second exon and the third exon is inducible in the presence of a small molecule splicing modifier (SMSM) compound.

[0012] In one aspect, in the absence of the SMSM compound, the RNA regulatory element is not present within the recombinant RNA sequence.

[0013] In one aspect, in the absence of the SMSM compound, the regulatory element is not present in the first, second or third exons.

[0014] In one aspect, the first and second exons are non-coding RNA sequences.

[0015] In one aspect, the third exon comprises a transgene's protein coding region.

[0016] In one aspect the regulatory element comprises a cis-acting RNA regulatory element.

[0017] In one aspect, the regulatory element comprises the protein coding region's AUG start codon.

[0018] In one aspect, the protein coding region's AUG start codon is not present within the recombinant RNA sequence.

[0019] In one aspect, the protein coding region's AUG start codon is not present in the first, second or third exons.

[0020] In one aspect, the nucleotide at the 3' end of the first exon is not adenosine.

[0021] In one aspect, the nucleotide at the 5' end of the third exon is not adenosine.

[0022] In one aspect, the inactive first portion of the RNA regulatory element at the 3' end of the second exon is the adenosine nucleotide of the protein coding region's AUG start codon.

[0023] In one aspect, the inactive second portion of the RNA regulatory element at the 5' end of the third exon is the UG dinucleotide of the protein coding region's AUG start codon.

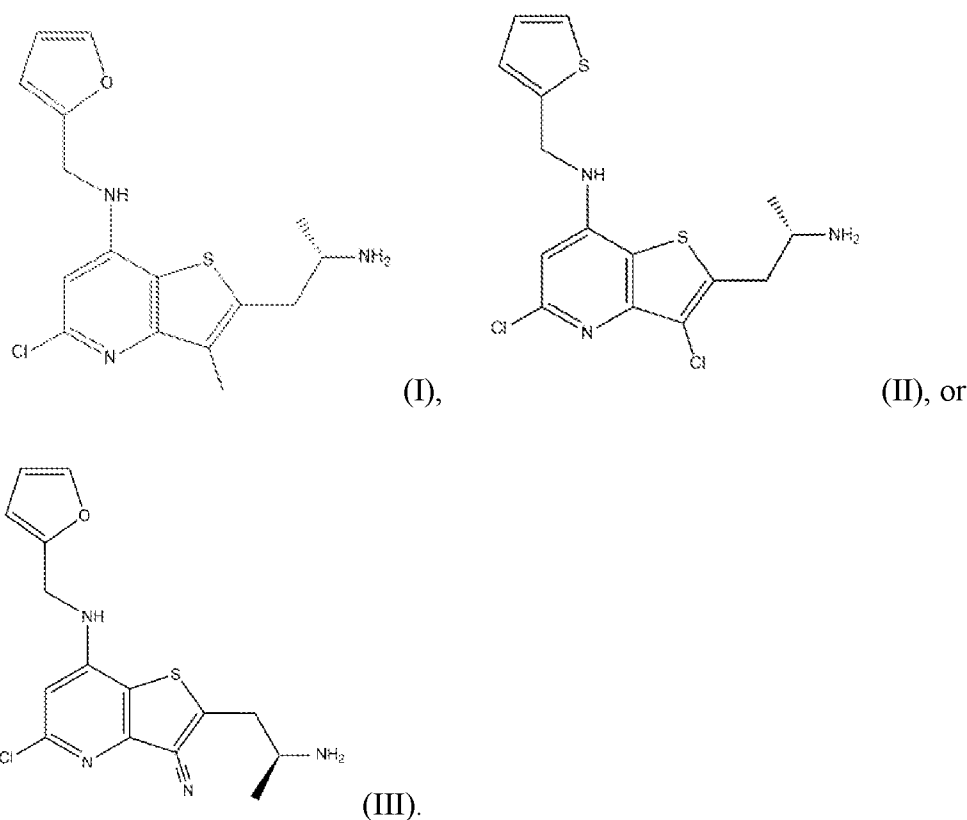
[0024] In one aspect, the second exon comprises a 3' splice site and a non-canonical 5' splice site.

[0025] In one aspect, the non-canonical 5' splice site comprises the inactive first portion of the RNA regulatory element at the 3' end of the second exon.

[0026] In one aspect, the non-canonical 5' splice site comprises an RNA sequence of 5'-CAAGu-3'.

[0027] In one aspect, splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an FD compound.

[0028] In one aspect, splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:

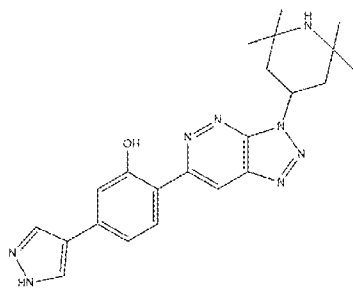


[0029] In one aspect, the non-canonical 5' splice site comprises an RNA sequence of 5'-NDGAg-3', wherein D is A, U or G and N is A, U, C or G.

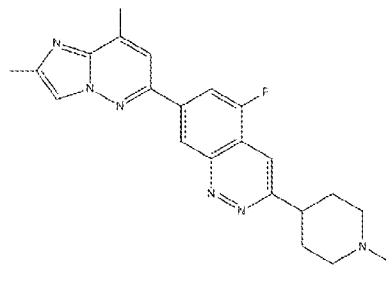
[0030] In one aspect, the non-canonical 5' splice site comprises the inactive first portion of the RNA regulatory element at the 3' end of the second exon.

[0031] In one aspect, splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an HD compound.

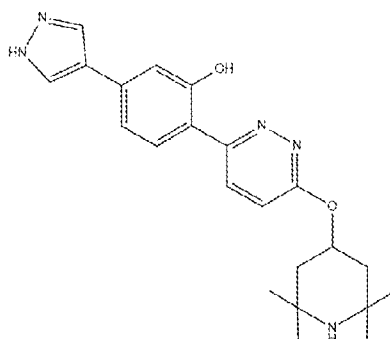
[0032] In one aspect, the splicing at the 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:



(IV),



(V), or

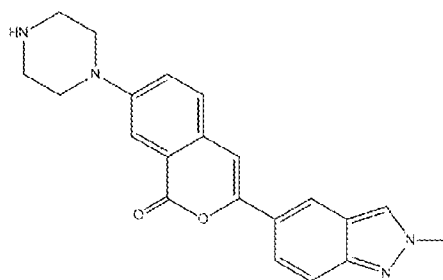


(VI).

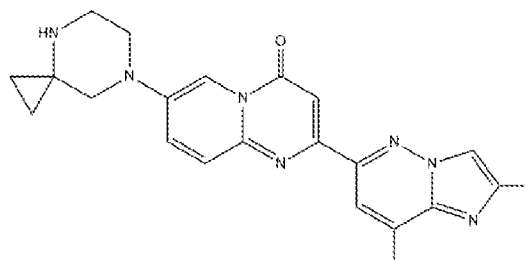
[0033] In one aspect, the non-canonical 5' splice site comprises an RNA sequence of 5'-ANGAg-3', wherein N is A, U, C or G.

[0034] In one aspect, splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an SMA compound.

[0035] In one aspect, splicing at the 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:



(VII), or



(VIII).

[0036] In a second aspect, a recombinant RNA sequence for regulating transgene expression is disclosed comprising in 5' to 3' order: a first exon having a transgene's AUG start codon at its 3' end, a non-coding second exon, and a third exon comprising a second codon of the transgene's protein coding region at its 5' end, wherein inducible splicing between the first and third exon prevents translation of the transgene's protein coding region.

[0037] In one aspect, the second exon does not comprise the AUG start codon of the protein coding region.

[0038] In one aspect, the second exon comprises a stop codon in frame with the protein coding region's AUG start codon.

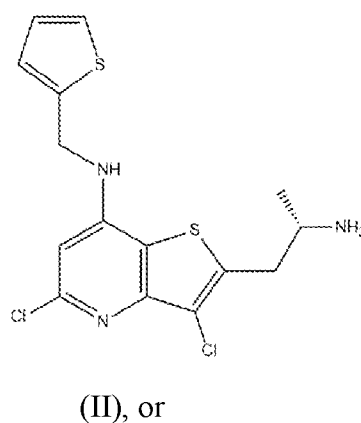
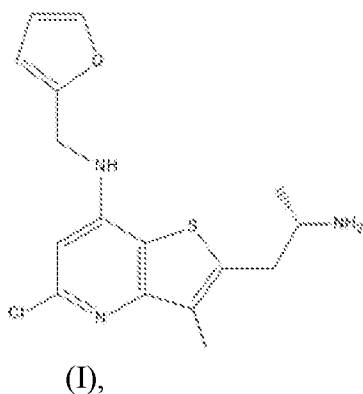
[0039] In one aspect, the second exon comprises a 3' splice site and a non-canonical 5' splice site.

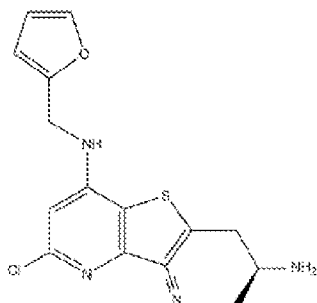
[0040] In one aspect, the non-canonical 5' splice site comprises an RNA sequence of 5'-CAAg-3'.

[0041]

[0042] In one aspect, splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an FD compound.

[0043] In one aspect, the splicing at the 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:





(III).

[0044] In one aspect, the SMSM inducible splicing between the second exon and the third exon prevents translation of the transgene's protein coding region.

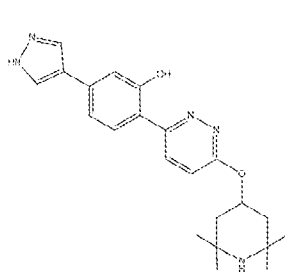
[0045] In one aspect, the splicing between the first exon and the third exon does not require the SMSM compound.

[0046] In one aspect, an expression vector is disclosed comprising a promoter operably linked to a nucleotide sequence encoding any one of the preceding recombinant cis-acting RNA sequences for regulating transgene expression.

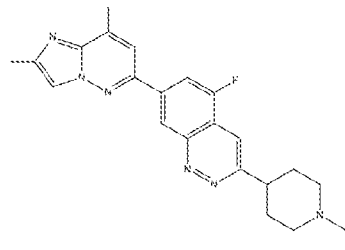
[0047] In one aspect, a recombinant adeno-associated virus (rAAV) is disclosed comprising the aforementioned expression vector.

[0048] In a third aspect, a method for regulating transgene expression *in vivo* is disclosed, comprising delivering a recombinant adeno-associated virus (rAAV) containing an expression cassette having a promoter operably linked to a nucleotide sequence encoding any one of the preceding recombinant cis-acting RNA sequences for regulating transgene expression into a subject in need thereof, and administering a small molecule splicing modifier (SMSM) composition, wherein the amount of the SMSM composition modulates the level of transgene expression in the subject.

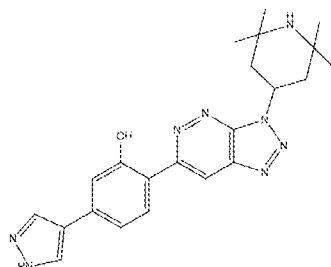
[0049] In one aspect, the small molecule splicing modifier (SMSM) composition comprises an effective amount of a compound having the structure of:



(IV),



(V), or



(VI).

BRIEF DESCRIPTION OF THE DRAWINGS

[0050] FIGs. 1Ai-iv shows exemplary non-canonical 5' splice site sequences, the splicing of which can be inducible with small molecule splicing modifier (SMSM) compounds. FIG. 1Ai and FIG. 1Aii depict 5' splice sites (SEQ ID NOs: 15-30) responsive to FD SMSM compounds. Depending on the exonic sequence of the 5' splice site, SMSM induced splicing leads to either exon inclusion or exon skipping. FIG. 1Aiii depicts 5' splice sites (SEQ ID NOs: 31-37) responsive to HD SMSM compounds. Splicing induced by HD SMSM compounds results in exon inclusion. FIG. 1Aiv depicts 5' splice sites (SEQ ID NOs: 38-44) responsive to SMA SMSM compounds, the splicing of which results in exon inclusion. FD: Familial Dysautonomia, HD: Huntington's Disease; SMA: spinal muscular atrophy. Nucleotides shaded in gray are conserved amongst 5' splice sites inducible by a particular family of small molecule compounds. Nucleotides shaded in black are exonic sequences that are required for small molecule induced splicing. Numbers are $-\log_{10}$ based P-value (Fisher's exact test) in k-mer analysis.

[0051] FIG. 1Bi depicts an exemplary minigene cassette containing Exon 1, Intron 1, Exon 2, Intron 2 and Exon 3. An RNA regulatory element (RRE) is split between the 3' end of Exon 2 (RRE(2)) and the 5' end of Exon 3 (RRE(2)). FIG. 1Bi shows that, in certain aspects, the minigene cassette can be inserted upstream of the transgene, e.g., in the 5'-UTR. In certain aspects, as shown in FIG. 1Bii, the minigene cassette can be inserted downstream of the transgene, e.g., in the 3'-UTR. FIG. 1Biii shows a schematic of the exon2-intron2 and intron2-exon3 boundaries.

[0052] FIG. 1C shows an exemplary schematic illustration of an RRE, e.g., an AUG start codon, in an inducible splicing cassette that, in concert with a small molecule splicing modifier (SMSM) compound (Cpd), can regulate the post-transcriptional expression of a transgene.

[0053] FIG. 1Ci shows an exemplary Splicing-Induced On (SION) splicing cassette. In the absence of an SMSM compound, exon skipping caused by splicing, or intron retention fails to reconstitute the transgene's AUG start codon thereby preventing translation of the transgene mRNA. In the presence of an SMSM compound, splicing induces exon inclusion and the generation of a functional AUG start codon that permits translation of the transgene mRNA.

[0054] FIG. 1Cii shows an exemplary Splicing-Induced Off (SIOFF) splicing cassette. In the absence of the SMSM compound, splicing induces exon skipping resulting in an AUG start codon placed in frame with the transgene's open reading frame thereby permitting translation of the transgene mRNA. In the presence of an SMSM compound, splicing results in inclusion of an intervening exon containing a nonsense UGA stop codon in frame with the transgene's AUG start codon which prevents translation of the transgene mRNA.

[0055] FIG. 1D shows an exemplary schematic illustration of an inducible polyadenylation cassette that, in concert with a small molecule splicing modifier (SMSM) compound (Cpd), can regulate the post-transcriptional expression of a transgene. In the presence of an SMSM compound, splicing induces exon inclusion and the generation of a functional AAUAAA polyadenylation signal that permits translation of the transgene mRNA. In the absence of an SMSM compound, exon skipping, or intron retention fails to reconstitute the transgene's AAUAAA polyadenylation signal. The ensuing mRNA decay prevents translation of the transgene mRNA.

[0056] FIG. 1E shows an exemplary SION configuration for SMA/HD SMSM compound induced exon inclusion. "N" means A, T/U, C or G; "D" means A, T/U or G; "ND" means at least an A is present. Nucleotide sequences in upper case are in an exon. Nucleotide sequences in lower case are in an intron.

[0057] FIG. 1F shows an exemplary SION configuration for FD SMSM compound induced exon inclusion. Nucleotide sequences in upper case are in an exon. Nucleotide sequences in lower case are in an intron.

[0058] FIG. 1G shows an exemplary SION configuration for FD SMSM compound induced exon skipping. Nucleotide sequences in upper case are in an exon. Nucleotide sequences in lower case are in an intron.

[0059] FIG. 1H shows an exemplary SIOFF configuration for FD SMSM compound induced exon skipping. Nucleotide sequences in upper case are in an exon. Nucleotide sequences in lower case are in an intron.

[0060] FIG. 1I shows an exemplary SIOFF configuration for FD SMSM compound induced exon inclusion. Nucleotide sequences in upper case are in an exon. Nucleotide sequences in lower case are in an intron.

[0061] FIG. 2A shows an exemplary map of the pAAV-GFP expression vector containing a CMV promoter, a SION/SIOFF SMSM compound inducible splicing cassette upstream of an Enhanced Green Fluorescent Protein (EGFP) transgene and a human growth hormone (hGH) poly(A) signal.

[0062] FIGs. 2Bi-vi show the sequence and length of each SMSM compound induced splicing cassette cloned into the pAAV-GFP expression vector of FIG. 2A. Nucleotide sequences in upper case are in an exon. Nucleotide sequences in lower case are in an intron. Sequences outlined in a box are exons. The AUG start codon of the EGFP transgene is in bold and underlined. Stop codons, e.g., TAA, TGA or TAG, in frame with the AUG start codon are shown in bold. SMA/HD SMSM compounds targeting 5' splice sites for exon inclusion are in dark gray, for example GA at positions -2 to -1 (see FIG. 1A). FD SMSM compounds targeting 5' splice sites for exon inclusion are shaded in black, for example CAA at positions -3 to -1 (see FIG. 1A). FD SMSM compounds targeting 5' splice sites for exon skipping have no shading, for example T at position -1 (see FIG. 1A). SMSM compound induced splicing cassettes cloned into the pAAV-GFP expression vector (SION 1-8 and SIOFF1-2) were transfected into HEK293 cells in the absence of SMSM compound. After 24 hours in culture, the transfected cells were screened for green fluorescence (see column entitled GFP expression). SION constructs having the lowest expression and SIOFF constructs with the highest expression were selected for further analysis, as highlighted in the first column by a double border.

[0063] FIG. 2Ci shows a Western blot of whole cell extracts of HEK293 cells transfected with the SION 1-8, SIOFF 1-2, pAAV-GFP constructs or a mock transfected control. The Western blot was probed with anti-GFP and β -actin antibodies.

[0064] FIG. 2Cii shows a bar graph of % expression compared to the fluorescence of pAAV-GFP DMSO.

[0065] FIGs. 3Ai-ii show chemical structures of exemplary SMA 1-2, HD 1-3 and FD 1-3 SMSM compounds.

[0066] FIGs. 3Bi-ii show GFP fluorescence in HEK293 cells transfected with SION-2, SION-3, pAAV-GFP (positive control) or mock transfected cells (negative control) in the presence of DMSO or SMSM SMA 1, SMA2, HD1, HD2 or HD3 compounds.

[0067] FIGs. 3Biii-iv show the expression of GFP in HEK293 cells transfected with SION-5, SION-6, SIOFF-1, pAAV-GFP (positive control) or mock transfected cells (negative control) in the presence of DMSO or SMSM FD1, FD2 or FD3 compounds.

[0068] FIG. 4 shows Western blot analysis of GFP expression in HEK293 transfected with SION/SIOFF constructs in the presence of SMSM compounds.

[0069] FIG. 4A shows a Western blot of whole cell extracts of HEK293 cells transfected with the SION-2 and SION 3 in the presence of 1 μ M SMA 1, SMA2, HD1, HD2, HD3 compounds or DMSO. HEK293 cells transfected with pAAV-GFP provided a positive control. Mock transfected cells in the presence of DMSO was used as a negative control. The Western blot was probed with anti-GFP and β -actin antibodies.

[0070] FIG. 4B shows the fold GFP expression in the SION2 and SION3 transfected HEK293 cells in the presence of 1 μ M SMA 1, SMA2, HD1, HD2, HD3 compounds or DMSO over the GFP expression in DMSO mock transfected cells.

[0071] FIG. 4C shows the GFP expression in SION2 and SION3 transfected HEK293 cells in the presence of 1 μ M SMA 1, SMA2, HD1, HD2, HD3 compounds or DMSO as compared to the GFP expression of HEK293 cells transfected with pAAV-GFP.

[0072] FIG. 4D shows a Western blot of whole cell extracts of HEK293 cells transfected with the SION-5 and SION 6 in the presence of DMSO or 1 μ M FD1, FD2 or FD3 compounds. HEK293 cells transfected with pAAV-GFP provided a positive control. Mock transfected cells in the presence of DMSO was used as a negative control. The Western blot was probed with anti-GFP and β -actin antibodies.

[0073] FIG. 4E shows the fold GFP expression in the SION 5 and SION6 transfected HEK293 cells in the presence of 1 μ M FD1, FD2 or DMSO over the GFP expression in DMSO mock transfected cells.

[0074] FIG. 4F shows the GFP expression in SION5 and SION6 transfected HEK293 cells in the presence of 1 μ M FD1, FD2 or DMSO as compared to the GFP expression of HEK293 cells transfected with pAAV-GFP.

[0075] FIG. 4G shows the GFP expression in SIOFF1 transfected HEK293 cells in the presence of 1 μ M FD1, FD2 or DMSO as compared to the GFP expression of HEK293 cells transfected with pAAV-GFP.

[0076] FIG. 5 shows an RT-PCR analysis of RNA splicing generated by the inducible splicing constructs transfected into HEK293 cells in the presence or absence of SMSM compounds.

[0077] FIG. 5A shows the location of PCR primers (black arrows) and the PCR products (hashed bar) produced from exon skipping, exon 2 inclusion or with the intron retained (no splicing).

[0078] FIG. 5B shows the expected sizes of the PCR fragments generated by SION 1-8, SIOFF 1-2 constructs, the positive control AAV-GFP and DMSO negative control transfected into HEK293 cells in the presence or absence of an SMSM compound as indicated.

[0079] FIGs. 5Ci-ii depict an exemplary RT-PCR analysis of the splicing of GFP pre-mRNA expressed in HEK293 cells transfected with the SION 1-8, SIOFF 1-2, and AAV-GFP constructs in the presence of DMSO or 1 μ M of the indicated SMSM compounds.

[0080] FIGs. 5Ci-ii further shows an exemplary RT-PCR analysis of the splicing of the endogenous genes POMT2, c12orf4, HTT, ZNF37BP (on which the inducible splicing cassettes SION1, SION2, SION3 and SION4 respectively are modeled) in response to DMSO, 1 μ M HD1 and HSD17B4, ZNF207, RPP14, HSD17B4 and FANCI (on which the inducible splicing cassettes SION5, SION6, SION7, SION8, SIOFF1 and SIOFF2 respectively are modeled) in response to DMSO, 1 μ M FD1 or 1 μ M FD2.

[0081] FIGs. 5Di-ii shows an exemplary dose response RT-PCR analysis of the splicing of GFP pre-mRNA expressed in HEK293 cells transfected with the SION1, SION2, SION3, SION5, SION6, SION8 and SIOFF1 constructs in the presence of DMSO, 10 nM, 100 nM, 1 μ M HD1 (for HD cassettes: SION1, SION2 and SION3) and DMSO, 10 nM, 100 nM, 1 μ M FD1 (for FD cassettes: SION5, SION6, SION8 and SIOFF1).

[0082] FIGs. 5Di-ii further shows an exemplary dose response RT-PCR analysis of the splicing of the endogenous genes POMT2, c12orf4, HTT49a (on which the inducible splicing cassettes

SION1, SION2, and SION3 respectively are modeled) in response to DMSO, 10 nM, 100 nM, and 1 μ M HD1 and HSD17B4, RPP14, and HSD17B4 (on which the inducible splicing cassettes SION5, SION8, and SIOFF1 respectively are modeled) in response to DMSO, 10 nM, 100 nM, and 1 μ M FD2.

[0083] FIG. 6A shows an exemplary schematic illustration of SION3 inducible splicing cassette deletion mutants SION3 T1-10. Each construct was transfected into HEK293 cells in the presence or absence of 1 μ M HD1 SMSM compound. pAAV-GFP vector provided a positive control. DMSO mock transfected cells was the negative control. The Western blot data of pseudoexon 49a inclusion and associated bar graph depict the fold increase in HD1 induced splicing over splicing observed in the presence of DMSO. The nucleotide “t” present in SION3T4, SION3T6, and SION3T7 indicates a g->t mutation at position +6 of the pseudoexon 49a’s 5’ splice site. The nucleotide “A” in SION3 T9 denotes a C->A mutation in the pseudoexon 49a’s 5’ splice site.

[0084] FIGs. 6Bi-iv show the nucleotide sequences of exemplary truncated SION3 inducible splicing minigene cassettes (SION3 T1-T10).

[0085] FIGs. 6Ci-ii show an exemplary dose response RT-PCR analysis of the splicing of GFP pre-mRNA expressed in HEK293 cells transfected with pAAV-GFP, SION1, SION3, SION3 T1, SION3 T2, SION3 T3, SION3 T4, SION3 T5, SION3 T6, SION3 T7, SION3 T8, SION3 T9, and SION3 T10 constructs in the presence of DMSO, 10 nM, or 1 μ M HD1. Endpoint PCR primers: SION-F-KE (5’-GGCAAAGAATTGGGATTCGAACAT-3’) (SEQ ID NO: 58) and SION-R-KE (5’-CACCCCGGTGAACAGCTC-3’) (SEQ ID NO: 59).

[0086] FIGs. 6Ciii show the expected sizes of the GFP RT-PCR fragments generated in HEK293 cells transfected with pAAV-GFP, SION1, SION3 and SION3 T1-10 constructs in the presence or absence of 1 μ M HD1. RT-PCR of GFP pre-mRNA splicing can detect exon skipping (short fragment), exon inclusion (long fragment) and the absence of splicing resulting in intron retention (extra-long fragment).

[0087] FIG. 6Civ shows the location where RT-PCR primers (black arrows) anneal to sequences flanking the inducible splicing cassette together with potential PCR fragments generated depending on GFP pre-mRNA splicing (hashed bar).

[0088] FIGs. 6Di-ii show a dose response RT-PCR analysis of endogenous POMT2, HTT, c12orf4, and CENPI gene splicing in HEK293 cells transfected with SION1, SION3, SION3

T1, SION3 T2, SION3 T3, SION3 T4, SION3 T5, SION3 T6, SION3 T7, SION3 T8, SION3 T9, and SION3 T10 constructs in the presence of DMSO, 10 nM, or 1 μ M HD1.

[0089] FIG. 7A shows an exemplary schematic illustration of the SION3 inducible splicing cassette and the location where RT-PCR primers (black and gray arrows) anneal to sequences flanking the inducible splicing cassette.

[0090] FIG. 7B shows an exemplary dose response RT-PCR analysis of the splicing of GFP pre-mRNA expressed in HEK293 cells transfected with no plasmid, SION1, SION3, SION3 T1, SION3 T2, SION3 T3, SION3 T8, and SION3 T10 constructs in the presence of DMSO, 10 nM, or 1 μ M HD1. Endpoint PCR primers used were as described in FIG. 7A corresponding to Cassette: SION-F-KE (5'-GGCAAAGAATTGGGATTCGAACAT-3') (SEQ ID NO: 58) and SION-R-KE (5'-CACCCCGGTGAACAGCTC-3') (SEQ ID NO: 59); Outside 1: β -globin-F1-SION-KE (5'-CTCCATAGAAGACACCGGGAC-3') (SEQ ID NO: 62) and SION-R-KE (5'-CACCCCGGTGAACAGCTC-3') (SEQ ID NO: 59) and Outside 2: β -globin-F1-SION-KE (5'-CTCCATAGAAGACACCGGGAC-3') (SEQ ID NO: 63) and SION-Rev (5'-CCGGACACGCTGAACTTGTG-3') (SEQ ID NO: 59).

[0091] FIG. 8A shows an exemplary schematic illustration of an Ampliseq workflow.

[0092] FIG. 8B is an exemplary Sashimi plot showing undesired splice sites detected by Ampliseq within the SION3 cassette transfected in HEK293 cells in the presence of DMSO, HD1 (1 μ M) and HD1 (10nM). Exon 49 and 50 are indicated as E49 and E50 respectively. Undesired splice sites (ss) were identified and shown. "a" and "d" represent acceptor and donor sites respectively.

[0093] FIG. 8C shows exemplary Ampliseq results for SION3. Individual read mapping to the cassette suggesting splicing of undesired splice sites was visualized in an Integrated Genome Viewer (IGV). "a" and "d" represent undesired acceptor and donor site respectively.

[0094] FIG. 8D shows the structure of SION3 and undesired acceptor sites (a) or donor sites (d) being deleted in SION3T1 and SION3T3. "a1_247" and "a2_146" are undesired acceptor sites in SION3 that when spliced generate a 247nt and a 146nt psiExon, respectively (when the downstream desired donor site of HTT-psiExon49a is also used). "a1_247" and "d1" were deleted in SION3T1. "d1", "a2_146" and the acceptor site creating the 115nt psiExon (3'ss_115) were deleted in SION3T3. SION3T3 uses "a1_247" instead as the acceptor site of the psiExon.

[0095] FIG. 8E is an exemplary Sashimi plot showing undesired splice sites detected by Ampliseq within the SION2 cassette transfected in HEK293 cells in the presence of DMSO, HD1 (1 μ M) and HD1 (10nM). Desired splicing of C12orf4 psiExon1a is shown. Undesired splice sites (ss) were identified and shown. “a” and “d” represent acceptor and donor sites respectively.

[0096] FIG. 8F shows Ampliseq results for SION2. Individual read mapping to the cassette suggesting splicing of undesired splice sites was visualized in an Integrated Genome Viewer (IGV). “a” and “d” represent undesired acceptor and donor site respectively.

[0097] FIG. 8G shows parameters used in Ampliseq percent Desired Splicing (pDS) calculation method. Percent of Desired Splicing (pDS) is calculated for each target and treatment (sample).

[0098] FIGs. 8H-I show the Ampliseq Percent of Desired Splicing (pDS, %) for the endogenous HTT e49_50 as well as SION1, SION2, SION3, SION3T1 and SION3T3 transfected into HEK293 cells in the presence of DMSO, 10 nM, or 1 μ M HD1 and SION5 and SION6 in the presence of DMSO, 10 nM, and 1 μ M FD1.

[0099] FIGs. 8J-K present the Ampliseq fold over DMSO for the endogenous HTT e49_50 as well as SION1, SION2, SION3, SION3T1 and SION3T3 transfected into HEK293 cells in the presence of DMSO, 10 nM, or 1 μ M HD1 and SION5 and SION6 in the presence of DMSO, 10 nM, and 1 μ M FD1.

[0100] FIGs. 9A-D show the sequence of mutated induced splicing cassettes (ON1m2, ON2m1, ON2m2, ON6m2, ON6m3, ON1m2, ON2m1, ON2m2, ON6m2, ON6m3) cloned into the pAAV-GFP expression vector (SEQ ID NOs: 47-55). Mutations targeted cryptic splice sites identified by Ampliseq, CG dinucleotides, upstream ATG trinucleotides in frame with the GFP's AUG start codon, and upstream TATA box sequences. Nucleotide sequences in upper case are in an exon. Nucleotide sequences in lower case are in an intron. Sequences outlined in a box are exons. The AUG start codon of the EFGR transgene is in bold with a wavy underline. Stop codons, e.g., TAA, TGA or TAG, in frame with the AUG start codon are shown in bold with dotted underline. SMA/HD SMSM compounds targeting 5' splice sites for exon inclusion are in dark gray and underlined, for example, GA at positions -2 to -1 (see FIG. 1A). FD SMSM compounds targeting 5' splice sites for exon inclusion are shaded in black, for example, CAA at positions -3 to -1 (see FIG. 1A).

[0101] FIG. 10A and FIG. 10B are exemplary Sashimi plots showing the removal of undesired splice sites in SION2m1 and SION3m1 respectively results in inducible splicing of GFP pre-mRNA and exon inclusion in HEK393 cells in the presence of 10nM and 1 μ M HD1. DMSO mock transfected cells denotes the negative control.

[0102] FIG. 10C compares the sequence of the a3 splice site in SION3 with the mutated splice acceptor site in SION3m1.

[0103] FIG. 10D shows the Ampliseq Percent of Desired Splicing (pDS, %) for the SION2m1, SION3m1, SION3T1m2 and SION3T3m2 transfected into HEK293 cells in the presence of DMSO, 10 nM, or 1 μ M HD1.

[0104] FIG. 10E shows the Ampliseq fold over DMSO for SION2m1, SION3m1, and SION3T3m2 transfected into HEK293 cells in the presence of DMSO, 10 nM, or 1 μ M HD1.

[0105] FIG. 11A depicts an exemplary dose response RT-PCR analysis of the splicing of GFP pre-mRNA expressed in HEK293 cells transfected with pAAV-GFP, SION1, SION1m2, SION2, SION2m1, SION2m2, SION3, SION3m1, SION3m2, SION3T1, SION3T1m2, SION3T3, SION3T3m2, in the presence of DMSO, 10 nM, and 1 μ M HD1 and SION6, SION6m2 and SION6m3 constructs in the presence of DMSO, 10 nM, and 1 μ M FD1.

[0106] FIG. 11B shows the sequence of cassette a, b and c PCR primers.

[0107] FIG. 11C shows the predicted length of RT-PCR fragments from exon skipping (skip) or exon inclusion (incl.) produced using the cassette a, b or c PCR primers.

[0108] FIGs. 11Di-iii show an exemplary dose response RT-PCR analysis of splicing of endogenous POMT2, c12orf4 and HTT gene pre-mRNAs in HEK293 cells transfected with pAAV-GFP, SION1, SION1m2, SION2, SION2m1, SION2m2, SION3, SION3m1, SION3m2, SION3T1, SION3T1m2, SION3T3, and SION3T3m2 constructs in the presence of DMSO, 10 nM, and 1 μ M HD1. An exemplary dose response RT-PCR analysis is also shown of the splicing of the endogenous LOC150776 gene pre-mRNA in HEK293 cells transfected with pAAV-GFP, SION1, SION1m2, SION2, SION2m1, SION2m2, SION3, SION3m1, SION3m2, SION3T1, SION3T1m2, SION3T3, and SION3T3m2 constructs in the presence of DMSO, 10 nM, and 1 μ M FD1.

[0109] FIG. 11E depicts an exemplary dose response RT-PCR analysis of the splicing of GFP pre-mRNA expressed in HEK293 cells transfected with pAAV-GFP, SION3, SION3T3,

SION3m2, and SION2m1, in the presence of DMSO, 10 nM, and 1 μ M HD1 using the outside (specific), outside (universal) and psiExon primer sets.

[0110] FIG. 11F shows the predicted length of RT-PCR fragments from exon skipping (skip), exon inclusion (incl.) or intron retention (upper, downstream or both upper and downstream introns) using the outside (specific), outside (universal) and psiExon primer sets.

[0111] FIGs. 12Ai-ii show a graph depicting the position of predicted enhancer and silencer intronic sequences within the SF3B3 intron identified using the Human splicing finder website at www.umd.be/HSF3. The position of the LMI070-induced exon (psiExon 2a) and the intronic regions with a high density of silencer sequences are indicated. The location of SF3B3 nucleotide sequences within the SION9 minigene are displayed as black bars.

[0112] FIGs. 12Bi-iii depicts the nucleotide sequences between exons 2 and 3 of the SF3B3 gene aligned with those sequences within the SION9 and SION10 minigene cassettes.

[0113] FIGs. 12Ci-ii shows the nucleotide sequences of the SION2m1, SION9 and SION10 minigene cassettes. The Table also provides the total length of each minigene cassette and the length of the pseudoexon.

[0114] FIG. 12D shows a Western blot of whole HEK293 cell extracts transfected with the SION2m1, SION-9 and SION 10 in the presence of DMSO, 10nM or 1 μ M HD1 compound. HEK293 cells transfected with pAAV-GFP provided a positive control. Mock transfected cells in the presence of DMSO were used as a negative control. The Western blot was probed with anti-GFP and β -actin antibodies.

[0115] FIG. 12Ei shows the GFP expression in the SION2m1, SION-9 and SION 10 transfected HEK293 cells in the presence of DMSO, 10nM or 1 μ M HD1 compound relative to GFP expression in pAAV-GFP transfected cells.

[0116] FIG. 12Eii shows the fold GFP expression in the SION2m1, SION-9 and SION 10 transfected HEK293 cells in the presence of DMSO, 10nM or 1 μ M HD1 compound over the GFP expression in DMSO mock transfected cells.

[0117] FIG. 13A shows a Western blot of whole HEK293 cell extracts transfected with the SION-3, SION 3T3, SION3T3m2 and SION2m1 in the presence of DMSO, 1.6 nM, 8nM, 40 nM, 200nM, 1 μ M or 5 μ M HD1 compound. HEK293 cells transfected with pAAV-GFP

provided a positive control. Mock transfected cells in the presence of DMSO were used as a negative control.

[0118] FIGs. 13B-D shows exemplary graphs of the GFP expression in the SION-3, SION3T3, SION3T3m2 and SION2m1 transfected HEK293 cells in the presence of DMSO, 1.6 nM, 8nM, 40 nM, 200nM, 1 μ M or 5 μ M HD1 compound relative to GFP expression in pAAV-GFP transfected cells (denoted as “+”) or as a fold increase over the GFP expression in DMSO mock transfected cells (denoted by “x”).

[0119] FIG. 14A shows an exemplary rAAV vector comprising at each end an inverted terminal repeat (ITR), an enhancer, a promoter, a minigene cassette operably linked to a transgene, a post-transcriptional regulatory element (PRE) and polyadenylation sequence (polyA).

[0120] FIG. 14B shows an exemplary protocol where a SION2m1 AAV eGFP vector is administered to post-natal day 0 (PND 0) CD1 mice by bilateral intracerebroventricular injection. After 5 weeks, the HD1 compound is administered orally at 2 doses (10 mg/kg and 20 mg/kg) at 3 time points (at 3 days, 7 days, and 14 days).

[0121] FIG. 14C depicts experimental parameters for testing GFP expression in mice administered a SION AAV GFP virus by bilateral intracerebroventricular injection followed by orally administered HD1 compound. The parameters include number of mice, vector name, dose (vg/mouse), dose concentration (vg/ml), volume (μ l), dose 0, 10 or 20 mg/kg), and time of euthanasia after the initiation of compound dosing (day 3, 7, or 14, 4 hours post dose).

[0122] FIG. 14D shows exemplary body weights of the test animals from 0 to 55 days.

[0123] FIG. 14E shows an RT-PCR analysis of SION2m1 pre-mRNA extracted from brain tissue taken each of the test groups 1-9 treated as described in FIG. 14C. The band corresponding to the correct splice product is depicted by the arrow.

[0124] FIG. 14Fi shows a quantification of GFP protein measured by ELISA assay or fold increase in GFP fluorescence over the GFP fluorescence of an ON2m1 vehicle (FIG. 14Fii) for each of the test animal groups 1, 3-9 treated as described in FIG. 14C.

[0125] FIG. 14Gi shows GFP fluorescence in a brain section taken from a mouse injected ICV with SION2m1 and treated with HD3 (10mg/kg) over a period of 14 days. FIG. 14Gii shows the quantification of the corresponding GFP fluorescence in the olfactory bulb of mice injected ICV with SION2m1 and treated with or without HD3 (10mg/kg) over a 14 day period. The

Table shows the fold increase in GFP expression in the presence of the HD3 compound either in vitro, in whole brain or by immunohistochemistry. FIG. 14H shows HD3 induced GFP fluorescence in olfactory bulb tissue and the corresponding quantification of GFP intensity and fold over ON2m1 with vehicle (FIG. 14Ii-iii).

[0126] FIG. 15A shows an exemplary schematic describing a study design used to test AAV9-SION3T3 in ICV injected mice treated with either with 0, 10 or 20mg/kg HD3.

[0127] FIG. 15B shows an exemplary experimental protocol including AAV vector, viral dose (vg/mouse), volume, drug (HD1 or HD3), drug dose, and time of euthanasia for each of the test groups 1-8. FIG. 15C shows the quantification of brain GFP protein for each of the test groups 1-8 of FIG. 15B.

[0128] FIG. 15D shows GFP fluorescence in brain cross sections taken from mice injected ICV with two different doses of AAV9-SION3T3 and treated with either 0 or 20mg/kg HD3. AAV-GFP was using as a positive control. AAV9-SION3T3 + vehicle was the negative control.

[0129] FIG. 16A shows an exemplary schematic describing a study design used to test AAV9-SION3T3 in subretinally injected mice treated daily with 0 or 20mg/kg HD3 starting 2 weeks post-injection.

[0130] FIG. 16B shows an exemplary experimental protocol for the subretinal injection of AAV9-SION3T3 including AAV dose, oral dosing, number of mice/group, and type of assays.

[0131] FIG. 16C shows GFP fluorescence in fundus imaging of the treated mice (Groups 1-4 of FIGs. 16A and 16B).

[0132] FIG. 16D shows GFP fluorescence in retinal flat mounts harvested from the treated mice (Groups 1-4 of FIGs. 16A and 16B).

[0133] FIG. 16E shows GFP fluorescence in cross section of eyes taken from the treated mice (Groups 1-4 of FIGs. 16A and 16B).

[0134] FIG. 16Fi shows GFP imaging in retinal cross sections taken from the treated mice (Groups 1-4 of FIGs. 16A and 16B).

[0135] FIG. 16Fii shows GFP quantification by ELISA as fold over Grp 3 (AAV9-SION3T3 with vehicle) of the treated mice (Groups 1-4 of FIGs. 16A and 16B).

[0136] FIG. 16G shows GFP and Arrestin expression in the retina of mice from Groups 2, 3 and 4 of FIG. 16B.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0137] Unless explained otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the materials, methods, and examples are illustrative only and not intended to be limiting. Other features of the disclosure are apparent from the following detailed description and the claims.

[0138] Titles or subtitles may be used in the specification for the sole convenience of the reader but are not intended to influence the scope of the present disclosure or to limit any aspect of the disclosure to any subsection, subtitle, or paragraph.

I. DEFINITIONS

[0139] As used herein, the singular forms “a,” “an,” and “the,” are intended to include the plural forms as well, unless the context clearly indicates otherwise.

[0140] The phrase “and/or,” as used herein and in the claims, is understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Thus, as a non-limiting example, a reference to “A and/or B,” when used in conjunction with open-ended language such as “comprising” can refer, in one aspect, to A only (optionally including elements other than B); in another aspect, to B only (optionally including elements other than A); in yet another aspect, to both A and B (optionally including other elements); etc

[0141] As used herein and in the claims, the phrase “at least one,” in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements, and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase “at least one” refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, “at least one of A and B” (or, equivalently, “at least one of A or B,” or, equivalently “at least one of A and/or B”) can refer, in one aspect, to at least one, optionally including more than one, A, with no B present (and

optionally including elements other than B); in another aspect, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another aspect, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

[0142] The term “or combinations thereof” as used herein refers to all permutations and combinations of the listed items preceding the term. For example, “A, B, C, or combinations thereof” is intended to include at least one of: A, B, C, AB, AC, BC, or ABC, and if order is important in a particular context, also BA, CA, CB, CBA, BCA, ACB, BAC, or CAB. Continuing with this example, expressly included are combinations that contain repeats of one or more item or term, such as BB, AAA, BBC, AAABCCCC, CBBAAA, CABABB, and so forth. The skilled artisan will understand that typically there is no limit on the number of items or terms in any combination, unless otherwise apparent from the context.

[0143] In the present application, a first element is upstream of a second element when the first element is 5' to the second element, and conversely a first element is downstream of a second element when the first element is 3' to the second element. When referring to elements being upstream or downstream of one another in the construct, this is in the context of the construct and its elements being in the forward orientation. If the construct is inverted, i.e. placed in the reverse orientation, upstream and downstream are reversed.

[0144] A "fragment" of a defined nucleotide sequence, as defined herein, is a segment of the sequence in which the 5' and/or 3' end is truncated relative to the defined nucleotide sequence. The sequence of the fragment is present within the defined nucleotide sequence as a single, contiguous nucleotide sequence.

[0145] The term "sequence identity" and "sequence homology" are used interchangeably herein, and as used in connection with a polynucleotide or polypeptide, refers to the percentage of bases or amino acids that are the same, and are in the same relative position, when comparing or aligning two sequences of polynucleotides or polypeptides. Methods for determining the level of sequence identity between two or more sequences are well known in the art and any convenient or available method may be used (e.g., BLAST, T-COFFEE, MAFFT, etc, see Altschul et al., (1990) J. Mol. Biol., 215:403-10). For example, computer programs that make pair-wise or multiple alignments of sequences are useful. For example, the programs EMBOSS Needle or EMBOSS stretcher (both Rice,

P. et al., Trends Genet., 16, (6) pp 276-277, 2000; for example, using the parameters of matrix DNAsfull, gap opening penalty 10, gap extension penalty 0.5, end gap penalty false) may be used for pairwise sequence alignments while Clustal Omega (Sievers Fetal., Mol. Syst. Biol. 7:539, 2011) or MUSCLE (Edgar, R. C., Nucleic Acids Res. 32(5):1792-1797, 2004) may be used for multiple sequence alignments. Sequence alignments and % identity calculations may also be determined using standard Clustal Omega parameters, for example, matrix Gannet, gap opening penalty 6, gap extension penalty. Alternatively, any other suitable parameters may be used. For the purposes of this disclosure, where there is dispute between sequence identity values obtained by different methods, the value obtained by global pairwise alignment using EMBOSS Needle with default parameters shall be considered valid.

[0146] When the term “about” is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below those numerical values. In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of 20%, 10%, 5%, or 1%. In certain aspects, the term “about” is used to modify a numerical value above and below the stated value by a variance of 10%. In certain aspects, the term “about” is used to modify a numerical value above and below the stated value by a variance of 5%. In certain aspects, the term “about” is used to modify a numerical value above and below the stated value by a variance of 1%. Thus, for example, if the term “about” (or “around”) in all numerical values allows for a 5% variation, i.e. a value of about 1.25% would mean from between 1.19%-1.31%.

[0147] As used herein, the terms “subject” and “patient” are used interchangeably to refer to an animal or any living organism having sensation and the power of voluntary movement, and which requires for its existence oxygen and organic food. Non-limiting examples include members of the human, equine, porcine, bovine, rattus, murine, canine and feline species. In some aspects, the subject is a mammal or a warm-blooded vertebrate animal. In certain aspects, the subject is a non-human animal. In specific aspects, the subject is a human. As used herein, the term “elderly human” refers to a human 65 years old or older. As used herein, the term “human adult” refers to a human that is 18 years or older. As used herein, the term “human child” refers to a human that is 1 year to 18 years old. As used herein, the term “human infant” refers to a newborn to 1 year old human. As used herein, the term “human toddler” refers to a human that is 1 year to 3 years old.

[0148] When a range of values is listed herein, it is intended to encompass each value and sub-range within that range. For example, “1-5 ng” or a range of “1 ng to 5 ng” is intended to encompass 1 ng, 2 ng, 3 ng, 4 ng, 5 ng, 1-2 ng, 1-3 ng, 1-4 ng, 1-5 ng, 2-3 ng, 2-4 ng, 2-5 ng, 3-4 ng, 3-5 ng, and 4-5 ng.

[0149] It will be further understood that the terms “comprises,” “comprising,” “includes,” and/or “including,” when used herein, specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof.

[0150] As used herein, the terms “treat,” “treatment,” and “treating” refer to therapeutic treatments, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a disorder. The term “treating” includes reducing or alleviating at least one adverse effect or symptom of a condition, disease, or disorder. Treatment is generally “effective” if one or more symptoms or clinical markers are reduced. Alternatively, treatment is “effective” if the progression of a disorder is reduced or halted. That is, “treatment” includes not just the improvement of symptoms or markers, but also a cessation of, or at least slowing of, progress or worsening of symptoms compared to what would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, remission (whether partial or total), and/or decreased mortality, whether detectable or undetectable. The term “treatment” of a disease also includes providing relief from the symptoms or side-effects of the disease (including palliative treatment).

[0151] A “vector” can be any genetic element that contains a nucleic acid of interest (e.g., a transgene) that is capable of being expressed in a host cell, e.g., a nucleic acid of interest within a larger nucleic acid sequence or structure suitable for delivery to a cell, tissue, and/or organism, such as a plasmid, phage, transposon, cosmid, chromosome, virus, virion, etc. For instance, a vector may comprise an insert (e.g., a heterologous nucleic acid comprising a transgene encoding a gene to be expressed or an open reading frame of that gene) and one or more additional elements, e.g., a minigene cassette as described herein, and/or elements suitable for delivering or controlling expression of the insert. The vector may be capable of replication and/or expression, e.g., when associated

with the proper control elements, and it may be capable of transferring genetic information to a cell. In some aspects, a vector may be a replication deficient vector suitable for expression in a host cell, e.g., an adeno-associated virus (AAV) vector. In some aspects, a vector may be a plasmid suitable for expression and/or replication, e.g., in a cell or bioreactor. In some aspects, vectors designed specifically for the expression of a heterologous nucleic acid sequence, e.g., a transgene encoding a protein of interest, a non-coding RNA, e.g., recombinant U snRNA, RNAi, shRNA, piwiRNA and the like, in the target cell may be referred to as expression vectors, and generally have a promoter sequence that drives expression of the transgene.

[0152] The terms “recombinant” or “engineered” as used herein means that the vector, polynucleotide, polypeptide or cell is the product of various combinations of cloning, restriction or ligation steps (e.g., relating to a polynucleotide or polypeptide comprised therein), and/or other procedures that result in a construct that is distinct from a product found in nature. A recombinant virus or vector is a viral particle comprising a recombinant polynucleotide. The terms respectively include replicates of the original polynucleotide construct and progeny of the original virus construct.

[0153] As used herein, the term “RNA” means a molecule comprising at least one ribonucleotide residue. By “ribonucleotide” is meant a nucleotide with a hydroxyl group at the 2' position of a beta-D-ribo-furanose moiety. The terms include double stranded RNA, single stranded RNA, isolated RNA such as partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA, as well as altered RNA that differs from naturally occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides. RNAs can be synthesized in a cell by RNA polymerase I, II or III.

[0154] The term “mRNA” refers to any RNA that is produced in a cell by RNA polymerase transcription of a gene. In one aspect, the mRNA of the disclosure is capped and polyadenylated. In one aspect, an mRNA of the disclosure encodes one or more proteins. In one aspect, the mRNA does not encode a protein. In another aspect, mRNA can refer to processed or unprocessed pre-mRNA. In another aspect, the mRNA of this disclosure includes, but is not limited to, pre-mRNA, spliced mRNA, partially spliced mRNA and alternatively spliced mRNA. In one aspect, the mRNA of the disclosure is a transcript that undergoes nonsense-mediated decay (NMD).

[0155] A "pre-mRNA" is the first form of RNA created through transcription of DNA (e.g., of a nucleic acid molecule described herein) that has not yet undergone further processing, such as, for example, splicing. Thus, a pre-mRNA can include both introns and exons. Pre-mRNA molecules are further processed, e.g., through splicing, to form the "mature-RNA," "spliced RNA" or "mRNA."

[0156] As used herein, the term "contiguous" refers to those nucleotides that are immediately adjacent to each other in a polynucleotide chain.

[0157] The term "align" refers to the process of comparing the nucleotide sequence of two or more nucleotide sequences to assess their degree of sequence identity. As used herein, a "match" refers to the alignment of two or more nucleotide sequences having 100% sequence identity.

[0158] A "minigene," otherwise called "an inducible splicing cassette," "minigene cassette" or simply "cassette," as the term is used herein refers to a nucleic acid sequence comprising a plurality of introns and exons, where at least one exon comprises the -4 to -1 nucleotide sequence of a SMSM compound inducible non-canonical 5' splice site, as defined herein, at its 3' end (see, for example, FIG. 1). In certain aspects, the presence or absence of SMSM compound controls the number of the minigene cassette exons present in a mature mRNA.

[0159] As used herein, the terms pseudoexon, psiExon, iExon or, in certain instances referred to as "Exon 2" or "middle exon" or "middle exon 2" are used interchangeably throughout this disclosure to refer a small molecule-inducible intronic sequence that can be converted, by SMSM compound-induced alternative splicing, into an "intron-derived exon."

[0160] A "small molecule splicing modifier" (SMSM) compound is a small organic molecule that can modulate the splicing of a pre-mRNA molecule, for example, a pre-mRNA molecule transcribed from a DNA molecule described herein. In certain aspects, the splice modulator increases the inclusion of one or more exons into the mature mRNA molecule. In other aspects, the small molecule splice modulator decreases the inclusion of an exon in the mature mRNA molecule by exon skipping. In certain aspects, the SMSM compound induces splicing at an otherwise dormant non-canonical 5' splice site.

[0161] As used herein, the term "isolated" means the physical state of an SMSM compound after being isolated and/or purified from a synthetic process (e.g., from a reaction mixture) or natural source or combination thereof according to an isolation or purification process or

processes described herein or which are well known to the skilled artisan (e.g., chromatography, recrystallization and the like) in sufficient purity to be characterized by standard analytical techniques well known to the skilled artisan.

[0162] A “therapeutically effective amount” means a minimal amount of active agent which is necessary to impart therapeutic benefit to a subject. In one example, a “therapeutically effective amount” is an amount which induces, ameliorates, stabilizes, slows down the progression or otherwise causes an improvement in the pathological symptoms, disease progression or physiological conditions associated with or resistance to succumbing to a disorder. In this instance, a therapeutically effective amount can mean an amount of SMSM compound needed to induce transgene expression in an amount sufficient to reduce at least one or more symptom(s) of a disease or disorder. In another example, the term “therapeutically effective amount” can refer to an amount of the transgene encoded product that is sufficient to produce a therapeutically or prophylactically significant reduction in a symptom or clinical marker associated with a disease or disorder when administered to a typical subject who has said condition, disease, or disorder.

[0163] In certain aspects, a transgene can mean a polynucleotide containing at least one open reading frame encoding a polypeptide or protein.

[0164] The term “coding sequence” or “coding region” means a sequence which encodes a protein or “encoding nucleic acid,” denotes a nucleic acid sequence which is transcribed (in the case of DNA) and translated (in the case of mRNA) into a polypeptide *in vitro* or *in vivo* when placed under the control of (operably linked to) appropriate regulatory sequences, e.g. a promoter. The boundaries of a protein coding mRNA sequence are delineated by a start AUG codon at the 5' end and a translation stop (UAA, UAG or UGA) codon at the 3' end. A coding sequence can include, but is not limited to, cDNA from prokaryotic or eukaryotic mRNA, genomic DNA sequences from prokaryotic or eukaryotic DNA, and even synthetic DNA sequences.

[0165] The chemical terms used throughout the description, unless specifically defined otherwise, shall be understood by one of ordinary skill in the art to have the following indicated meanings.

[0166] As used herein, the term “C₁₋₈alkyl” generally refers to saturated hydrocarbon radicals having from one to eight carbon atoms in a straight or branched chain configuration, including,

but not limited to, methyl, ethyl, n-propyl (also referred to as propyl or propanyl), isopropyl, n-butyl (also referred to as butyl or butanyl), isobutyl, sec-butyl, tert-butyl, n-pentyl (also referred to as pentyl or pentanyl), n-hexyl (also referred to as hexyl or hexanyl), n-heptyl (also referred to as heptyl or heptanyl), n-octyl and the like. In certain aspects, C₁₋₈alkyl includes, but is not limited to, C₁₋₆alkyl, C₁₋₄alkyl and the like. A C₁₋₈alkyl radical is optionally substituted with substituent species as described herein where allowed by available valences.

[0167] As used herein, the term “C₂₋₈alkenyl” generally refers to partially unsaturated hydrocarbon radicals having from two to eight carbon atoms in a straight or branched chain configuration and one or more carbon-carbon double bonds therein, including, but not limited to, ethenyl (also referred to as vinyl), allyl, propenyl and the like. In certain aspects, C₂₋₈alkenyl includes, but is not limited to, C₂₋₆alkenyl, C₂₋₄alkenyl and the like. A C₂₋₈alkenyl radical is optionally substituted with substituent species as described herein where allowed by available valences.

[0168] As used herein, the term “C₂₋₈alkynyl” generally refers to partially unsaturated hydrocarbon radicals having from two to eight carbon atoms in a straight or branched chain configuration and one or more carbon-carbon triple bonds therein, including, but not limited to, ethynyl, propynyl, butynyl and the like. In certain aspects, C₂₋₈alkynyl includes, but is not limited to, C₂₋₆alkynyl, C₂₋₄alkynyl and the like. A C₂₋₈alkynyl radical is optionally substituted with substituent species as described herein where allowed by available valences.

[0169] As used herein, the term “C₁₋₈alkoxy” generally refers to saturated hydrocarbon radicals having from one to eight carbon atoms in a straight or branched chain configuration of the formula: -O-C₁₋₈alkyl, including, but not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, n-hexoxy and the like. In certain aspects, C₁₋₈alkoxy includes, but is not limited to, C₁₋₆alkoxy, C₁₋₄alkoxy and the like. A C₁₋₈alkoxy radical is optionally substituted with substituent species as described herein where allowed by available valences.

[0170] As used herein, the term “C₃₋₁₄cycloalkyl” generally refers to a saturated or partially unsaturated monocyclic, bicyclic or polycyclic hydrocarbon radical, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, 1*H*-indanyl, indenyl, tetrahydro-naphthalenyl and the like. In certain aspects, C₃₋₁₄cycloalkyl includes, but is not limited to, C₃₋₈cycloalkyl, C₅₋₈cycloalkyl, C₃₋₁₀cycloalkyl and the like. A

C₃₋₁₄cycloalkyl radical is optionally substituted with substituent species as described herein where allowed by available valences.

[0171] As used herein, the term “aryl” generally refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical, including, but not limited to, phenyl, naphthyl, anthracenyl, fluorenyl, azulenyl, phenanthrenyl and the like. An aryl radical is optionally substituted with substituent species as described herein where allowed by available valences.

[0172] As used herein, the term “heteroaryl” generally refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms, such as an O, S or N atom, including, but not limited to, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, 1,3-thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, indolyl, indazolyl, indolizynyl, isoindolyl, benzofuranyl, benzothienyl, benzoimidazolyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, 1,3-diazinyl, 1,2-diazinyl, 1,2-diazolyl, 1,4-diazanaphthalenyl, acridinyl, furo[3,2-*b*]pyridinyl, furo[3,2-*c*]pyridinyl, furo[2,3-*c*]pyridinyl, 6*H*-thieno[2,3-*b*]pyrrolyl, thieno[3,2-*c*]pyridinyl, thieno[2,3-*d*]pyrimidinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, 1*H*-pyrrolo[3,2-*b*]pyridinyl, pyrrolo[1,2-*a*]pyrazinyl, pyrrolo[1,2-*b*]pyridazinyl, pyrazolo[1,5-*a*]pyridinyl, pyrazolo[1,5-*a*]pyrazinyl, imidazo[1,2-*a*]pyridinyl, 3*H*-imidazo[4,5-*b*]pyridinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*c*]pyrimidinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[2,1-*b*][1,3]thiazolyl, imidazo[2,1-*b*][1,3,4]thiadiazolyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl and the like. A heteroaryl radical is optionally substituted on a carbon or nitrogen atom ring member with substituent species as described herein where allowed by available valences.

[0173] In certain aspects, the nomenclature for a heteroaryl radical may differ, such as in non-limiting examples where furanyl may also be referred to as furyl, thienyl may also be referred to as thiophenyl, pyridinyl may also be referred to as pyridyl, benzothienyl may also be referred to as benzothiophenyl and 1,3-benzoxazolyl may also be referred to as 1,3-benzooxazolyl.

[0174] In certain other aspects, the term for a heteroaryl radical may also include other regioisomers, such as in non-limiting examples where the term pyrrolyl may also include 2*H*-pyrrolyl, 3*H*-pyrrolyl and the like, the term pyrazolyl may also include 1*H*-pyrazolyl and

the like, the term imidazolyl may also include *1H*-imidazolyl and the like, the term triazolyl may also include *1H*-1,2,3-triazolyl and the like, the term oxadiazolyl may also include 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl and the like, the term tetrazolyl may also include *1H*-tetrazolyl, *2H*-tetrazolyl and the like, the term indolyl may also include *1H*-indolyl and the like, the term indazolyl may also include *1H*-indazolyl, *2H*-indazolyl and the like, the term benzoimidazolyl may also include *1H*-benzoimidazolyl and the term purinyl may also include *9H*-purinyl and the like.

[0175] As used herein, the term “heterocyclyl” generally refers to a saturated or partially unsaturated monocyclic, bicyclic or polycyclic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with a heteroatom, such as an O, S or N atom, including, but not limited to, oxiranyl, oxetanyl, azetidiny, tetrahydrofuranyl, pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, isoxazolinyl, isoxazolidinyl, isothiazolinyl, isothiazolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, triazolinyl, triazolidinyl, oxadiazolinyl, oxadiazolidinyl, thiadiazolinyl, thiadiazolidinyl, tetrazolinyl, tetrazolidinyl, pyranyl, dihydro-*2H*-pyranyl, thiopyranyl, 1,3-dioxanyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,4-diazepanyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, 2,3-dihydro-1,4-benzodioxinyl, hexahydropyrrolo[3,4-*b*]pyrrol-(*1H*)-yl, (3*aS*,6*aS*)-hexahydropyrrolo[3,4-*b*]pyrrol-(*1H*)-yl, (3*aR*,6*aR*)-hexahydropyrrolo[3,4-*b*]pyrrol-(*1H*)-yl, hexahydropyrrolo[3,4-*b*]pyrrol-(*2H*)-yl, (3*aS*,6*aS*)-hexahydropyrrolo[3,4-*b*]pyrrol-(*2H*)-yl, (3*aR*,6*aR*)-hexahydropyrrolo[3,4-*b*]pyrrol-(*2H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-(*1H*)-yl, (3*aR*,6*aS*)-hexahydropyrrolo[3,4-*c*]pyrrol-(*1H*)-yl, (3*aR*,6*aR*)-hexahydropyrrolo[3,4-*c*]pyrrol-(*1H*)-yl, octahydro-*5H*-pyrrolo[3,2-*c*]pyridinyl, octahydro-*6H*-pyrrolo[3,4-*b*]pyridinyl, (4*aR*,7*aR*)-octahydro-*6H*-pyrrolo[3,4-*b*]pyridinyl, (4*aS*,7*aS*)-octahydro-*6H*-pyrrolo[3,4-*b*]pyridinyl, hexahydropyrrolo[1,2-*a*]pyrazin-(*1H*)-yl, (7*R*,8*aS*)-hexahydropyrrolo[1,2-*a*]pyrazin-(*1H*)-yl, (8*aS*)-hexahydropyrrolo[1,2-*a*]pyrazin-(*1H*)-yl, (8*aR*)-hexahydropyrrolo[1,2-*a*]pyrazin-(*1H*)-yl, (8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-(*1H*)-yl, (8*aR*)-octahydropyrrolo[1,2-*a*]pyrazin-(*1H*)-yl, hexahydropyrrolo[1,2-*a*]pyrazin-(*2H*)-one, octahydro-*2H*-pyrido[1,2-*a*]pyrazinyl, 3-azabicyclo[3.1.0]hexyl, (1*R*,5*S*)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]octyl,

8-azabicyclo[3.2.1]oct-2-enyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl, (1*R*,5*S*)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 3,8-diazabicyclo[3.2.1]octyl, (1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, azaspiro[3.3]heptyl, 2,6-diazaspiro[3.3]heptyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 2,7-diazaspiro[4.4]nonyl, 6,9-diazaspiro[4.5]decyl and the like. A heterocyclyl radical is optionally substituted on a carbon or nitrogen atom ring member with substituent species as described herein where allowed by available valences.

[0176] In certain aspects, the nomenclature for a heterocyclyl radical may differ, such as in non-limiting examples where 1,3-benzodioxolyl may also be referred to as benzo[*d*][1,3]dioxolyl and 2,3-dihydro-1,4-benzodioxinyl may also be referred to as 2,3-dihydrobenzo[*b*][1,4]dioxinyl.

[0177] As used herein, the term “heteroaryl-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-heteroaryl.

[0178] As used herein, the term “C₁₋₈alkoxy-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-O-C₁₋₈alkyl.

[0179] As used herein, the term “C₁₋₈alkoxy-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-O-C₁₋₈alkyl.

[0180] As used herein, the term “(C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino” refers to a radical of the formula: -N(C₁₋₈alkyl-O-C₁₋₈alkyl)₂.

[0181] As used herein, the term “C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-NH-C₁₋₈alkyl-O-C₁₋₈alkyl.

[0182] As used herein, the term “(C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-N(C₁₋₈alkyl-O-C₁₋₈alkyl)₂.

[0183] As used herein, the term “(C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-N(C₁₋₈alkyl)(C₁₋₈alkyl-O-C₁₋₈alkyl).

[0184] As used herein, the term “C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-NH-C₁₋₈alkyl-O-C₁₋₈alkyl.

[0185] As used herein, the term “(C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-N(C₁₋₈alkyl-O-C₁₋₈alkyl)₂.

[0186] As used herein, the term “(C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-N(C₁₋₈alkyl)(C₁₋₈alkyl-O-C₁₋₈alkyl).

[0187] As used herein, the term “C₁₋₈alkoxy-carbonyl” refers to a radical of the formula: -C(O)-O-C₁₋₈alkyl.

[0188] As used herein, the term “C₁₋₈alkoxy-carbonyl-C₂₋₈alkenyl” refers to a radical of the formula: -C₂₋₈alkenyl-C(O)-O-C₁₋₈alkyl.

[0189] As used herein, the term “C₁₋₈alkoxy-carbonyl-amino” refers to a radical of the formula: -NH-C(O)-O-C₁₋₈alkyl.

[0190] As used herein, the term “heteroaryl-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-heteraryl.

[0191] As used herein, the term “C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl.

[0192] As used herein, the term “(C₁₋₈alkyl)₂-amino” refers to a radical of the formula: -N(C₁₋₈alkyl)₂.

[0193] As used herein, the term “C₁₋₈alkyl-amino-C₂₋₈alkenyl” refers to a radical of the formula: -C₂₋₈alkenyl-NH-C₁₋₈alkyl.

[0194] As used herein, the term “(C₁₋₈alkyl)₂-amino-C₂₋₈alkenyl” refers to a radical of the formula: -C₂₋₈alkenyl-N(C₁₋₈alkyl)₂.

[0195] As used herein, the term “C₁₋₈alkyl-amino-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-NH-C₁₋₈alkyl.

[0196] As used herein, the term “(C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-N(C₁₋₈alkyl)₂.

[0197] As used herein, the term “C₁₋₈alkyl-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-NH-C₁₋₈alkyl.

[0198] As used herein, the term “(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-N(C₁₋₈alkyl)₂.

[0199] As used herein, the term “C₁₋₈alkyl-amino-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-NH-C₁₋₈alkyl.

[0200] As used herein, the term “(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-N(C₁₋₈alkyl)₂.

[0201] As used herein, the term “(C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino” refers to a radical of the formula: -N(C₁₋₈alkyl-NH-C₁₋₈alkyl)₂.

[0202] As used herein, the term “[C(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl]₂-amino” refers to a radical of the formula: -N[C₁₋₈alkyl-N(C₁₋₈alkyl)₂]₂.

[0203] As used herein, the term “(C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)(C₁₋₈alkyl-NH-C₁₋₈alkyl).

[0204] As used herein, the term “[C(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)[C₁₋₈alkyl-N(C₁₋₈alkyl)₂].

[0205] As used herein, the term “C₁₋₈alkyl-amino-C₂₋₈alkynyl” refers to a radical of the formula: -C₂₋₈alkynyl-NH-C₁₋₈alkyl.

[0206] As used herein, the term “(C₁₋₈alkyl)₂-amino-C₂₋₈alkynyl” refers to a radical of the formula: -C₂₋₈alkynyl-N(C₁₋₈alkyl)₂.

[0207] As used herein, the term “C₁₋₈alkyl-carbonyl” refers to a radical of the formula: -C(O)-C₁₋₈alkyl.

[0208] As used herein, the term “C₁₋₈alkyl-carbonyl-amino” refers to a radical of the formula: -NH-C(O)-C₁₋₈alkyl.

[0209] As used herein, the term “C₁₋₈alkyl-thio” refers to a radical of the formula: -S-C₁₋₈alkyl.

[0210] As used herein, the term “amino-C₂₋₈alkenyl” refers to a radical of the formula: -C₂₋₈alkenyl-NH₂.

[0211] As used herein, the term “amino-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-NH₂.

[0212] As used herein, the term “amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-NH₂.

[0213] As used herein, the term “amino-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-NH₂.

[0214] As used herein, the term “(amino-C₁₋₈alkyl)₂-amino” refers to a radical of the formula: -N(C₁₋₈alkyl-NH₂)₂.

[0215] As used herein, the term “(amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)(C₁₋₈alkyl-NH₂).

[0216] As used herein, the term “amino-C₂₋₈alkynyl” refers to a radical of the formula: -C₂₋₈alkynyl-NH₂.

[0217] As used herein, the term “aryl-C₁₋₈alkoxy-carbonyl” refers to a radical of the formula: -C(O)-O-C₁₋₈alkyl-aryl.

[0218] As used herein, the term “aryl-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-aryl.

[0219] As used herein, the term “aryl-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-aryl.

[0220] As used herein, the term “(aryl-C₁₋₈alkyl)₂-amino” refers to a radical of the formula: -N(C₁₋₈alkyl-aryl)₂.

[0221] As used herein, the term “(aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)(C₁₋₈alkyl-aryl).

[0222] As used herein, the term “aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-NH-C₁₋₈alkyl-aryl.

[0223] As used herein, the term “(aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-N(C₁₋₈alkyl-aryl)₂.

[0224] As used herein, the term “(aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-N(C₁₋₈alkyl)(C₁₋₈alkyl-aryl).

[0225] As used herein, the term “aryl-amino” refers to a radical of the formula: -NH-aryl.

[0226] As used herein, the term “aryl-amino-carbonyl” refers to a radical of the formula: -C(O)-NH-aryl.

[0227] As used herein, the term “aryl-sulfonyloxy-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-O-SO₂-aryl.

[0228] As used herein, the term “benzoxycarbonyl” refers to a radical of the formula: -C(O)-O-CH₂-phenyl.

[0229] As used herein, the term “C₃₋₁₄cycloalkyl-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-C₃₋₁₄cycloalkyl.

[0230] As used herein, the term “C₃₋₁₄cycloalkyl-amino” refers to a radical of the formula: -NH-C₃₋₁₄cycloalkyl.

[0231] As used herein, the term “C₃₋₁₄cycloalkyl-oxy” refers to a radical of the formula: -O-C₃₋₁₄cycloalkyl.

[0232] As used herein, the term “aryl-oxy” refers to a radical of the formula: -O-aryl.

[0233] As used herein, the term “halo” or “halogen” generally refers to a halogen atom radical, including fluoro, chloro, bromo and iodo.

[0234] As used herein, the term “halo-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-halo, wherein C₁₋₈alkyl is partially or completely substituted with one or more halogen atoms where allowed by available valences.

[0235] As used herein, the term “halo-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-halo, wherein C₁₋₈alkyl is partially or completely substituted with one or more halogen atoms where allowed by available valences.

[0236] As used herein, the term “halo-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-halo.

[0237] As used herein, the term “(halo-C₁₋₈alkyl)(C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)(C₁₋₈alkyl-halo).

[0238] As used herein, the term “(halo-C₁₋₈alkyl)₂-amino” refers to a radical of the formula: -N(C₁₋₈alkyl-halo)₂.

[0239] As used herein, the term “heteroaryl-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-heteroaryl.

[0240] As used herein, the term “heteroaryl-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-heteroaryl.

[0241] As used herein, the term “heteroaryl-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-heteroaryl.

[0242] As used herein, the term “(heteroaryl-C₁₋₈alkyl)₂-amino” refers to a radical of the formula: -N(C₁₋₈alkyl-heteroaryl)₂.

[0243] As used herein, the term “(heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)(C₁₋₈alkyl-heteroaryl).

[0244] As used herein, the term “heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-NH-C₁₋₈alkyl-heteroaryl.

[0245] As used herein, the term “(heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-N(C₁₋₈alkyl-heteroaryl)₂.

[0246] As used herein, the term “(heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-N(C₁₋₈alkyl)(C₁₋₈alkyl-heteroaryl).

[0247] As used herein, the term “heteroaryl-amino” refers to a radical of the formula: -NH-heteroaryl.

[0248] As used herein, the term “heterocyclyl-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-heterocyclyl.

[0249] As used herein, the term “heterocyclyl-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-heterocyclyl.

[0250] As used herein, the term “heterocyclyl-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-heterocyclyl.

[0251] As used herein, the term “(heterocyclyl-C₁₋₈alkyl)₂-amino” refers to a radical of the formula: -N(C₁₋₈alkyl-heterocyclyl)₂.

[0252] As used herein, the term “(heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)(C₁₋₈alkyl-heterocyclyl).

[0253] As used herein, the term “heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-NH-C₁₋₈alkyl-heterocyclyl.

[0254] As used herein, the term “(heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-N(C₁₋₈alkyl-heterocyclyl)₂.

[0255] As used herein, the term “(heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-N(C₁₋₈alkyl)(C₁₋₈alkyl-heterocyclyl).

[0256] As used herein, the term “heterocyclyl-amino” refers to a radical of the formula: -NH-heterocyclyl.

[0257] As used herein, the term “(heterocyclyl)(C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)(heterocyclyl).

[0258] As used herein, the term “heterocyclyl-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-NH-heterocyclyl.

[0259] As used herein, the term “heterocyclyl-carbonyl” refers to a radical of the formula: -C(O)-heterocyclyl.

[0260] As used herein, the term “heterocyclyl-carbonyl-oxy” refers to a radical of the formula: -O-C(O)-heterocyclyl.

[0261] As used herein, the term “heterocyclyl-oxy” refers to a radical of the formula: -O-heterocyclyl.

[0262] As used herein, the term “hydroxy” refers to a radical of the formula: -OH.

[0263] As used herein, the term “hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-O-C₁₋₈alkyl-OH.

[0264] As used herein, the term “hydroxy-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-OH, wherein C₁₋₈alkyl is partially or completely substituted with one or more hydroxy radicals where allowed by available valences.

[0265] As used herein, the term “hydroxy-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-OH.

[0266] As used herein, the term “(hydroxy-C₁₋₈alkyl)₂-amino” refers to a radical of the formula: -N(C₁₋₈alkyl-OH)₂.

[0267] As used herein, the term “(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)(C₁₋₈alkyl-OH).

[0268] As used herein, the term “hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-NH-C₁₋₈alkyl-OH.

[0269] As used herein, the term “(hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-N(C₁₋₈alkyl-OH)₂.

[0270] As used herein, the term “(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-N(C₁₋₈alkyl)(C₁₋₈alkyl-OH).

[0271] As used herein, the term “hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-NH-C₁₋₈alkyl-OH.

[0272] As used herein, the term “(hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-N(C₁₋₈alkyl-OH)₂.

[0273] As used herein, the term “(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy” refers to a radical of the formula: -O-C₁₋₈alkyl-N(C₁₋₈alkyl)(C₁₋₈alkyl-OH).

[0274] As used herein, the term “hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-NH-C₁₋₈alkyl-OH.

[0275] As used herein, the term “(hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino” refers to a radical of the formula: -N(C₁₋₈alkyl-NH-C₁₋₈alkyl-OH)₂.

[0276] As used herein, the term “(hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-N(C₁₋₈alkyl-OH)₂.

[0277] As used herein, the term “(hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl) (C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)(C₁₋₈alkyl-NH-C₁₋₈alkyl-OH).

[0278] As used herein, the term “[(hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)[C₁₋₈alkyl-N(C₁₋₈alkyl-OH)₂].

[0279] As used herein, the term “(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl-amino” refers to a radical of the formula: -NH-C₁₋₈alkyl-N(C₁₋₈alkyl,C₁₋₈alkyl-OH).

[0280] As used herein, the term “[(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl](C₁₋₈alkyl)amino” refers to a radical of the formula: -N(C₁₋₈alkyl)[C₁₋₈alkyl-N(C₁₋₈alkyl)(C₁₋₈alkyl-OH)].

[0281] As used herein, the term “substituent” means positional variables on the atoms of a core molecule that are substituted at a designated atom position, replacing one or more hydrogens on the designated atom, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. A person of ordinary skill in the art should note that any carbon as well as heteroatom with valences that appear to be unsatisfied as described or shown herein is assumed to have a sufficient number of hydrogen atom(s) to satisfy the valences described or shown. In certain instances one or more substituents having a double bond (e.g., “oxo” or “=O”) as the point of attachment may

be described, shown or listed herein within a substituent group, wherein the structure may only show a single bond as the point of attachment to the core structure of Formula (I). A person of ordinary skill in the art would understand that, while only a single bond is shown, a double bond is intended for those substituents.

[0282] As used herein, the term “and the like,” with reference to the definitions of chemical terms provided herein, means that variations in chemical structures that could be expected by one skilled in the art include, without limitation, isomers (including chain, branching or positional structural isomers), hydration of ring systems (including saturation or partial unsaturation of monocyclic, bicyclic or polycyclic ring structures) and all other variations where allowed by available valences which result in a stable compound.

[0283] For the purposes of this description, where one or more substituent variables for a compound of Formula (I) or a form thereof, encompass functionalities incorporated into a compound of Formula (I), each functionality appearing at any location within the disclosed compound may be independently selected, and as appropriate, independently and/or optionally substituted.

[0284] As used herein, the terms “independently selected,” or “each selected” refer to functional variables in a substituent list that may occur more than once on the structure of Formula (I), the pattern of substitution at each occurrence is independent of the pattern at any other occurrence. Further, the use of a generic substituent variable on any formula or structure for a compound described herein is understood to include the replacement of the generic substituent with species substituents that are included within the particular genus, *e.g.*, aryl may be replaced with phenyl or naphthalenyl and the like, and that the resulting compound is to be included within the scope of the compounds described herein.

[0285] As used herein, the terms “each instance of” or “in each instance, when present,” when used preceding a phrase such as “...C₃₋₁₄cycloalkyl, C₃₋₁₄cycloalkyl-C₁₋₄alkyl, aryl, aryl-C₁₋₄alkyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heterocyclyl and heterocyclyl-C₁₋₄alkyl,” are intended to refer to the C₃₋₁₄cycloalkyl, aryl, heteroaryl and heterocyclyl ring systems when each are present either alone or as a substituent.

[0286] As used herein, the term “optionally substituted” means optional substitution with the specified substituent variables, groups, radicals or moieties.

II. SMALL MOLECULE SPLICING MODIFIER (SMSM) COMPOUNDS

[0287] Splicing processes primary messenger ribonucleic acid (mRNA) transcribed from deoxyribonucleic acid (DNA) before the mRNA is translated into a protein. Splicing involves removing one or more contiguous segments of mRNA and is directed, in part, by a spliceosome. The segments that are removed are often referred to as introns, but the spliceosome may remove segments that contain both introns and exons.

[0288] An “exon” can be any part of a gene that is a part of the final mature RNA produced by that gene after introns have been removed by RNA splicing. The term “exon” refers to both the DNA sequence within a gene and to the corresponding sequence in RNA transcripts. Exons may contain translated (e.g., protein coding region) or untranslated regions (e.g., 5' or 3' untranslated regions or UTRs).

[0289] The term “intron” refers to both the DNA sequence within a gene and the corresponding sequence in the unprocessed RNA transcript. As part of the RNA processing pathway, introns can be removed by RNA splicing either shortly after or concurrent with transcription. They can be found in a wide range of genes, including those that generate proteins, ribosomal RNA (rRNA), and transfer RNA (tRNA).

[0290] In one aspect, the terms "canonical splice site" or "consensus splice site" can be used interchangeably and refer to splice sites that are conserved across species. Consensus sequences for the 5' splice site and the 3' splice site used in eukaryotic RNA splicing are well known in the art (see, e.g., Gesteland et al. (eds.), *The RNA World*, 3rd Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, (2006), Watson et al, *supra*, and Mount, *Nucleic Acid Res.*, 10: 459-472 (1982), the contents of which are incorporated by reference herein in their entirety). These consensus sequences include nearly invariant dinucleotides at each end of the intron: GT at the 5' end of the intron, and AG at the 3' end of an intron.

[0291] In one aspect, a “canonical 5' splice site” or splice donor site consensus sequence can be (for DNA) CAG/GTRAG (where A is adenosine, T is thymine, G is guanine, C is cytosine, R is a purine and "/" indicates the site of cleavage).

[0292] In one aspect, a “non-canonical 5' splice site” can be (for DNA) the sequence NNNN/GTNNNN (SEQ ID NO: 68) where N can be any one of adenosine, thymine, guanine, cytosine and "/" is the splice site except for a canonical 5' splice site having the sequence of CAG/GTRAG (where A is adenosine, T is thymine, G is guanine, C is cytosine, R is a purine

and "/" indicates the site of cleavage). In some aspects, a non-canonical 5' splice site is dormant in the absence of both a proximal pseudo-ESE and SMSM compound as described herein.

[0293] In one aspect, the splice acceptor site consists of three separate sequence elements: the branch point or branch site, a polypyrimidine tract and the 3' splice site consensus sequence. The branch point consensus sequence in eukaryotes is YNYTRAC (where Y is a pyrimidine, N is any nucleotide, and R is a purine; the underlined A is the site of branch formation. The 3' splice site consensus sequence is YAG (where Y is a pyrimidine) (see, e.g., Griffiths et al, eds., Modern Genetic Analysis, 2nd edition, W.H. Freeman and Company, New York (2002), the contents of which are incorporated by reference herein in their entirety).

[0294] In one aspect, a proximal splicing enhancer sequence is required but not sufficient for splicing at a non-canonical 5' splice site.

[0295] The compounds of the disclosure, referred to herein as "small molecules," "compounds," "small molecule compounds," or "small molecule splicing modifier" (SMSM) compounds, are molecules that can induce splicing at an otherwise dormant non-canonical 5' splice site having a specific -4 to -1 nucleotide sequence (FIG. 1A). Because these sequences can also be found in genes causing certain monogenic genetic diseases such as spinal muscular atrophy (SMA), Huntington's Disease (HTT) and Familial dysautonomia (FD), the compounds are identified herein as SMA, HD or FD compounds, respectively.

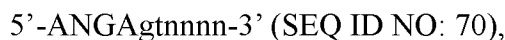
Exemplary SMA compounds

[0296] Spinal Muscular Atrophy (SMA) refers to a group of hereditary diseases that damages and kills specialized nerve cells in the brain and spinal cord (called motor neurons). Motor neurons control movement in the arms, legs, face, chest, throat, and tongue, as well as skeletal muscle activity including speaking, walking, swallowing, and breathing.

[0297] SMA is caused by an inactivating mutation or deletion of the telomeric copy of the gene (SMN1) in both chromosomes, resulting in the loss of SMN1 gene function. However, all patients retain the centromeric copy of the gene (SMN2), and the copy number of the SMN2 gene in SMA patients generally correlates inversely with the disease severity; i.e., patients with less severe SMA have more copies of SMN2. Nevertheless, SMN2 is unable to compensate completely for the loss of SMN1 function due to alternative splicing of exon 7 caused by a translationally silent C to T mutation in exon 7. As a result, the majority of transcripts produced

from SMN2 lack exon 7 (SMN2 $\Delta 7$) and encode a truncated SMN protein that has an impaired function and is rapidly degraded.

[0298] In one aspect, as disclosed herein, SMA SMSM compounds, also referred to herein simply as “SMA compounds,” can induce splicing at 5' splice sites having the nucleotide sequence of:

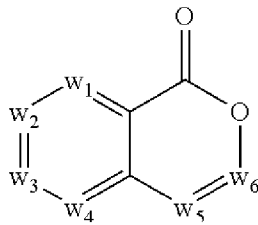


where N is A, G, C or T and “/” indicates the splice site, including the mutated 5' splice site in exon 7 of the SMN I gene (see FIG. 1Aiv).

SMA Compounds of Formula (IX) – (X)

[0299] In one aspect, an SMA compound of the disclosure can refer to a compound as disclosed in the U.S. Patent Nos. 9,399,649 and 9,969,754, the content of each patent is incorporated by reference herein in its entirety.

[0300] In one aspect, an SMA compound of the disclosure can refer to a compound of Formula (IX):



(IX)

or a form thereof, wherein:

w_1 is C— R_b or N;

w_2 and w_6 are C— R_1 or C— R_2 ;

w_3 , w_4 and w_5 are C— R_a or N;

wherein one of w_2 and w_6 is C— R_1 and the other is C— R_2 , provided that, when w_2 is C— R_1 , then w_6 is C— R_2 ; or, when w_2 is C— R_2 , then w_6 is C— R_1 ; and,

wherein anyone, two or three of the remaining w_1 , w_3 , w_4 and w_5 may simultaneously be N;

R_1 is C_{1-8} alkyl, amino, C_{1-8} alkyl-amino, $(C_{1-8}$ alkyl) $_2$ -amino, C_{1-8} alkoxy- C_{1-8} alkyl-amino, $(C_{1-8}$ alkoxy- C_{1-8} alkyl) $_2$ -amino, $(C_{1-8}$ alkoxy- C_{1-8} alkyl)(C_{1-8} alkyl)amino, amino- C_{1-8} alkyl, C_{1-8} alkyl-amino- C_{1-8} alkyl, $(C_{1-8}$ alkyl) $_2$ -amino- C_{1-8} alkyl, C_{1-8} alkoxy- C_{1-8} alkyl-

amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, (amino-C₁₋₈alkyl)₂-amino, (amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, amino-C₁₋₈alkoxy, C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, amino-C₂₋₈alkenyl, C₁₋₈alkyl-amino-C₂₋₈alkenyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkenyl, amino-C₂₋₈alkynyl, C₁₋₈alkyl-amino-C₂₋₈alkynyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkynyl, halo-C₁₋₈alkyl-amino, (halo-C₁₋₈alkyl)₂-amino, (halo-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl-amino, [(hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, [(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, heterocyclyl, heterocyclyl-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkoxy, heterocyclyl-amino, (heterocyclyl)(C₁₋₈alkyl)amino, heterocyclyl-amino-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkyl-amino, (heterocyclyl-C₁₋₈alkyl)₂-amino, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl-oxy, heterocyclyl-carbonyl, heterocyclyl-carbonyl-oxy, aryl-C₁₋₈alkyl-amino, (aryl-C₁₋₈alkyl)₂-amino, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heteroaryl, heteroaryl-C₁₋₈alkyl, heteroaryl-C₁₋₈alkoxy, heteroaryl-amino, heteroaryl-C₁₋₈alkyl-amino, (heteroaryl-C₁₋₈alkyl)₂-amino, (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl;

wherein, each instance of heterocyclyl and heteroaryl is optionally substituted with one, two or three R₃ substituents and one additional, optional R₄ substituent; and, wherein, alternatively, each instance of heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R₃ substituents;

R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino;

wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with one, two or three R₆ substituents and one additional, optional R₇ substituent;

R_a is, in each instance, independently selected from hydrogen, halogen or C₁₋₈alkyl;

R_b is hydrogen, halogen, C₁₋₈alkyl or C₁₋₈alkoxy;

R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, oxo, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkyl-carbonyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl]₂-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, C₁₋₈alkyl-carbonyl-amino, C₁₋₈alkoxy-carbonyl-amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino or (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino;

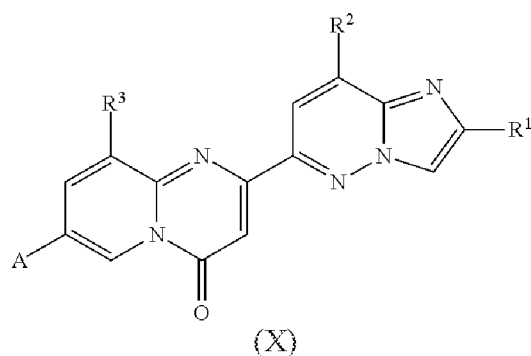
R₄ is C₃₋₁₄cycloalkyl, C₃₋₁₄cycloalkyl-C₁₋₈alkyl, C₃₋₁₄cycloalkyl-amino, aryl-C₁₋₈alkyl, aryl-C₁₋₈alkoxy-carbonyl, aryl-sulfonyloxy-C₁₋₈alkyl, heterocyclyl or heterocyclyl-C₁₋₈alkyl; wherein, each instance of C₃₋₁₄cycloalkyl, aryl and heterocyclyl is optionally substituted with one, two or three R₅ substituents;

R₅ is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino or C₁₋₈alkyl-thio;

R₆ is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C₁₋₈alkyl, C₂₋₈alkenyl, halo-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino or C₁₋₈alkyl-thio; and,

R₇ is C₃₋₁₄cycloalkyl, C₃₋₁₄cycloalkyl-oxy, aryl, heterocyclyl or heteroaryl.

[0301] In one aspect, an SMA compound of the disclosure can also refer to a compound of Formula (X):



wherein

R^1 is hydrogen or C_{1-7} -alkyl;

R^2 is hydrogen, cyano, C_{1-7} -haloalkyl or C_{3-8} -cycloalkyl;

R^3 is hydrogen, C_{1-7} -alkyl, or C_{3-8} -cycloalkyl;

A is N-heterocycloalkyl or $NR^{12}R^{13}$, wherein N-heterocycloalkyl comprises 1 or 2 nitrogen ring atoms and is optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14} ;

R^{12} is heterocycloalkyl comprising 1 nitrogen ring atom, wherein heterocycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents selected from R^{14} ;

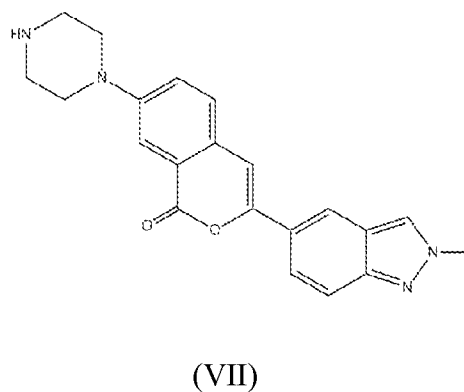
R^{13} is hydrogen, C_{1-7} -alkyl or C_{3-8} -cycloalkyl;

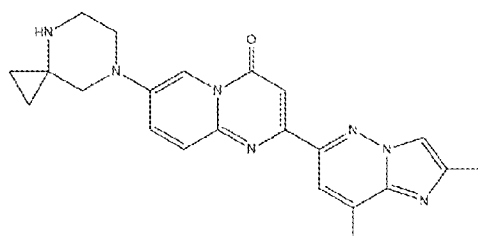
R^{14} is independently selected from hydrogen, C_{1-7} -alkyl, amino, amino- C_{1-7} -alkyl, C_{3-8} -cycloalkyl and heterocycloalkyl or two R^{14} together form C_{1-7} -alkylene;

with the proviso that if A is N-heterocycloalkyl comprising only 1 nitrogen ring atom, then at least one R^{14} substituent is amino or amino- C_{1-7} -alkyl;

and pharmaceutically acceptable salts thereof.

[0302] In one aspect, an SMA compound may have the structure of





(VIII)

[0303] In one aspect, an SMA compound may include, but is not limited to, compounds disclosed in U.S. Patent No. 9,399,649, the content of which is incorporated by reference herein in its entirety, and compounds disclosed in U.S. Patent No. 9,969,754, the content of which is incorporated by reference herein in its entirety.

[0304] In one aspect, as described herein, an SMA compound, or a pharmaceutically acceptable salt thereof, may be prepared by those skilled in the art, such as, by the synthetic methods set forth in, for example, International Application Number PCT/EP2018/075282, filed September 19, 2018 and published as WO/2019/057740 on March 28, 2019 and in International Application Number PCT/EP2019/078313, filed October 18, 2019 and published as WO/2020/079203 on April 23, 2020. All these references are incorporated by reference herein in their entireties as if fully set forth herein.

[0305] In addition to the correction of aberrant splicing of the SMN 1 gene transcripts, SMA compounds can also impact the splicing of endogenous genes identified in the published U.S. patent application No. 2019/0330615 and Singh et al. (2020) Neuroscience Insights 15: 1-11, the contents of which are incorporated by reference herein in their entireties).

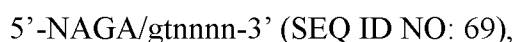
[0306] For example, SMA/HD compounds can induce exon inclusion via splicing endogenous genes, including but not limited to, for example, POMT2 (Protein O-Mannosyltransferase 2; HGNC: 19743, Entrez Gene: 29954); c12orf4 (Chromosome 12 Open Reading Frame 4; HGNC: 1184; Entrez Gene: 57102), CENPI (Centromere Protein I; HGNC: 3968; Entrez Gene: 2491), XRN2 (5'-3' Exoribonuclease 2, HGNC: 12836; Entrez Gene: 22803); STRN3 (Striatin 3; HGNC: 15720; Entrez Gene: 29966), FOXM1 (Forkhead Box M1; HGNC: 3818; Entrez Gene: 2305), MADD (MAP Kinase Activating Death Domain; HGNC: 6766, Entrez Gene: 8567); APLP2 (Amyloid Beta Precursor Like Protein 2; HGNC: 598; Entrez Gene: 334), SLC25A17 (Solute Carrier Family 25 Member 17, HGNC: 10987 Entrez Gene: 10478), and ZNF37BP_i4s (Zinc Finger Protein 37B, Pseudogene; HGNC: 13103 Entrez Gene: 100129482).

Exemplary HD compounds

[0307] Huntington's disease (HD) is an autosomal dominant, progressive, neurodegenerative disorder. HD is characterized by motor, cognitive, and psychiatric symptoms due to progressive atrophy of the striatum as well as of cortical and other extra-striatal areas of the brain. In advanced cases, there is also loss of neurons in the thalamus, substantia nigra pars reticulata and in the subthalamic nucleus. The huntingtin (HTT) gene is widely expressed and is required for normal development. HD pathology is caused by an expanded, unstable trinucleotide repeat in the huntingtin gene leading to the production of a mutant HTT protein (mHTT) having an extended polyglutamine repeat. A range of 10-35 trinucleotide repeats is found in wild type HTT protein but repeat numbers greater than 36 are generally pathogenic by a dominant toxic gain of function mechanism.

[0308] HD SMSM compounds induce alternative splicing of an intronic sequence, pseudoexon 49a, which can be spliced into a fully spliced mRNA (exon inclusion), an event which leads to a frameshift in the mRNA's open reading frame and the production of premature stop codons. The ensuing premature termination of translation triggers nonsense mediated decay (NMD) of the mRNA and a concomitant reduction in the amount of protein encoded by the mRNA. HD SMSM compounds are therefore being developed as a treatment for HD.

[0309] In one aspect, as disclosed herein, HD SMSM compounds, also referred to herein simply as "HD compounds," induce splicing at a non-canonical 5' splice sites having the nucleotide sequence of:

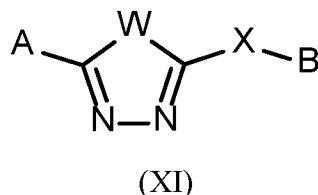


where N is A, G, C or T and "/" is the splice site (see FIG. 1Aiii).

HD Compounds of Formula (XI)

[0310] In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in U.S. Patent No. 10,874,672, the content of which is incorporated by reference herein in its entirety.

[0311] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XI):



or a form thereof, wherein

W is CH=CH or S;

X is CH₂, CH(C₁₋₄alkyl), C(C₁₋₄alkyl)₂, CH=CH, O, NR₅, or a bond;

A is aryl, heteroaryl, heterocyclyl, or C₉₋₁₀cycloalkyl,

wherein aryl is selected from phenyl and naphthyl, each optionally substituted with 1, 2, 3, or 4 substituents each selected from R₁,

wherein heteroaryl is a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms, such as an O, S, or N atom each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₁,

wherein heterocyclyl is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₂, and

wherein C₉₋₁₀cycloalkyl is a saturated or partially unsaturated bicyclic ring system optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₂;

B is heterocyclyl,

wherein heterocyclyl is a saturated or partially unsaturated monocyclic, bicyclic or polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₄;

R₁ is halogen, hydroxyl, cyano, C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, (C₁₋₄alkyl)₂-amino-C₁₋₄alkyl, amino-carbonyl, C₁₋₄alkyl-amino-carbonyl, (C₁₋₄alkyl)₂-amino-carbonyl, C₁₋₄alkyl-amino-carbonyl-C₁₋₄alkyl, (C₁₋₄alkyl)₂-amino-carbonyl-C₁₋₄alkyl, C₁₋₄alkyl-carbonyl-amino, C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkyl-carbonyl, C₁₋₄alkoxy, halo-C₁₋₄alkoxy, amino-C₁₋₄alkoxy, hydroxyl-C₁₋₄alkoxy, C₁₋₄alkyl-C₁₋₄alkoxy, C₁₋₄alkyl-amino-C₁₋₄alkoxy,

(C₁₋₄alkyl)₂-amino-C₁₋₄alkoxy, C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkoxy, C₁₋₄alkoxy-C₁₋₄alkoxy, C₁₋₄alkoxy-carbonyl, C₁₋₄alkoxy-carbonyl-amino, C₁₋₄alkoxy-carbonyl-amino-C₁₋₄alkoxy, C₂₋₄alkenyl, C₂₋₄alkenyl-amino-carbonyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkyl-C₁₋₄alkoxy, C₃₋₇cycloalkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl-amino, heteroaryl-C₁₋₄alkyl-amino-carbonyl, heteroaryl-C₁₋₄alkyl-carbonyl-amino, heteroaryl-C₁₋₄alkyl-amino-carbonyl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkyl, heterocyclyl, heterocyclyl-C₁₋₄alkyl, heterocyclyl-C₁₋₄alkoxy, phenyl, or phenyl-C₁₋₄alkoxy,

wherein heteroaryl is a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms such as an O, S, or N atom,

wherein heterocyclyl is a saturated or partially unsaturated monocyclic or bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R₃;

R₂ is halogen, hydroxyl, cyano, oxo, hydroxyl-imino, C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, (C₁₋₄alkyl)₂-amino-C₁₋₄alkyl, amino-carbonyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxy-carbonyl, C₂₋₄alkenyl, C₃₋₇cycloalkyl, or heterocyclyl-C₁₋₄alkyl,

wherein heterocyclyl is a saturated or partially unsaturated monocyclic or bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R₃;

R₃ is halogen, hydroxyl, nitro, oxo, hydroxyl-imino, C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, (C₁₋₄alkyl)₂-amino-C₁₋₄alkyl, amino-carbonyl, C₁₋₄alkyl-amino-carbonyl, (C₁₋₄alkyl)₂-amino-carbonyl, C₁₋₄alkyl-amino-carbonyl-C₁₋₄alkyl, (C₁₋₄alkyl)₂-amino-carbonyl-C₁₋₄alkyl, C₁₋₄alkyl-carbonyl-amino, C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkyl-carbonyl, C₁₋₄alkoxy, halo-C₁₋₄alkoxy, amino-C₁₋₄alkoxy, hydroxyl-C₁₋₄alkoxy, C₁₋₄alkyl-C₁₋₄alkoxy, C₁₋₄alkyl-amino-C₁₋₄alkoxy, (C₁₋₄alkyl)₂-amino-C₁₋₄alkoxy, C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkoxy, C₁₋₄alkoxy-C₁₋₄alkoxy, C₁₋₄alkoxy-carbonyl, C₁₋₄alkoxy-carbonyl-amino, C₁₋₄alkoxy-carbonyl-

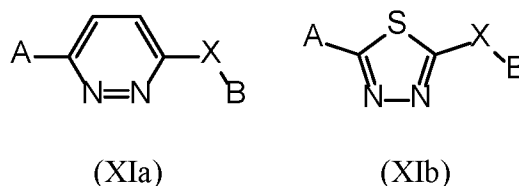
amino-C₁₋₄alkoxy, C₂₋₄alkenyl, C₂₋₄alkenyl-amino-carbonyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkyl-C₁₋₄alkoxy, C₃₋₇cycloalkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl-amino, heteroaryl-C₁₋₄alkyl-amino-carbonyl, heteroaryl-C₁₋₄alkyl-carbonyl-amino, heteroaryl-C₁₋₄alkyl-amino-carbonyl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkyl, heterocyclyl, heterocyclyl-C₁₋₄alkyl, phenyl, or phenyl-C₁₋₄alkoxy;

R₄ is independently selected from halogen, C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino or hydroxyl-C₁₋₄alkyl-amino; and

R₅ is hydrogen, C₁₋₄alkyl, or hydroxyl-C₁₋₄alkyl;

wherein a form of the compound is selected from the group consisting of a prodrug, salt, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

[0312] In certain aspects, an HD compound of the disclosure can refer to a compound of Formula (XI) selected from a compound of Formula (XIa) and Formula (XIb):



or a form thereof, wherein

X is CH₂, CH(C₁₋₄alkyl), C(C₁₋₄alkyl)₂, CH=CH, O, NR₅, or a bond;

A is aryl, heteroaryl, heterocyclyl, or C₉₋₁₀cycloalkyl,

wherein aryl is selected from phenyl and naphthyl, each optionally substituted with 1, 2, 3, or 4 substituents each selected from R₁,

wherein heteroaryl is a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms, such as an O, S, or N atom each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₁,

wherein heterocyclyl is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₂, and

wherein C₉₋₁₀cycloalkyl is a saturated or partially unsaturated bicyclic ring system optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₂;

B is heterocyclyl,

wherein heterocyclyl is a saturated or partially unsaturated monocyclic, bicyclic or polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₄;

R₁ is halogen, hydroxyl, cyano, C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, (C₁₋₄alkyl)₂-amino-C₁₋₄alkyl, amino-carbonyl, C₁₋₄alkyl-amino-carbonyl, C₁₋₄alkyl-amino-carbonyl-C₁₋₄alkyl, C₁₋₄alkyl-carbonyl-amino, C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkyl-carbonyl, C₁₋₄alkoxy, halo-C₁₋₄alkoxy, amino-C₁₋₄alkoxy, hydroxyl-C₁₋₄alkoxy, C₁₋₄alkyl-C₁₋₄alkoxy, C₁₋₄alkyl-amino-C₁₋₄alkoxy, (C₁₋₄alkyl)₂-amino-C₁₋₄alkoxy, C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkoxy, C₁₋₄alkoxy-C₁₋₄alkoxy, C₁₋₄alkoxy-carbonyl, C₁₋₄alkoxy-carbonyl-amino, C₁₋₄alkoxy-carbonyl-amino-C₁₋₄alkoxy, C₂₋₄alkenyl, C₂₋₄alkenyl-amino-carbonyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkyl-C₁₋₄alkoxy, C₃₋₇cycloalkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl-amino, heteroaryl-C₁₋₄alkyl-amino-carbonyl, heteroaryl-C₁₋₄alkyl-carbonyl-amino, heteroaryl-C₁₋₄alkyl-amino-carbonyl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkyl, heterocyclyl, heterocyclyl-C₁₋₄alkyl, heterocyclyl-C₁₋₄alkoxy, phenyl, or phenyl-C₁₋₄alkoxy,

wherein heteroaryl is a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms such as an O, S, or N atom,

wherein heterocyclyl is a saturated or partially unsaturated monocyclic or bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R₃;

R₂ is halogen, hydroxyl, cyano, oxo, hydroxyl-imino, C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, amino-C₁₋₄alkyl, amino-carbonyl,

hydroxyl-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxy-carbonyl, C₂₋₄alkenyl, C₃₋₇cycloalkyl, or heterocyclyl-C₁₋₄alkyl;

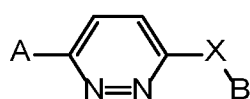
R₃ is halogen, hydroxyl, nitro, oxo, hydroxyl-imino, C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, (C₁₋₄alkyl)₂-amino-C₁₋₄alkyl, amino-carbonyl, C₁₋₄alkyl-amino-carbonyl, C₁₋₄alkyl-amino-carbonyl-C₁₋₄alkyl, C₁₋₄alkyl-carbonyl-amino, C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkyl-carbonyl, C₁₋₄alkoxy, halo-C₁₋₄alkoxy, amino-C₁₋₄alkoxy, hydroxyl-C₁₋₄alkoxy, C₁₋₄alkyl-C₁₋₄alkoxy, C₁₋₄alkyl-amino-C₁₋₄alkoxy, (C₁₋₄alkyl)₂-amino-C₁₋₄alkoxy, C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkoxy, C₁₋₄alkoxy-C₁₋₄alkoxy, C₁₋₄alkoxy-carbonyl, C₁₋₄alkoxy-carbonyl-amino, C₁₋₄alkoxy-carbonyl-amino-C₁₋₄alkoxy, C₂₋₄alkenyl, C₂₋₄alkenyl-amino-carbonyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkyl-C₁₋₄alkoxy, C₃₋₇cycloalkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl-amino, heteroaryl-C₁₋₄alkyl-amino-carbonyl, heteroaryl-C₁₋₄alkyl-carbonyl-amino, heteroaryl-C₁₋₄alkyl-amino-carbonyl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkyl, heterocyclyl, heterocyclyl-C₁₋₄alkyl, phenyl, or phenyl-C₁₋₄alkoxy;

R₄ is independently selected from halogen, C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino or hydroxyl-C₁₋₄alkyl-amino; and

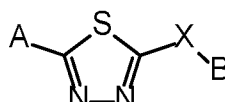
R₅ is hydrogen, C₁₋₄alkyl, or hydroxyl-C₁₋₄alkyl;

wherein a form of the compound is selected from the group consisting of a prodrug, salt, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

Another aspect of the present description further relates to a compound of Formula (XI) selected from a compound of Formula (XIa) and Formula (XIb):



(XIa)



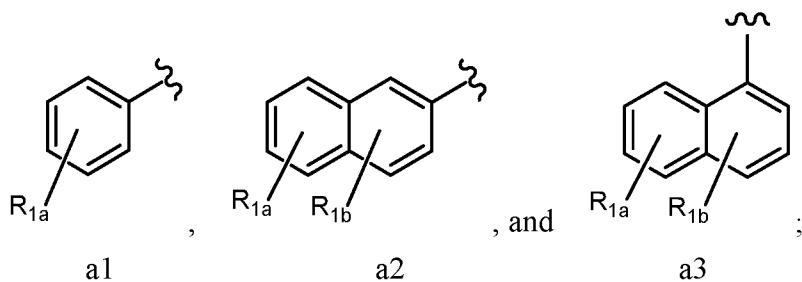
(XIb)

or a form thereof,

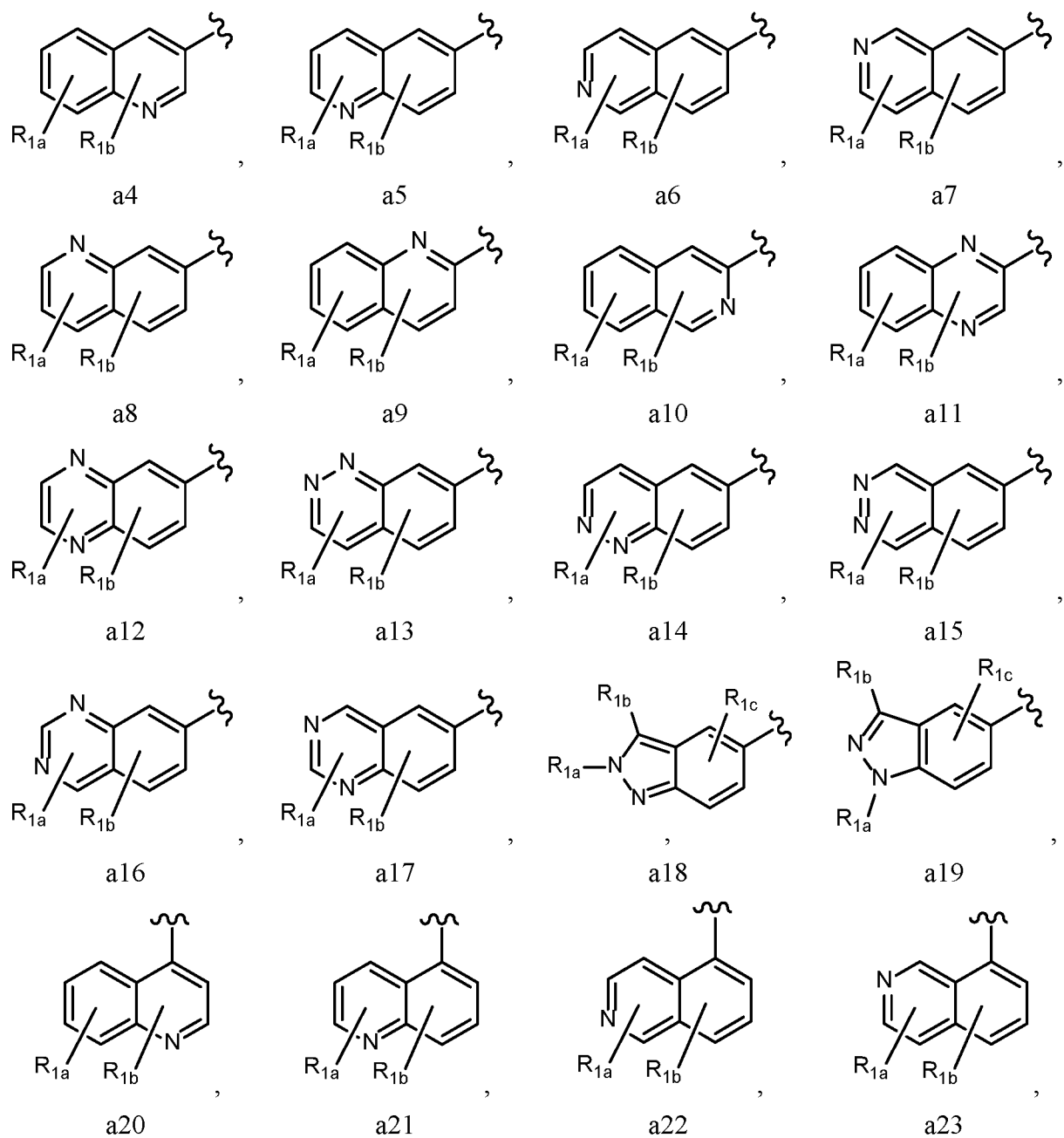
wherein X is O, NH, N(CH₃) or a bond;

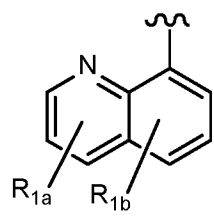
A is aryl, heteroaryl or heterocyclyl,

wherein aryl is selected from the group consisting of

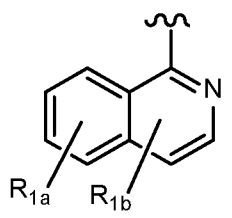


wherein heteroaryl is selected from the group consisting of

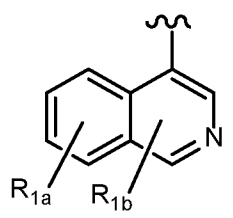




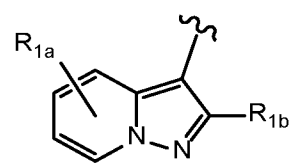
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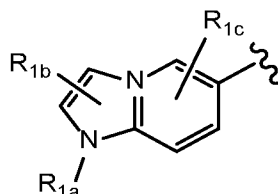
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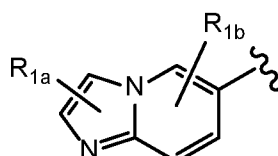
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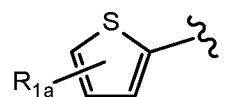
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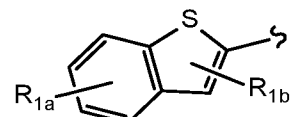
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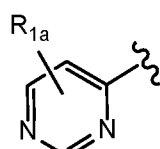
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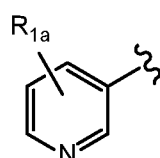
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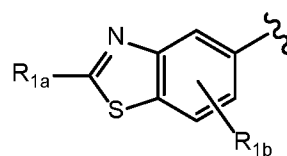
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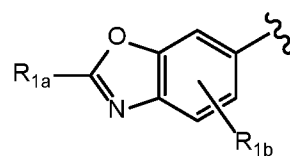
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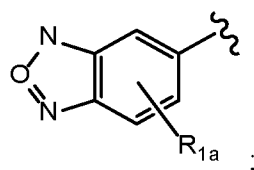
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a34

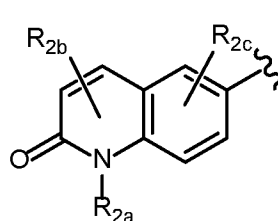


a35, and

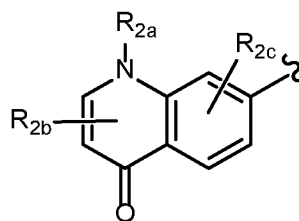


a36

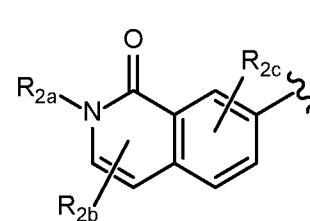
wherein heterocyclyl is selected from the group consisting of



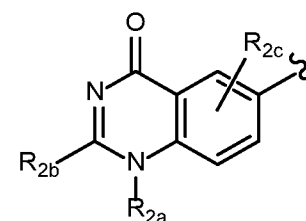
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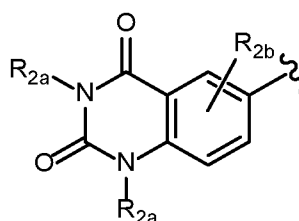
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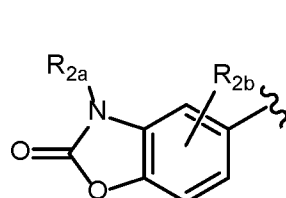
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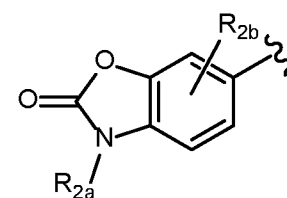
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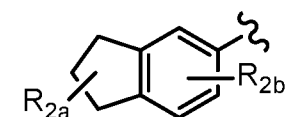
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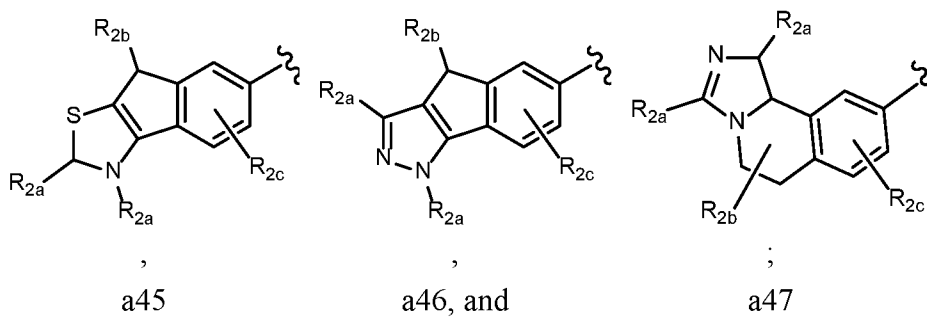
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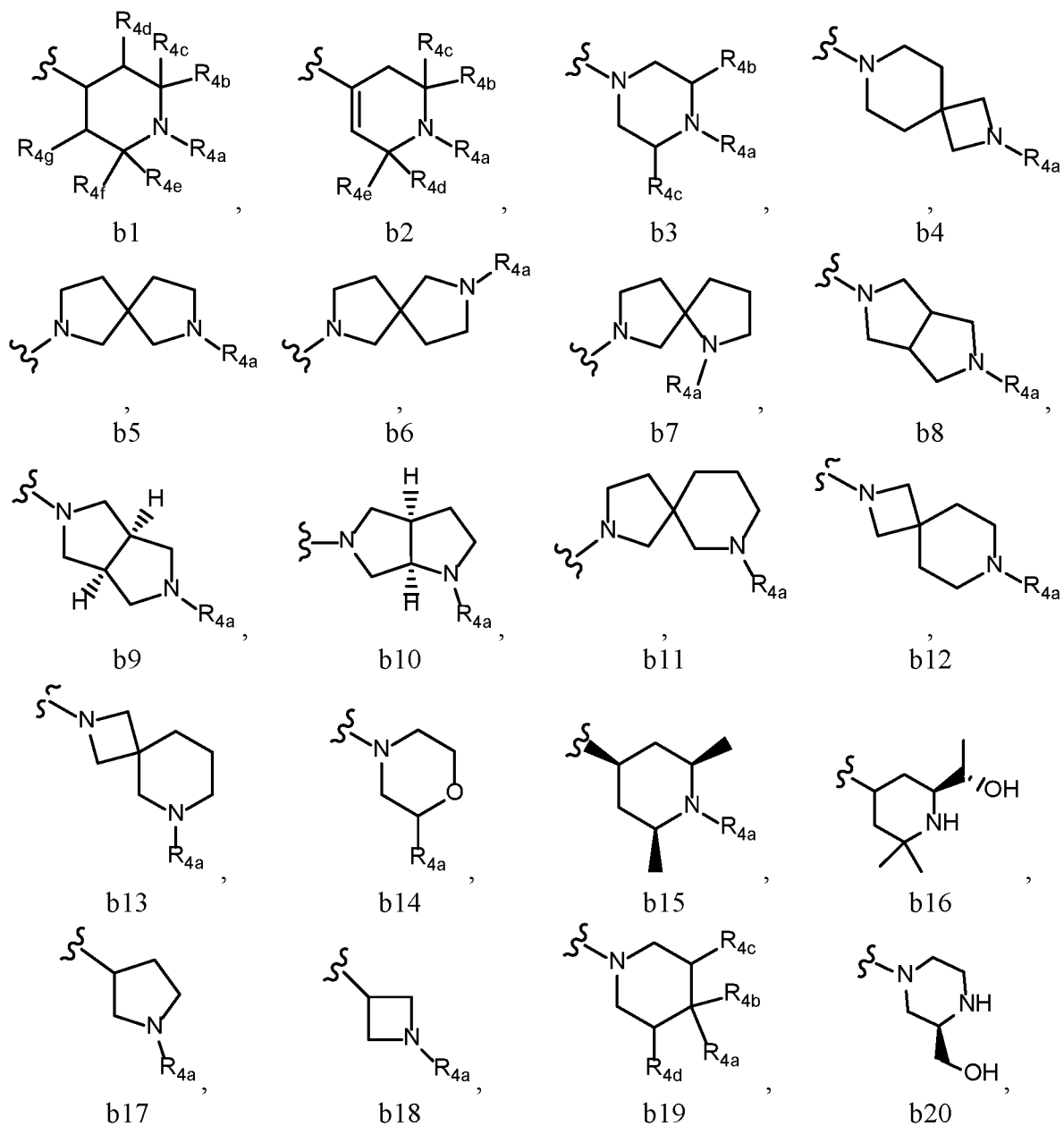
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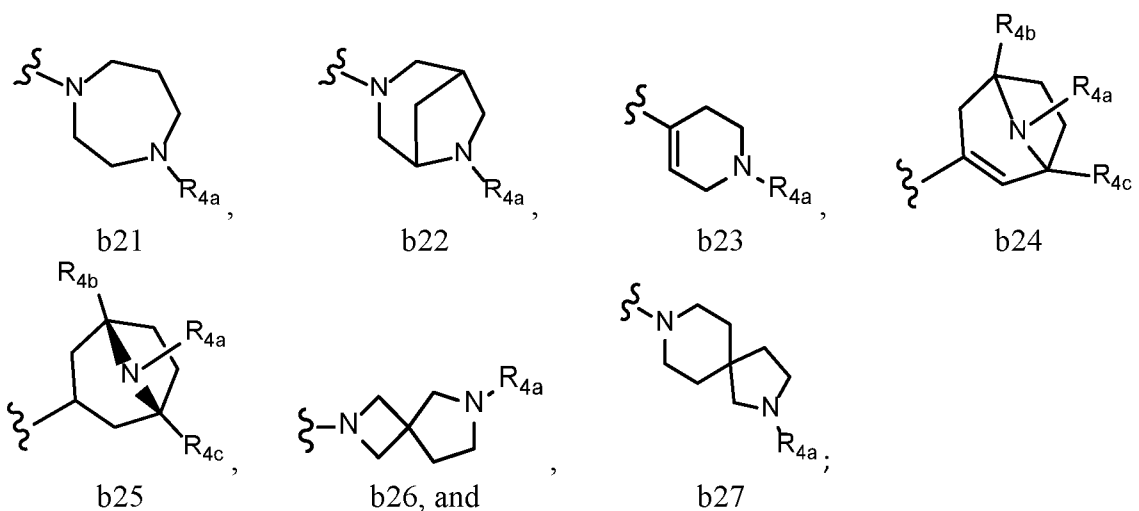


a44



B is heterocyclyl selected from the group consisting of





R_{1a} , R_{1b} and R_{1c} are each, where allowed by available valences, one or more substituents each selected from halogen, hydroxyl, cyano, C_{1-4} alkyl, halo- C_{1-4} alkyl, amino, C_{1-4} alkyl-amino, $(C_{1-4}$ alkyl)₂-amino, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, $(C_{1-4}$ alkyl)₂-amino- C_{1-4} alkyl, amino-carbonyl, C_{1-4} alkyl-amino-carbonyl, $(C_{1-4}$ alkyl)₂-amino-carbonyl, C_{1-4} alkyl-amino-carbonyl- C_{1-4} alkyl, $(C_{1-4}$ alkyl)₂-amino-carbonyl- C_{1-4} alkyl, C_{1-4} alkyl-carbonyl-amino, C_{1-4} alkyl-carbonyl-amino- C_{1-4} alkyl, hydroxyl- C_{1-4} alkyl, C_{1-4} alkyl-carbonyl, C_{1-4} alkoxy, halo- C_{1-4} alkoxy, amino- C_{1-4} alkoxy, hydroxyl- C_{1-4} alkoxy, C_{1-4} alkyl- C_{1-4} alkoxy, C_{1-4} alkyl-amino- C_{1-4} alkoxy, $(C_{1-4}$ alkyl)₂-amino- C_{1-4} alkoxy, C_{1-4} alkyl-carbonyl-amino- C_{1-4} alkoxy, C_{1-4} alkoxy- C_{1-4} alkoxy, C_{1-4} alkoxy-carbonyl, C_{1-4} alkoxy-carbonyl-amino, C_{1-4} alkoxy-carbonyl-amino- C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkenyl-amino-carbonyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl- C_{1-4} alkoxy, C_{3-7} cycloalkenyl, heteroaryl, heteroaryl- C_{1-4} alkyl, heteroaryl- C_{1-4} alkyl-amino, heteroaryl- C_{1-4} alkyl-amino-carbonyl, heteroaryl- C_{1-4} alkyl-carbonyl-amino, heteroaryl- C_{1-4} alkyl-amino-carbonyl- C_{1-4} alkyl, heteroaryl- C_{1-4} alkyl-carbonyl-amino- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, heterocyclyl- C_{1-4} alkoxy, phenyl, or phenyl- C_{1-4} alkoxy,

wherein heteroaryl is a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms such as an O, S, or N atom,

wherein heterocyclyl is a saturated or partially unsaturated monocyclic or bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R₃;

R_{2a}, R_{2b} and R_{2c} are each, where allowed by available valences, one or more substituents each selected from halogen, hydroxyl, cyano, oxo, hydroxyl-imino, C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, (C₁₋₄alkyl)₂-amino-C₁₋₄alkyl, amino-carbonyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxy-carbonyl, C₂₋₄alkenyl, C₃₋₇cycloalkyl, or heterocyclyl-C₁₋₄alkyl,

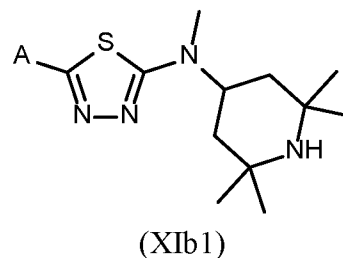
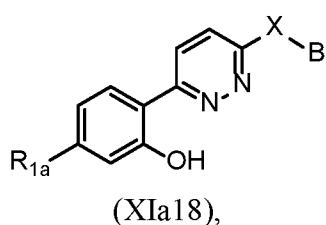
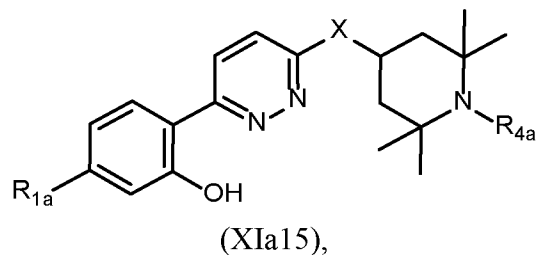
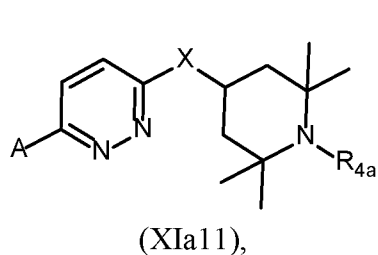
wherein heterocyclyl is a saturated or partially unsaturated monocyclic or bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and wherein each instance of heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R₃;

R₃ is halogen, hydroxyl, nitro, oxo, hydroxyl-imino, C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, (C₁₋₄alkyl)₂-amino-C₁₋₄alkyl, amino-carbonyl, C₁₋₄alkyl-amino-carbonyl, (C₁₋₄alkyl)₂-amino-carbonyl, C₁₋₄alkyl-amino-carbonyl-C₁₋₄alkyl, (C₁₋₄alkyl)₂-amino-carbonyl-C₁₋₄alkyl, C₁₋₄alkyl-carbonyl-amino, C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkyl-carbonyl, C₁₋₄alkoxy, halo-C₁₋₄alkoxy, amino-C₁₋₄alkoxy, hydroxyl-C₁₋₄alkoxy, C₁₋₄alkyl-C₁₋₄alkoxy, C₁₋₄alkyl-amino-C₁₋₄alkoxy, (C₁₋₄alkyl)₂-amino-C₁₋₄alkoxy, C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkoxy, C₁₋₄alkoxy-C₁₋₄alkoxy, C₁₋₄alkoxy-carbonyl, C₁₋₄alkoxy-carbonyl-amino, C₁₋₄alkoxy-carbonyl-amino-C₁₋₄alkoxy, C₂₋₄alkenyl, C₂₋₄alkenyl-amino-carbonyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkyl-C₁₋₄alkoxy, C₃₋₇cycloalkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl-amino, heteroaryl-C₁₋₄alkyl-amino-carbonyl, heteroaryl-C₁₋₄alkyl-carbonyl-amino, heteroaryl-C₁₋₄alkyl-amino-carbonyl-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl-carbonyl-amino-C₁₋₄alkyl, heterocyclyl, heterocyclyl-C₁₋₄alkyl, phenyl, or phenyl-C₁₋₄alkoxy; and

R_{4a}, R_{4b}, R_{4c}, R_{4d}, R_{4e}, R_{4f} and R_{4g} are independently selected from halogen, C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino or hydroxyl-C₁₋₄alkyl-amino;

wherein a form of the compound is selected from the group consisting of a prodrug, salt, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

[0313] Another aspect of the present description relates to a compound of Formula (XI) selected from a compound of Formula (XIa11), Formula (XIa15), Formula (XIa18) or Formula (XIb1):



or a form thereof, wherein (when present),

X is selected from O, NR₅, or a bond;

A is selected from phenyl, thiophenyl, indazolyl, pyridinyl, pyrimidinyl or phenoxy, wherein phenyl and phenoxy are each optionally substituted with 1, 2 or 3 substituents each selected from R_{1a},

wherein thiophenyl, indazolyl, pyridinyl, pyrimidinyl are each optionally substituted with 1 or 2 substituents each selected from R_{1a},

B is selected from 1H-pyrazolyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, 2,6-diazaspiro[3.4]octyl or 2,7-diazaspiro[3.5]nonyl, each optionally substituted with 1 or 2 substituents each selected from R_{4a};

R_{1a} is selected from halogen, hydroxyl, C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkoxy, or heteroaryl,

wherein heteroaryl is a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms such as an O, S, or N atom, optionally substituted with 1 or 2 substituents each selected from R_{3a};

R_{3a} is selected from nitro or C₁₋₄alkyl; and,

R_{4a} is C₁₋₄alkyl;

R_{5a} is hydrogen, C₁₋₄alkyl, or hydroxyl-C₁₋₄alkyl;

wherein a form of the compound is selected from the group consisting of a prodrug, salt, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

Another aspect of the present description relates to a compound of Formula (XI) selected from a compound of Formula (XIa11), Formula (XIa15), Formula (XIa18) or Formula (XIb1):

or a form thereof, wherein (when present),

R_{1a} is selected from fluoro, chloro, hydroxyl, methyl, difluoromethyl, amino, methoxy or 1H-pyrazolyl or 1H-imidazol-1-yl,

wherein 1H-pyrazolyl is optionally substituted with 1 or 2 substituents each selected from R_{3a};

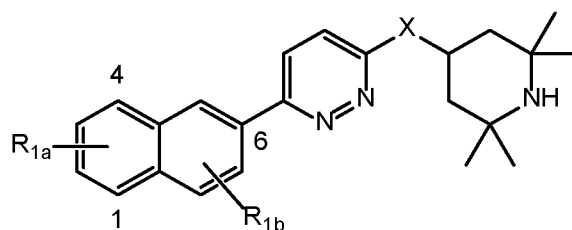
R_{3a} is selected from nitro or methyl or amino; and,

R_{4a} is methyl or ethyl;

R_{5a} is hydrogen or methyl;

wherein a form of the compound is selected from the group consisting of a prodrug, salt, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

[0314] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa), or a form thereof, selected from a compound of Formula (XIa1) or a form thereof, wherein substituents R_{1a}, R_{1b}, and X, when present, are indicated in the table below with multiple substituents separated by a comma; and, "--" indicates that one or more R_{1a}, R_{1b}, and X substituents are not present:

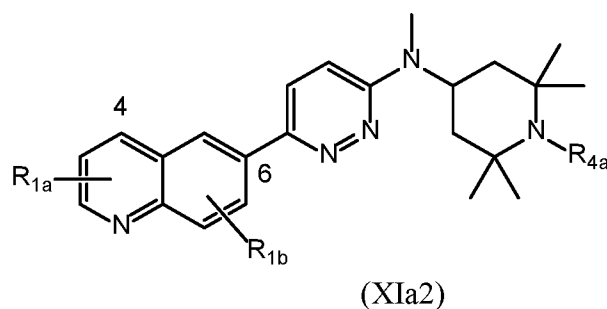


(XIa1)

Cpd	R _{1a}	R _{1b}	X
1	--	--	NH
8	2-OH	--	N(CH ₃)

Cpd	R _{1a}	R _{1b}	X
40	1-CH ₂ CH=CH ₂ , 2-OH	--	N(CH ₃)
106	1-Br, 2-OH	7-OH	N(CH ₃)
107	1-Cl, 2-OH	7-OH	N(CH ₃)

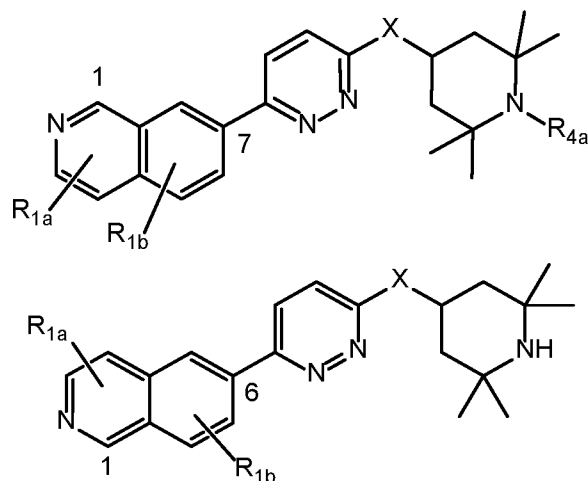
[0315] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa2) or a form thereof, wherein substituents R_{1a}, R_{1b}, and R_{4a}, when present, are indicated in the table below with multiple substituents separated by a comma; and, "--" indicates that one or more R_{1a}, R_{1b}, and R_{4a} substituents are not present:



Cpd	R _{1a}	R _{1b}	R _{4a}
13	--	--	--
207	--	7-OH	--
208	--	7-OH	CH ₃
210	2-CH ₃	7-OH	--
222	3-Cl	7-OH	--
223	3-Br	7-OH	--
224	3-CN	7-OH	--
225	3-(1-CH ₃ -1H-imidazol-4-yl)	7-OH	--
226	3-(1H-imidazol-1-yl)	7-OH	--
227	3-OH	7-OH	--
228	3-CH ₂ CH ₃	7-OH	--
229	3-CH(CH ₃) ₂	7-OH	--
232	2-CH ₃ , 4-OCH ₃ ,	7-OH	--
233	2-CH ₃ , 4-(pyrrolidin-1-yl)	7-OH	--

Cpd	R _{1a}	R _{1b}	R _{4a}
234	2-CH ₃ , 4-(morpholin-4-yl)	7-OH	--
235	2-CH ₃ , 4-N(CH ₃) ₂	7-OH	--
236	2-CH ₃ , 4-OCH ₂ CH ₃	7-OH	--
237	2-CH ₃ , 4-(1-CH ₃ -1H-pyrazol-4-yl)	7-OH	--
240	3-(tetrahydro-2H-pyran-4-yl)	7-OH	--
249	4-OCH ₃	7-OH	--
250	2-CH ₃ , 4-(azetidin-1-yl)	7-OH	--
251	2-CH ₃ , 4-CN	7-OH	--
252	2-CH ₃ , 4-cyclopropyl	7-OH	--
253	2-CH ₃ , 4-(3,6-dihydro-2H-pyran-4-yl)	7-OH	--
254	2-CH ₃ , 4-(tetrahydro-2H-pyran-4-yl)	7-OH	--
255	2-CH ₃ , 4-(oxetan-3-yl)	7-OH	--
256	4-N(CH ₃) ₂	7-OH	--
262	2-CN	7-OH	--
265	2-C(O)NH ₂	7-OH	--
293	3-Cl	7-OH	--
294	3-CH(CH ₃) ₂	7-OH	--
296	2-CH ₃ , 4-Cl	7-OH	--

[0316] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa3) or a form thereof, wherein substituents R_{1a}, R_{1b} and X, when present, are indicated in the table below with multiple substituents separated by a comma; and, "--" indicates that one or more R_{1a}, R_{1b} and X substituents are not present:



(XIa3)

Cpd	R _{1a}	R _{1b}	X
11	--	--	O
15	--	--	N(CH ₃)
218	--	7-OH	N(CH ₃)
261	1-CN	7-OH	N(CH ₃)
272	1-CH ₃	7-OH	N(CH ₃)
275	1-CN, 3-CH ₃	7-OH	N(CH ₃)
292	3-(OCH ₂ -phenyl)	--	N(CH ₃)

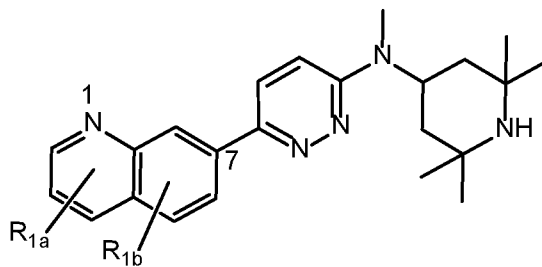
[0317] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa4) or a form thereof, wherein substituents X, R_{1a}, R_{1b} and R_{4a}, when present, are indicated in the table below; and, "--" indicates that one or more X, R_{1a}, R_{1b} and R_{4a} substituents are not present:

(XIa4)

Cpd	R _{1a}	R _{1b}	X	R _{4a}
10	--	--	O	--
14	--	--	N(CH ₃)	--
159	1-(OCH ₂ -phenyl)	--	N(CH ₃)	--
211	--	6-OH	N(CH ₃)	CH ₃
212	--	6-OH	N(CH ₃)	--
213	--	6-OH	O	--
215	1-cyclopropyl	6-OH	N(CH ₃)	--
216	1-OH	6-OH	N(CH ₃)	--

Cpd	R _{1a}	R _{1b}	X	R _{4a}
217	1-CN	6-OH	N(CH ₃)	--
264	1-C(O)NH ₂	6-OH	N(CH ₃)	--
273	1-CH ₃	6-OH	N(CH ₃)	--
274	1,3-(CH ₃) ₂	6-OH	N(CH ₃)	--
276	1-NH ₂	6-OH	N(CH ₃)	--
283	1-OCH ₂ CH ₃	6-OH	N(CH ₃)	--
284	1-OH	6-OH	O	--
285	3-phenyl	6-OH	N(CH ₃)	--
286	3-CH ₃	6-OH	N(CH ₃)	--
287	3-cyclopropyl	6-OH	N(CH ₃)	--
288	3-CH(CH ₃) ₂	6-OH	N(CH ₃)	--
289	3-(CH ₂) ₂ CH ₃	6-OH	N(CH ₃)	--
290	3-CH(CH ₃) ₂	6-OH	O	--

[0318] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa5) or a form thereof, wherein substituents R_{1a} and R_{1b}, when present, are indicated in the table below with multiple substituents separated by a comma; and, "--" indicates that one or more R_{1a} and R_{1b} substituents are not present:

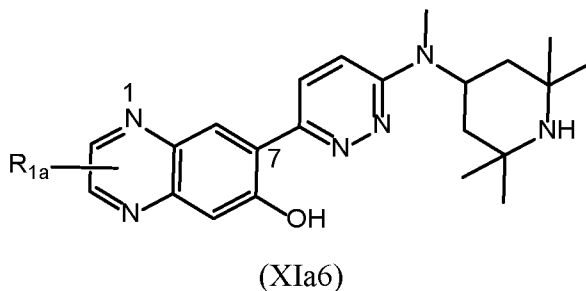


(XIa5)

Cpd	R _{1a}	R _{1b}
12	--	--
220	--	6-OH
221	2-CH ₃	6-OH
238	4-OCH ₃	6-OH
241	3-Cl	6-OH
242	3-Br	6-OH
243	3-CH ₃	6-OH

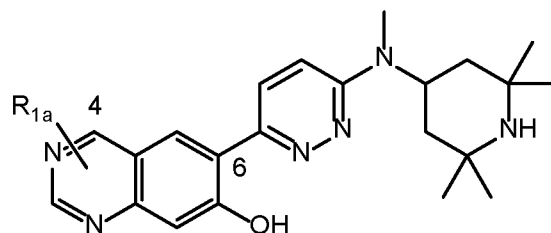
Cpd	R _{1a}	R _{1b}
244	3-CH ₃	5-Br, 6-OH
263	2-CN	6-OH
266	2-C(O)NH ₂	6-OH
267	2-CO ₂ CH ₃	6-OH
297	4-Cl	6-OH
300	--	6-OH

[0319] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa6) or a form thereof, wherein substituents R_{1a}, when present, are indicated in the table below; and, "--" indicates that one or more R_{1a} substituents are not present:



Cpd	R _{1a}
239	--
246	2,3-(CH ₃) ₂
247	2-CH ₃
248	3-CH ₃

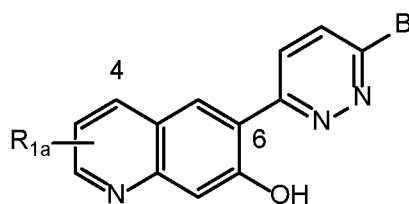
[0320] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa7) or a form thereof, wherein substituents R_{1a}, when present, are indicated in the table below; and, "--" indicates that one or more R_{1a} substituents are not present:



(XIa7)

Cpd	R _{1a}
258	--
260	2-CH ₃

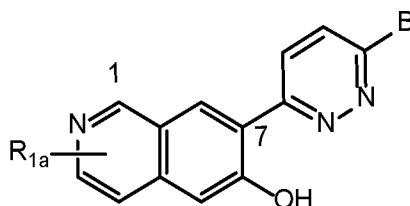
[0321] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa), or a form thereof, selected from a compound of Formula (XIa8) or a form thereof, wherein substituents R_{1a} and B, when present, are indicated in the table below; and, "--" indicates that one or more R_{1a} and B substituents are not present:



(XIa8)

Cpd	R _{1a}	B
209	--	6-((3aR,6aS)-5-CH ₃ -hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)
269	2-CN	piperazin-1-yl

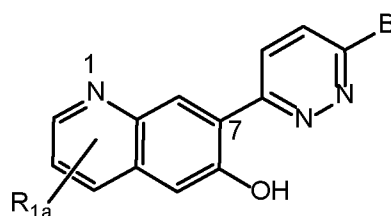
[0322] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa9) or a form thereof, wherein substituents R_{1a} and B, when present, are indicated in the table below; and, "--" indicates that one or more R_{1a} and B substituents are not present:



(XIa9)

Cpd	R _{1a}	B
214	--	6-((3aR,6aS)-5-CH ₃ -hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)
270	--	piperazin-1-yl
291	3-CH ₃	piperazin-1-yl

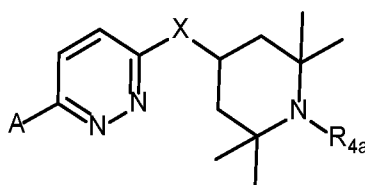
[0323] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa10) or a form thereof, wherein substituents R_{1a} and B, when present, are indicated in the table below; and, "--" indicates that one or more R_{1a} and B substituents are not present:



(XIa10)

Cpd	R _{1a}	B
268	2-CN	piperazin-1-yl
271	--	1,2,3,6-tetrahydropyridin-4-yl

[0324] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa11) or a form thereof, wherein substituents A, X and R_{4a}, when present, are indicated in the table below; and, "--" indicates that one or more A, X and R_{4a} substituents are not present:



(XIa11)

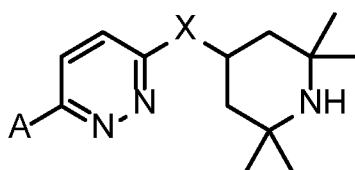
Cpd	A	X	R _{4a}
2	benzo[b]thiophen-2-yl	N(CH ₃)	--
4	5-CN-benzo[b]thiophen-2-yl	N(CH ₃)	--
5	quinolin-3-yl	NH	--
6	benzo[b]thiophen-2-yl	O	--
9	benzo[b]thiophen-2-yl	NH	--
16	imidazo[1,2-a]pyridin-6-yl	N(CH ₃)	--

Cpd	A	X	R _{4a}
17	6-phenyl-pyridin-3-yl	N(CH ₃)	--
18	6-(1H-pyrrol-1-yl)-pyridin-3-yl	N(CH ₃)	--
19	6-(1H-pyrazol-1-yl)-pyridin-3-yl	N(CH ₃)	--
20	quinoxalin-2-yl	N(CH ₃)	--
21	quinolin-3-yl	N(CH ₃)	--
22	phthalazin-6-yl	N(CH ₃)	--
23	benzo[c][1,2,5]oxadiazol-5-yl	NH	--
24	benzo[d]thiazol-5-yl	NH	--
25	2-CH ₃ -benzo[d]oxazol-6-yl	NH	--
30	2-(4-CN-phenol)	N(CH ₃)	--
32	2-(4-CF ₃ -phenol)	N(CH ₃)	--
33	6-(2-F-phenol)	N(CH ₃)	--
34	2-[3,5-(OCH ₃) ₂ -phenol]	N(CH ₃)	--
35	2-[4,5-(OCH ₃) ₂ -phenol]	N(CH ₃)	--
37	2-(4,5-F ₂ -phenol)	N(CH ₃)	--
41	benzo[b]thiophen-2-yl	NH	CH ₃
53	2-[4-(1H-pyrazol-1-yl)-phenol]	N(CH ₃)	--
115	2-[3-OH-5-(1H-pyrazol-4-yl)-phenol]	N(CH ₃)	--
116	2-[3-OCH ₃ -5-(1H-pyrazol-4-yl)-phenol]	N(CH ₃)	--
117	2-[5-(1H-pyrazol-4-yl)-3-OCF ₃ -phenol]	NH	--
118	2-[5-(1-CH ₃ -1H-pyrazol-4-yl)-3-OCF ₃ -phenol]	N(CH ₃)	--
119	2-[5-(1H-pyrazol-4-yl)-3-OCF ₃ -phenol]	N(CH ₃)	--
120	2-[5-(1-CH ₃ -pyridin-2(1H)-one)-3-OCF ₃ -phenol]	N(CH ₃)	--
121	2-[3-OCH ₃ -5-(1-CH ₃ -1H-pyrazol-4-yl)-phenol]	N(CH ₃)	--
122	2-[3-OCH ₃ -5-(5,6,7,8-tetrahydroimidazo-[1,2-a]pyridin-3-yl)-phenol]	N(CH ₃)	--
123	2-[3-OCH ₃ -5-(pyridin-3-yl)-phenol]	N(CH ₃)	--
124	2-[3-OCH ₃ -5-(1-cyclopentyl-1H-pyrazol-4-yl)-phenol]	N(CH ₃)	--
125	2-[5-(3-OCH ₃ -phenyl)-3-OCH ₃ -phenol]	N(CH ₃)	--
126	2-[3-benzyloxy-5-(5-CH ₃ -oxazol-2-yl)-phenol]	N(CH ₃)	--
127	2-[3-OCH ₂ CH ₃ -5-(5-CH ₃ -oxazol-2-yl)-phenol]	N(CH ₃)	--
128	2-[3-(OCH ₂ -cyclopropyl)-5-(5-CH ₃ -oxazol-2-yl)-phenol]	N(CH ₃)	--
129	5-(2-CH ₃ -1H-benzo[d]imidazol-6-ol)	N(CH ₃)	--
134	2-[4-(1H-pyrazol-4-yl)-phenol]	N(CH ₃)	--

Cpd	A	X	R _{4a}
135	2-[4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)-phenol]	N(CH ₃)	--
136	2-[4-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)-phenol]	N(CH ₃)	--
137	2-[4-(1H-indol-2-yl)-phenol]	N(CH ₃)	--
138	2-[4-(cyclopent-1-en-1-yl)-phenol]	N(CH ₃)	--
139	2-[4-(1H-pyrazol-3-yl)-phenol]	N(CH ₃)	--
140	2-[4-(2-OH-pyridin-4-yl)-phenol]	N(CH ₃)	--
141	2[4-(1-CH ₃ -pyridin-2(1H)-one)-phenol]	O	--
142	2-[4-(2-OH-pyridin-4-yl)-phenol]	O	--
144	2-[4-Cl-5-(1H-pyrazol-4-yl)-phenol]	N(CH ₃)	--
145	2-[4-F-5-(1H-pyrazol-4-yl)-phenol]	N(CH ₃)	--
146	2-[5-F-4-(1H-imidazol-4-yl)-phenol]	N(CH ₃)	--
147	2-[5-F-4-(1H-pyrazol-4-yl)-phenol]	N(CH ₃)	--
148	2-[5-F-(1H-pyrazol-5-yl)-phenol]	N(CH ₃)	--
149	6-OH-1-oxo-2,3-dihydro-1H-inden-5-yl	N(CH ₃)	--
150	6-(1,4-dihydroindeno[1,2-c]-1H-pyrazol-7-ol)	N(CH ₃)	--
151	6-OH-1-OH-imino-2,3-dihydro-1H-inden-5-yl	N(CH ₃)	--
152	6-OH-1-OH-2,3-dihydro-1H-inden-5-yl	N(CH ₃)	--
153	6-(2-NH ₂ -8H-indeno[1,2-d]thiazol-5-ol)	N(CH ₃)	--
154	9-(5,6-dihydroimidazo[5,1-a]isoquinolin-8-ol)	N(CH ₃)	--
155	2-{4-[C(O)NHCH ₂ -(1-CH ₃ -1H-pyrazol-4-yl)]-phenol}	N(CH ₃)	--
156	2-[4-(4-CH ₂ OH-1H-pyrazol-1-yl)-phenol]	N(CH ₃)	--
158	3-(OCH ₂ -phenyl)-isoquinolin-6-yl	N(CH ₃)	--
160	2-[3-F-5-(2-OCH ₃ -pyridin-4-yl)-phenol]	N(CH ₃)	--
161	4-[1-(4-pyridin-2(1H)-one)-3-F-5-OH-phenyl]	N(CH ₃)	--
162	4-{1-[4-(1-CH ₃ -pyridin-2(1H)-one)]-3-F-5-OH-phenyl}	N(CH ₃)	--
163	4-{1-[5-(1-CH ₃ -pyridin-2(1H)-one)]-3-F-5-OH-phenyl}	N(CH ₃)	--
164	2-[3-F-5-(1H-pyrazol-4-yl)-phenol]	O	--
165	2-(5-Cl-3-F-phenol)	N(CH ₃)	--
166	2-[3-F-5-(1H-pyrazol-4-yl)-phenol]	N(CH ₃)	--
167	2-[3-F-5-(1-CH ₃ -1H-pyrazol-4-yl)-phenol]	N(CH ₃)	--
219	8-(quinolin-7-ol)	N(CH ₃)	--
230	6-(7-OH-quinolin-2(1H)-one)	N(CH ₃)	--

Cpd	A	X	R _{4a}
231	6-(7-OH-1-CH ₃ -quinolin-2(1H)-one)	N(CH ₃)	--
245	7-(6-OH-1-CH ₃ -quinolin-4(1H)-one)	N(CH ₃)	--
257	6-(7-OH-quinazolin-4(1H)-one)	N(CH ₃)	--
259	6-(7-OH-1-CH ₃ -3,4-dihydroquinolin-2(1H)-one)	N(CH ₃)	--
277	7-OH-1,3-(CH ₃) ₂ -quinazolin-6-yl-2,4(1H,3H)-dione	N(CH ₃)	--
278	6-OH-benzo[d]oxazol-5-yl-2(3H)-one	N(CH ₃)	--
279	2-CH ₃ -6-OH-2H-indazol-5-yl	N(CH ₃)	--
280	1-CH ₃ -6-OH-1H-indazol-5-yl	N(CH ₃)	--
281	7-(6-OH-2-CH ₃ -isoquinolin-1(2H)-one)	N(CH ₃)	--
282	7-(6-OH-2-CH ₂ CH ₃ -isoquinolin-1(2H)-one)	O	--

[0325] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa), or a form thereof, selected from a compound of Formula (XIa11) or a form thereof, wherein substituents A, X and R_{4a}, when present, are indicated in the table below; and, "--" indicates that one or more A, X and R_{4a} substituents are not present:

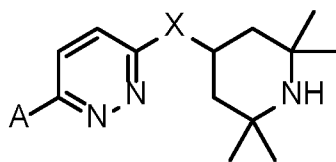


(XIa11)

Cpd	A	X
420	2-OCH ₃ -4-(4-NO ₂ -1H-pyrazol-1-yl)phenyl	N(CH ₃)
428	2,5-F ₂ -4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)
430	2,3-F ₂ -4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)
431	2,5-F ₂ -4-(1H-pyrazol-4-yl)phenyl	O
434	2-OCH ₃ -4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)
435	4-(1H-pyrazol-4-yl)phenyl	O
437	2-F-4-(1H-pyrazol-4-yl)phenyl	O
438	4-(1-CH ₃ -1H-pyrazol-4-yl)thiophen-2-yl	O
440	2-F-4-OH-phenyl	N(CH ₃)

Cpd	A	X
442	2-CH ₃ -2H-indazol-5-yl	N(CH ₃)
443	2-CH ₃ -2H-indazol-5-yl	O
444	4-Cl-2-OCH ₃ -phenyl	O
445	2-CH ₃ -pyrazolo[1,5-a]pyridin-3-yl	N(CH ₃)
446	imidazo[1,2-a]pyridin-6-yl	O
447	2-OCH ₃ -4-(1H-pyrazol-1-yl)phenyl	O
448	5-(1H-pyrazol-4-yl)thiophen-2-yl	O
449	5-(1-CH ₃ -1H-pyrazol-4-yl)thiophen-2-yl	O
450	4-(1H-pyrazol-4-yl)thiophen-2-yl	O
451	2-OH-4-[3,5-(CH ₃) ₂ -1H-pyrazol-4-yl]phenyl	O
452	2-F-4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)
453	2-OCH ₃ -4-OH-phenyl	O
454	2-OCH ₃ -4-(4-NO ₂ -1H-pyrazol-1-yl)phenyl	O
455	2,4-(OH) ₂ -phenyl	O
456	2-Cl-4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)
457	5-amino-2-(1H-pyrazol-4-yl)pyrimidin-4-yl	O
458	2,6-F ₂ -4-(1H-pyrazol-4-yl)phenyl	O
464	2-(CHF ₂)-4-(1H-pyrazol-4-yl)phenyl	O
465	2-(CHF ₂)-4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)

[0326] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa11) or a form thereof, wherein substituents A, X and R_{4a}, when present, are indicated in the table below; and, "--" indicates that one or more A, X and R_{4a} substituents are not present:

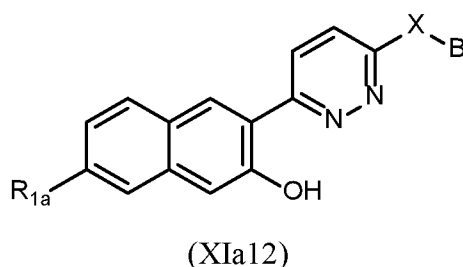


(XIa11)

Cpd	A	X
420	2-OCH ₃ -4-(4-NO ₂ -1H-pyrazol-1-yl)phenyl	N(CH ₃)
428	2,5-F ₂ -4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)
430	2,3-F ₂ -4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)
431	2,5-F ₂ -4-(1H-pyrazol-4-yl)phenyl	O
434	2-OCH ₃ -4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)
435	4-(1H-pyrazol-4-yl)phenyl	O
437	2-F-4-(1H-pyrazol-4-yl)phenyl	O
438	4-(1-CH ₃ -1H-pyrazol-4-yl)thiophen-2-yl	O
440	2-F-4-OH-phenyl	N(CH ₃)
442	2-CH ₃ -2H-indazol-5-yl	N(CH ₃)
443	2-CH ₃ -2H-indazol-5-yl	O
444	4-Cl-2-OCH ₃ -phenyl	O
445	2-CH ₃ -pyrazolo[1,5-a]pyridin-3-yl	N(CH ₃)
446	imidazo[1,2-a]pyridin-6-yl	O
447	2-OCH ₃ -4-(1H-pyrazol-1-yl)phenyl	O
448	5-(1H-pyrazol-4-yl)thiophen-2-yl	O
449	5-(1-CH ₃ -1H-pyrazol-4-yl)thiophen-2-yl	O
450	4-(1H-pyrazol-4-yl)thiophen-2-yl	O
451	2-OH-4-[3,5-(CH ₃) ₂ -1H-pyrazol-4-yl]phenyl	O
452	2-F-4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)
453	2-OCH ₃ -4-OH-phenyl	O
454	2-OCH ₃ -4-(4-NO ₂ -1H-pyrazol-1-yl)phenyl	O
455	2,4-(OH) ₂ -phenyl	O

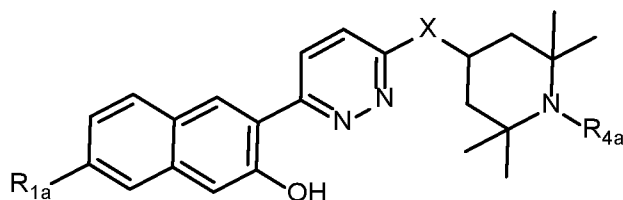
Cpd	A	X
456	2-Cl-4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)
457	5-amino-2-(1H-pyrazol-4-yl)pyrimidin-4-yl	O
458	2,6-F ₂ -4-(1H-pyrazol-4-yl)phenyl	O
464	2-(CHF ₂)-4-(1H-pyrazol-4-yl)phenyl	O
465	2-(CHF ₂)-4-(1H-pyrazol-4-yl)phenyl	N(CH ₃)

[0327] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa12) or a form thereof, wherein substituents X, R_{1a} and B, when present, are indicated in the table below; and, "--" indicates that one or more X, R_{1a} and B substituents are not present:



Cpd	R _{1a}	X	B
66	H	NH	azetidin-3-yl
82	OH	--	piperazin-1-yl
85	H	--	1,2,3,6-tetrahydropyridin-4-yl
86	OH	--	1,2,3,6-tetrahydropyridin-4-yl
87	OH	--	2,2,6,6-tetramethyl-(1,2,3,6-tetrahydropyridin-4-yl)
88	OH	--	1-CH ₃ -(1,2,3,6-tetrahydropyridin-4-yl)
89	OH	--	piperidin-4-yl
99	H	CH ₂	piperidin-4-yl

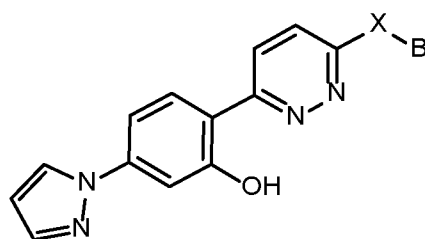
[0328] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa13) or a form thereof, wherein substituents X, R_{1a} and R_{4a}, when present, are indicated in the table below; and, "--" indicates that one or more X, R_{1a} and R_{4a} substituents are not present:



(XIa13)

Cpd	X	R _{1a}	R _{4a}
26	N(CH ₃)	H	--
28	NH	H	--
31	O	H	--
90	O	OH	--
91	N(CH ₃)	OH	--
92	NH	OH	--
93	N(CH ₃)	O(CH ₂) ₃ NHCO ₂ C(CH ₃) ₃	--
94	N(CH ₃)	O(CH ₂) ₃ NH ₂	--
95	N(CH ₃)	O(CH ₂) ₃ NHCO ₂ CH ₃	--
96	N(CH ₃)	O(CH ₂) ₃ OH	--
97	N(CH ₃)	O(CH ₂) ₃ OCH ₃	--
98	O	O(CH ₂) ₃ -morpholin-4-yl	--
103	N(CH ₃)	CN	--
104	N(CH ₃)	CH ₂ -1-piperidiny	--
105	N(CH ₃)	CH ₂ -pyrrolidin-1-yl	--
108	N(CH ₃)	OCH ₃	--
109	N(CH ₃)	OCH ₃	CH ₃
110	N(CH ₃)	3,6-dihydro-2H-pyran-4-yl	--
111	N(CH ₃)	tetrahydro-2H-pyran-4-yl	--
112	N(CH ₃)	CHF ₂	--
113	N(CH ₃)	OC(CH ₃) ₂ (CH ₂) ₂ OH	--
114	N(CH ₃)	O(CH ₂) ₂ C(CH ₃) ₂ OH	--

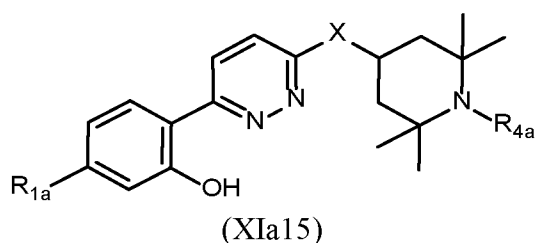
[0329] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa14) or a form thereof, wherein substituents X and B, when present, are indicated in the table below; and, "--" indicates that one or more X and B substituents are not present:



(XIa14)

Cpd	X	B
55	O	piperidin-4-yl
56	O	(2S,4R,6R)-2,6-(CH ₃) ₂ -piperidin-4-yl
57	O	2,6-(CH ₃) ₂ -piperidin-4-yl
58	O	pyrrolidin-3-yl
59	O	2-CH ₃ -piperidin-4-yl
60	OCH ₂	1H-pyrrolidin-3-yl
61	O	3-F-piperidin-4-yl
65	--	piperazin-1-yl
67	NH	azetidin-3-yl
68	--	3,5-(CH ₃) ₂ -piperazin-1-yl
69	--	7-CH ₃ -2,7-diazaspiro[4.4]non-2-yl
70	--	[1,4]diazepan-1-yl
71	--	4-CH ₂ CH ₂ OH-piperazin-1-yl
72	--	2,7-diazaspiro[3.5]non-7-yl
73	--	2,7-diazaspiro[3.5]non-7-yl
74	--	3-CH ₂ OH-piperazin-1-yl
75	--	1,7-diazaspiro[4.4]non-7-yl
76	--	4-NH ₂ -4-CH ₃ -piperidin-1-yl
77	--	3-N(CH ₃) ₂ -piperidin-1-yl
79	--	3,3-(CH ₃) ₂ -piperazin-1-yl
80	--	7-CH ₂ CH ₂ OH-2,7-diazaspiro[4.4]-nonan-2-yl
83	--	1,2,3,6-tetrahydropyridin-4-yl
84	--	piperidin-4-yl
102	O	(6S)-6-[(S)-CH(OH)CH ₃]-2,2-(CH ₃) ₂ -piperidin-4-yl
133	O	2,2-(CH ₃) ₂ -piperidin-4-yl

[0330] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa15) or a form thereof, wherein substituents X, R_{1a} and R_{4a}, when present, are indicated in the table below; and, "--" indicates that one or more X, R_{1a} and R_{4a} substituents are not present:

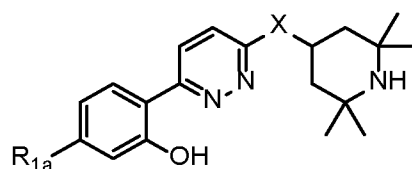


Cpd	X	R _{1a}	R _{4a}
3	NH	H	--
7	N(CH ₃)	H	--
27	N(CH ₃)	Cl	CH ₃
29	NH	Cl	CH ₃
36	N(CH ₃)	OCH ₃	--
38	N(CH ₃)	F	--
39	N(CH ₃)	CN	--
42	N(CH ₃)	C(O)NHCH ₂ CH=CH ₂	--
43	N(CH ₃)	1H-pyrazol-1-yl	--
44	N(CH ₃)	5-CH ₃ -oxazol-2-yl	--
45	N(CH ₃)	4-CH ₂ OH-1H-pyrazole-1-yl	--
46	N(CH ₃)	1H-imidazole-1-yl	--
47	N(CH ₃)	4-NH ₂ -1H-pyrazol-1-yl	--
48	N(CH ₃)	1H-pyrazol-4-yl	--
49	N(CH ₃)	3-NH ₂ -1H-pyrazol-1-yl	--
50	N(CH ₃)	1-(CH ₂ CH ₂ -morpholin-4-yl)-1H-pyrazol-4-yl	--
51	N(CH ₃)	1-CH ₃ -1H-pyrazol-4-yl	--
52	N(CH ₃)	5-NH ₂ -1H-pyrazol-1-yl	--
54	N(CH ₂ CH ₂ OH)	1H-pyrazol-1-yl	--
62	O	1H-pyrazol-1-yl	CH ₃
63	O	1H-pyrazol-1-yl	--
64	O	1H-pyrazol-4-yl	--
78	NH	1H-pyrazol-1-yl	CH ₃
100	CH ₂	1H-pyrazol-1-yl	--
130	N(CH ₃)	Cl	--
131	NH	1H-pyrazol-1-yl	--
132	NH	CN	--
143	N(CH ₃)	1H-indazol-7-yl	--
157	CH ₂	1H-pyrazol-4-yl	--
168	N(CH ₃)	5-OCH ₃ -pyridin-3-yl	--

Cpd	X	R _{1a}	R _{4a}
169	N(CH ₃)	5-pyridin-2-ol	--
170	N(CH ₃)	4-pyridin-2-ol	--
171	N(CH ₃)	6-OCH ₃ -pyridin-3-yl	--
172	N(CH ₃)	5-(3-CF ₃ -pyridin-2-ol)	--
173	N(CH ₃)	5-(1-CH ₃ -pyridin-2(1H)-one)	--
174	N(CH ₃)	4-(1-CH ₃ -pyridin-2(1H)-one)	--
175	N(CH ₃)	2-OCH ₃ -pyridin-4-yl	--
176	O	4-pyridin-2-ol	--
177	N(CH ₃)	6-N(CH ₃) ₂ -pyridin-3-yl	--
178	O	4-(1-CH ₃ -pyridin-2(1H)-one)	--
179	N(CH ₃)	pyrimidin-5-yl	--
180	N(CH ₃)	5-pyridin-3-ol	--
181	N(CH ₃)	4-(1-cyclopropyl-pyridin-2(1H)-one)	--
182	N(CH ₃)	1,2,3,6-tetrahydropyridin-4-yl	--
183	N(CH ₃)	cyclopent-1-en-1-yl	--
184	N(CH ₃)	3,6-dihydro-2H-pyran-4-yl	--
185	N(CH ₃)	imidazo[1,5-a]pyridin-7-yl	--
186	N(CH ₃)	imidazo[1,2-a]pyridin-7-yl	--
187	N(CH ₃)	2-CH ₃ -pyridin-4-yl	--
188	N(CH ₃)	1H-imidazol-2-yl	--
189	N(CH ₃)	1H-imidazol-4-yl	--
190	N(CH ₃)	imidazo[1,2-a]pyrazin-3-yl	--
191	N(CH ₃)	5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl	--
192	N(CH ₃)	4-CH ₃ -1H-imidazol-2-yl	--
193	N(CH ₃)	1-CH ₃ -1H-imidazol-4-yl	--
194	N(CH ₃)	1-CH ₃ -1H-imidazol-5-yl	--
195	N(CH ₃)	4-NO ₂ -1H-imidazol-2-yl	--
196	N(CH ₃)	2-CH ₃ -1H-imidazol-4-yl	--
197	N(CH ₃)	1,2-(CH ₃) ₂ -1H-imidazol-4-yl	--
198	N(CH ₃)	4-C(O)NH ₂ -1H-pyrazol-1-yl	--
206	N(CH ₃)	H	--

[0331] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa), or a form thereof, selected from a compound of Formula (XIa15) or a form thereof,

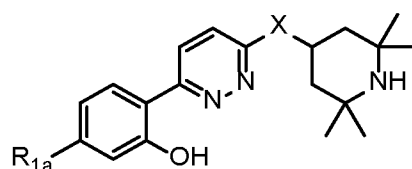
wherein substituents X, R_{1a} and R_{4a}, when present, are indicated in the table below; and, "--" indicates that one or more X, R_{1a} and R_{4a} substituents are not present:



(XIa15)

Cpd	X	R _{1a}	R _{4a}
413	NH	1H-pyrazol-4-yl	--
414	O	1-CH ₃ -1H-pyrazol-4-yl	--
416	N(CH ₃)	5-CH ₃ -1H-pyrazol-4-yl	--
417	O	1H-imidazol-1-yl	--
418	O	5-CH ₃ -1H-pyrazol-4-yl	--
419	N(CH ₃)	4-NO ₂ -1H-pyrazol-1-yl	--
421	O	4-NH ₂ -1H-pyrazol-1-yl	--
423	O	4-NO ₂ -1H-pyrazol-1-yl	--
460	N(CH ₃)	1H-pyrazol-4-yl	--
461	O	1H-pyrazol-4-yl	--

[0332] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa15) or a form thereof, wherein substituents X, R_{1a} and R_{4a}, when present, are indicated in the table below; and, "--" indicates that one or more X, R_{1a} and R_{4a} substituents are not present:

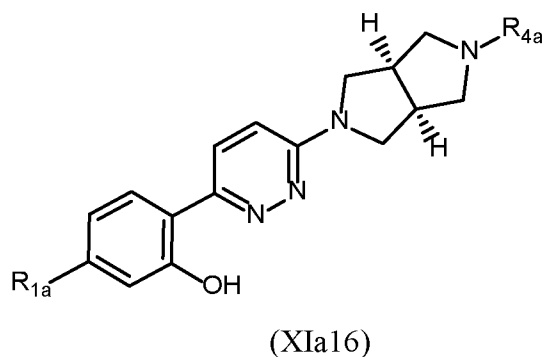


(XIa15)

Cpd	X	R _{1a}
413	NH	1H-pyrazol-4-yl
414	O	1-CH ₃ -1H-pyrazol-4-yl
416	N(CH ₃)	5-CH ₃ -1H-pyrazol-4-yl
417	O	1H-imidazol-1-yl
418	O	5-CH ₃ -1H-pyrazol-4-yl
419	N(CH ₃)	4-NO ₂ -1H-pyrazol-1-yl
421	O	4-NH ₂ -1H-pyrazol-1-yl

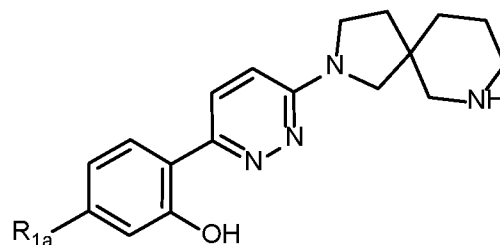
Cpd	X	R _{1a}
423	O	4-NO ₂ -1H-pyrazol-1-yl
460	N(CH ₃)	1H-pyrazol-4-yl
461	O	1H-pyrazol-4-yl

[0333] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa16) or a form thereof, wherein substituents R_{1a} and R_{4a}, when present, are indicated in the table below; and, "--" indicates that one or more R_{1a} and R_{4a} substituents are not present:



Cpd	R _{1a}	R _{4a}
81	1H-pyrazol-1-yl	--
199	1H-pyrazol-4-yl	(CH ₂) ₂ OH
200	1H-pyrazol-4-yl	--
201	1H-pyrazol-4-yl	CH ₃
202	4-(1-CH ₃ -pyridin-2(1H)-one)	CH ₃
203	4-(1-CH ₃ -pyridin-2(1H)-one)	CH ₃

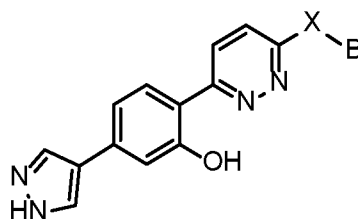
[0334] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa), or a form thereof, selected from a compound of Formula (XIa17) or a form thereof, wherein substituent R_{1a}, when present, is indicated in the table below; and, "--" indicates that one or more R_{1a} substituents are not present:



(XIa17)

Cpd	R _{1a}
204	1H-pyrazol-4-yl
205	4-(1-CH ₃ -pyridin-2(1H)-one)

[0335] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa), or a form thereof, selected from a compound of Formula (XIa18) or a form thereof, wherein substituents X and B, when present, are indicated in the table below; and, "--" indicates that one or more X and B substituents are not present:

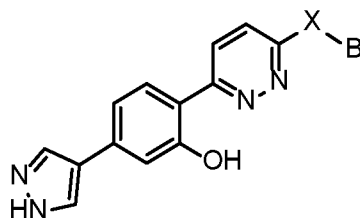


(XIa18)

Cpd	X	B
411	N(CH ₃)	(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-yl
412	NH	(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-yl
415	O	(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-yl
422	--	1-CH ₃ -(1,2,3,6-tetrahydropyridin-4-yl)
424	--	1,2,3,6-tetrahydropyridin-4-yl
425	--	1-CH ₃ CH ₂ -(1,2,3,6-tetrahydropyridin-4-yl)
426	N(CH ₃)	piperidin-4-yl
427	NH	piperidin-4-yl
429	--	8-azabicyclo[3.2.1]oct-2-en-3-yl
432	O	piperidin-4-yl
433	NH	(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-yl
436	O	2,6-(CH ₃) ₂ -piperidin-4-yl
439	--	2,7-diazaspiro[3.5]non-2-yl
441	O	2,6-(CH ₃) ₂ -piperidin-4-yl

Cpd	X	B
459	--	2,6-diazaspiro[3.4]oct-2-yl

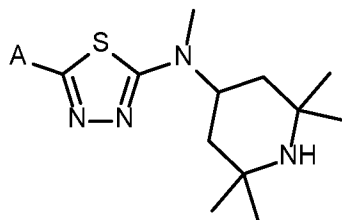
[0336] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIa) or a form thereof, selected from a compound of Formula (XIa18) or a form thereof, wherein substituents X, R_{1a} and B, when present, are indicated in the table below; and, "--" indicates that one or more X, R_{1a} and B substituents are not present:



(XIa18)

Cpd	X	B
411	N(CH ₃)	(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-yl
412	NH	(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-yl
415	O	(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-yl
422	--	1-CH ₃ -(1,2,3,6-tetrahydropyridin-4-yl)
424	--	1,2,3,6-tetrahydropyridin-4-yl
425	--	1-CH ₃ CH ₂ -(1,2,3,6-tetrahydropyridin-4-yl)
426	N(CH ₃)	piperidin-4-yl
427	NH	piperidin-4-yl
429	--	8-azabicyclo[3.2.1]oct-2-en-3-yl
432	O	piperidin-4-yl
433	NH	(1 <i>R</i> ,5 <i>S</i>)-8-azabicyclo[3.2.1]oct-3-yl
436	O	2,6-(CH ₃) ₂ -piperidin-4-yl
439	--	2,7-diazaspiro[3.5]non-2-yl
441	O	2,6-(CH ₃) ₂ -piperidin-4-yl
459	--	2,6-diazaspiro[3.4]oct-2-yl

[0337] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIb), or a form thereof, selected from a compound of Formula (XIb1) or a form thereof, wherein substituent A is indicated in the table below:



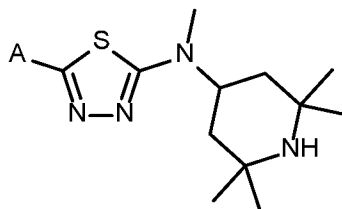
(XIb1)

Cpd	A
302	6-(naphthalen-2-yl)
320	6-(naphthalen-2,7-diol)
331	7-OCH ₃ -quinolin-6-yl
332	7-OH-quinolin-6-yl
337	2-CN-7-OCH ₃ -quinolin-6-yl
355	3-F-5-(1H-pyrazol-4-yl)-pyridin-2-yl
364	2-(6-OCH ₃ -3,4-dihydroisoquinolin-1(2H)-one)
392	6-OH-1-oxo-2,3-dihydro-1H-inden-5-yl
401	3-(4-OCH ₃ -1-CH ₃ -quinolin-2(1H)-one)
402	3-(4-OH-1-CH ₃ -quinolin-2(1H)-one)
403	3-(quinolin-2(1H)-one)
404	3-(1-OCH ₃ -quinolin-2(1H)-one)
408	5-CN-benzo[b]thiophen-2-yl
409	3-Cl-benzo[b]thiophen-2-yl

[0338] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIb) or a form thereof, selected from a compound of Formula (XIb1) or a form thereof, wherein substituent A is indicated in the table below:

Cpd	A
462	3-(1H-pyrazol-4-yl)phenoxy
463	4-(1H-pyrazol-4-yl)phenoxy

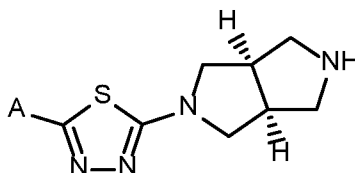
[0339] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIb) or a form thereof, selected from a compound of Formula (XIb1) or a form thereof, wherein substituent A is indicated in the table below:



(XIb1)

Cpd	A
462	3-(1H-pyrazol-4-yl)phenoxy
463	4-(1H-pyrazol-4-yl)phenoxy

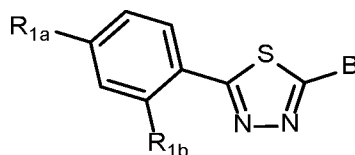
[0340] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIb) or a form thereof, selected from a compound of Formula (XIb2) or a form thereof, wherein substituent A is indicated in the table below:



(XIb2)

Cpd	A
321	6-naphthalen-2,7-diol

[0341] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIb) or a form thereof, selected from a compound of Formula (XIb3) or a form thereof, wherein substituents R_{1a}, R_{1b} and B, when present, are indicated in the table below; and, "--" indicates that one or more R_{1a}, R_{1b} and B substituents are not present:

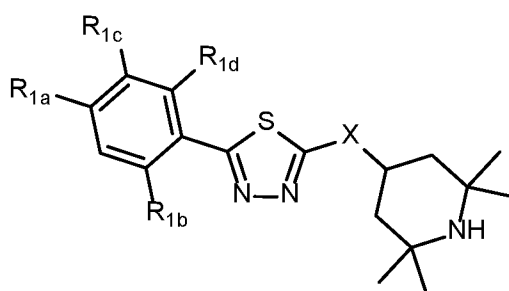


(XIb3)

Cpd	R _{1a}	R _{1b}	B
329	1H-pyrazol-1-yl	OCH ₃	1,2,3,6-tetrahydropyridin-4-yl
330	1H-pyrazol-1-yl	OH	piperazin-1-yl
381	1H-pyrazol-1-yl	Cl	5-((3aR,6aR)-1-CH ₃ -hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)
382	1H-pyrazol-1-yl	Cl	2-NHCH(CH ₃) ₂ -morpholin-4-yl

Cpd	R _{1a}	R _{1b}	B
383	1H-pyrazol-1-yl	Cl	2-OCH ₃ -2,7-diazaspiro[4.5]decan-7-yl
385	1-CH ₃ -1H-pyrazol-4-yl	OCH ₃	5-((3aR,6aS)-5-CH ₃ -hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)
394	1-CH ₃ -1H-pyrazol-4-yl	OH	5-((3aR,6aS)-5-CH ₃ -hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)
406	1H-pyrazol-1-yl	Cl	2,7-diazaspiro[4.5]decan-2-yl
407	1H-pyrazol-1-yl	Cl	(3R)-(3-(R)-CH ₂ OH)-piperazin-1-yl

[0342] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIb) or a form thereof, selected from a compound of Formula (XIb4) or a form thereof, wherein substituents R_{1a}, R_{1b}, R_{1c}, R_{1d} (each representative of the scope of R₁) and X, when present, are indicated in the table below; and, "--" indicates that one or more R_{1a}, R_{1b}, R_{1c}, R_{1d} and X substituents are not present:



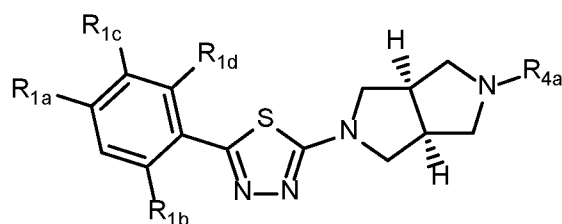
(XIb4)

Cpd	R _{1a}	R _{1b}	R _{1c}	R _{1d}	X
301	1H-pyrazol-1-yl	OCH ₃	H	H	N(CH ₃)
305	1H-pyrazol-1-yl	OCH ₃	H	H	N(CH ₃)
306	1-CH ₃ -1H-pyrazol-4-yl	OCH ₃	H	H	N(CH ₃)
307	1H-pyrazol-4-yl	OCH ₃	H	H	N(CH ₃)
308	4-(1-CH ₃ -pyridin-2(1H)-one)	OCH ₃	H	H	N(CH ₃)
309	5-pyridin-2-ol	OCH ₃	H	H	N(CH ₃)
310	5-(1-CH ₃ -pyridin-2(1H)-one)	OCH ₃	H	H	N(CH ₃)
311	1-CH ₃ -1H-pyrazol-4-yl	CH ₃	H	H	N(CH ₃)
312	4-(1-CH ₃ -pyridin-2(1H)-one)	OCF ₃	H	H	N(CH ₃)
313	3,5-(CH ₃) ₂ -1H-pyrazol-4-yl	OCH ₃	H	H	N(CH ₃)
314	1-CH ₃ -1H-pyrazol-4-yl	CF ₃	H	H	N(CH ₃)
315	1-CH ₃ -1H-pyrazol-4-yl	OH	H	H	N(CH ₃)
316	1H-pyrazol-1-yl	OH	H	H	N(CH ₃)
317	5-(1-CH ₃ -pyridin-2(1H)-one)	OH	H	H	N(CH ₃)

Cpd	R _{1a}	R _{1b}	R _{1c}	R _{1d}	X
318	4-(1-CH ₃ -pyridin-2(1H)-one)	OH	H	H	N(CH ₃)
319	5-pyridin-2-ol	OH	H	H	N(CH ₃)
324	H	OH	1H-pyrazol-1-yl	H	N(CH ₃)
325	1-CH ₃ -1H-pyrazol-4-yl	H	H	Cl	N(CH ₃)
326	1-CH ₃ -1H-pyrazol-4-yl	OH	H	Cl	N(CH ₃)
327	1-CH ₃ -1H-pyrazol-4-yl	H	H	Cl	N(CH ₃)
328	5-CH ₃ -oxazol-2-yl	OH	H	OCH ₃	N(CH ₃)
333	CN	OCH ₃	H	H	N(CH ₃)
334	CN	F	H	H	N(CH ₃)
335	CO ₂ CH ₃	F	H	H	N(CH ₃)
336	3-NHCH ₃ -1H-pyrazol-1-yl	OCH ₃	H	H	N(CH ₃)
338	4-(1-CH ₃ -pyridin-2(1H)-one)	OCH ₃	H	H	N(CH ₃)
339	4-(1-CH ₃ -pyridin-2(1H)-one)	Cl	H	H	N(CH ₃)
340	1H-pyrazol-4-yl	Cl	H	H	N(CH ₃)
341	4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl	Cl	H	H	N(CH ₃)
343	1-CH ₃ -1H-pyrazol-4-yl	Cl	H	H	O
344	6-OCH ₃ -pyridin-3-yl	Cl	H	H	N(CH ₃)
345	6-NH ₂ -pyridin-3-yl	F	H	H	N(CH ₃)
346	3-CH ₃ -1H-pyrazol-5-yl	F	H	H	N(CH ₃)
347	1H-pyrazol-5-yl	F	H	H	N(CH ₃)
348	1H-pyrazol-4-yl	H	F	F	N(CH ₃)
349	1H-pyrazol-5-yl	H	F	F	N(CH ₃)
350	1H-pyrazol-4-yl	F	F	H	N(CH ₃)
351	1H-pyrazol-5-yl	F	F	H	N(CH ₃)
352	1H-pyrazol-4-yl	F	H	F	N(CH ₃)
354	1H-pyrazol-4-yl	Cl	F	H	N(CH ₃)
356	2-NH ₂ -pyrimidin-4-yl	Cl	H	H	N(CH ₃)
357	H	Cl	2-NH ₂ -pyrimidin-4-yl	H	N(CH ₃)
358	2,4-(CH ₃) ₂ -thiazol-5-yl	F	F	H	N(CH ₃)
359	2,4-(CH ₃) ₂ -thiazol-5-yl	H	F	F	N(CH ₃)
360	4-(1-CH ₃ -pyridin-2(1H)-one)	OH	H	OCF ₃	N(CH ₃)
361	1H-pyrazol-4-yl	OCH ₃	H	F	N(CH ₃)
363	1H-pyrazol-4-yl	OCH ₃	F	F	N(CH ₃)
365	1H-pyrazol-1-yl	Cl	H	H	N(CH ₃)

Cpd	R _{1a}	R _{1b}	R _{1c}	R _{1d}	X
366	1H-1,2,3-triazol-1-yl	Cl	H	H	N(CH ₃)
367	2H-1,2,3-triazol-2-yl	Cl	H	H	N(CH ₃)
368	1H-1,2,4-triazol-1-yl	Cl	H	H	N(CH ₃)
369	3-NH ₂ -1H-pyrazol-1-yl	Cl	H	H	N(CH ₃)
371	1H-imidazol-1-yl	Cl	H	H	N(CH ₃)
372	1H-imidazol-1-yl	F	H	H	N(CH ₃)
373	1H-pyrazol-5-yl	OCH ₃	H	H	N(CH ₃)
374	2,4-(CH ₃) ₂ -thiazol-5-yl	OCH ₃	H	H	N(CH ₃)
375	pyridin-3-yl	OCH ₃	H	H	N(CH ₃)
376	1H-pyrazol-4-yl	F	H	H	N(CH ₃)
377	2-OCH ₃ -pyridin-4-yl	OCH ₃	H	H	N(CH ₃)
378	6-OCH ₃ -pyridin-3-yl	OCH ₃	H	H	N(CH ₃)
387	1H-pyrazol-1-yl	OH	H	H	N(CH ₃)
388	5-(pyridin-2(1H)-one)	Cl	H	H	N(CH ₃)
389	3-NHCH ₃ -1H-pyrazol-1-yl	OH	H	H	N(CH ₃)
390	1H-pyrazol-4-yl	OH	H	F	N(CH ₃)
391	1H-pyrazol-4-yl	OH	F	F	N(CH ₃)
393	1H-pyrazol-4-yl	OH	H	H	N(CH ₃)
397	1H-pyrazol-4-yl	OH	H	Cl	N(CH ₃)
398	1H-pyrazol-1-yl	OCH ₃	H	H	CH ₂
410	1H-pyrazol-4-yl	OCH ₃	H	H	N(CH ₃)

[0343] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIb) or a form thereof, selected from a compound of Formula (XIb5) or a form thereof, wherein substituents R_{1a}, R_{1b}, R_{1c}, R_{1d} (each representative of the scope of R₁) and R_{4a}, when present, are indicated in the table below; and, "--" indicates that one or more R_{1a}, R_{1b}, R_{1c}, R_{1d} and R_{4a} substituents are not present:

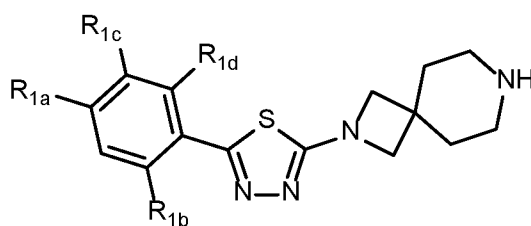


(XIb5)

Cpd	R _{1a}	R _{1b}	R _{1c}	R _{1d}	R _{4a}
353	1H-pyrazol-4-yl	F	F	H	--

Cpd	R _{1a}	R _{1b}	R _{1c}	R _{1d}	R _{4a}
362	1H-pyrazol-4-yl	OCH ₃	H	F	CH ₃
370	1H-imidazol-1-yl	Cl	H	H	CH ₃
379	1-CH ₃ -1H-pyrazol-4-yl	Cl	H	H	CH ₃
380	1H-pyrazol-4-yl	Cl	H	H	CH ₃
384	1H-pyrazol-4-yl	F	H	H	CH ₃
396	1H-pyrazol-4-yl	F	H	OH	--
405	1H-pyrazol-4-yl	Cl	H	H	--

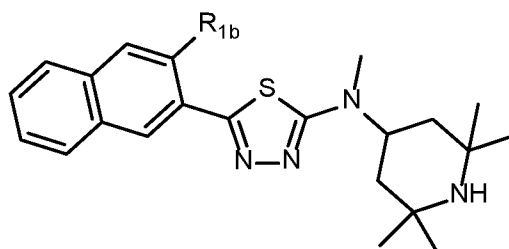
[0344] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIb) or a form thereof, for use of the present description, selected from a compound of Formula (XIb6) or a form thereof, wherein substituents R_{1a}, R_{1b}, R_{1c} and R_{1d} (each representative of the scope of R₁), when present, are indicated in the table below; and, "--" indicates that one or more R_{1a}, R_{1b}, R_{1c} and R_{1d} substituents are not present:



(XIb6)

Cpd	R _{1a}	R _{1b}	R _{1c}	R _{1d}
386	1-CH ₃ -1H-pyrazol-4-yl	OCH ₃	H	H
395	1-CH ₃ -1H-pyrazol-4-yl	OH	H	H
399	1H-pyrazol-4-yl	H	F	F
400	1H-pyrazol-4-yl	OH	H	F

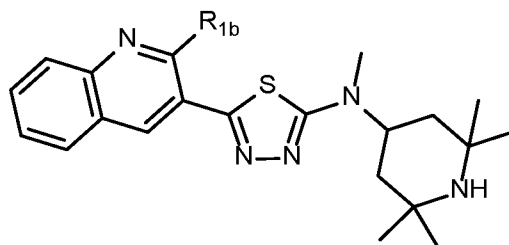
[0345] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIb) or a form thereof, selected from a compound of Formula (XIb7) or a form thereof, wherein substituent R_{1b}, when present, is indicated in the table below:



(XIb7)

Cpd	R _{1b}
304	OCH ₃
322	OH

[0346] In other aspects, an HD compound of the disclosure can refer to a compound of Formula (XIb) or a form thereof, selected from a compound of Formula (XIb8) or a form thereof, wherein substituent R_{1b}, when present, is indicated in the table below:



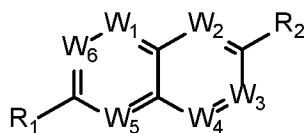
(XIb8)

Cpd	R _{1b}
303	OCH ₃
323	OH

HD Compounds of Formula (XII)

[0347] In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in the published U.S. Patent Application No. 2020/0165256, the content of which is incorporated by reference herein in its entirety.

[0348] In one aspect, an HD compound of the disclosure can refer to a compound of Formula (VI.1):



(VI.1)

or a form thereof, wherein:

W₁, W₂, W₃, W₄, W₅ and W₆ are independently C-R_a, C-R_b or N,

wherein, when one, two or three of W₁, W₅ and W₆ are N, then W₂, W₃ and W₄ are C-R_a or C-R_b, and

wherein, when one, two or three of W₂, W₃ and W₄ are N, then W₁, W₅ and W₆ are C-R_a or C-R_b;

R₁ is C₁₋₈alkyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, (amino-C₁₋₈alkyl)₂-amino, (amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, amino-C₁₋₈alkoxy, C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, amino-C₂₋₈alkenyl, C₁₋₈alkyl-amino-C₂₋₈alkenyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkenyl, amino-C₂₋₈alkynyl, C₁₋₈alkyl-amino-C₂₋₈alkynyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkynyl, halo-C₁₋₈alkyl-amino, (halo-C₁₋₈alkyl)₂-amino, (halo-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl-amino, [(hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, [(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, C₃₋₁₄cycloalkyl, aryl, aryl-C₁₋₈alkyl-amino, (aryl-C₁₋₈alkyl)₂-amino, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl, heterocyclyl-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkoxy, heterocyclyl-amino, (heterocyclyl)(C₁₋₈alkyl)amino, heterocyclyl-amino-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkyl-amino, (heterocyclyl-C₁₋₈alkyl)₂-amino, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl,

(heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl-oxy, heterocyclyl-carbonyl, heterocyclyl-carbonyl-oxy, heteroaryl, heteroaryl-C₁₋₈alkyl, heteroaryl-C₁₋₈alkoxy, heteroaryl-amino, heteroaryl-C₁₋₈alkyl-amino, (heteroaryl-C₁₋₈alkyl)₂-amino, (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl,

wherein, each instance of C₃₋₁₄cycloalkyl, aryl, heterocyclyl and heteroaryl is optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent, or,

wherein, alternatively, each instance of C₃₋₁₄cycloalkyl, aryl, heterocyclyl and heteroaryl is optionally substituted with one, two, three or four R₃ substituents;

R₂ is aryl, heteroaryl, heteroaryl-amino or (heterocyclyl)(C₁₋₈alkyl)amino,

wherein, each instance of aryl and heteroaryl is optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent;

R_a is, in each instance, independently selected from hydrogen, or C₁₋₈alkyl;

R_b is, in each instance, independently selected from hydrogen, or halogen;

R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkyl-carbonyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl]₂-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, C₁₋₈alkyl-carbonyl-amino, C₁₋₈alkoxy-carbonyl-amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino or (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino;

R₄ is C₃₋₁₄cycloalkyl, C₃₋₁₄cycloalkyl-C₁₋₈alkyl, C₃₋₁₄cycloalkyl-amino, aryl-C₁₋₈alkyl, aryl-C₁₋₈alkoxy-carbonyl, aryl-sulfonyloxy-C₁₋₈alkyl, heterocyclyl, heterocyclyl-C₁₋₈alkyl,

heteroaryl or heteroaryl-C₁₋₈alkyl; wherein, each instance of C₃₋₁₄cycloalkyl, aryl, heterocyclyl and heteroaryl is optionally substituted with one, two or three R₅ substituents; R₅ is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, hydroxy-C₁₋₈alkyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, C₁₋₈alkyl-thio or heteroaryl-C₁₋₈alkyl; R₆ is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C₁₋₈alkyl, C₂₋₈alkenyl, cyano-C₁₋₈alkyl, halo-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, (C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkoxy-C₁₋₈alkoxy, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, (C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkyl)amino or C₁₋₈alkyl-thio; and, R₇ is C₃₋₁₄cycloalkyl, C₃₋₁₄cycloalkyl-oxy, aryl, heterocyclyl, heteroaryl or heteroaryl-C₁₋₈alkoxy.

[0349] One aspect includes a compound of Formula (XII), wherein W₁ is N.

[0350] Another aspect includes a compound of Formula (XII), wherein W₁ is N, W₄ is C-R_b and W₂, W₃, W₅ and W₆ are C-R_a.

[0351] One aspect includes a compound of Formula (XII), wherein W₂ is N.

[0352] Another aspect includes a compound of Formula (XII), wherein W₂ is N, W₄ is C-R_b and W₁, W₃, W₅ and W₆ are C-R_a.

[0353] One aspect includes a compound of Formula (XII), wherein W₃ is N.

[0354] Another aspect includes a compound of Formula (XII), wherein W₃ is N, W₄ is C-R_b and W₁, W₂, W₅ and W₆ are C-R_a.

[0355] One aspect includes a compound of Formula (XII), wherein W₄ is N.

[0356] Another aspect includes a compound of Formula (XII), wherein W₄ is N and W₁, W₂, W₃, W₅ and W₆ are independently C-R_a.

[0357] One aspect includes a compound of Formula (XII), wherein W₅ is N.

[0358] Another aspect includes a compound of Formula (XII), wherein W₅ is N, W₄ is C-R_b and W₁, W₂, W₃ and W₆ are C-R_a.

[0359] One aspect includes a compound of Formula (XII), wherein W₆ is N.

[0360] Another aspect includes a compound of Formula (XII), wherein W_6 is N, W_4 is C- R_b and W_1 , W_2 , W_3 and W_5 are C- R_a .

[0361] Another aspect includes a compound of Formula (XII), wherein R_1 is aryl, heterocyclyl, heterocyclyl-amino, (heterocyclyl)(C_{1-8} alkyl)amino, or heteroaryl.

[0362] Another aspect includes a compound of Formula (XII), wherein R_1 is aryl or heteroaryl.

[0363] Another aspect includes a compound of Formula (XII), wherein R_1 is aryl.

[0364] Another aspect includes a compound of Formula (XII), wherein R_1 is heteroaryl.

[0365] Another aspect includes a compound of Formula (XII), wherein R_1 is heterocyclyl, heterocyclyl-amino or (heterocyclyl)(C_{1-8} alkyl)amino.

[0366] Another aspect includes a compound of Formula (XII), wherein R_1 is heterocyclyl.

[0367] Another aspect includes a compound of Formula (XII), wherein R_1 is heterocyclyl-amino.

[0368] Another aspect includes a compound of Formula (XII), wherein R_1 is (heterocyclyl)(C_{1-8} alkyl)amino.

[0369] Another aspect includes a compound of Formula (XII), wherein R_a is hydrogen or C_{1-8} alkyl.

[0370] Another aspect includes a compound of Formula (XII), wherein R_b is hydrogen or halogen.

[0371] Another aspect includes a compound of Formula (XII), wherein R_4 is heterocyclyl- C_{1-8} alkyl or heteroaryl- C_{1-8} alkyl.

[0372] Another aspect includes a compound of Formula (XII), wherein R_5 is hydroxy- C_{1-8} alkyl, (C_{1-8} alkyl)₂-amino- C_{1-8} alkyl, or heteroaryl- C_{1-8} alkyl.

[0373] Another aspect includes a compound of Formula (XII), wherein R_6 is halogen, hydroxy, cyano, C_{1-8} alkyl, cyano- C_{1-8} alkyl, halo- C_{1-8} alkyl, hydroxy- C_{1-8} alkyl, C_{1-8} alkoxy, (C_{1-8} alkyl)₂-amino- C_{1-8} alkoxy- C_{1-8} alkoxy- C_{1-8} alkoxy, or C_{1-8} alkoxy- C_{1-8} alkyl-amino.

[0374] Another aspect includes a compound of Formula (XII), wherein R_7 is C_{3-14} cycloalkyl, heterocyclyl, or heteroaryl- C_{1-8} alkoxy.

[0375] One aspect includes a compound of Formula (XII), wherein W_1 and W_5 are N.

[0376] Another aspect includes a compound of Formula (XII), wherein W_1 and W_5 are N, W_4 is C- R_b and W_2 , W_3 and W_6 are C- R_a .

[0377] One aspect includes a compound of Formula (XII), wherein W_1 and W_6 are N.

[0378] Another aspect includes a compound of Formula (XII), wherein W_1 and W_6 are N, W_4 is C- R_b and W_2 , W_3 and W_5 are C- R_a .

[0379] One aspect includes a compound of Formula (XII), wherein W_2 and W_3 are N.

[0380] Another aspect includes a compound of Formula (XII), wherein W_2 and W_3 are N, W_4 is C- R_b and W_1 , W_5 and W_6 are C- R_a .

[0381] One aspect includes a compound of Formula (XII), wherein W_2 and W_4 are N.

[0382] Another aspect includes a compound of Formula (XII), wherein W_2 and W_4 are N, and W_1 , W_3 , W_5 and W_6 are independently C- R_a .

[0383] One aspect includes a compound of Formula (XII), wherein W_3 and W_4 are N.

[0384] Another aspect includes a compound of Formula (XII), wherein W_3 and W_4 are N, and W_1 , W_2 , W_5 and W_6 are independently C- R_a .

[0385] One aspect includes a compound of Formula (XII), wherein W_5 and W_6 are N.

[0386] Another aspect includes a compound of Formula (XII), wherein W_5 and W_6 are N, W_4 is C- R_b and W_1 , W_2 and W_3 are C- R_a .

[0387] Another aspect includes a compound of Formula (XII), wherein W_5 and W_6 are N, W_2 is C- R_b and W_1 , W_3 and W_4 are C- R_a .

[0388] Another aspect includes a compound of Formula (XII), wherein W_5 and W_6 are N, W_3 is C- R_b and W_1 , W_2 and W_4 are C- R_a .

[0389] One aspect includes a compound of Formula (XII), wherein W_1 , W_5 and W_6 are N.

[0390] Another aspect includes a compound of Formula (XII), wherein W_1 , W_5 and W_6 are N, W_4 is C- R_b and W_2 and W_3 are C- R_a .

[0391] One aspect includes a compound of Formula (XII), wherein W_2 , W_3 and W_4 are N.

[0392] Another aspect includes a compound of Formula (XII), wherein W_2 , W_3 and W_4 are N, and W_1 , W_5 and W_6 are independently C- R_a .

[0393] One aspect includes a compound of Formula (XII), wherein R₁ is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, 1,4-diazepanyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydropyrrolo[3,4-*b*]pyrrol-(1*H*)-yl, (3*aS*,6*aS*)-hexahydropyrrolo[3,4-*b*]pyrrol-(1*H*)-yl, (3*aR*,6*aR*)-hexahydropyrrolo[3,4-*b*]pyrrol-(1*H*)-yl, hexahydropyrrolo[3,4-*b*]pyrrol-(2*H*)-yl, (3*aS*,6*aS*)-hexahydropyrrolo[3,4-*b*]pyrrol-(2*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-(1*H*)-yl, (3*aR*,6*aS*)-hexahydropyrrolo[3,4-*c*]pyrrol-(1*H*)-yl, octahydro-5*H*-pyrrolo[3,2-*c*]pyridinyl, octahydro-6*H*-pyrrolo[3,4-*b*]pyridinyl, (4*aR*,7*aR*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridinyl, (4*aS*,7*aS*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridinyl, hexahydropyrrolo[1,2-*a*]pyrazin-(2*H*)-one, hexahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, (7*R*,8*aS*)-hexahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, (8*aS*)-hexahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, (8*aR*)-hexahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, hexahydro-1*H*-cyclobuta[1.2-*c*:1,4-*c'*]dipyrrol-(3*H*)-yl, (8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, (8*aR*)-octahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, octahydro-2*H*-pyrido[1,2-*a*]pyrazinyl, 3-azabicyclo[3.1.0]hexyl, (1*R*,5*S*)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl, (1*R*,5*S*)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptyl, 1,4-diazabicyclo[3.1.1]heptyl, 3,6-diazabicyclo[3.2.0]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 1,4-diazabicyclo[3.2.1]octyl, 3,8-diazabicyclo[3.2.1]octyl, (1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, azaspiro[3.3]heptyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonyl, 2,6-diazaspiro[3.5]nonyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 2,7-diazaspiro[4.4]nonyl, 2,7-diazaspiro[4.5]decanyl or 6,9-diazaspiro[4.5]decyl; wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0394] Another aspect includes a compound of Formula (XII), wherein R₁ is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-4-yl, piperazin-1-yl, azepan-4-yl, 1,4-diazepan-1-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl, (3*aS*,6*aS*)-hexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl,

(3a*S*,6a*S*)-hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl,
 (3a*R*,6a*R*)-hexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-1(1*H*)-yl,
 hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-5(1*H*)-yl,
 (3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, octahydro-5*H*-pyrrolo[3,2-*c*]pyridin-5-yl,
 octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl,
 (4a*R*,7a*R*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl,
 (4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl,
 hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one, hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl,
 (7*R*,8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl,
 (8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl,
 (8a*R*)-hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl,
 hexahydro-1*H*-cyclobuta[1.2-*c*:1,4-*c'*]dipyrrol-2(3*H*)-yl,
 (8a*S*)-octahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl,
 (8a*R*)-octahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl, octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-yl,
 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl,
 (1*R*,5*S*)-8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl,
 (1*R*,5*S*)-8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl,
 (1*R*,5*S*)-9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl,
 (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl,
 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl,
 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl,
 3,8-diazabicyclo[3.2.1]octan-3-yl, (1*R*,5*S*)-3,8-diazabicyclo[3.2.1]ocant-3-yl,
 1,4-diazabicyclo[3.2.2]nonan-4-yl, azaspiro[3.3]heptan-2-yl, 4,7-diazaspiro[2.5]octan-4-yl,
 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 2,6-diazaspiro[3.4]octan-2-yl,
 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl,
 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl,
 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl,
 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl
 or 6,9-diazaspiro[4.5]decan-9-yl; wherein, each instance of heterocyclyl is optionally
 substituted with R₃ and R₄ substituents.

[0395] Another aspect includes a compound of Formula (XII), wherein R₁ is heterocyclyl
 selected from pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, 1,2,5,6-tetrahydropyridinyl,
 1,2,3,6-tetrahydropyridinyl, 3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl,

2,5-diazabicyclo[2.2.1]heptyl, 2,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.5]nonyl, 2,7-diazaspiro[3.5]nonyl.

[0396] Another aspect includes a compound of Formula (XII), wherein R₁ is heterocyclyl selected from pyrrolidin-3-yl, piperidin-4-yl, piperazin-1-yl, azepan-4-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-2-yl, and 2,7-diazaspiro[3.5]nonan-7-yl.

[0397] Another aspect includes a compound of Formula (XII), wherein R₁ is substituted heterocyclyl selected from *N,N*-dimethylpyrrolidin-3-amine, *N,N*-dimethylpiperidin-4-amine, *N,N*-4-trimethylpiperidin-4-amine, 1-methylpiperidin-4-yl, 1-ethylpiperidin-4-yl, 1-(propan-2-yl)piperidin-4-yl, 2-hydroxyethylpiperidin-4-yl, 2-fluoroethylpiperidin-4-yl, 2,2-difluoroethylpiperidin-4-yl, *N,N*-dimethyl-2-(piperidin-1-yl)ethan-1-amine, *N,N*-dimethyl-2-(piperidin-1-yl)propan-1-amine, (2*S*,6*S*)-2,6-dimethylpiperidin-4-yl, (2*R*,6*S*)-2,6-dimethylpiperidin-4-yl, (2*S*,6*S*)-2,6-diethylpiperidin-4-yl, (2*S*,6*S*)-(2,6-diethyl-1-methyl)piperidin-4-yl, (2*S*,6*S*)-1,2,6-trimethylpiperidin-4-yl, (2*R*,6*S*)-1,2,6-trimethylpiperidin-4-yl, (2*S*,4*R*,6*R*)-1,2,6-trimethylpiperidin-4-yl, (2*R*,6*R*)-1-ethyl-2,6-dimethylpiperidin-4-yl, (2*R*,6*S*)-[1-(2-fluoroethyl)-2,6-dimethyl]piperidin-4-yl, (ethyl-1-ol)piperidin-1-yl, 2,6-dimethylpiperidin-1-yl-ethan-1-ol, 3-(1*H*-pyrazol-1-yl)propylpiperidin-4-yl, 3-(1*H*-benzimidazol-1-yl)propylpiperidin-4-yl, 2-(1*H*-benzimidazol-1-yl)ethylpiperidin-4-yl, 1-ethyl-1,2,3,6-tetrahydropyridin-4-yl, 2,2,6,6-tetramethylpiperidin-4-yl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl, (3*R*,5*S*)-3,5-dimethylpiperazin-1-yl, 1-methylazepan-4-yl, 1-ethylazepan-4-yl, 2-fluoroethylazepan-4-yl, azepan-1-yl-ethan-1-ol, 4-methyl-1,4-diazepan-1-yl, (3*aS*,6*aS*)-1-methylhexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl, (3*aS*,6*aS*)-5-methylhexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl, (3*aR*,6*aR*)-1-methylhexahydropyrrolo[3,4-*b*]pyrrol-5(1*H*)-yl, (3*aR*,6*aS*)-5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, (3*aR*,6*aS*)-5-(2-hydroxyethyl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, (3*aR*,6*aS*)-5-(propan-2-yl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, (3*aR*,6*aS*)-5-ethylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, (4*aR*,7*aR*)-1-methyloctahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl,

(4a*R*,7a*R*)-1-ethyloctahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl,
 (4a*R*,7a*R*)-1-(2-hydroxyethyl)octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl,
 (4a*S*,7a*S*)-1-methyloctahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl,
 (4a*S*,7a*S*)-1-(2-hydroxyethyl)octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl,
 (7*R*,8a*S*)-7-hydroxyhexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl,
 (8a*S*)-8a-methyloctahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl,
 (8a*R*)-8a-methyloctahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl,
 (1*R*,5*S*,6*s*)-6-(dimethylamino)-3-azabicyclo[3.1.0]hex-3-yl,
N,N-dimethyl-3-azabicyclo[3.1.0]hexan-6-amine,
 (1*R*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, 9-methyl-9-azabicyclo[3.3.1]non-3-yl,
 (3-*exo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl,
 (1*R*,5*S*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl, 5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl,
 (1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl,
 (1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl or
 (1*S*,4*S*)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl.

[0398] Another aspect includes a compound of Formula (XII), wherein R₁ is substituted heterocyclyl selected from *N,N*-dimethylpyrrolidin-3-amine, *N,N*-dimethylpiperidin-4-amine, *N,N*-4-trimethylpiperidin-4-amine, 1-methylpiperidin-4-yl, 1-ethyl-piperidin-4-yl, 1-(propan-2-yl)piperidin-4-yl, 2-hydroxyethylpiperidin-4-yl, 2-fluoroethylpiperidin-4-yl, 2,2-difluoroethylpiperidin-4-yl, *N,N*-dimethyl-2-(piperidin-1-yl)ethan-1-amine, *N,N*-dimethyl-2-(piperidin-1-yl)propan-1-amine, (2*S*,6*S*)-2,6-dimethylpiperidin-4-yl, (2*R*,6*S*)-2,6-dimethylpiperidin-4-yl, (2*S*,6*S*)-2,6-diethylpiperidin-4-yl, (2*S*,6*S*)-2,6-diethyl-1-methylpiperidin-4-yl, (2*S*,6*S*)-1,2,6-trimethylpiperidin-4-yl, (2*R*,6*S*)-1,2,6-trimethylpiperidin-4-yl, (2*S*,4*R*,6*R*)-1,2,6-trimethylpiperidin-4-yl, (2*R*,6*R*)-1-ethyl-2,6-dimethylpiperidin-4-yl, (2*R*,6*S*)-1-(2-fluoroethyl)-2,6-dimethylpiperidin-4-yl, piperidin-1-yl-ethan-1-ol, 2,6-dimethylpiperidin-1-yl-ethan-1-ol, 3-(1*H*-pyrazol-1-yl)propyl]piperidin-4-yl, 3-(1*H*-benzimidazol-1-yl)propyl]piperidin-4-yl, 2-(1*H*-benzimidazol-1-yl)ethyl]piperidin-4-yl, 1-ethyl-1,2,3,6-tetrahydropyridin-4-yl, 2,2,6,6-tetramethylpiperidin-4-yl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl, (3*R*,5*S*)-3,5-dimethylpiperazin-1-yl, 1-methylazepan-4-yl, 1-ethylazepan-4-yl, 2-fluoroethylazepan-4-yl, azepan-1-yl-ethan-1-ol, *N,N*-dimethyl-3-azabicyclo[3.1.0]hexan-6-amine, 5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl or (1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl.

[0399] One aspect includes a compound of Formula (XII), wherein R₁ is heterocyclyl-amino, wherein heterocyclyl is selected from azetidiny, pyrrolidiny, piperidiny, 9-azabicyclo[3.3.1]nonyl or (1*R*,5*S*)-9-azabicyclo[3.3.1]nonyl; and, wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0400] Another aspect includes a compound of Formula (XII), wherein R₁ is heterocyclyl-amino selected from azetidin-3-yl-amino, pyrrolidin-3-yl-amino, piperidin-4-yl-amino, 9-azabicyclo[3.3.1]non-3-yl-amino, (1*R*,5*S*)-9-azabicyclo[3.3.1]non-3-yl-amino, 9-methyl-9-azabicyclo[3.3.1]non-3-yl-amino, (3-*exo*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl-amino or (1*R*,5*S*)-9-methyl-9-azabicyclo[3.3.1]non-3-yl-amino; wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0401] One aspect includes a compound of Formula (XII), wherein R₁ is (heterocyclyl)(C₁₋₈alkyl)amino, wherein heterocyclyl is selected from pyrrolidiny or piperidiny; and, wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0402] Another aspect includes a compound of Formula (XII), wherein R₁ is (heterocyclyl)(C₁₋₈alkyl)amino wherein heterocyclyl is piperidiny.

[0403] Another aspect includes a compound of Formula (XII), wherein R₁ is (heterocyclyl)(C₁₋₈alkyl)amino selected from (pyrrolidin-3-yl)(methyl)amino or (piperidin-4-yl)(methyl)amino; wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0404] One aspect includes a compound of Formula (XII), wherein R₃ is selected from cyano, halogen, hydroxy, oxo, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkyl-carbonyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, C₁₋₈alkyl-carbonyl-amino, C₁₋₈alkoxy-carbonyl-amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino or (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino.

[0405] Another aspect includes a compound of Formula (XII), wherein R₃ is selected from cyano, halogen, hydroxy, oxo, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, C₁₋₈alkoxy-carbonyl-amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino or (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino.

[0406] Another aspect includes a compound of Formula (XII), wherein R₃ is C₁₋₈alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl.

[0407] Another aspect includes a compound of Formula (XII), R₃ is C₁₋₈alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl.

[0408] Another aspect includes a compound of Formula (XII), wherein R₃ is halo-C₁₋₈alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, halo-ethyl, trihalo-propyl, dihalo-propyl or halo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0409] Another aspect includes a compound of Formula (XII), wherein R₃ is halo-C₁₋₈alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, trihalo-propyl or dihalo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0410] Another aspect includes a compound of Formula (XII), wherein R₃ is hydroxy-C₁₋₈alkyl selected from hydroxy-methyl, hydroxy-ethyl, hydroxy-propyl, dihydroxy-propyl, hydroxy-butyl or dihydroxy-butyl.

[0411] Another aspect includes a compound of Formula (XII), wherein R₃ is hydroxy-C₁₋₈alkyl selected from hydroxy-methyl, hydroxy-ethyl, dihydroxy-propyl, hydroxy-butyl or dihydroxy-butyl.

[0412] Another aspect includes a compound of Formula (XII), wherein R₃ is C₁₋₈alkoxy selected from methoxy, ethoxy, propoxy or isopropoxy.

[0413] Another aspect includes a compound of Formula (XII), wherein R₃ is halo-C₁₋₈alkoxy selected from trihalo-methoxy, dihalo-methoxy, halo-methoxy, trihalo-ethoxy, dihalo-ethoxy, halo-ethoxy, trihalo-propoxy, dihalo-propoxy or halo-propoxy; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0414] Another aspect includes a compound of Formula (XII), wherein R₃ is C₁₋₈alkoxy-carbonyl-amino selected from methoxy-carbonyl-amino, ethoxy-carbonyl-amino, propoxy-carbonyl-amino, isopropoxy-carbonyl-amino, tert-butoxy-carbonyl-amino.

[0415] Another aspect includes a compound of Formula (XII), wherein R₄ is C₃₋₁₄cycloalkyl, C₃₋₁₄cycloalkyl-C₁₋₈alkyl, C₃₋₁₄cycloalkyl-amino, aryl-C₁₋₈alkyl, aryl-C₁₋₈alkoxy-carbonyl, aryl-sulfonyloxy-C₁₋₈alkyl, heterocyclyl, heterocyclyl-C₁₋₈alkyl or heteroaryl; wherein, each instance of C₃₋₁₄cycloalkyl, aryl, heterocyclyl and heteroaryl is optionally substituted with one, two or three R₅ substituents.

[0416] Another aspect includes a compound of Formula (XII), wherein R₅ is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, hydroxy-C₁₋₈alkyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, C₁₋₈alkyl-thio or heteroaryl-C₁₋₈alkyl.

[0417] One aspect includes a compound of Formula (XII), wherein R₂ is aryl, heteroaryl, heteroaryl-amino, (heteroaryl)(C₁₋₈alkyl)amino or (heterocyclyl)(C₁₋₈alkyl)amino.

[0418] Another aspect includes a compound of Formula (XII), wherein R₂ is aryl, heteroaryl, heteroaryl-amino or (heteroaryl)(C₁₋₈alkyl)amino.

[0419] Another aspect includes a compound of Formula (XII), wherein R₂ is aryl.

[0420] Another aspect includes a compound of Formula (XII), wherein R₂ is heteroaryl.

[0421] Another aspect includes a compound of Formula (XII), wherein R₂ is heteroaryl-amino.

[0422] Another aspect includes a compound of Formula (XII), wherein R₂ is (heteroaryl)(C₁₋₈alkyl)amino.

[0423] Another aspect includes a compound of Formula (XII), wherein R₂ is (heterocyclyl)(C₁₋₈alkyl)amino.

[0424] One aspect includes a compound of Formula (XII), wherein R₂ is heteroaryl selected from thienyl, 1*H*-pyrazolyl, 1*H*-imidazolyl, 1,3-thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrimidinyl, 1*H*-indolyl, 2*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1*H*-benzimidazolyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, 9*H*-purinyl, furo[3,2-*b*]pyridinyl, furo[3,2-*c*]pyridinyl, furo[2,3-*c*]pyridinyl, thieno[3,2-*c*]pyridinyl, thieno[2,3-*d*]pyrimidinyl,

1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, pyrrolo[1,2-*a*]pyrimidinyl, pyrrolo[1,2-*a*]pyrazinyl, pyrrolo[1,2-*b*]pyridazinyl, pyrazolo[1,5-*a*]pyridinyl, 2*H*-pyrazolo[3,4-*c*]pyridinyl, 2*H*-pyrazolo[4,3-*b*]pyridinyl, 2*H*-pyrazolo[4,3-*c*]pyridinyl, pyrazolo[1,5-*a*]pyrazinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*c*]pyrimidinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, 3*H*-imidazo[4,5-*b*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, imidazo[2,1-*b*][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-*b*]pyridinyl, [1,3]oxazolo[4,5-*c*]pyridinyl, [1,3]thiazolo[4,5-*c*]pyridinyl, [1,3]thiazolo[5,4-*b*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl or quinoxalinyl; wherein, each instance of heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0425] Another aspect includes a compound of Formula (XII), wherein R₂ is heteroaryl selected from thien-2-yl, thien-3-yl, 1*H*-pyrazol-3-yl, 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1*H*-imidazol-1-yl, 1*H*-imidazol-4-yl, 1,3-thiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-4-yl, 1*H*-indol-3-yl, 1*H*-indol-4-yl, 1*H*-indol-5-yl, 1*H*-indol-6-yl, 1*H*-indazol-5-yl, 2*H*-indazol-5-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1*H*-benzimidazol-2-yl, 1*H*-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 9*H*-purin-8-yl, furo[3,2-*b*]pyridin-2-yl, furo[3,2-*c*]pyridin-2-yl, furo[2,3-*c*]pyridin-2-yl, thieno[3,2-*c*]pyridin-2-yl, thieno[2,3-*d*]pyrimidin-6-yl, 1*H*-pyrrolo[2,3-*b*]pyridin-5-yl, 1*H*-pyrrolo[2,3-*c*]pyridin-2-yl, 1*H*-pyrrolo[2,3-*c*]pyridin-4-yl, pyrrolo[1,2-*a*]pyrimidin-7-yl, pyrrolo[1,2-*a*]pyrazin-7-yl, pyrrolo[1,2-*b*]pyridazin-2-yl, pyrazolo[1,5-*a*]pyridin-2-yl, pyrazolo[1,5-*a*]pyridin-5-yl, 2*H*-pyrazolo[3,4-*c*]pyridin-5-yl, 2*H*-pyrazolo[4,3-*b*]pyridin-5-yl, 2*H*-pyrazolo[4,3-*c*]pyridin-5-yl, pyrazolo[1,5-*a*]pyrazin-2-yl, imidazo[1,2-*a*]pyridin-2-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyrimidin-2-yl, imidazo[1,2-*a*]pyrimidin-6-yl, imidazo[1,2-*c*]pyrimidin-2-yl, imidazo[1,2-*b*]pyridazin-2-yl, imidazo[1,2-*b*]pyridazin-6-yl, imidazo[1,2-*a*]pyrazin-2-yl, imidazo[1,2-*a*]pyrazin-6-yl, 3*H*-imidazo[4,5-*b*]pyridin-5-yl, imidazo[2,1-*b*][1,3]thiazol-6-yl, imidazo[2,1-*b*][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-*b*]pyridin-2-yl, [1,3]oxazolo[4,5-*c*]pyridin-2-yl, [1,3]thiazolo[5,4-*b*]pyridin-5-yl, [1,3]thiazolo[5,4-*c*]pyridin-2-yl, [1,2,4]triazolo[1,5-*a*]pyridin-6-yl, or quinoxalin-2-yl; wherein, each instance of heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0426] One aspect includes a compound of Formula (XII), wherein R₆ is selected from halogen, hydroxy, cyano, nitro, C₁₋₈alkyl, halo-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl, C₁₋₈alkoxy,

halo-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkoxy-C₁₋₈alkoxy, (C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, heteroaryl-C₁₋₈alkoxy, aryl-oxy, (C₁₋₈alkyl)₂-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, C₁₋₈alkyl-thio, C₃₋₁₄cycloalkyl; wherein, halogen and halo is selected from fluoro, chloro, bromo or iodo.

[0427] Another aspect includes a compound of Formula (XII), wherein R₆ is C₁₋₈alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl.

[0428] Another aspect includes a compound of Formula (XII), wherein R₆ is C₁₋₈alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl.

[0429] Another aspect includes a compound of Formula (XII), wherein R₆ is halo-C₁₋₈alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, halo-ethyl, trihalo-propyl, dihalo-propyl or halo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo.

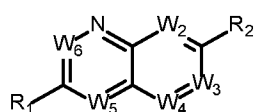
[0430] Another aspect includes a compound of Formula (XII), wherein R₇ is C₃₋₁₄cycloalkyl, C₃₋₁₄cycloalkyl-oxy, aryl, heterocyclyl or heteroaryl.

[0431] One aspect includes a compound of Formula (XII), wherein R_a is hydrogen or C₁₋₈alkyl.

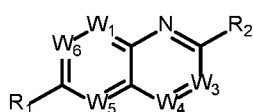
[0432] One aspect includes a compound of Formula (XII), wherein R_b is hydrogen or C₁₋₈alkyl.

[0433] Another aspect includes a compound of Formula (XII), wherein R_b is halo.

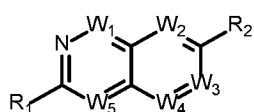
[0434] One aspect of the compound of Formula (XII) includes a compound selected from Formula (XIIa), Formula (XIIb), Formula (XIIc), Formula (XIId), Formula (XIIe), Formula (XIIf), Formula (XIIg), Formula (XIIh), Formula (XIIi), Formula (XIIj), Formula (XIIk), Formula (XIII), Formula (XIIIm) or Formula (XIIn):



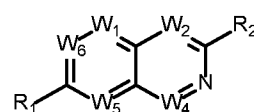
(XIIa),



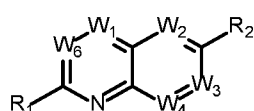
(XIIb),



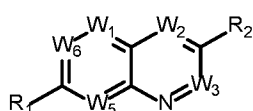
(XIIc),



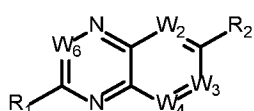
(XIId),



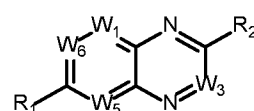
(XIIe),



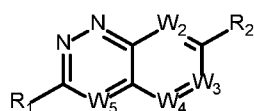
(XIIf),



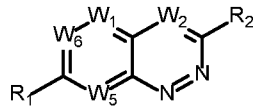
(XIIg),



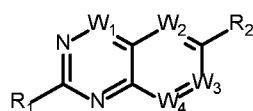
(XIIh),



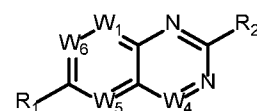
(XIIi),



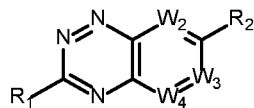
(XIIj),



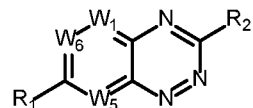
(XIIk),



(XIII),



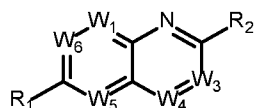
(XIIIm) and



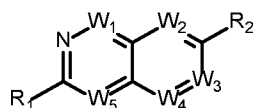
(XIIn),

or a form thereof.

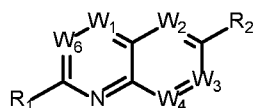
[0435] Another aspect of the compound of Formula (XII) includes the compound selected from Formula (XIIb), Formula (XIIc), Formula (XIId), Formula (XIIe), Formula (XIIf), Formula (XIIg), Formula (XIIh), Formula (XIIi), Formula (XIIj), Formula (XIIk), Formula (XIIl), Formula (XIIm) or Formula (XIIn):



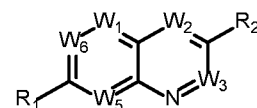
(XIIb),



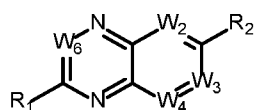
(XIIc),



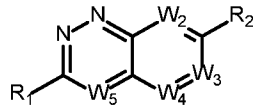
(XIId),



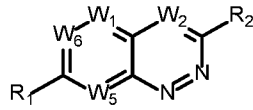
(XIIe),



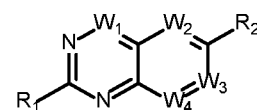
(XIIf),



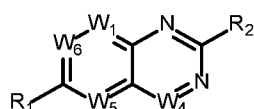
(XIIg),



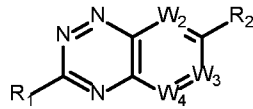
(XIIh),



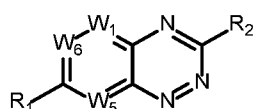
(XIIi),



(XIII),



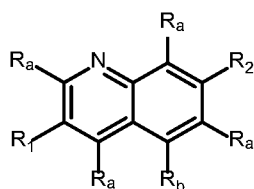
(XIIIm) and



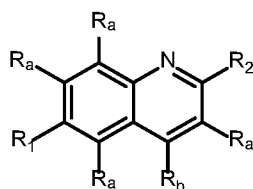
(XIIn),

or a form thereof.

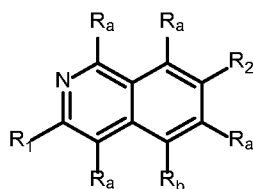
[0436] Another aspect of the compound of Formula (XII) includes the compound selected from of Formula (XIIa1), Formula (XIIb1), Formula (XIIc1), Formula (XIId1), Formula (XIIe1), Formula (XIIf1), Formula (XIIg1), Formula (XIIh1), Formula (XIIi1), Formula (XIIj1), Formula (XIIk1), Formula (XIIl1), Formula (XIIm1) or Formula (XIIn1), respectively:



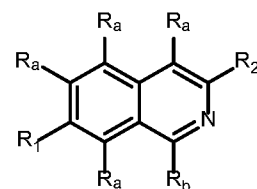
(XIIa1),



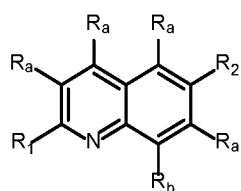
(XIIb1),



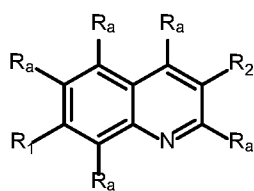
(XIIc1),



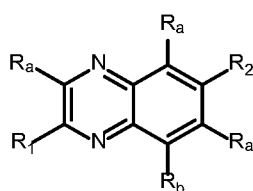
(XIId1),



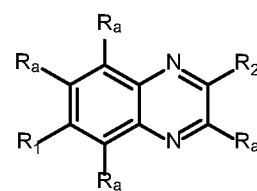
(XIIe1),



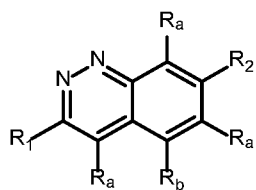
(XIIIf1),



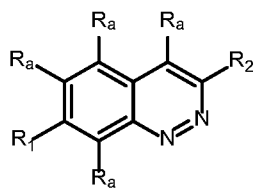
(XIIg1)



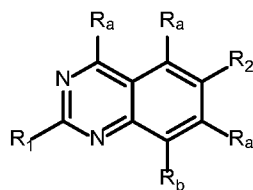
(XIIh1)



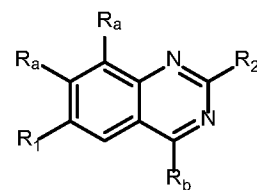
(XIIi)



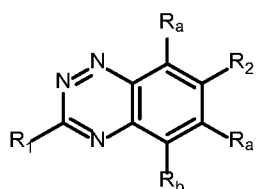
(XIIj1),



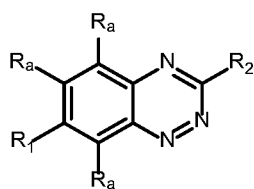
(XIIk1),



(XIII1),



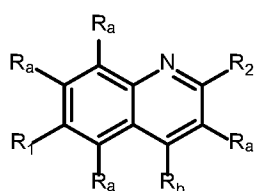
(XIIIm1) and



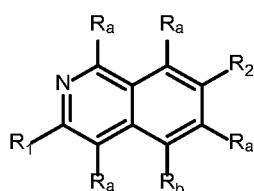
(XIIn1),

or a form thereof.

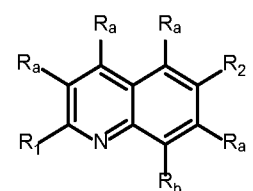
[0437] Another aspect of the compound of of Formula (XII) includes the compound selected from Formula (XIIb1), Formula (XIIc1), Formula (XIIe1), Formula (XIIIf1), Formula (XIIg1), Formula (XIII1), Formula (XIIj1), Formula (XIIk1), Formula (XIII1), Formula (XIIIm1) or Formula (XIIn1), respectively:



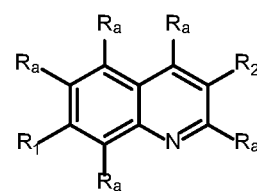
(XIIb1),



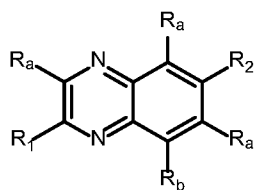
(XIIc1),



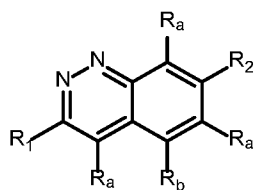
(XIIe1),



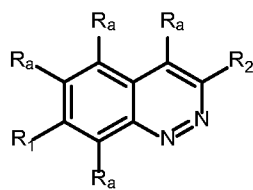
(XIIIf1),



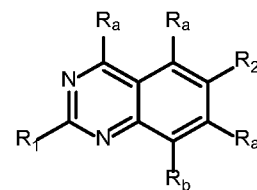
(XIIg1)



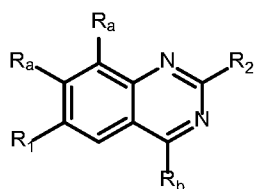
(XIII1),



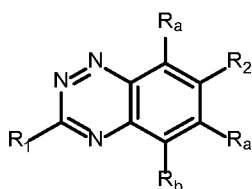
(XIIj1),



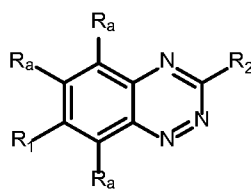
(XIIk1),



(XIII1)



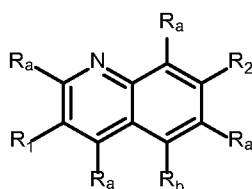
(XIIIm1) or



(XIIn1),

or a form thereof.

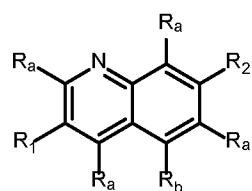
[0438] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIa1):



(XIIa1)

or a form thereof.

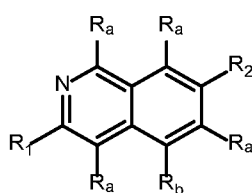
[0439] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIb1):



(XIIb1)

or a form thereof.

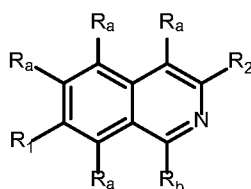
[0440] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIc1):



(XIIc1)

or a form thereof.

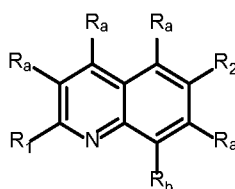
[0441] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIId1):



(XIId1)

or a form thereof.

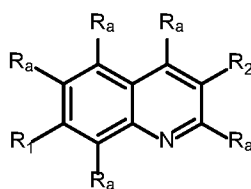
[0442] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIe1):



(XIIe1)

or a form thereof.

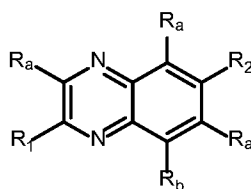
[0443] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIf1):



(XIIf1)

or a form thereof.

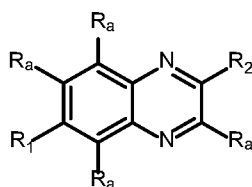
[0444] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIf1):



(XIIf1)

or a form thereof.

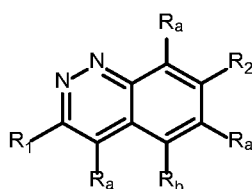
[0445] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIh1):



(XIIh1)

or a form thereof.

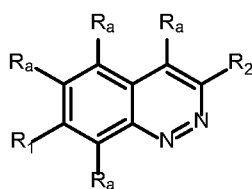
[0446] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIi1):



(XIIi1)

or a form thereof.

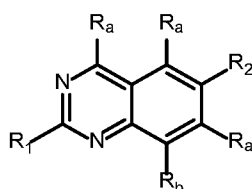
[0447] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIj1):



(XIIj1)

or a form thereof.

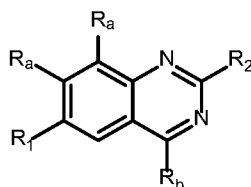
[0448] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIk1):



(XIIk1)

or a form thereof.

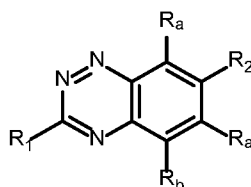
[0449] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIII1):



(XIII1)

or a form thereof.

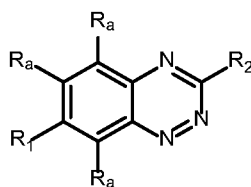
[0450] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIIm1):



(XIIIm1)

or a form thereof.

[0451] Another aspect of the compound of Formula (XII) includes the compound of Formula (XIIn1):



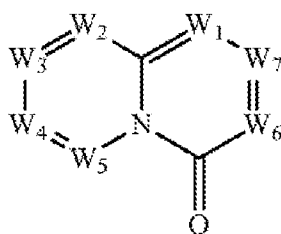
(XIIn1)

or a form thereof.

HD Compounds of Formula (XIII)

[0452] In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in the published U.S. Patent Application No. 2020/0163973, the content of which is incorporated by reference herein in its entirety.

[0453] In one aspect, an HD compound of the disclosure can refer to a compound of Formula (XIII)



(XIII)

or a form thereof, wherein:

w_1 and w_5 are independently C—R_a or N;

w₂ is C—R_b or N;

w₃, w₄ and w₇ are independently C—R₁, C—R₂, C—R_a or N;

w₆ is C—R₁, C—R₂, C—R_e or N;

wherein one of w₃, w₄, w₆ and w₇ is C—R₁ and one other of w₃, w₄, w₆ and w₇ is C—R₂, provided that,

when w_3 is C—R₁, then w_6 is C—R₂ and w_4 and w_7 are independently C—R_a or N; or,

when w_3 is C—R₂, then w_6 is C—R₁ and w_4 and w_7 are independently C—R_a or N; or,

when w_4 is C—R₁, then w_7 is C—R₂ and w_3 is C—R_a or N and w_6 is C—R_e or N; or,

when w_4 is C—R₂, then w_7 is C—R₁ and w_3 is C—R_a or N and w_6 is C—R_e or N; and,

wherein any one, two or three of w_1 , w_2 , w_3 , w_4 , w_5 , w_6 and w_7 may optionally be N;

R₁ is C₁₋₈alkyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, (amino-C₁₋₈alkyl)₂-amino, (amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, amino-C₁₋₈alkoxy, C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, amino-C₂₋₈alkenyl, C₁₋₈alkyl-amino-C₂₋₈alkenyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkenyl, amino-C₂₋₈alkynyl, C₁₋₈alkyl-amino-C₂₋₈alkynyl, (C₁₋

8alkyl)₂-amino-C₂₋₈alkynyl, halo-C₁₋₈alkyl-amino, (halo-C₁₋₈alkyl)₂-amino, (halo-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl-amino, [(hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, [(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, heterocyclyl, heterocyclyl-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkoxy, heterocyclyl-amino, (heterocyclyl)(C₁₋₈alkyl)amino, heterocyclyl-amino-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkyl-amino, (heterocyclyl-C₁₋₈alkyl)₂-amino, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl-oxy, heterocyclyl-carbonyl, heterocyclyl-carbonyl-oxy, C₃₋₁₄cycloalkyl, aryl-C₁₋₈alkyl-amino, (aryl-C₁₋₈alkyl)₂-amino, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heteroaryl, heteroaryl-C₁₋₈alkyl, heteroaryl-C₁₋₈alkoxy, heteroaryl-amino, heteroaryl-C₁₋₈alkyl-amino, (heteroaryl-C₁₋₈alkyl)₂-amino, (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl;

wherein, each instance of heterocyclyl, C₃₋₁₄cycloalkyl, aryl and heteroaryl is optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent; or,

wherein, each instance of heterocyclyl, C₃₋₁₄cycloalkyl, aryl and heteroaryl is optionally substituted with one, two, three or four R₃ substituents;

R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino; wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent;

R_a is, in each instance, independently selected from hydrogen, halogen or C₁₋₈alkyl;

R_b is hydrogen, halogen, C₁₋₈alkyl or C₁₋₈alkoxy;

R_c is hydrogen, halogen or C₁₋₈alkyl;

R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, oxo, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkyl-carbonyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl]₂-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, C₁₋₈alkyl-carbonyl-amino, C₁₋₈alkoxy-carbonyl-amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino or (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino;

R₄ is C₃₋₁₄cycloalkyl, C₃₋₁₄cycloalkyl-C₁₋₈alkyl, C₃₋₁₄cycloalkyl-amino, aryl-C₁₋₈alkyl, aryl-C₁₋₈alkoxy-carbonyl, aryl-sulfonyloxy-C₁₋₈alkyl, heterocyclyl or heterocyclyl-C₁₋₈alkyl; wherein, each instance of C₃₋₁₄cycloalkyl, aryl and heterocyclyl is optionally substituted with one, two or three R₅ substituents;

R₅ is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino or C₁₋₈alkyl-thio;

R₆ is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C₁₋₈alkyl, C₂₋₈alkenyl, halo-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino or C₁₋₈alkyl-thio; and,

R₇ is C₃₋₁₄cycloalkyl, C₃₋₁₄cycloalkyl-oxy, aryl, heterocyclyl or heteroaryl; and, wherein the form of the compound is selected from the group consisting of a salt, prodrug, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

[0454] In one aspect of the compound of Formula (XIII), w1 is C—Ra.

[0455] In another aspect of the compound of Formula (XIII), w1 is N.

- [0456] In one aspect of the compound of Formula (XIII), w₂ is C—R_b.
- [0457] In another aspect of the compound of Formula (XIII), w₂ is N.
- [0458] In one aspect of the compound of Formula (XIII), w₃ is C—R_a.
- [0459] In another aspect of the compound of Formula (XIII), w₃ is N.
- [0460] In one aspect of the compound of Formula (XIII), w₄ is C—R_a.
- [0461] In another aspect of the compound of Formula (XIII), w₄ is N.
- [0462] In one aspect of the compound of Formula (XIII), w₅ is C—R_a.
- [0463] In another aspect of the compound of Formula (XIII), w₅ is N.
- [0464] In one aspect of the compound of Formula (XIII), w₆ is C—R_e.
- [0465] In another aspect of the compound of Formula (XIII), w₆ is N.
- [0466] In one aspect of the compound of Formula (XIII), w₇ is C—R_a.
- [0467] In another aspect of the compound of Formula (XIII), w₇ is N.
- [0468] In one aspect of the compound of Formula (XIII), w₃ is C—R₁ and w₆ is C—R₂.
- [0469] In another aspect of the compound of Formula (XIII), w₃ is C—R₂ and w₆ is C—R₁.
- [0470] In one aspect of the compound of Formula (XIII), w₄ is C—R₁ and w₇ is C—R₂.
- [0471] In another aspect of the compound of Formula (XIII), w₄ is C—R₂ and w₇ is C—R₁.
- [0472] In one aspect of the compound of Formula (XIII), w₃ is C—R₁, w₆ is C—R₂ and w₁, w₄, w₅ and w₇ are independently C—R_a or N and w₂ is C—R_b or N.
- [0473] In another aspect of the compound of Formula (XIII), w₃ is C—R₂, w₆ is C—R₁ and w₁, w₄, w₅ and w₇ are independently C—R_a or N and w₂ is C—R_b or N.
- [0474] In one aspect of the compound of Formula (XIII), w₄ is C—R₁, w₇ is C—R₂, w₁, w₃ and w₅ are independently C—R_a or N, w₂ is C—R_b or N and w₆ is C—R_e or N.
- [0475] In another aspect of the compound of Formula (XIII), w₄ is C—R₂, w₇ is C—R₁, w₁, w₃ and w₅ are independently C—R_a or N, w₂ is C—R_b or N and w₆ is C—R_e or N.
- [0476] In one aspect of the compound of Formula (XIII), w₁ and w₂ are N.
- [0477] In one aspect of the compound of Formula (XIII), w₁ and w₃ are N.

[0478] In one aspect of the compound of Formula (XIII), w1 and w4 are N.

[0479] In one aspect of the compound of Formula (XIII), w1 and w5 are N.

[0480] In one aspect of the compound of Formula (XIII), w1 and w6 are N.

[0481] In one aspect of the compound of Formula (XIII), w1 and w7 are N.

[0482] In one aspect of the compound of Formula (XIII),

R₁ is C₁₋₈alkyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, (amino-C₁₋₈alkyl)₂-amino, (amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, amino-C₁₋₈alkoxy, C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, amino-C₂₋₈alkenyl, C₁₋₈alkyl-amino-C₂₋₈alkenyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkenyl, amino-C₂₋₈alkynyl, C₁₋₈alkyl-amino-C₂₋₈alkynyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkynyl, halo-C₁₋₈alkyl-amino, (halo-C₁₋₈alkyl)₂-amino, (halo-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl-amino, [(hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, [(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, heterocyclyl, heterocyclyl-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkoxy, heterocyclyl-amino, (heterocyclyl)(C₁₋₈alkyl)amino, heterocyclyl-amino-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkyl-amino, (heterocyclyl-C₁₋₈alkyl)₂-amino, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl-oxy, heterocyclyl-carbonyl, heterocyclyl-carbonyl-oxy, C₃₋₁₄cycloalkyl, aryl-C₁₋

8alkyl-amino, (aryl-C₁₋₈alkyl)₂-amino, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heteroaryl, heteroaryl-C₁₋₈alkyl, heteroaryl-C₁₋₈alkoxy, heteroaryl-amino, heteroaryl-C₁₋₈alkyl-amino, (heteroaryl-C₁₋₈alkyl)₂-amino, (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl; wherein, each instance of heterocyclyl, C₃₋₁₄cycloalkyl, aryl and heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0483] In another aspect of the compound of Formula (XIII),

R₁ is amino, (C₁₋₈alkyl)₂-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, (amino-C₁₋₈alkyl)₂-amino, (amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, amino-C₁₋₈alkoxy, C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, amino-C₂₋₈alkenyl, C₁₋₈alkyl-amino-C₂₋₈alkenyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkenyl, amino-C₂₋₈alkynyl, C₁₋₈alkyl-amino-C₂₋₈alkynyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkynyl, halo-C₁₋₈alkyl-amino, (halo-C₁₋₈alkyl)₂-amino, (halo-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl-amino, [(hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, [(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, heterocyclyl, heterocyclyl-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkoxy, heterocyclyl-amino, (heterocyclyl)(C₁₋₈alkyl)amino, heterocyclyl-amino-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkyl-amino, (heterocyclyl-C₁₋₈alkyl)₂-amino, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl,

(heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl-oxy, heterocyclyl-carbonyl, heterocyclyl-carbonyl-oxy, C₃₋₁₄cycloalkyl, aryl-C₁₋₈alkyl-amino, (aryl-C₁₋₈alkyl)₂-amino, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heteroaryl, heteroaryl-C₁₋₈alkyl, heteroaryl-C₁₋₈alkoxy, heteroaryl-C₁₋₈alkyl-amino, (heteroaryl-C₁₋₈alkyl)₂-amino, (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl; wherein, each instance of heterocyclyl, C₃₋₁₄cycloalkyl, aryl and heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0484] In another aspect of the compound of Formula (XIII),

R₁ is C₁₋₈alkyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, (amino-C₁₋₈alkyl)₂-amino, (amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, amino-C₁₋₈alkoxy, C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, amino-C₂₋₈alkenyl, C₁₋₈alkyl-amino-C₂₋₈alkenyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkenyl, amino-C₂₋₈alkynyl, C₁₋₈alkyl-amino-C₂₋₈alkynyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkynyl, halo-C₁₋₈alkyl-amino, (halo-C₁₋₈alkyl)₂-amino, (halo-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl-amino, [(hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino or [(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl](C₁₋₈alkyl)amino.

[0485] In another aspect of the compound of Formula (XIII),

R₁ is heterocyclyl, heterocyclyl-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkoxy, heterocyclyl-amino, (heterocyclyl)(C₁₋₈alkyl)amino, heterocyclyl-amino-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkyl-amino, (heterocyclyl-C₁₋₈alkyl)₂-amino, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl-oxy, heterocyclyl-carbonyl, heterocyclyl-carbonyl-oxy, C₃₋₁₄cycloalkyl, aryl-C₁₋₈alkyl-amino, (aryl-C₁₋₈alkyl)₂-amino, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heteroaryl, heteroaryl-C₁₋₈alkyl, heteroaryl-C₁₋₈alkoxy, heteroaryl-amino, heteroaryl-C₁₋₈alkyl-amino, (heteroaryl-C₁₋₈alkyl)₂-amino, (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl; wherein, each instance of heterocyclyl, C₃₋₁₄cycloalkyl, aryl and heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0486] In another aspect of the compound of Formula (XIII),

R₁ is heterocyclyl, heterocyclyl-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkoxy, heterocyclyl-amino, (heterocyclyl)(C₁₋₈alkyl)amino, heterocyclyl-amino-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkyl-amino, (heterocyclyl-C₁₋₈alkyl)₂-amino, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl-oxy, heterocyclyl-carbonyl or heterocyclyl-carbonyl-oxy; wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0487] In another aspect of the compound of Formula (XIII), R₁ is heterocyclyl optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituents; or, optionally, with one, two, three or four R₃ substituents.

[0488] In another aspect of the compound of Formula (XIII), R₁ is C₃₋₁₄cycloalkyl optionally substituted with R₃ and R₄ substituents.

[0489] In another aspect of the compound of Formula (XIII),

R₁ is aryl-C₁₋₈alkyl-amino, (aryl-C₁₋₈alkyl)₂-amino, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl; wherein, each instance of aryl is optionally substituted with R₃ and R₄ substituents.

[0490] In another aspect of the compound of Formula (XIII), R₁ is aryl-C₁₋₈alkyl-amino optionally substituted with R₃ and R₄ substituents.

[0491] In another aspect of the compound of Formula (XIII),

R₁ is heteroaryl, heteroaryl-C₁₋₈alkyl, heteroaryl-C₁₋₈alkoxy, heteroaryl-amino, heteroaryl-C₁₋₈alkyl-amino, (heteroaryl-C₁₋₈alkyl)₂-amino, (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl; wherein, each instance of heterocyclyl, C₃₋₁₄cycloalkyl, aryl and heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0492] In another aspect of the compound of Formula (XIII), R₁ is heteroaryl optionally substituted with R₃ and R₄ substituents.

[0493] In one aspect of the compound of Formula (XIII),

R₁ is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,4-diazepanyl, 3,6-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl, (8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl, (8aS)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazinyl, (8aR)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazinyl, (8aS)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, (3aR,4aR,7aS)-hexahydro-1H-cyclobuta[1,2-c:1,4-c']dipyrrol-(3H)-yl, 3-azabicyclo[3.1.0]hexyl, (1R,5S)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1R,5S)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl, (1R,5S)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1S,4S)-2,5-diazabicyclo[2.2.1]heptyl, 2,5-

diazabicyclo[2.2.2]octyl, 3,6-diazabicyclo[3.2.0]heptyl, 3,8-diazabicyclo[3.2.1]octyl, (1R,5S)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, azaspiro[3.3]heptyl, 2,6-diazaspiro[3.3]heptyl, 4,7-diazaspiro[2.5]octyl, 2,6-diazaspiro[3.4]octyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 2,7-diazaspiro[4.4]nonyl or 6,9-diazaspiro[4.5]decyl; wherein, each instance of heterocyclyl is optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent; or, optionally, with one, two, three or four R₃ substituents.

[0494] In another aspect of the compound of Formula (XIII),

R₁ is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 3,6-dihydropyridin-4-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl, (8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl, (8aS)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl, (8aR)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl, (8aS)-octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aR)-octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, (3aR,4aR,7aS)-hexahydro-1H-cyclobuta[1,2-c:1,4-c']dipyrrol-2(3H)-yl, 3-azabicyclo[3.1.0]hex-3-yl, 8-azabicyclo[3.2.1]oct-3-yl, (1R,5S)-8-azabicyclo[3.2.1]oct-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]non-3-yl, (1R,5S)-9-azabicyclo[3.3.1]non-3-yl, 2,5-diazabicyclo[2.2.1]hept-2-yl, (1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl, 2,5-diazabicyclo[2.2.2]oct-2-yl, 3,6-diazabicyclo[3.2.0]hept-3-yl, 3,8-diazabicyclo[3.2.1]oct-3-yl, (1R,5S)-3,8-diazabicyclo[3.2.1]oct-3-yl, 1,4-diazabicyclo[3.2.2]non-4-yl, azaspiro[3.3]hept-2-yl, 2,6-diazaspiro[3.3]hept-2-yl, 4,7-diazaspiro[2.5]oct-7-yl, 2,6-diazaspiro[3.4]oct-2-yl, 2,7-diazaspiro[3.5]non-2-yl, 2,7-diazaspiro[3.5]non-7-yl, 5,8-diazaspiro[3.5]non-8-yl, 2,7-

diazaspiro[4.4]non-2-yl or 6,9-diazaspiro[4.5]dec-9-yl; wherein, each instance of heterocyclyl is optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent; or, optionally, with one, two, three or four R₃ substituents.

[0495] In another aspect of the compound of Formula (XIII),

R₁ is substituted heterocyclyl selected from (3R)-3-pyrrolidin-1-ylpyrrolidin-1-yl, 1-methylpiperidin-4-yl, 1-ethylpiperidin-4-yl, 2,2,6,6-tetramethylpiperidin-4-yl, (3 S)-3-methylpiperazin-1-yl, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, 3-(trifluoromethyl)piperazin-1-yl, 1-tert-butoxy-carbonyl-3,6-dihydropyridin-4-yl, 1-ethyl-1,2,3,6-tetrahydropyridin-4-yl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl, 4-methyl-1,4-diazepan-1-yl, (3 aS,6aS)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, (3 aS,6aS)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1 (2H)-yl, (3 aR, 6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5 (1H)-yl, (3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (3aR,6aS)-5-(2-hydroxyethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (3aR,6aS)-5-(propan-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (4aR,7aR)-1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aR,7aR)-1-ethyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aR,7aR)-1-(2-hydroxyethyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aS,7aS)-1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aS,7aS)-1-(2-hydroxyethyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (7R,8aS)-7-hydroxyhexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aS)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl, (8aR)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl, (8aS)-8a-methyloctahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aR)-8a-methyloctahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (1R,5S,6s)-6-(dimethylamino)-3-azabicyclo[3.1.0]hex-3-yl, (1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, 9-methyl-9-azabicyclo[3.3.1]non-3-yl, (3-exo)-9-methyl-9-azabicyclo[3.3.1]non-3-yl, (1R,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl, (1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl, (1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl or 6-methyl-2,6-diazaspiro[3.3]hept-2-yl.

[0496] In one aspect of the compound of Formula (XIII), R₁ is heterocyclyl-C1-8alkyl, wherein heterocyclyl is selected from morpholinyl, piperidinyl, piperazinyl, imidazolyl or pyrrolidinyl; and, wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0497] In another aspect of the compound of Formula (XIII), R₁ is heterocyclyl-C1-8alkyl selected from morpholin-4-yl-methyl, morpholin-4-yl-ethyl, morpholin-4-yl-propyl,

piperidin-1-yl-methyl, piperazin-1-yl-methyl, piperazin-1-yl-ethyl, piperazin-1-yl-propyl, piperazin-1-yl-butyl, imidazol-1-yl-methyl, imidazol-1-yl-ethyl, imidazol-1-yl-propyl, imidazol-1-yl-butyl, pyrrolidin-1-yl-methyl, pyrrolidin-1-yl-ethyl, pyrrolidin-1-yl-propyl or pyrrolidin-1-yl-butyl; wherein, each instance of heterocyclyl is optionally substituted with R3 and R4 substituents.

[0498] In one aspect of the compound of Formula (XIII), R1 is heterocyclyl-C1-8alkoxy, wherein heterocyclyl is selected from pyrrolidinyl, piperidinyl or morpholinyl; and, wherein, each instance of heterocyclyl is optionally substituted with R3 and R4 substituents.

[0499] In another aspect of the compound of Formula (XIII), R1 is heterocyclyl-C1-8alkoxy selected from pyrrolidin-2-yl-methoxy, pyrrolidin-2-yl-ethoxy, pyrrolidin-1-yl-methoxy, pyrrolidin-1-yl-ethoxy, piperidin-1-yl-methoxy, piperidin-1-yl-ethoxy, morpholin-4-yl-methoxy or morpholin-4-yl-ethoxy; wherein, each instance of heterocyclyl is optionally substituted with R3 and R4 substituents.

[0500] In one aspect of the compound of Formula (XIII), R1 is heterocyclyl-amino, wherein heterocyclyl is selected from azetidiny, pyrrolidinyl, piperidinyl, 9-azabicyclo[3.3.1]nonyl or (1R,5S)-9-azabicyclo[3.3.1]nonyl; and, wherein, each instance of heterocyclyl is optionally substituted with R3 and R4 substituents.

[0501] In another aspect of the compound of Formula (XIII), R1 is heterocyclyl-amino selected from azetidin-3-yl-amino, pyrrolidin-3-yl-amino, piperidin-4-yl-amino, 9-azabicyclo[3.3.1]non-3-yl-amino, (1R,5S)-9-azabicyclo[3.3.1]non-3-yl-amino, 9-methyl-9-azabicyclo[3.3.1]non-3-yl-amino, (3-exo)-9-methyl-9-azabicyclo[3.3.1]non-3-yl-amino or (1R,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl-amino; wherein, each instance of heterocyclyl is optionally substituted with R3 and R4 substituents.

[0502] In one aspect of the compound of Formula (XIII), R1 is (heterocyclyl)(C1-8alkyl)amino, wherein heterocyclyl is selected from pyrrolidinyl or piperidinyl; and, wherein, each instance of heterocyclyl is optionally substituted with R3 and R4 substituents.

[0503] In another aspect of the compound of Formula (XIII), R1 is (heterocyclyl)(C1-8alkyl)amino selected from (pyrrolidin-3-yl)(methyl)amino or (piperidin-4-yl)(methyl)amino; wherein, each instance of heterocyclyl is optionally substituted with R3 and R4 substituents.

[0504] In one aspect of the compound of Formula (XIII), R₁ is heterocyclyl-amino-C₁-8alkyl, wherein heterocyclyl is selected from tetrahydrofuranyl; and, wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0505] In another aspect of the compound of Formula (XIII), R₁ is heterocyclyl-amino-C₁-8alkyl, selected from 3-(tetrahydrofuran-3-yl-amino)propyl; wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0506] In one aspect of the compound of Formula (XIII), R₁ is heterocyclyl-C₁-8alkyl-amino-C₁-8alkyl, wherein heterocyclyl is selected from tetrahydrofuranyl, thienyl or pyridinyl; and, wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0507] In another aspect of the compound of Formula (XIII), R₁ is heterocyclyl-C₁-8alkyl-amino-C₁-8alkyl, selected from 3-[(tetrahydrofuran-2-ylmethyl)amino]propyl, 3-[(thienyl-3-ylmethyl)amino]propyl, 3-[(pyridin-2-ylmethyl)amino]propyl or 3-[(pyridin-4-ylmethyl)amino]propyl; wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0508] In one aspect of the compound of Formula (XIII), R₁ is heterocyclyl-oxy, wherein heterocyclyl is selected from pyrrolidinyl or piperidinyl; and, wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0509] In another aspect of the compound of Formula (XIII), R₁ is heterocyclyl-oxy selected from pyrrolidin-3-yl-oxy or piperidin-4-yl-oxy; wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0510] In one aspect of the compound of Formula (XIII), R₁ is heterocyclyl-carbonyl, wherein heterocyclyl is selected from piperazinyl; and, wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0511] In another aspect of the compound of Formula (XIII), R₁ is heterocyclyl-carbonyl selected from piperazin-1-yl-carbonyl; wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0512] In one aspect of the compound of Formula (XIII), R₁ is heterocyclyl-carbonyl-oxy, wherein heterocyclyl is selected from piperazinyl; and, wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0513] In another aspect of the compound of Formula (XIII), R₁ is heterocyclyl-carbonyl-oxy selected from piperazin-1-yl-carbonyl-oxy; wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents.

[0514] In one aspect of the compound of Formula (XIII), R₁ is C₃₋₁₄cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl or cycloheptyl; wherein, each instance of C₃₋₁₄cycloalkyl is optionally substituted with R₃ and R₄ substituents.

[0515] In another aspect of the compound of Formula (XIII), R₁ is C₃₋₈cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl or cycloheptyl; wherein, each instance of C₃₋₈cycloalkyl is optionally substituted with R₃ and R₄ substituents.

[0516] In one aspect of the compound of Formula (XIII), R₁ is aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, wherein aryl is selected from phenyl; and, wherein, each instance of aryl is optionally substituted with R₃ and R₄ substituents.

[0517] In another aspect of the compound of Formula (XIII), R₁ is aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl selected from 3-(benzylamino)propyl; wherein, each instance of aryl is optionally substituted with R₃ and R₄ substituents.

[0518] In one aspect of the compound of Formula (XIII), R₁ is heteroaryl, wherein heteroaryl is selected from pyridinyl; and, wherein, each instance of heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0519] In another aspect of the compound of Formula (XIII), R₁ is heteroaryl selected from pyridin-4-yl; wherein, each instance of heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0520] In one aspect of the compound of Formula (XIII), R₁ is heteroaryl-C₁₋₈alkyl, wherein heteroaryl is selected from 1H-imidazolyl; and, wherein, each instance of heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0521] In another aspect of the compound of Formula (XIII), R₁ is heteroaryl-C₁₋₈alkyl selected from 1H-imidazol-1-yl-methyl; wherein, each instance of heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0522] In one aspect of the compound of Formula (XIII), R₁ is (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, wherein heteroaryl is selected from pyridinyl; and, wherein, each instance of heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0523] In another aspect of the compound of Formula (XIII), R₁ is (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino selected from (pyridin-3-ylmethyl)(methyl)amino; wherein, each instance of heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0524] In one aspect of the compound of Formula (XIII), R₁ is heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, wherein heteroaryl is selected from thienyl or pyridinyl; and, wherein, each instance of heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0525] In another aspect of the compound of Formula (XIII), R₁ is heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl selected from thien-3-yl-methyl-amino-propyl, pyridin-2-yl-methyl-amino-propyl, pyridin-3-yl-methyl-amino-propyl or pyridin-4-yl-methyl-amino-propyl; wherein, each instance of heteroaryl is optionally substituted with R₃ and R₄ substituents.

[0526] In one aspect of the compound of Formula (XIII), R₃ is selected from cyano, halogen, hydroxy, oxo, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkyl-carbonyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, C₁₋₈alkyl-carbonyl-amino, C₁₋₈alkoxy-carbonyl-amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino or (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino.

[0527] In another aspect of the compound of Formula (XIII), R₃ is selected from cyano, halogen, hydroxy, oxo, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, C₁₋₈alkoxy-carbonyl-amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino or (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino.

[0528] In one aspect of the compound of Formula (XIII), R₃ is C₁₋₈alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl.

[0529] In another aspect of the compound of Formula (XIII), R₃ is C₁₋₈alkyl selected from ethyl, propyl, isopropyl or tert-butyl.

[0530] In one aspect of the compound of Formula (XIII), R₃ is halo-C₁₋₈alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, halo-ethyl, trihalo-

propyl, dihalo-propyl or halo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0531] In another aspect of the compound of Formula (XIII), R₃ is halo-C₁₋₈alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, trihalo-propyl or dihalo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0532] In one aspect of the compound of Formula (XIII), R₃ is hydroxy-C₁₋₈alkyl selected from hydroxy-methyl, hydroxy-ethyl, hydroxy-propyl, dihydroxy-propyl, hydroxy-butyl or dihydroxy-butyl.

[0533] In another aspect of the compound of Formula (XIII), R₃ is hydroxy-C₁₋₈alkyl selected from hydroxy-methyl, dihydroxy-propyl, hydroxy-butyl or dihydroxy-butyl.

[0534] In one aspect of the compound of Formula (XIII), R₃ is C₁₋₈alkoxy selected from methoxy, ethoxy, propoxy or isopropoxy.

[0535] In one aspect of the compound of Formula (XIII), R₃ is halo-C₁₋₈alkoxy selected from trihalo-methoxy, dihalo-methoxy, halo-methoxy, trihalo-ethoxy, dihalo-ethoxy, halo-ethoxy, trihalo-propoxy, dihalo-propoxy or halo-propoxy; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0536] In one aspect of the compound of Formula (XIII), R₃ is C₁₋₈alkoxy-carbonyl-amino selected from methoxy-carbonyl-amino, ethoxy-carbonyl-amino, propoxy-carbonyl-amino, isopropoxy-carbonyl-amino, tert-butoxy-carbonyl-amino.

[0537] In one aspect of the compound of Formula (XIII), R₄ is C₃₋₁₄cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; wherein, each instance of C₃₋₁₄cycloalkyl is optionally substituted with R₅ substituents.

[0538] In another aspect of the compound of Formula (XIII), R₄ is C₃₋₈cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; wherein, each instance of C₃₋₈cycloalkyl is optionally substituted with R₅ substituents.

[0539] In one aspect of the compound of Formula (XIII), R₄ is C₃₋₁₄cycloalkyl-C₁₋₈alkyl, wherein C₃₋₁₄cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; and, wherein, each instance of C₃₋₁₄cycloalkyl is optionally substituted with R₅ substituents.

[0540] In another aspect of the compound of Formula (XIII), R₄ is C₃₋₈cycloalkyl-C₁₋₈alkyl, wherein C₃₋₈cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; and, wherein, each instance of C₃₋₈cycloalkyl is optionally substituted with R₅ substituents.

[0541] In one aspect of the compound of Formula (XIII), R₄ is C₃₋₁₄cycloalkyl-amino, wherein C₃₋₁₄cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; and, wherein, each instance of C₃₋₁₄cycloalkyl is optionally substituted with R₅ substituents.

[0542] In another aspect of the compound of Formula (XIII), R₄ is C₃₋₈cycloalkyl-amino, wherein C₃₋₈cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; and, wherein, each instance of C₃₋₈cycloalkyl is optionally substituted with R₅ substituents.

[0543] In one aspect of the compound of Formula (XIII), R₄ is aryl-C₁₋₈alkyl, aryl-C₁₋₈alkoxy-carbonyl or aryl-sulfonyloxy-C₁₋₈alkyl, wherein aryl is selected from phenyl; and, wherein, each instance of aryl is optionally substituted with R₅ substituents.

[0544] In another aspect of the compound of Formula (XIII), R₄ is aryl-C₁₋₈alkyl or aryl-C₁₋₈alkoxy-carbonyl, wherein each instance of aryl is optionally substituted with R₅ substituents.

[0545] In one aspect of the compound of Formula (XIII), R₄ is heterocyclyl selected from oxetanyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,3-dioxanyl or morpholinyl, wherein each instance of heterocyclyl is optionally substituted with R₅ substituents.

[0546] In another aspect of the compound of Formula (XIII), R₄ is heterocyclyl selected from oxetan-3-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, 1,3-dioxan-5-yl or morpholin-4-yl, wherein each instance of heterocyclyl is optionally substituted with R₅ substituents.

[0547] In one aspect of the compound of Formula (XIII), R₄ is heterocyclyl-C₁₋₈alkyl, wherein each instance of heterocyclyl is selected from pyrrolidinyl or piperidinyl; and, wherein, each instance of heterocyclyl is optionally substituted with R₅ substituents.

[0548] In another aspect of the compound of Formula (XIII), R₄ is heterocyclyl-C₁₋₈alkyl selected from pyrrolidin-1-yl-C₁₋₈alkyl or piperidin-1-yl-C₁₋₈alkyl, wherein each instance of heterocyclyl is optionally substituted with R₅ substituents.

[0549] In one aspect of the compound of Formula (XIII), R₅ is selected from halogen, hydroxy, cyano, nitro, halo-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino or C₁₋₈alkyl-thio; wherein, halogen and halo is selected from fluoro, chloro, bromo or iodo.

[0550] In one aspect of the compound of Formula (XIII), R₅ is hydroxy.

[0551] In one aspect of the compound of Formula (XIII), R₅ is C₁₋₈alkyl selected from methyl, ethyl, propyl, isopropyl, n-butyl or tert-butyl.

[0552] In another aspect of the compound of Formula (XIII), R₅ is C₁₋₈alkyl selected from ethyl, propyl, isopropyl or tert-butyl.

[0553] In one aspect of the compound of Formula (XIII), R₅ is halo-C₁₋₈alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, halo-ethyl, trihalo-propyl, dihalo-propyl or halo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0554] In one aspect of the compound of Formula (XIII), R₅ is C₁₋₈alkoxy selected from methoxy, ethoxy, propoxy or isopropoxy.

[0555] In one aspect of the compound of Formula (XIII), R₅ is halo-C₁₋₈alkoxy selected from trihalo-methoxy, dihalo-methoxy, halo-methoxy, trihalo-ethoxy, dihalo-ethoxy, halo-ethoxy, trihalo-propoxy, dihalo-propoxy or halo-propoxy; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0556] In one aspect of the compound of Formula (XIII), R₂ is aryl selected from phenyl optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent.

[0557] In one aspect of the compound of Formula (XIII), R₂ is aryl-amino, wherein aryl is selected from phenyl; and, wherein, each instance of aryl is optionally substituted with R₆ and R₇ substituents.

[0558] In another aspect of the compound of Formula (XIII), R₂ is aryl-amino selected from phenyl-amino; wherein, each instance of aryl is optionally substituted with R₆ and R₇ substituents.

[0559] In one aspect of the compound of Formula (XIII), R₂ is aryl-amino-carbonyl, wherein aryl is selected from phenyl; and, wherein, each instance of aryl is optionally substituted with R₆ and R₇ substituents.

[0560] In another aspect of the compound of Formula (XIII), R₂ is aryl-amino-carbonyl selected from phenyl-amino-carbonyl; wherein, each instance of aryl is optionally substituted with R₆ and R₇ substituents.

[0561] In one aspect of the compound of Formula (XIII),

R₂ is heterocyclyl selected from 1,2,3,6-tetrahydropyridinyl, 1,3-benzodioxolyl or 2,3-dihydro-1,4-benzodioxinyl; wherein, each instance of heterocyclyl is optionally substituted with R₆ and R₇ substituents.

[0562] In another aspect of the compound of Formula (XIII),

R₂ is heterocyclyl selected from 1,2,3,6-tetrahydropyridin-4-yl, 1,3-benzodioxol-5-yl or 2,3-dihydro-1,4-benzodioxin-6-yl; wherein, each instance of heterocyclyl is optionally substituted with R₆ and R₇ substituents.

[0563] In one aspect of the compound of Formula (XIII),

R₂ is heteroaryl optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent.

[0564] In one aspect of the compound of Formula (XIII),

R₂ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrimidinyl, 1H-indolyl, 2H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, 9H-purinyl, quinazolinyl, quinoxalinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrazinyl, pyrazolo[4,3-b]pyridinyl, pyrazolo[3,4-c]pyridinyl, imidazo[1,2-a]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, [1,2,4]triazolo[1,5-

a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, pyrido[1,2-a]pyrimidinyl or pyrido[1,2-a]pyrimidinone; wherein, each instance of heteroaryl is optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent.

[0565] In another aspect of the compound of Formula (XIII),

R₂ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-4-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 2H-indazol-5-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 9H-purin-8-yl, quinazolin-6-yl, quinoxalin-2-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[4,3-b]pyridin-5-yl, pyrazolo[3,4-c]pyridin-5-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyrimidin-6-yl, [1,2,4]triazolo[1,5-b]pyridazin-6-yl, pyrido[1,2-a]pyrimidin-4-yl or pyrido[1,2-a]pyrimidin-4-one; wherein, each instance of heteroaryl is optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent.

[0566] In another aspect of the compound of Formula (XIII),

R₂ is substituted heteroaryl selected from 4-methylthien-2-yl, 1-methyl-1H-pyrazol-3-yl, 4-methyl-1H-pyrazol-3-yl, 1-phenyl-1H-pyrazol-3-yl, 1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl, 1-phenyl-1H-imidazol-4-yl, 2-methyl-1-(pyridin-2-yl)-1H-imidazol-4-yl, 4-methyl-1,3-thiazol-2-yl, 4-(trifluoromethyl)-1,3-thiazol-2-yl, 4-phenyl-1,3-thiazol-2-yl, 5-phenyl-1,2,4-oxadiazol-3-yl, 3-fluoropyridin-4-yl, 6-fluoropyridin-2-yl, 2-chloropyridin-4-yl, 4-chloropyridin-3-yl, 5-chloropyridin-2-yl, 6-methylpyridin-3-yl, 2-(trifluoromethyl)pyridin-3-yl, 4-(trifluoromethyl)pyridin-2-yl, 6-(trifluoromethyl)pyridin-2-yl, 2-methoxypyridin-4-yl,

4-methoxypyridin-3-yl, 6-methoxypyridin-2-yl, 2-ethoxypyridin-3-yl, 6-ethoxypyridin-2-yl, 6-(propan-2-yloxy)pyridin-2-yl, 6-(dimethylamino)pyridin-3-yl, 6-(methyl sulfanyl)pyridin-2-yl, 6-(cyclobutyloxy)pyridin-2-yl, 6-(pyrrolidin-1-yl)pyridin-2-yl, (5-fluoro-6-hydroxy)pyridin-3-yl, 2-methylpyrimidin-4-yl, 2-(propan-2-yl)pyrimidin-4-yl, 2-cyclopropylpyrimidin-4-yl, 1-methyl-1H-indol-3-yl, 1,7-dimethyl-1H-indazol-5-yl, 2-methyl-2H-indazol-5-yl, 2,7-dimethyl-2H-indazol-5-yl, 7-fluoro-2-methyl-2H-indazol-5-yl, 2-methyl-1-benzofuran-5-yl, 1-methyl-1H-benzimidazol-2-yl, 4-methyl-1H-benzimidazol-2-yl, 5-fluoro-1H-benzimidazol-2-yl, 4-fluoro-1,3-benzoxazol-2-yl, 5-fluoro-1,3-benzoxazol-2-yl, 4-chloro-1,3-benzoxazol-2-yl, 4-iodo-1,3-benzoxazol-2-yl, 2-methyl-1,3-benzoxazol-6-yl, 4-methyl-1,3-benzoxazol-2-yl, 4-(trifluoromethyl)-1,3-benzoxazol-2-yl, 7-(trifluoromethyl)-1,3-benzoxazol-2-yl, 2-methyl-1,3-benzothiazol-2-yl, 2-methyl-1,3-benzothiazol-5-yl, 2-methyl-1,3-benzothiazol-6-yl, 4-chloro-1,3-benzothiazol-2-yl, 7-chloro-1,3-benzothiazol-2-yl, 4-(trifluoromethyl)-1,3-benzothiazol-2-yl, (4-hydroxy-2-methyl)quinazolin-6-yl, 5-methylfuro[3,2-b]pyridin-2-yl, 4,6-dimethylfuro[3,2-c]pyridin-2-yl, 5,7-dimethylfuro[2,3-c]pyridin-2-yl, 4,6-dimethylthieno[3,2-c]pyridin-2-yl, 2,4-dimethylthieno[2,3-d]pyrimidin-6-yl, 1-methylpyrrolo[1,2-a]pyrazin-7-yl, 3-methylpyrrolo[1,2-a]pyrazin-7-yl, 1,3-dimethylpyrrolo[1,2-a]pyrazin-7-yl, 2-methylpyrrolo[1,2-b]pyridazin-2-yl, 2-methylpyrazolo[1,5-a]pyridin-5-yl, 5-methylpyrazolo[1,5-a]pyridin-2-yl, 4-(dimethyl amino)-6-methylpyrazolo[1,5-a]pyrazin-2-yl, 4,6-dimethylpyrazolo[1,5-a]pyrazin-2-yl, 4-ethyl-6-methylpyrazolo[1,5-a]pyrazin-2-yl, 1,7-dimethyl-1H-pyrazolo[4,3-b]pyridin-5-yl, 1,7-dimethyl-1H-pyrazolo[3,4-c]pyridin-5-yl, 2,7-dimethyl-2H-pyrazolo[3,4-c]pyridin-5-yl, 2,7-dimethyl-2H-pyrazolo[4,3-b]pyridin-5-yl, 2-chloroimidazo[2,1-b][1,3]thiazol-6-yl, 2-methylimidazo[2,1-b][1,3]thiazol-6-yl, 3-methylimidazo[2,1-b][1,3]thiazol-6-yl, 2-ethylimidazo[2,1-b][1,3]thiazol-6-yl, 2-methylimidazo[2,1-b][1,3,4]thiadiazol-6-yl, 6-cyanoimidazo[1,2-a]pyridin-2-yl (also referred to as 2-imidazo[1,2-a]pyridine-6-carbonitrile), 6-fluoroimidazo[1,2-a]pyridin-2-yl, 8-fluoroimidazo[1,2-a]pyridin-2-yl, 6,8-difluoroimidazo[1,2-a]pyridin-2-yl, 7-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl, 8-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl, 6-chloroimidazo[1,2-a]pyridin-2-yl, 7-chloroimidazo[1,2-a]pyridin-2-yl, 8-chloroimidazo[1,2-a]pyridin-2-yl, 8-bromoimidazo[1,2-a]pyridin-2-yl, 2-methylimidazo[1,2-a]pyridin-2-yl, 5-methylimidazo[1,2-a]pyridin-2-yl, 6-methylimidazo[1,2-a]pyridin-2-yl, 7-methylimidazo[1,2-a]pyridin-2-yl, 8-methylimidazo[1,2-a]pyridin-2-yl, 7-ethylimidazo[1,2-a]pyridin-2-yl, 8-ethylimidazo[1,2-a]pyridin-2-yl, 6,8-dimethylimidazo[1,2-a]pyridin-2-yl, 8-ethyl-6-methylimidazo[1,2-

a]pyridin-2-yl, 7-methoxyimidazo[1,2-a]pyridin-2-yl, 8-methoxyimidazo[1,2-a]pyridin-2-yl, 6-fluoro-8-methylimidazo[1,2-a]pyridin-2-yl, 8-fluoro-6-methylimidazo[1,2-a]pyridin-2-yl, 8-chloro-6-methylimidazo[1,2-a]pyridin-2-yl, 6-methyl-8-nitroimidazo[1,2-a]pyridin-2-yl, 8-cyclopropylimidazo[1,2-a]pyridin-2-yl, 2-methylimidazo[1,2-a]pyridin-6-yl, 2-ethylimidazo[1,2-a]pyridin-6-yl, 2,3-dimethylimidazo[1,2-a]pyridin-6-yl, 2,8-dimethylimidazo[1,2-a]pyridin-6-yl, 2-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl, 8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl, 8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl, 6-fluoroimidazo[1,2-a]pyrimidin-2-yl, 6-chloroimidazo[1,2-a]pyrimidin-2-yl, 6-methylimidazo[1,2-a]pyrimidin-2-yl, 7-methylimidazo[1,2-a]pyrimidin-2-yl, 2-methylimidazo[1,2-a]pyrimidin-6-yl, 6-methylimidazo[1,2-b]pyridazin-2-yl, 2-methylimidazo[1,2-b]pyridazin-6-yl, 2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl, 6-methylimidazo[1,2-a]pyrazin-2-yl, 8-methylimidazo[1,2-a]pyrazin-2-yl, 6,8-dimethylimidazo[1,2-a]pyrazin-2-yl, 6-chloro-8-methylimidazo[1,2-a]pyrazin-2-yl, 6-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyrazin-2-yl, 8-(methylsulfanyl)imidazo[1,2-a]pyrazin-2-yl, 2-methylimidazo[2,1-b][1,3]thiazol-6-yl, 3-methylimidazo[2,1-b][1,3]thiazol-6-yl, 2-methylimidazo[2,1-b][1,3,4]thiadiazol-6-yl, 2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl, 2-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl, 2-methyl-[1,2,4]triazolo[1,5-b]pyridazin-6-yl or 4H,4'H-2,7'-bipyrido[1,2-a]pyrimidine-4,4'-dione.

[0567] In another aspect of the compound of Formula (XIII),

R₂ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrimidinyl, 1H-indolyl, 2H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, 9H-purinyl, quinazolinyl or quinoxalinyl; wherein, each instance of heteroaryl is optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent.

[0568] In another aspect of the compound of Formula (XIII),

R₂ is heteroaryl selected from furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrazinyl, pyrazolo[4,3-b]pyridinyl, pyrazolo[3,4-c]pyridinyl, imidazo[1,2-a]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-

a]pyrazinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, pyrido[1,2-a]pyrimidinyl or pyrido[1,2-a]pyrimidinone; wherein, each instance of heteroaryl is optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent.

[0569] In one aspect of the compound of Formula (XIII), R₂ is heteroaryl-amino, wherein heteroaryl is selected from pyridinyl or pyrimidinyl; and, wherein, each instance of heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0570] In another aspect of the compound of Formula (XIII), R₂ is heteroaryl-amino selected from pyridin-2-yl-amino, pyridin-3-yl-amino or pyrimidin-2-yl-amino; wherein, each instance of heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0571] In one aspect of the compound of Formula (XIII), R₆ is selected from halogen, hydroxy, cyano, nitro, C1-8alkyl, halo-C1-8alkyl, hydroxy-C1-8alkyl, C1-8alkoxy, halo-C1-8alkoxy, C1-8alkoxy-C1-8alkyl, (C1-8alkyl)2-amino or C1-8alkyl-thio; wherein, halogen and halo is selected from fluoro, chloro, bromo or iodo.

[0572] In one aspect of the compound of Formula (XIII), R₆ is C1-8alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl.

[0573] In another aspect of the compound of Formula (XIII), R₆ is C1-8alkyl selected from ethyl, propyl, isopropyl or tert-butyl.

[0574] In one aspect of the compound of Formula (XIII), R₆ is C2-8alkenyl selected from ethenyl, allyl or buta-1,3-dienyl.

[0575] In another aspect of the compound of Formula (XIII), R₆ is C2-8alkenyl selected from ethenyl or allyl.

[0576] In one aspect of the compound of Formula (XIII), R₆ is halo-C1-8alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, halo-ethyl, trihalo-propyl, dihalo-propyl or halo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0577] In one aspect of the compound of Formula (XIII), R₆ is hydroxy-C1-8alkyl selected from hydroxy-methyl, hydroxy-ethyl, hydroxy-propyl, dihydroxy-propyl, hydroxy-butyl or dihydroxy-butyl.

[0578] In another aspect of the compound of Formula (XIII), R6 is hydroxy-C1-8alkyl selected from hydroxy-methyl, dihydroxy-propyl, hydroxy-butyl or dihydroxy-butyl.

[0579] In one aspect of the compound of Formula (XIII), R6 is C1-8alkoxy selected from methoxy, ethoxy, propoxy or isopropoxy.

[0580] In one aspect of the compound of Formula (XIII), R6 is halo-C1-8alkoxy selected from trihalo-methoxy, dihalo-methoxy, halo-methoxy, trihalo-ethoxy, dihalo-ethoxy, halo-ethoxy, trihalo-propoxy, dihalo-propoxy or halo-propoxy; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0581] In one aspect of the compound of Formula (XIII), R7 is C3-14cycloalkyl, C3-14cycloalkyl-oxy, aryl, heterocyclyl or heteroaryl; wherein C3-14cycloalkyl is selected from cyclopropyl or cyclobutoxy; wherein aryl is selected from phenyl; wherein heterocyclyl is selected from oxetanyl, pyrrolidinyl or 1,2,3,6-tetrahydropyridinyl; and, wherein heteroaryl is selected from thienyl or pyridinyl.

[0582] In another aspect of the compound of Formula (XIII), R7 is C3-14cycloalkyl or C3-14cycloalkyl-oxy, wherein each instance of C3-14cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

[0583] In another aspect of the compound of Formula (XIII), R7 is C3-8cycloalkyl or C3-8cycloalkyl-oxy, wherein each instance of C3-8cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

[0584] In one aspect of the compound of Formula (XIII), R7 is aryl selected from phenyl.

[0585] In one aspect of the compound of Formula (XIII), R7 is heterocyclyl selected from oxetanyl, pyrrolidinyl or 1,2,3,6-tetrahydropyridinyl.

[0586] In another aspect of the compound of Formula (XIII), R7 is heterocyclyl selected from oxetan-3-yl, pyrrolidin-1-yl or 1,2,3,6-tetrahydropyridin-4-yl.

[0587] In one aspect of the compound of Formula (XIII), R7 is heteroaryl selected from thienyl or pyridinyl.

[0588] In another aspect of the compound of Formula (XIII), R7 is heteroaryl selected from pyridinyl.

[0589] In one aspect of the compound of Formula (XIII), R7 is heteroaryl selected from thien-2-yl or pyridin-2-yl.

[0590] In another aspect of the compound of Formula (XIII), R7 is heteroaryl selected from pyridin-2-yl.

[0591] In one aspect of the compound of Formula (XIII), Rc is hydrogen or C1-8alkyl.

[0592] In another aspect of the compound of Formula (XIII),

R₁ is heterocyclyl, heterocyclyl-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkoxy, heterocyclyl-amino, (heterocyclyl)(C₁₋₈alkyl)amino, heterocyclyl-amino-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkyl-amino, (heterocyclyl-C₁₋₈alkyl)₂-amino, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl-oxy, heterocyclyl-carbonyl, heterocyclyl-carbonyl-oxy, C₃₋₁₄cycloalkyl, aryl-C₁₋₈alkyl-amino, (aryl-C₁₋₈alkyl)₂-amino, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heteroaryl, heteroaryl-C₁₋₈alkyl, heteroaryl-C₁₋₈alkoxy, heteroaryl-amino, heteroaryl-C₁₋₈alkyl-amino, (heteroaryl-C₁₋₈alkyl)₂-amino, (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl; wherein, each instance of heterocyclyl, C₃₋₁₄cycloalkyl, aryl and heteroaryl is optionally substituted with R₃ and R₄ substituents; and,

wherein, heterocyclyl is selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,4-diazepanyl, 3,6-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl, (8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl, (8aS)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazinyl, (8aR)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazinyl, (8aS)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, (3aR,4aR,7aS)-hexahydro-1H-

cyclobuta[1,2-c:1,4-c']dipyrrol-(3H)-yl, 3-azabicyclo[3.1.0]hexyl, (1R,5S)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1R,5S)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl, (1R,5S)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1S,4S)-2,5-diazabicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 3,6-diazabicyclo[3.2.0]hept-3-yl, 3,8-diazabicyclo[3.2.1]octyl, (1R,5S)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, azaspiro[3.3]heptyl, 2,6-diazaspiro[3.3]heptyl, 4,7-diazaspiro[2.5]oct-7-yl, 2,6-diazaspiro[3.4]oct-2-yl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 2,7-diazaspiro[4.4]nonyl or 6,9-diazaspiro[4.5]decyl.

[0593] In another aspect of the compound of Formula (XIII),

R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino; wherein, aryl is phenyl;

wherein, heterocyclyl is selected from 1,2,3,6-tetrahydropyridinyl, 1,3-benzodioxolyl or 2,3-dihydro-1,4-benzodioxinyl;

wherein, heteroaryl is selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrimidinyl, 1H-indolyl, 2H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, 9H-purinyl, quinazoliny, quinoxaliny, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrazinyl, pyrazolo[4,3-b]pyridinyl, pyrazolo[3,4-c]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, pyrido[1,2-a]pyrimidinyl or pyrido[1,2-a]pyrimidinone; and, wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0594] In another aspect of the compound of Formula (XIII),

R₁ is heterocyclyl, heterocyclyl-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkoxy, heterocyclyl-amino, (heterocyclyl)(C₁₋₈alkyl)amino, heterocyclyl-amino-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkyl-amino, (heterocyclyl-C₁₋₈alkyl)₂-amino, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl-oxy, heterocyclyl-carbonyl, heterocyclyl-carbonyl-oxy, C₃₋₁₄cycloalkyl, aryl-C₁₋₈alkyl-amino, (aryl-C₁₋₈alkyl)₂-amino, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heteroaryl, heteroaryl-C₁₋₈alkyl, heteroaryl-C₁₋₈alkoxy, heteroaryl-amino, heteroaryl-C₁₋₈alkyl-amino, (heteroaryl-C₁₋₈alkyl)₂-amino, (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl;

wherein, heterocyclyl is selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,4-diazepanyl, 3,6-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl, (8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl, (8aS)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazinyl, (8aR)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazinyl, (8aS)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, (3aR,4aR,7aS)-hexahydro-1H-cyclobuta[1,2-c:1,4-c']dipyrrol-(3H)-yl, 3-azabicyclo[3.1.0]hexyl, (1R,5S)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1R,5S)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl, (1R,5S)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1S,4S)-2,5-diazabicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 3,6-diazabicyclo[3.2.0]heptyl, 3,8-diazabicyclo[3.2.1]octyl, (1R,5S)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, azaspiro[3.3]heptyl, 2,6-

diazaspiro[3.3]heptyl, 4,7-diazaspiro[2.5]octyl, 2,6-diazaspiro[3.4]octyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 2,7-diazaspiro[4.4]nonyl or 6,9-diazaspiro[4.5]decyl; and, wherein, each instance of heterocyclyl, C₃₋₁₄cycloalkyl, aryl and heteroaryl is optionally substituted with R₃ and R₄ substituents; and

R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino; wherein, heterocyclyl is selected from 1,2,3,6-tetrahydropyridin-4-yl, 1,3-benzodioxol-5-yl or 2,3-dihydro-1,4-benzodioxin-6-yl;

wherein, heteroaryl is selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrimidinyl, 1H-indolyl, 2H-indolyl, 1H-indazolyl, 2H-indazolyl, indoliziny, benzofuranyl, benzothieryl, 1H-benzimidazolyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, 9H-puriny, quinazoliny, quinoxaliny, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrazinyl, pyrazolo[4,3-b]pyridinyl, pyrazolo[3,4-c]pyridinyl, imidazo[1,2-a]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, pyrido[1,2-a]pyrimidinyl or pyrido[1,2-a]pyrimidinone; and, wherein, each instance of heterocyclyl and heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0595] In another aspect of the compound of Formula (XIII),

R₁ is C₁₋₈alkyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, (amino-C₁₋₈alkyl)₂-amino, (amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, amino-C₁₋₈alkoxy, C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkyl)₂-amino-

C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, amino-C₂₋₈alkenyl, C₁₋₈alkyl-amino-C₂₋₈alkenyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkenyl, amino-C₂₋₈alkynyl, C₁₋₈alkyl-amino-C₂₋₈alkynyl, (C₁₋₈alkyl)₂-amino-C₂₋₈alkynyl, halo-C₁₋₈alkyl-amino, (halo-C₁₋₈alkyl)₂-amino, (halo-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkoxy, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkoxy, hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl-amino, [(hydroxy-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino or [(hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl](C₁₋₈alkyl)amino; and R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino, wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0596] In another aspect of the compound of Formula (XIII),

R₁ is heterocyclyl, heterocyclyl-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkoxy, heterocyclyl-amino, (heterocyclyl)(C₁₋₈alkyl)amino, heterocyclyl-amino-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkyl-amino, (heterocyclyl-C₁₋₈alkyl)₂-amino, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl-oxy, heterocyclyl-carbonyl, heterocyclyl-carbonyl-oxy, C₃₋₁₄cycloalkyl, aryl-C₁₋₈alkyl-amino, (aryl-C₁₋₈alkyl)₂-amino, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heteroaryl, heteroaryl-C₁₋₈alkyl, heteroaryl-C₁₋₈alkoxy, heteroaryl-amino, heteroaryl-C₁₋₈alkyl-amino, (heteroaryl-C₁₋₈alkyl)₂-amino, (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl; wherein, each instance of heterocyclyl, C₃₋₁₄cycloalkyl, aryl and heteroaryl is optionally substituted with R₃ and R₄ substituents; and

R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino, wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0597] In another aspect of the compound of Formula (XIII),

R₁ is heterocyclyl, heterocyclyl-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkoxy, heterocyclyl-amino, (heterocyclyl)(C₁₋₈alkyl)amino, heterocyclyl-amino-C₁₋₈alkyl, heterocyclyl-C₁₋₈alkyl-amino, (heterocyclyl-C₁₋₈alkyl)₂-amino, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heterocyclyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, (heterocyclyl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl, heterocyclyl-oxy, heterocyclyl-carbonyl or heterocyclyl-carbonyl-oxy; wherein, each instance of heterocyclyl is optionally substituted with R₃ and R₄ substituents; and R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino, wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0598] In another aspect of the compound of Formula (XIII), R₁ is heterocyclyl optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituents; or, optionally, with one, two, three or four R₃ substituents; and

R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino, wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0599] In another aspect of the compound of Formula (XIII),

R₁ is C₃₋₁₄cycloalkyl optionally substituted with R₃ and R₄ substituents; and

R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino, wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0600] In another aspect of the compound of Formula (XIII),

R₁ is aryl-C₁₋₈alkyl-amino, (aryl-C₁₋₈alkyl)₂-amino, (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, aryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (aryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (aryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl; wherein, each instance of aryl is optionally substituted with R₃ and R₄ substituents; and R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino, wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0601] In another aspect of the compound of Formula (XIII),

R₁ is aryl-C₁₋₈alkyl-amino optionally substituted with R₃ and R₄ substituents; and

R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino, wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0602] In another aspect of the compound of Formula (XIII),

R₁ is heteroaryl, heteroaryl-C₁₋₈alkyl, heteroaryl-C₁₋₈alkoxy, heteroaryl-amino, heteroaryl-C₁₋₈alkyl-amino, (heteroaryl-C₁₋₈alkyl)₂-amino, (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino, heteroaryl-C₁₋₈alkyl-amino-C₁₋₈alkyl, (heteroaryl-C₁₋₈alkyl)₂-amino-C₁₋₈alkyl or (heteroaryl-C₁₋₈alkyl)(C₁₋₈alkyl)amino-C₁₋₈alkyl; wherein, each instance of heterocyclyl, C₃₋₁₄cycloalkyl, aryl and heteroaryl is optionally substituted with R₃ and R₄ substituents; and

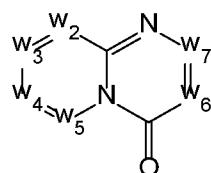
R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino, wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with R₆ and R₇ substituents.

[0603] In another aspect of the compound of Formula (XIII),

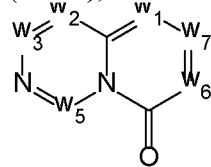
R₁ is heteroaryl optionally substituted with R₃ and R₄ substituents; and

R₂ is aryl, aryl-amino, aryl-amino-carbonyl, heterocyclyl, heteroaryl or heteroaryl-amino, wherein, each instance of aryl, heterocyclyl and heteroaryl is optionally substituted with R₆ and R₇ substituents.

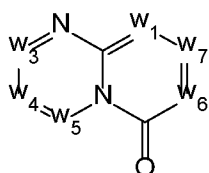
[0604] An aspect of the use of the compound of Formula (XIII) is the use of a compound selected from Formula (XXX), Formula (XXXI), Formula (XXXII), Formula (XXXIII), Formula (XXXIV), Formula (XXXV), Formula (XXXVI), Formula (XXXVII), Formula (XXXVIII), Formula (XXXIX), Formula (XL), Formula (XLI) or Formula (XLII):



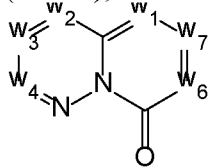
(XXX),



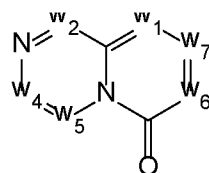
(XXXIII),



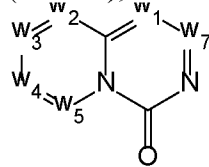
(XXXI),



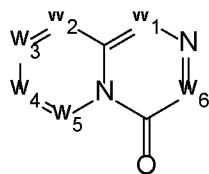
(XXXIV),



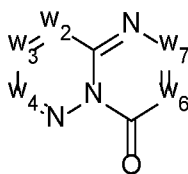
(XXXII),



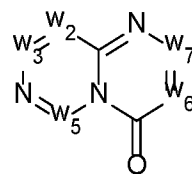
(XXXV),



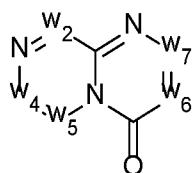
(XXXVI),



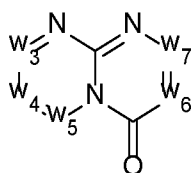
(XXXVII),



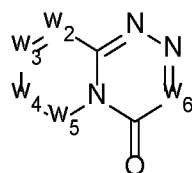
(XXXVIII),



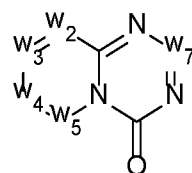
(XXXIX),



(XL),



(XLI) or



(XLII)

or a form thereof.

[0605] In an aspect of the use of the compound of Formula (XIII), w_3 is C-R₁, w_6 is C-R₂, w_1 , w_4 , w_5 and w_7 are independently C-R_a or N and w_2 is C-R_b or N.

[0606] In another aspect of the use of the compound of Formula (XIII), w_3 is C-R₂, w_6 is C-R₁, w_1 , w_4 , w_5 and w_7 are independently C-R_a or N and w_2 is C-R_b or N.

[0607] In another aspect of the use of the compound of Formula (XIII), w_4 is C-R₁, w_7 is C-R₂, w_1 , w_3 and w_5 are independently C-R_a or N, w_2 is C-R_b or N and w_6 is C-R_c or N.

[0608] In another aspect of the use of the compound of Formula (XIII), w_4 is C-R₂, w_7 is C-R₁, w_1 , w_3 and w_5 are independently C-R_a or N, w_2 is C-R_b or N and w_6 is C-R_c or N.

[0609] In an aspect of the use of the compound of Formula (XXX), w_3 is C-R₁, w_6 is C-R₂, w_4 , w_5 and w_7 are independently C-R_a or N and w_2 is C-R_b or N.

[0610] In another aspect of the use of the compound of Formula (XXX), w_3 is C-R₂, w_6 is C-R₁, w_4 , w_5 and w_7 are independently C-R_a or N and w_2 is C-R_b or N.

[0611] In another aspect of the use of the compound of Formula (XXX), w_4 is C-R₁, w_7 is C-R₂, w_3 and w_5 are independently C-R_a or N, w_2 is C-R_b or N and w_6 is C-R_c or N.

[0612] In another aspect of the use of the compound of Formula (XXX), w_4 is C-R₂, w_7 is C-R₁, w_3 and w_5 are independently C-R_a or N, w_2 is C-R_b or N and w_6 is C-R_c or N.

[0613] In an aspect of the use of the compound of Formula (XXXI), w_3 is C-R₁, w_6 is C-R₂ and w_1 , w_4 , w_5 and w_7 are independently C-R_a or N.

[0614] In another aspect of the use of the compound of Formula (XXXI), w_3 is C-R₂, w_6 is C-R₁ and w_1 , w_4 , w_5 and w_7 are independently C-R_a or N.

[0615] In another aspect of the use of the compound of Formula (XXXI), w_4 is C-R₁, w_7 is C-R₂, w_1 , w_3 and w_5 are independently C-R_a or N and w_6 is C-R_c or N.

[0616] In another aspect of the use of the compound of Formula (XXXI), w_4 is C-R₂, w_7 is C-R₁, w_1 , w_3 and w_5 are independently C-R_a or N and w_6 is C-R_c or N.

[0617] In an aspect of the use of the compound of Formula (XXXII), w_4 is C-R₁, w_7 is C-R₂, w_1 and w_5 are independently C-R_a or N, w_2 is C-R_b or N and w_6 is C-R_c or N.

[0618] In another aspect of the use of the compound of Formula (XXXII), w_4 is C-R₂, w_7 is C-R₁, w_1 and w_5 are independently C-R_a or N, w_2 is C-R_b or N and w_6 is C-R_c or N.

[0619] In an aspect of the use of the compound of Formula (XXXIII), w_3 is C-R₁, w_6 is C-R₂, w_1 , w_5 and w_7 are independently C-R_a or N and w_2 is C-R_b or N.

[0620] In another aspect of the use of the compound of Formula (XXXIII), w_3 is C-R₂, w_6 is C-R₁, w_1 , w_5 and w_7 are independently C-R_a or N and w_2 is C-R_b or N.

[0621] In an aspect of the use of the compound of Formula (XXXIV), w_3 is C-R₁, w_6 is C-R₂, w_1 , w_4 and w_7 are independently C-R_a or N and w_2 is C-R_b or N.

[0622] In another aspect of the use of the compound of Formula (XXXIV), w_3 is C-R₂, w_6 is C-R₁, w_1 , w_4 and w_7 are independently C-R_a or N and w_2 is C-R_b or N.

[0623] In another aspect of the use of the compound of Formula (XXXIV), w_4 is C-R₁, w_7 is C-R₂, w_1 and w_3 are independently C-R_a or N, w_2 is C-R_b or N and w_6 is C-R_c or N.

[0624] In another aspect of the use of the compound of Formula (XXXIV), w_4 is C-R₂, w_7 is C-R₁, w_1 and w_3 are independently C-R_a or N, w_2 is C-R_b or N and w_6 is C-R_c or N.

[0625] In another aspect of the use of the compound of Formula (XXXV), w_4 is C-R₁, w_7 is C-R₂, w_1 , w_3 and w_5 are C-R_a or N and w_2 is C-R_b or N.

[0626] In another aspect of the use of the compound of Formula (XXXV), w_4 is C-R₂, w_7 is C-R₁, w_1 , w_3 and w_5 are C-R_a or N and w_2 is C-R_b or N.

[0627] In another aspect of the use of the compound of Formula (XXXVI), w_3 is C-R₁, w_6 is C-R₂, w_1 , w_4 and w_5 are C-R_a or N and w_2 is C-R_b or N.

[0628] In another aspect of the use of the compound of Formula (XXXVI), w_3 is C-R₂, w_6 is C-R₁, w_1 , w_4 and w_5 are C-R_a or N and w_2 is C-R_b or N.

[0629] In an aspect of the use of the compound of Formula (XXXVII), w_3 is C-R₁, w_6 is C-R₂, w_4 and w_7 are independently C-R_a or N and w_2 is C-R_b or N.

[0630] In another aspect of the use of the compound of Formula (XXXVII), w_3 is C-R₂, w_6 is C-R₁, w_4 and w_7 are independently C-R_a or N and w_2 is C-R_b or N.

[0631] In another aspect of the use of the compound of Formula (XXXVII), w_4 is C-R₁, w_7 is C-R₂, w_2 is C-R_b or N, w_3 is C-R_a or N and w_6 is C-R_c or N.

[0632] In another aspect of the use of the compound of Formula (XXXVII), w_4 is C-R₂, w_7 is C-R₁, w_2 is C-R_b or N, w_3 is C-R_a or N and w_6 is C-R_c or N.

[0633] In an aspect of the use of the compound of Formula (XXXVIII), w_3 is C-R₁, w_6 is C-R₂, w_2 is C-R_b or N and w_5 and w_7 are independently C-R_a or N.

[0634] In another aspect of the use of the compound of Formula (XXXVIII), w_3 is C-R₂, w_6 is C-R₁, w_2 is C-R_b or N and w_5 and w_7 are independently C-R_a or N.

[0635] In an aspect of the use of the compound of Formula (XXXIX), w_4 is C-R₁, w_7 is C-R₂, w_2 is C-R_b or N, w_5 is C-R_a or N and w_6 is C-R_c or N.

[0636] In another aspect of the use of the compound of Formula (XXXIX), w_4 is C-R₂, w_7 is C-R₁, w_2 is C-R_b or N, w_5 is C-R_a or N and w_6 is C-R_c or N.

[0637] In an aspect of the use of the compound of Formula (XL), w_3 is C-R₁, w_6 is C-R₂ and w_4 , w_5 and w_7 are independently C-R_a or N.

[0638] In another aspect of the use of the compound of Formula (XL), w_3 is C-R₂, w_6 is C-R₁ and w_4 , w_5 and w_7 are independently C-R_a or N.

[0639] In another aspect of the use of the compound of Formula (XL), w_4 is C-R₁, w_7 is C-R₂, w_3 and w_5 are independently C-R_a or N and w_6 is C-R_c or N.

[0640] In another aspect of the use of the compound of Formula (XL), w_4 is C-R₂, w_7 is C-R₁, w_3 and w_5 are independently C-R_a or N and w_6 is C-R_c or N.

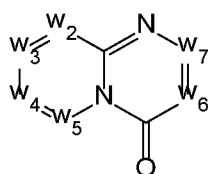
[0641] In an aspect of the use of the compound of Formula (XLI), w_3 is C-R₁, w_6 is C-R₂, w_2 is C-R_b or N and w_4 and w_5 are independently C-R_a or N.

[0642] In another aspect of the use of the compound of Formula (XLI), w_3 is C-R₂, w_6 is C-R₁, w_2 is C-R_b or N and w_4 and w_5 are independently C-R_a or N.

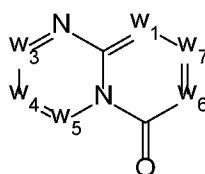
[0643] In an aspect of the use of the compound of Formula (XLII), w_4 is C-R₁, w_7 is C-R₂, w_2 is C-R_b or N and w_3 and w_5 are independently C-R_a or N.

[0644] In another aspect of the use of the compound of Formula (XLII), w_4 is C-R₂, w_7 is C-R₁, w_2 is C-R_b or N and w_3 and w_5 are independently C-R_a or N.

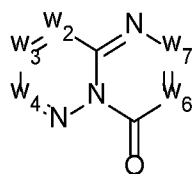
[0645] Another aspect of the use of the compound of Formula (XIII) is the use of the compound selected from Formula (XXX), Formula (XXXI), Formula (XXXVII), Formula (XXXIX) or Formula (XL):



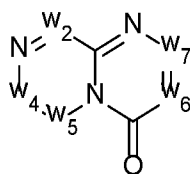
(XXX),



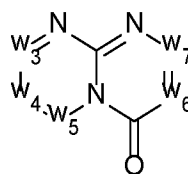
(XXXI),



(XXXVII),



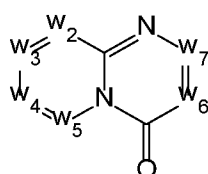
(XXXIX), or



(XL)

or a form thereof.

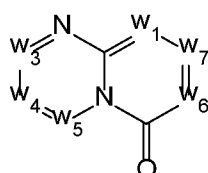
[0646] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XXX):



(XXX)

or a form thereof.

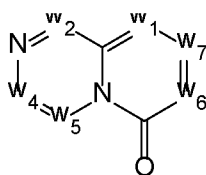
[0647] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XXXI):



(XXXI)

or a form thereof.

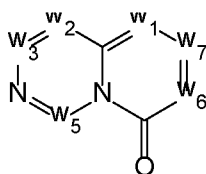
[0648] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XXXII):



(XXXII)

or a form thereof.

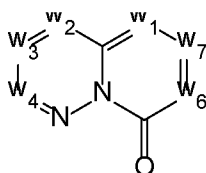
[0649] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XXXIII):



(XXXIII)

or a form thereof.

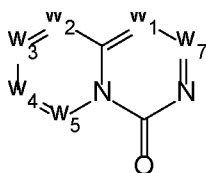
[0650] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XXXIV):



(XXXIV)

or a form thereof.

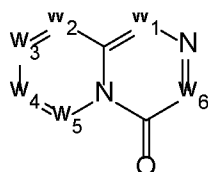
[0651] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XXXV):



(XXXV)

or a form thereof.

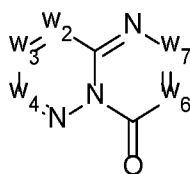
[0652] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XXXVI):



(XXXVI)

or a form thereof.

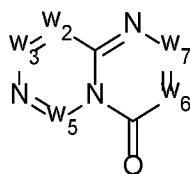
[0653] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XXXVII):



(XXXVII)

or a form thereof.

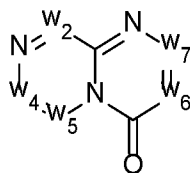
[0654] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XXXVIII):



(XXXVIII)

or a form thereof.

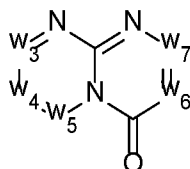
[0655] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XXXIX):



(XXXIX)

or a form thereof.

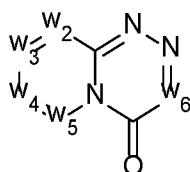
[0656] Another aspect of the compound of Formula (XIII) is the use of the compound of Formula (XL):



(XL)

or a form thereof.

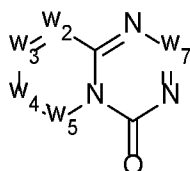
[0657] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XLI):



(XLI)

or a form thereof.

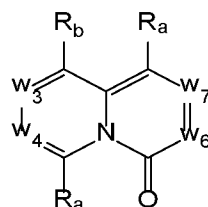
[0658] Another aspect of the use of the compound of Formula (XIII) is the use of the compound of Formula (XLII):



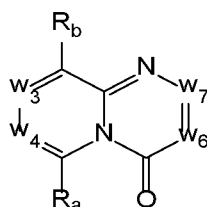
(XLII)

or a form thereof.

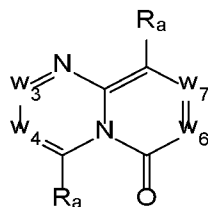
[0659] An aspect of the use of the compound of Formula (XIII), Formula (XXX), Formula (XXXI), Formula (XXXII), Formula (XXXIII), Formula (XXXIV), Formula (XXXV), Formula (XXXVI), Formula (XXXVII), Formula (XXXVIII), Formula (XXXIX), Formula (XL), Formula (XLI) or Formula (XLII) is the use of a compound selected from Formula (XXXVa), Formula (XXXa), Formula (XXXIa), Formula (XXXIIa), Formula (XXXIIIa), Formula (XXXIVa), Formula (XXXVa), Formula (XXXVIa), Formula (XXXVIIa), Formula (XXXVIIIa), Formula (XXXIXa), Formula (XLa), Formula (XLIa) or Formula (XLIIa), respectively:



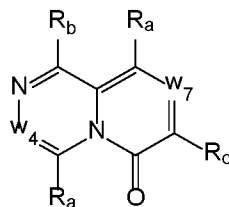
(XXXVa),



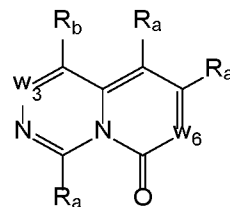
(XXXa),



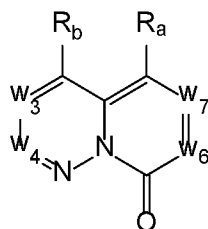
(XXXIa),



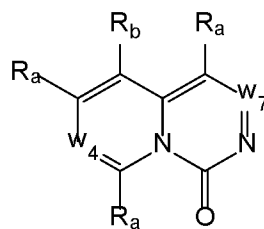
(XXXIIa),



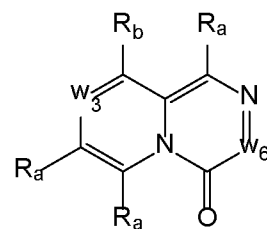
(XXXIIIa),



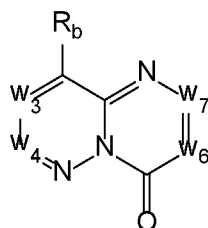
(XXXIVa)



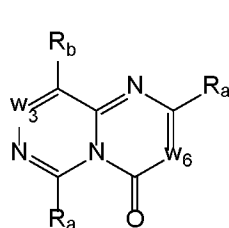
(XXXVa),



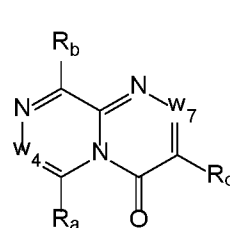
(XXXVIa),



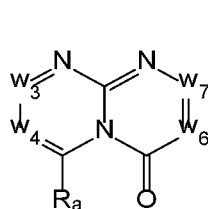
(XXXVIIa),



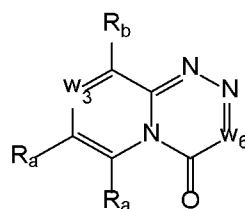
(XXXVIIIa),



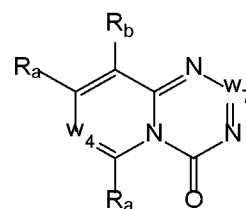
(XXXIXa),



(XLa),



(XLIa), or



(XLIIa)

or a form thereof.

[0660] In an aspect of the use of the compound of Formula (XXXVa), one of w₃, w₄, w₆ and w₇ is C-R₁ and one other of w₃, w₄, w₆ and w₇ is C-R₂, provided that,

when w₃ is C-R₁, then w₆ is C-R₂ and w₄ and w₇ are independently C-R_a or N; or,

when w₃ is C-R₂, then w₆ is C-R₁ and w₄ and w₇ are independently C-R_a or N; or,

when w_4 is C-R₁, then w_7 is C-R₂ and w_3 is C-R_a or N and w_6 is C-R_c or N; or,

when w_4 is C-R₂, then w_7 is C-R₁ and w_3 is C-R_a or N and w_6 is C-R_c or N.

[0661] In an aspect of the use of the compound of Formula (XXXa), one of w_3 , w_4 , w_6 and w_7 is C-R₁ and one other of w_3 , w_4 , w_6 and w_7 is C-R₂, provided that,

when w_3 is C-R₁, then w_6 is C-R₂ and w_4 and w_7 are independently C-R_a or N; or,

when w_3 is C-R₂, then w_6 is C-R₁ and w_4 and w_7 are independently C-R_a or N; or,

when w_4 is C-R₁, then w_7 is C-R₂ and w_3 is C-R_a or N and w_6 is C-R_c or N; or,

when w_4 is C-R₂, then w_7 is C-R₁ and w_3 is C-R_a or N and w_6 is C-R_c or N.

[0662] In an aspect of the use of the compound of Formula (XXXIa), one of w_3 , w_4 , w_6 and w_7 is C-R₁ and one other of w_3 , w_4 , w_6 and w_7 is C-R₂, provided that,

when w_3 is C-R₁, then w_6 is C-R₂ and w_4 and w_7 are independently C-R_a or N; or,

when w_3 is C-R₂, then w_6 is C-R₁ and w_4 and w_7 are independently C-R_a or N; or,

when w_4 is C-R₁, then w_7 is C-R₂ and w_3 is C-R_a or N and w_6 is C-R_c or N; or,

when w_4 is C-R₂, then w_7 is C-R₁ and w_3 is C-R_a or N and w_6 is C-R_c or N.

[0663] In an aspect of the use of the compound of Formula (XXXIIa), one of w_4 and w_7 is C-R₁ and the other is C-R₂, provided that, when w_4 is C-R₁, then w_7 is C-R₂; or, when w_4 is C-R₂, then w_7 is C-R₁.

[0664] In an aspect of the use of the compound of Formula (XXXIIIa), one of w_3 and w_6 is C-R₁ and the other is C-R₂, provided that, when w_3 is C-R₁, then w_6 is C-R₂; or, when w_3 is C-R₂, then w_6 is C-R₁.

[0665] In an aspect of the use of the compound of Formula (XXXIVa), one of w_3 , w_4 , w_6 and w_7 is C-R₁ and one other of w_3 , w_4 , w_6 and w_7 is C-R₂, provided that,

when w_3 is C-R₁, then w_6 is C-R₂ and w_4 and w_7 are independently C-R_a or N; or,

when w_3 is C-R₂, then w_6 is C-R₁ and w_4 and w_7 are independently C-R_a or N; or,

when w_4 is C-R₁, then w_7 is C-R₂ and w_3 is C-R_a or N and w_6 is C-R_c or N; or,

when w_4 is C-R₂, then w_7 is C-R₁ and w_3 is C-R_a or N and w_6 is C-R_c or N.

[0666] In an aspect of the use of the compound of Formula (XXXVa), one of w_4 and w_7 is C-R₁ and the other is C-R₂, provided that, when w_4 is C-R₁, then w_7 is C-R₂; or, when w_4 is C-R₂, then w_7 is C-R₁.

[0667] In an aspect of the use of the compound of Formula (XXXVIa), one of w_3 and w_6 is C-R₁ and the other is C-R₂, provided that, when w_3 is C-R₁, then w_6 is C-R₂; or, when w_3 is C-R₂, then w_6 is C-R₁.

[0668] In an aspect of the use of the compound of Formula (XXXVIIa), one of w_3 , w_4 , w_6 and w_7 is C-R₁ and one other of w_3 , w_4 , w_6 and w_7 is C-R₂, provided that,

when w_3 is C-R₁, then w_6 is C-R₂ and w_4 and w_7 are independently C-R_a or N; or,

when w_3 is C-R₂, then w_6 is C-R₁ and w_4 and w_7 are independently C-R_a or N; or,

when w_4 is C-R₁, then w_7 is C-R₂ and w_3 is C-R_a or N and w_6 is C-R_c or N; or,

when w_4 is C-R₂, then w_7 is C-R₁ and w_3 is C-R_a or N and w_6 is C-R_c or N.

[0669] In an aspect of the use of the compound of Formula (XXXVIIIa), one of w_3 and w_6 is C-R₁ and the other is C-R₂, provided that, when w_3 is C-R₁, then w_6 is C-R₂; or, when w_3 is C-R₂, then w_6 is C-R₁.

[0670] In an aspect of the use of the compound of Formula (XXXIIIa), one of w_4 and w_7 is C-R₁ and the other is C-R₂, provided that, when w_4 is C-R₁, then w_7 is C-R₂; or, when w_4 is C-R₂, then w_7 is C-R₁.

[0671] In an aspect of the use of the compound of Formula (XLa), one of w_3 , w_4 , w_6 and w_7 is C-R₁ and one other of w_3 , w_4 , w_6 and w_7 is C-R₂, provided that,

when w_3 is C-R₁, then w_6 is C-R₂ and w_4 and w_7 are independently C-R_a or N; or,

when w_3 is C-R₂, then w_6 is C-R₁ and w_4 and w_7 are independently C-R_a or N; or,

when w_4 is C-R₁, then w_7 is C-R₂ and w_3 is C-R_a or N and w_6 is C-R_c or N; or,

when w_4 is C-R₂, then w_7 is C-R₁ and w_3 is C-R_a or N and w_6 is C-R_c or N.

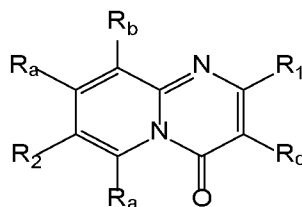
[0672] In an aspect of the use of the compound of Formula (XLIa), one of w_3 and w_6 is C-R₁ and the other is C-R₂, provided that, when w_3 is C-R₁, then w_6 is C-R₂; or, when w_3 is C-R₂, then w_6 is C-R₁.

[0673] In an aspect of the use of the compound of Formula (XLIIa), one of w_4 and w_7 is C-R₁ and the other is C-R₂, provided that, when w_4 is C-R₁, then w_7 is C-R₂; or, when w_4 is C-R₂, then w_7 is C-R₁.

HD Compounds of Formula (XIV)

In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in the published U.S. Patent Application No. 2020/0147087, the content of which is incorporated by reference herein in its entirety.

[0342] In one aspect, an HD compound of the disclosure can refer to a compound of Formula (XIV):



(XIV)

or a form thereof, wherein:

R₁ is heterocyclyl optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent; or, optionally substituted with one, two, three or four R₃ substituents;

R₂ is heteroaryl optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent;

R_a is, in each instance, independently selected from hydrogen, halogen or C₁₋₈alkyl;

R_b and R_c are, in each instance, independently selected from hydrogen, halogen or C₁₋₈alkyl;

R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, oxo, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkyl-carbonyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)₂-amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl]₂-amino, (C₁₋₈alkyl-amino-C₁₋₈alkyl)(C₁₋₈alkyl)amino, [(C₁₋₈alkyl)₂-amino-C₁₋₈alkyl](C₁₋₈alkyl)amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)₂-amino, (C₁₋₈alkoxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino, C₁₋₈alkyl-carbonyl-amino, C₁₋₈alkoxy-carbonyl-amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino or (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino;

R₄ is C₃₋₁₄cycloalkyl, C₃₋₁₄cycloalkyl-C₁₋₈alkyl, C₃₋₁₄cycloalkyl-amino, aryl-C₁₋₈alkyl, aryl-C₁₋₈alkoxy-carbonyl, aryl-sulfonyloxy-C₁₋₈alkyl, heterocyclyl or heterocyclyl-C₁₋₈alkyl; wherein, each instance of C₃₋₁₄ cycloalkyl, aryl and heterocyclyl is optionally substituted with one, two or three R₅ substituents;

R₅ is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino or C₁₋₈alkyl-thio;

R₆ is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C₁₋₈alkyl, C₂₋₈alkenyl, halo-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino or C₁₋₈alkyl-thio; and,

R₇ is C₃₋₁₄ cycloalkyl, C₃₋₁₄ cycloalkyl-oxy, aryl, heterocyclyl or heteroaryl; and,

wherein the form of the compound is selected from the group consisting of a salt, prodrug, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

[0674] In one aspect of the compound of Formula (XIV),

R₁ is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidiny, piperidiny, piperaziny, 1,4-diazepany, 3,6-dihydropyridiny, 1,2,5,6-tetrahydropyridiny, 1,2,3,6-tetrahydropyridiny, hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl, octahydro-5H-pyrrolo[3,2-c]pyridiny, octahydro-6H-pyrrolo[3,4-b]pyridiny, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridiny, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridiny, hexahydropyrrolo[1,2-c]pyrazin-(2H)-one, hexahydropyrrolo[1,2-c]pyrazin-(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-c]pyrazin-(1H)-yl, (8aS)-hexahydropyrrolo[1,2-c]pyrazin-(1H)-yl, (8aR)-hexahydropyrrolo[1,2-c]pyrazin-(1H)-yl, (8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyraziny, (8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyraziny, (8aS)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyraziny, (8aR)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyraziny, (8aS)-octahydropyrrolo[1,2-c]pyrazin-(1H)-yl, (8aR)-octahydropyrrolo[1,2-c]pyrazin-(1H)-yl, octahydro-2H-pyrrolo[1,2-c]pyraziny, (3aR,4aR,7aS)-hexahydro-1H-cyclobuta[1,2-c:1,4-c']dipyrrol-(3H)-yl, 3-azabicyclo[3.1.0]hexyl, (1R,5S)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1R,5S)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl, (1R,5S)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1S,4S)-2,5-diazabicyclo[2.2.1]heptyl, 2,5-

diazabicyclo[2.2.2]octyl, 3,6-diazabicyclo[3.2.0]heptyl, 3,8-diazabicyclo[3.2.1]octyl, (1R,5S)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, azaspiro[3.3]heptyl, 2,6-diazaspiro[3.3]heptyl, 4,7-diazaspiro[2.5]octyl, 2,6-diazaspiro[3.4]octyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 2,7-diazaspiro[4.4]nonyl or 6,9-diazaspiro[4.5]decyl; wherein, each instance of heterocyclyl is optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent; or, optionally, with one, two, three or four R₃ substituents.

[0675] In another aspect of the compound of Formula (XIV),

R₁ is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, 1,4-diazepanyl, hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl, hexahydropyrrolo[1,2-c]pyrazin-(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-c]pyrazin-(1H)-yl, (8aS)-hexahydropyrrolo[1,2-c]pyrazin-(1H)-yl, (8aR)-hexahydropyrrolo[1,2-c]pyrazin-(1H)-yl, (8aS)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl, (8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazinyl, (8aS)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazinyl, (8aR)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazinyl, (3aR,4aR,7aS)-hexahydro-1H-cyclobuta[1,2-c:1,4-c']dipyrrol-(3H)-yl, 3,6-diazabicyclo[3.2.0]heptyl, 2,6-diazaspiro[3.3]heptyl, 4,7-diazaspiro[2.5]octyl, 2,6-diazaspiro[3.4]octyl or 2,7-diazaspiro[3.5]nonyl; wherein, each instance of heterocyclyl is optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent; or, optionally, with one, two, three or four R₃ substituents.

[0676] In another aspect of the compound of Formula (XIV),

R₁ is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 3,6-dihydropyridin-4-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-c]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-c]pyrazin-2(1H)-yl, (7R, 8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aS)-3,4,6,7,8,8a-

hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl, (8aR)-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl, (8aS)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl, (8aR)-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl, (8aS)-octahydropyrrolo[1,2-c]pyrazin-2(1H)-yl, (8aR)-octahydropyrrolo[1,2-c]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-c]pyrazin-2-yl, (3aR,4aR,7aS)-hexahydro-1H-cyclobuta[1,2-c:1,4-c']dipyrrol-2(3H)-yl, 3-azabicyclo[3.1.0]hex-3-yl, 8-azabicyclo[3.2.1]oct-3-yl, (1R,5S)-8-azabicyclo[3.2.1]oct-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]non-3-yl, (1R,5S)-9-azabicyclo[3.3.1]non-3-yl, 2,5-diazabicyclo[2.2.1]hept-2-yl, (1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl, 2,5-diazabicyclo[2.2.2]oct-2-yl, 3,6-diazabicyclo[3.2.0]hept-3-yl, 3,8-diazabicyclo[3.2.1]oct-3-yl, (1R,5S)-3,8-diazabicyclo[3.2.1]oct-3-yl, 1,4-diazabicyclo[3.2.2]non-4-yl, azaspiro[3.3]hept-2-yl, 2,6-diazaspiro[3.3]hept-2-yl, 4,7-diazaspiro[2.5]oct-7-yl, 2,6-diazaspiro[3.4]oct-2-yl, 2,7-diazaspiro[3.5]non-2-yl, 2,7-diazaspiro[3.5]non-7-yl, 5,8-diazaspiro[3.5]non-8-yl, 2,7-diazaspiro[4.4]non-2-yl or 6,9-diazaspiro[4.5]dec-9-yl; wherein, each instance of heterocyclyl is optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent; or, optionally, with one, two, three or four R₃ substituents.

[0677] In another aspect of the compound of Formula (XIV),

R₁ is substituted heterocyclyl selected from (3R)-3-pyrrolidin-1-ylpyrrolidin-1-yl, 1-methylpiperidin-4-yl, 1-ethylpiperidin-4-yl, 2,2,6,6-tetramethylpiperidin-4-yl, (3S)-3-methylpiperazin-1-yl, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, 3-(trifluoromethyl)piperazin-1-yl, 1-tert-butoxy-carbonyl-3,6-dihydropyridin-4-yl, 1-ethyl-1,2,3,6-tetrahydropyridin-4-yl, 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl, 4-methyl-1,4-diazepan-1-yl, (3aS,6aS)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, (3aS,6aS)-5-methylhexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, (3aR,6aR)-1-methylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, (3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (3aR,6aS)-5-(2-hydroxyethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (3aR,6aS)-5-(propan-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, (4aR,7aR)-1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aR,7aR)-1-ethyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aR,7aR)-1-(2-hydroxyethyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aS,7aS)-1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aS,7aS)-1-(2-hydroxyethyl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (7R, 8aS)-7-hydroxyhexahydropyrrolo[1,2-c]pyrazin-2(1H)-yl, (8aS)-8a-methyl-1,3,4,6,7,8-

hexahydropyrrolo[1,2-a]pyrazin-2-yl, (8aR)-8a-methyl-1,3,4,6,7,8-hexahydropyrrolo[1,2-a]pyrazin-2-yl, (8aS)-8a-methyloctahydropyrrolo[1,2-c]pyrazin-2(1H)-yl, (8aR)-8a-methyloctahydropyrrolo[1,2-c]pyrazin-2(1H)-yl, (1R,5S,6s)-6-(dimethylamino)-3-azabicyclo[3.1.0]hex-3-yl, (1R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl, 9-methyl-9-azabicyclo[3.3.1]non-3-yl, (3-exo)-9-methyl-9-azabicyclo[3.3.1]non-3-yl, (1R,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl, (1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl, (1S,4S)-5-ethyl-2,5-diazabicyclo[2.2.1]hept-2-yl or 6-methyl-2,6-diazaspiro[3.3]hept-2-yl.

[0678] In one aspect of the compound of Formula (XIV), R₃ is selected from cyano, halogen, hydroxy, oxo, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkyl-carbonyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₁₋₈alkoxy-carbonyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, C₁₋₈alkyl-carbonyl-amino, C₁₋₈alkoxy-carbonyl-amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino or (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino.

[0679] In another aspect of the compound of Formula (XIV), R₃ is selected from cyano, halogen, hydroxy, oxo, C₁₋₈alkyl, halo-C₁₋₈alkyl, C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, C₁₋₈alkoxy-carbonyl-amino, hydroxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkoxy-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl-amino, (hydroxy-C₁₋₈alkyl)₂-amino or (hydroxy-C₁₋₈alkyl)(C₁₋₈alkyl)amino.

[0680] In another aspect of the compound of Formula (XIV), R₃ is C₁₋₈alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl.

[0681] In another aspect of the compound of Formula (XIV), R₃ is halo-C₁₋₈alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, halo-ethyl, trihalo-propyl, dihalo-propyl or halo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0682] In another aspect of the compound of Formula (XIV), R₃ is hydroxy-C₁₋₈alkyl selected from hydroxy-methyl, hydroxy-ethyl, hydroxy-propyl, dihydroxy-propyl, hydroxy-butyl or dihydroxy-butyl.

[0683] In another aspect of the compound of Formula (XIV), R3 is C1-8alkoxy selected from methoxy, ethoxy, propoxy or isopropoxy.

[0684] In another aspect of the compound of Formula (XIV), R3 is halo-C1-8alkoxy selected from trihalo-methoxy, dihalo-methoxy, halo-methoxy, trihalo-ethoxy, dihalo-ethoxy, halo-ethoxy, trihalo-propoxy, dihalo-propoxy or halo-propoxy; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0685] In another aspect of the compound of Formula (XIV), R3 is C1-8alkoxy-carbonyl-amino selected from methoxy-carbonyl-amino, ethoxy-carbonyl-amino, propoxy-carbonyl-amino, isopropoxy-carbonyl-amino, tert-butoxy-carbonyl-amino.

[0686] In one aspect of the compound of Formula (XIV), R4 is C3-14cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; wherein, each instance of C3-14cycloalkyl is optionally substituted with one, two or three R5 substituents.

[0687] In another aspect of the compound of Formula (XIV), R4 is C3-14cycloalkyl-C1-8alkyl, wherein C₃₋₁₄cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; and, wherein, each instance of C₃₋₁₄cycloalkyl is optionally substituted with one, two or three R5 substituents.

[0688] In another aspect of the compound of Formula (XIV), R4 is C3-14cycloalkyl-amino, wherein C₃₋₁₄cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; and, wherein, each instance of C3-14cycloalkyl is optionally substituted with one, two or three R5 substituents.

[0689] In another aspect of the compound of Formula (XIV), R4 is aryl-C1-8alkoxy-carbonyl or aryl-sulfonyloxy-C1-8alkyl, wherein aryl is selected from phenyl; and, wherein, each instance of aryl is optionally substituted with one, two or three R5 substituents.

[0690] In another aspect of the compound of Formula (XIV), R4 is heterocyclyl selected from oxetanyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,3-dioxanyl or morpholinyl, wherein each instance of heterocyclyl is optionally substituted with one, two or three R5 substituents.

[0691] In another aspect of the compound of Formula (XIV), R4 is heterocyclyl selected from oxetan-3-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, 1,3-dioxan-5-yl or morpholin-4-yl, wherein each instance of heterocyclyl is optionally substituted with one, two or three R5 substituents.

[0692] In another aspect of the compound of Formula (XIV), R₄ is heterocycl-yl-C₁-8alkyl, wherein each instance of heterocycl-yl is selected from pyrrolidin-yl or piperidin-yl; and, wherein, each instance of heterocycl-yl is optionally substituted with one, two or three R₅ substituents.

[0693] In another aspect of the compound of Formula (XIV), R₄ is heterocycl-yl-C₁-8alkyl selected from pyrrolidin-1-yl-C₁-8alkyl or piperidin-1-yl-C₁-8alkyl, wherein each instance of heterocycl-yl is optionally substituted with one, two or three R₅ substituents.

[0694] In one aspect of the compound of Formula (XIV), R₅ is selected from halogen, hydroxy, cyano, nitro, halo-C₁-8alkyl, C₁-8alkoxy, halo-C₁-8alkoxy, amino, C₁-8alkyl-amino, (C₁-8alkyl)₂-amino or C₁-8alkyl-thio; wherein, halogen and halo is selected from fluoro, chloro, bromo or iodo.

[0695] In another aspect of the compound of Formula (XIV), R₅ is C₁-8alkyl selected from methyl, ethyl, propyl, isopropyl, n-butyl or tert-butyl.

[0696] In another aspect of the compound of Formula (XIV), R₅ is halo-C₁-8alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, halo-ethyl, trihalo-propyl, dihalo-propyl or halo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0697] In another aspect of the compound of Formula (XIV), R₅ is C₁-8alkoxy selected from methoxy, ethoxy, propoxy or isopropoxy.

[0698] In another aspect of the compound of Formula (XIV), R₅ is halo-C₁-8alkoxy selected from trihalo-methoxy, dihalo-methoxy, halo-methoxy, trihalo-ethoxy, dihalo-ethoxy, halo-ethoxy, trihalo-propoxy, dihalo-propoxy or halo-propoxy; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0699] In one aspect of the compound of Formula (XIV),

R₂ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrimidinyl, 1H-indolyl, 2H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizynyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, 9H-purinyl, quinazolinyl, quinoxalinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-c]pyrimidinyl, pyrrolo[1,2-c]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl,

pyrazolo[1,5-a]pyrazinyl, pyrazolo[4,3-b]pyridinyl, pyrazolo[3,4-c]pyridinyl, imidazo[1,2-c]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrazinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, pyrido[1,2-a]pyrimidinyl or pyrido[1,2-a]pyrimidinone; wherein, each instance of heteroaryl is optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent.

[0700] In another aspect of the compound of Formula (XIV),

R₂ is heteroaryl selected from 1,3-benzoxazolyl, pyrazolo[1,5-c]pyrazinyl, imidazo[1,2-c]pyridinyl, imidazo[1,2-b]pyridazinyl, [1,2,4]triazolo[1,5-c]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl or [1,2,4]triazolo[1,5-b]pyridazinyl; wherein, each instance of heteroaryl is optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent.

[0701] In another aspect of the compound of Formula (XIV),

R₂ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-4-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 2H-indazol-5-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 9H-purin-8-yl, quinazolin-6-yl, quinoxalin-2-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-c]pyrimidin-7-yl, pyrrolo[1,2-c]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[4,3-b]pyridin-5-yl, pyrazolo[3,4-c]pyridin-5-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-c]pyrimidin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrazin-2-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyrimidin-6-yl, [1,2,4]triazolo[1,5-

b]pyridazin-6-yl, pyrido[1,2-a]pyrimidin-4-yl or pyrido[1,2-a]pyrimidin-4-one; wherein, each instance of heteroaryl is optionally substituted with one, two or three R₆ substituents and optionally, with one additional R₇ substituent.

[0702] In another aspect of the compound of Formula (XIV),

R₂ is substituted heteroaryl selected from 4-methylthien-2-yl, 1-methyl-1H-pyrazol-3-yl, 4-methyl-1H-pyrazol-3-yl, 1-phenyl-1H-pyrazol-3-yl, 1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl, 1-phenyl-1H-imidazol-4-yl, 2-methyl-1-(pyridin-2-yl)-1H-imidazol-4-yl, 4-methyl-1,3-thiazol-2-yl, 4-(trifluoromethyl)-1,3-thiazol-2-yl, 4-phenyl-1,3-thiazol-2-yl, 5-phenyl-1,2,4-oxadiazol-3-yl, 3-fluoropyridin-4-yl, 6-fluoropyridin-2-yl, 2-chloropyridin-4-yl, 4-chloropyridin-3-yl, 5-chloropyridin-2-yl, 6-methylpyridin-3-yl, 2-(trifluoromethyl)pyridin-3-yl, 4-(trifluoromethyl)pyridin-2-yl, 6-(trifluoromethyl)pyridin-2-yl, 2-methoxypyridin-4-yl, 4-methoxypyridin-3-yl, 6-methoxypyridin-2-yl, 2-ethoxypyridin-3-yl, 6-ethoxypyridin-2-yl, 6-(propan-2-yloxy)pyridin-2-yl, 6-(dimethylamino)pyridin-3-yl, 6-(methyl sulfanyl)pyridin-2-yl, 6-(cyclobutyloxy)pyridin-2-yl, 6-(pyrrolidin-1-yl)pyridin-2-yl, (5-fluoro-6-hydroxy)pyridin-3-yl, 2-methylpyrimidin-4-yl, 2-(propan-2-yl)pyrimidin-4-yl, 2-cyclopropylpyrimidin-4-yl, 1-methyl-1H-indol-3-yl, 1,7-dimethyl-1H-indazol-5-yl, 2-methyl-2H-indazol-5-yl, 2,7-dimethyl-2H-indazol-5-yl, 7-fluoro-2-methyl-2H-indazol-5-yl, 2-methyl-1-benzofuran-5-yl, 1-methyl-1H-benzimidazol-2-yl, 4-methyl-1H-benzimidazol-2-yl, 5-fluoro-1H-benzimidazol-2-yl, 4-fluoro-1,3-benzoxazol-2-yl, 5-fluoro-1,3-benzoxazol-2-yl, 4-chloro-1,3-benzoxazol-2-yl, 4-iodo-1,3-benzoxazol-2-yl, 2-methyl-1,3-benzoxazol-6-yl, 4-methyl-1,3-benzoxazol-2-yl, 4-(trifluoromethyl)-1,3-benzoxazol-2-yl, 7-(trifluoromethyl)-1,3-benzoxazol-2-yl, 2-methyl-1,3-benzothiazol-2-yl, 2-methyl-1,3-benzothiazol-5-yl, 2-methyl-1,3-benzothiazol-6-yl, 4-chloro-1,3-benzothiazol-2-yl, 7-chloro-1,3-benzothiazol-2-yl, 4-(trifluoromethyl)-1,3-benzothiazol-2-yl, (4-hydroxy-2-methyl)quinazolin-6-yl, 5-methylfuro[3,2-b]pyridin-2-yl, 4,6-dimethylfuro[3,2-c]pyridin-2-yl, 5,7-dimethylfuro[2,3-c]pyridin-2-yl, 4,6-dimethylthieno[3,2-c]pyridin-2-yl, 2,4-dimethylthieno[2,3-d]pyrimidin-6-yl, 1-methylpyrrolo[1,2-c]pyrazin-7-yl, 3-methylpyrrolo[1,2-c]pyrazin-7-yl, 1,3-dimethylpyrrolo[1,2-c]pyrazin-7-yl, 2-methylpyrrolo[1,2-b]pyridazin-2-yl, 2-methylpyrazolo[1,5-a]pyridin-5-yl, 5-methylpyrazolo[1,5-a]pyridin-2-yl, 4-(dimethylamino)-6-methylpyrazolo[1,5-a]pyrazin-2-yl, 4,6-dimethylpyrazolo[1,5-a]pyrazin-2-yl, 4-ethyl-6-methylpyrazolo[1,5-a]pyrazin-2-yl, 1,7-dimethyl-1H-pyrazolo[4,3-b]pyridin-5-yl, 1,7-dimethyl-1H-pyrazolo[3,4-c]pyridin-5-yl, 2,7-dimethyl-2H-pyrazolo[3,4-c]pyridin-5-yl, 2,7-

dimethyl-2H-pyrazolo[4,3-b]pyridin-5-yl, 2-chloroimidazo[2,1-b][1,3]thiazol-6-yl, 2-methylimidazo[2,1-b][1,3]thiazol-6-yl, 3-methylimidazo[2,1-b][1,3]thiazol-6-yl, 2-ethylimidazo[2,1-b][1,3]thiazol-6-yl, 2-methylimidazo[2,1-b][1,3,4]thiadiazol-6-yl, 6-cyanoimidazo[1,2-c]pyridin-2-yl (also referred to as 2-imidazo[1,2-a]pyridine-6-carbonitrile), 6-fluoroimidazo[1,2-a]pyridin-2-yl, 8-fluoroimidazo[1,2-a]pyridin-2-yl, 6,8-difluoroimidazo[1,2-a]pyridin-2-yl, 7-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl, 8-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl, 6-chloroimidazo[1,2-a]pyridin-2-yl, 7-chloroimidazo[1,2-a]pyridin-2-yl, 8-chloroimidazo[1,2-a]pyridin-2-yl, 8-bromoimidazo[1,2-a]pyridin-2-yl, 2-methylimidazo[1,2-a]pyridin-2-yl, 5-methylimidazo[1,2-a]pyridin-2-yl, 6-methylimidazo[1,2-a]pyridin-2-yl, 7-methylimidazo[1,2-a]pyridin-2-yl, 8-methylimidazo[1,2-a]pyridin-2-yl, 7-ethylimidazo[1,2-a]pyridin-2-yl, 8-ethylimidazo[1,2-a]pyridin-2-yl, 6,8-dimethylimidazo[1,2-a]pyridin-2-yl, 8-ethyl-6-methylimidazo[1,2-a]pyridin-2-yl, 7-methoxyimidazo[1,2-a]pyridin-2-yl, 8-methoxyimidazo[1,2-a]pyridin-2-yl, 6-fluoro-8-methylimidazo[1,2-a]pyridin-2-yl, 8-fluoro-6-methylimidazo[1,2-a]pyridin-2-yl, 8-chloro-6-methylimidazo[1,2-a]pyridin-2-yl, 6-methyl-8-nitroimidazo[1,2-a]pyridin-2-yl, 8-cyclopropylimidazo[1,2-a]pyridin-2-yl, 2-methylimidazo[1,2-a]pyridin-6-yl, 2-ethylimidazo[1,2-a]pyridin-6-yl, 2,3-dimethylimidazo[1,2-a]pyridin-6-yl, 2,8-dimethylimidazo[1,2-a]pyridin-6-yl, 2-(trifluoromethyl)imidazo[1,2-a]pyridin-6-yl, 8-chloro-2-methylimidazo[1,2-a]pyridin-6-yl, 8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl, 6-fluoroimidazo[1,2-a]pyrimidin-2-yl, 6-chloroimidazo[1,2-a]pyrimidin-2-yl, 6-methylimidazo[1,2-a]pyrimidin-2-yl, 7-methylimidazo[1,2-a]pyrimidin-2-yl, 2-methylimidazo[1,2-a]pyrimidin-6-yl, 6-methylimidazo[1,2-b]pyridazin-2-yl, 2-methylimidazo[1,2-b]pyridazin-6-yl, 2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl, 6-methylimidazo[1,2-a]pyrazin-2-yl, 8-methylimidazo[1,2-a]pyrazin-2-yl, 6,8-dimethylimidazo[1,2-a]pyrazin-2-yl, 6-chloro-8-methylimidazo[1,2-a]pyrazin-2-yl, 6-methyl-8-(trifluoromethyl)imidazo[1,2-a]pyrazin-2-yl, 8-(methylsulfanyl)imidazo[1,2-a]pyrazin-2-yl, 2-methylimidazo[2,1-b][1,3]thiazol-6-yl, 3-methylimidazo[2,1-b][1,3]thiazol-6-yl, 2-methylimidazo[2,1-b][1,3,4]thiadiazol-6-yl, 2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl, 2-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl, 2-methyl-[1,2,4]triazolo[1,5-b]pyridazin-6-yl or 4H,4'H-2,7'-bipyrido[1,2-a]pyrimidine-4,4'-dione.

In one aspect of the compound of Formula (XIV), R₆ is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C₁₋₈alkyl, C₂₋₈alkenyl, halo-C₁₋₈alkyl, hydroxy-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, amino, C₁₋₈alkyl-amino, (C₁₋

alkyl)₂-amino or C₁₋₈alkyl-thio; wherein, halogen and halo is selected from fluoro, chloro, bromo or iodo.

[0703] In another aspect of the compound of Formula (XIV), R₆ is C₁₋₈alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl.

[0704] In another aspect of the compound of Formula (XIV), R₆ is C₂₋₈alkenyl selected from ethenyl, allyl or buta-1,3-dienyl.

[0705] In another aspect of the compound of Formula (XIV), R₆ is halo-C₁₋₈alkyl selected from trihalo-methyl, dihalo-methyl, halo-methyl, trihalo-ethyl, dihalo-ethyl, halo-ethyl, trihalo-propyl, dihalo-propyl or halo-propyl; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0706] In another aspect of the compound of Formula (XIV), R₆ is hydroxy-C₁₋₈alkyl selected from hydroxy-methyl, hydroxy-ethyl, hydroxy-propyl, dihydroxy-propyl, hydroxy-butyl or dihydroxy-butyl.

[0707] In another aspect of the compound of Formula (XIV), R₆ is C₁₋₈alkoxy selected from methoxy, ethoxy, propoxy or isopropoxy.

[0708] In another aspect of the compound of Formula (XIV), R₆ is halo-C₁₋₈alkoxy selected from trihalo-methoxy, dihalo-methoxy, halo-methoxy, trihalo-ethoxy, dihalo-ethoxy, halo-ethoxy, trihalo-propoxy, dihalo-propoxy or halo-propoxy; wherein, halo is selected from fluoro, chloro, bromo or iodo.

[0709] In one aspect of the compound of Formula (XIV), R₇ is C₃₋₁₄cycloalkyl, C₃₋₁₄cycloalkyl-oxy, aryl, heterocyclyl or heteroaryl; wherein C₃₋₁₄cycloalkyl is selected from cyclopropyl or cyclobutoxy; wherein aryl is selected from phenyl; wherein heterocyclyl is selected from oxetanyl, pyrrolidinyl or 1,2,3,6-tetrahydropyridinyl; and, wherein heteroaryl is selected from thienyl or pyridinyl. In another aspect of the compound of Formula (XIV), R₇ is C₃₋₁₄cycloalkyl or C₃₋₁₄cycloalkyl-oxy, wherein each instance of C₃₋₁₄cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

[0710] In another aspect of the compound of Formula (XIV), R₇ is aryl selected from phenyl.

[0711] In another aspect of the compound of Formula (XIV), R₇ is heterocyclyl selected from oxetanyl, pyrrolidinyl or 1,2,3,6-tetrahydropyridinyl.

[0712] In another aspect of the compound of Formula (XIV), R₇ is heterocyclyl selected from oxetan-3-yl, pyrrolidin-1-yl or 1,2,3,6-tetrahydropyridin-4-yl.

[0713] In another aspect of the compound of Formula (XIV), R₇ is heteroaryl selected from thienyl or pyridinyl.

[0714] In another aspect of the compound of Formula (XIV), R₇ is heteroaryl selected from thien-2-yl or pyridin-2-yl.

[0715] In one aspect of the compound of Formula (XIV), R_a, R_b and R_c are each independently selected from hydrogen or C₁-8alkyl.

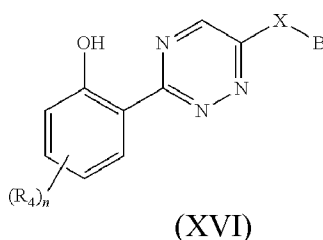
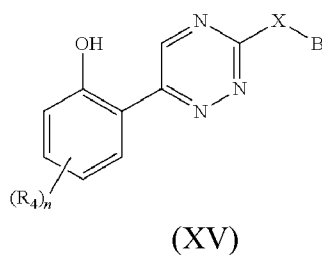
[0716] In another aspect of the compound of Formula (XIV), R_a, R_b and R_c are each independently selected from hydrogen or C₁-8alkyl.

[0717] In another aspect of the compound of Formula (XIV), R_a, R_b and R_c are each independently C₁-8alkyl selected from methyl, ethyl, propyl, isopropyl or tert-butyl.

HD Compounds of Formula (XV) and (XVI)

[0718] In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in the published U.S. Patent Application No. 2021/0024525, the content of which is incorporated by reference herein in its entirety.

[0719] In one aspect, an HD compound of the disclosure can refer to a compound of Formula (XV) or Formula (XVI):



or a form thereof, wherein:

X is CHR_{1a} , $\text{C}=\text{O}$, O, NR_{1b} , or a bond;

R_{1a} is hydrogen, halogen, hydroxyl, cyano, C_{1-4} alkyl, deuterio- C_{1-4} alkyl, halo- C_{1-4} alkyl, amino or hydroxyl- C_{1-4} alkyl;

R_{1b} is hydrogen, C_{1-4} alkyl, deuterio- C_{1-4} alkyl, halo- C_{1-4} alkyl or hydroxyl- C_{1-4} alkyl;

B is heterocyclyl,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2 ;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4} alkyl, deuterio- C_{1-4} alkyl, halo- C_{1-4} alkyl, amino, C_{1-4} alkyl-amino, $(\text{C}_{1-6}$ alkyl)₂-amino, halo- C_{1-4} alkyl-amino, (halo- C_{1-6} alkyl)₂-amino, hydroxy- C_{1-4} alkyl-amino, C_{1-4} alkoxy- C_{1-4} alkyl-amino, amino- C_{1-4} alkyl, C_{1-4} alkyl-amino- C_{1-4} alkyl, $(\text{C}_{1-4}$ alkyl-amino)₂- C_{1-4} alkyl, C_{1-4} alkoxy, halo- C_{1-4} alkoxy, hydroxyl- C_{1-4} alkoxy, C_{1-4} alkyl- C_{1-4} alkoxy, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-amino, C_{3-10} cycloalkyl-amino- C_{1-4} alkyl, heteroaryl- C_{1-4} alkyl, heteroaryl-amino, heteroaryl- C_{1-4} alkyl-amino, heterocyclyl, heterocyclyl- C_{1-4} alkyl, heterocyclyl-amino, heterocyclyl-amino- C_{1-4} alkyl, heterocyclyl- C_{1-4} alkoxy, heterocyclyl-amino- C_{3-10} cycloalkyl, phenyl, and phenyl- C_{1-4} alkoxy,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S,

wherein C_{3-10} cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10} cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3 ;

R₃ is independently selected from halogen, hydroxyl, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkoxy, and halo-C₁₋₄alkoxy;

n is 0, 1, or 2;

R₄ is independently selected from halogen, hydroxyl, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, C₁₋₄alkoxy, halo-C₁₋₄alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R₅;

R₅ is independently selected from halogen, hydroxyl, cyano, nitro, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkyl-carbonyl, C₁₋₄alkoxy, C₁₋₄alkylthio, halo-C₁₋₄alkoxy, and C₃₋₁₀cycloalkyl.

[0720] One aspect includes a compound of Formula (XV) or Formula (XVI), wherein X is selected from CHR_{1a}, C=O, O, NR_{1b}, and a bond.

[0721] Another aspect includes a compound of Formula (XV) wherein X is CHR_{1a}.

[0722] Another aspect includes a compound of Formula (XV) or Formula (XVI) wherein X is C=O.

[0723] Another aspect includes a compound of Formula (XV) or Formula (XVI) wherein X is O.

[0724] Another aspect includes a compound of Formula (XV) or Formula (XVI) wherein X is NR_{1b}.

[0725] Another aspect includes a compound of Formula (XV) or Formula (XVI) wherein X is a bond.

[0726] One aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_{1a} is selected from hydrogen, halogen, hydroxyl, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, and hydroxyl-C₁₋₄alkyl.

[0727] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_{1a} is selected from hydrogen, cyano, C₁₋₄alkyl, and amino.

[0728] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_{1a} is hydrogen.

[0729] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_{1a} is cyano.

[0730] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_{1a} is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[0731] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_{1a} is methyl.

[0732] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_{1a} is amino.

[0733] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_{1b} is selected from hydrogen and C₁₋₄alkyl.

[0734] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_{1b} is hydrogen.

[0735] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_{1b} is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[0736] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_{1b} is methyl.

[0737] One aspect includes a compound of Formula (XV) or Formula (XVI), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₂.

[0738] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, (8aS)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, (8aR)-octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, (1R,5S)-8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, (1R,5S)-9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, (1S,4S)-2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, (1R,5S)-3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, azaspiro[3.3]heptanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, and 7-azadispiro[5.1.5^{8.3}]⁶]hexadecanyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₂.

[0739] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl,

hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-(1H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 9-azabicyclo[3.3.1]nonanyl, 2,6-diazaspiro[3.3]heptanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, and 2,9-diazaspiro[5.5]undecanyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₂.

[0740] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, and 2,7-diazaspiro[3.5]nonanyl, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₂.

[0741] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aR,7aR)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, (4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (7R,8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aS)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aR)-hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, (8aS)-octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, (8aR)-octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 2-oxa-6-

azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, (1R,5S)-8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, (1R,5S)-8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, (1R,5S)-9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, (1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, (1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, azaspiro[3.3]heptan-2-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₂.

[0742] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-4-yl, piperazin-1-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, (3aR,6aR)-hexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, and 2,9-diazaspiro[5.5]undecan-9-yl, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₂.

[0743] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-4-yl, 2,7-diazaspiro[3.5]nonan-2-yl, and 2,7-diazaspiro[3.5]nonan-7-yl, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R₂.

[0744] One aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is selected from halogen, hydroxyl, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₆alkyl)₂-amino, halo-C₁₋₄alkyl-amino, (halo-C₁₋₆alkyl)₂-amino, hydroxy-C₁₋₄alkyl-amino, C₁₋₄alkoxy-C₁₋₄alkyl-amino, amino-C₁₋₄alkyl, C₁₋₄alkyl-amino-C₁₋₄alkyl, (C₁₋₄alkyl-amino)₂-C₁₋₄alkyl, C₁₋₄alkoxy, halo-C₁₋₄alkoxy, hydroxyl-C₁₋₄alkoxy, C₁₋₄alkyl-C₁₋₄alkoxy, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-amino, C₃₋₁₀cycloalkyl-amino-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl, heteroaryl-amino, heteroaryl-C₁₋₄alkyl-amino, heterocyclyl, heterocyclyl-C₁₋₄alkyl, heterocyclyl-amino, heterocyclyl-amino-C₁₋₄alkyl, heterocyclyl-C₁₋₄alkoxy, heterocyclyl-amino-C₃₋₁₀cycloalkyl, phenyl, and phenyl-C₁₋₄alkoxy,

wherein heteroaryl is a saturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S,

wherein C₃₋₁₀cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C₃₋₁₀cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R₃.

[0745] One aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is selected from halogen, hydroxyl, C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₆alkyl)₂-amino, halo-C₁₋₄alkyl-amino, hydroxy-C₁₋₄alkyl-amino, C₁₋₄alkoxy-C₁₋₄alkyl-amino, C₁₋₄alkyl-amino-C₁₋₄alkyl, (C₁₋₄alkyl-amino)₂-C₁₋₄alkyl, C₁₋₄alkoxy, C₃₋₁₀cycloalkyl-amino, C₃₋₁₀cycloalkyl-amino-C₁₋₄alkyl, heteroaryl-C₁₋₄alkyl-amino, heterocyclyl-amino, heterocyclyl-amino-C₁₋₄alkyl, and heterocyclyl-amino-C₃₋₁₀cycloalkyl,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S,

wherein C₃₋₁₀cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of heteroaryl, heterocyclyl, or C₃₋₁₀cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R₃.

[0746] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is halogen selected from bromo, chloro, fluoro, and iodo.

[0747] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is fluoro.

[0748] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is hydroxyl.

[0749] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[0750] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is C₁₋₄alkyl selected from methyl or ethyl.

[0751] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is methyl.

[0752] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is ethyl.

[0753] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is amino.

[0754] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is C₁₋₆alkyl-amino, wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 2-methylbutyl, and 3-methylpentyl.

[0755] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is C_{1-6} alkyl-amino, wherein C_{1-4} alkyl is selected from methyl, ethyl, isopropyl, tert-butyl, 2-methylbutyl, and 3-methylpentyl.

[0756] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is methylamino.

[0757] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is ethylamino.

[0758] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is isopropylamino.

[0759] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is tert-butylamino.

[0760] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is 2-methylbutyl-2-amino.

[0761] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is 3-methylpentyl-3-amino.

[0762] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is $(C_{1-6}$ alkyl)₂-amino, wherein C_{1-4} alkyl is each independently selected from selected from methyl, ethyl, isopropyl, tert-butyl, 2-methylbutyl, and 3-methylpentyl.

[0763] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is $(C_{1-6}$ alkyl)₂-amino, wherein C_{1-4} alkyl is methyl or ethyl.

[0764] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is dimethylamino or diethylamino.

[0765] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is dimethylamino.

[0766] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is diethylamino.

[0767] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is halo- C_{1-4} alkyl-amino, wherein C_{1-4} alkyl is selected from methyl, ethyl, propyl,

isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl, partially or completely substituted with one or more halogen atoms where allowed by available valences.

[0768] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is halo- C_{1-4} alkyl-amino, wherein C_{1-4} alkyl is selected from isopropyl and tert-butyl, partially or completely substituted with one or more halogen atoms where allowed by available valences.

[0769] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is 1-fluoro-2-methylpropan-2-amino or 1-fluoropropan-2-amino.

[0770] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is hydroxy- C_{1-4} alkyl-amino, wherein C_{1-4} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl, partially or completely substituted with one or more hydroxy groups where allowed by available valences.

[0771] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is hydroxy- C_{1-4} alkyl-amino, wherein C_{1-4} alkyl is selected from ethyl and propyl, partially or completely substituted with one or more hydroxy groups where allowed by available valences.

[0772] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is 2-hydroxyethylamino or 3-hydroxypropylamino.

[0773] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is C_{1-4} alkoxy- C_{1-4} alkyl-amino, wherein C_{1-4} alkoxy is selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy, and C_{1-4} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[0774] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is C_{1-4} alkoxy- C_{1-4} alkyl-amino, wherein C_{1-4} alkoxy is methoxy and C_{1-4} alkyl is selected propyl, isopropyl, and tert-butyl.

[0775] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is 1-methoxypropan-2-amino or 1-methoxy-2-methylpropan-2-amino.

[0776] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is C_{1-4} alkyl-amino- C_{1-4} alkyl, wherein each C_{1-4} alkyl is independently selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[0777] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is C_{1-4} alkyl-amino- C_{1-4} alkyl, wherein each C_{1-4} alkyl is independently selected from methyl, ethyl, isopropyl, and tert-butyl.

[0778] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is methylaminomethyl, propan-2-yl-aminomethyl, propan-2-yl-aminoethyl, or tert-butylaminomethyl.

[0779] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is $(C_{1-4}$ alkyl-amino) $_2$ - C_{1-4} alkyl, wherein each C_{1-4} alkyl is independently selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[0780] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is $(C_{1-4}$ alkyl-amino) $_2$ - C_{1-4} alkyl, wherein each C_{1-4} alkyl is methyl.

[0781] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is dimethylaminomethyl.

[0782] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is C_{1-4} alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

[0783] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 methoxy.

[0784] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is C_{3-10} cycloalkyl-amino, wherein C_{3-10} cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantyl.

[0785] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is C_{3-10} cycloalkyl-amino, wherein C_{3-10} cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, bicyclo[2.2.1]hexanyl, and adamantyl.

[0786] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is C_{3-10} cycloalkyl-amino- C_{1-4} alkyl, wherein C_{3-10} cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantyl and C_{1-4} alkyl is selected from methyl, ethyl, propyl, and butyl.

[0787] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is C_{3-10} cycloalkyl-amino- C_{1-4} alkyl, wherein C_{3-10} cycloalkyl is selected from cyclopropyl, cyclobutyl, and cyclopentyl, and C_{1-4} alkyl is methyl.

[0788] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is cyclopropylaminomethyl, cyclobutylaminomethyl, or cyclopentylaminomethyl.

[0789] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is heteroaryl-C₁₋₄alkyl-amino, wherein heteroaryl is selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, and C₁₋₄alkyl is selected from methyl, ethyl, propyl, and butyl.

[0790] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is heteroaryl-C₁₋₄alkyl-amino, wherein heteroaryl is pyridinyl, and C₁₋₄alkyl is methyl.

[0791] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is pyridin-2-yl-methylamino.

[0792] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is heterocyclyl-amino, wherein heterocyclyl is selected from azetidiny, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, 8-azabicyclo[3.2.1]octanyl, and 8-oxabicyclo[3.2.1]octanyl.

[0793] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is heterocyclyl-amino, wherein heterocyclyl is selected from oxetanyl and tetrahydropyranyl.

[0794] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is oxetanylamino or tetrahydropyranylamino.

[0795] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is heterocyclyl-amino-C₁₋₄alkyl, wherein heterocyclyl is selected from azetidiny, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, oxanyl, 8-azabicyclo[3.2.1]octanyl, and 8-oxabicyclo[3.2.1]octanyl, and C₁₋₄alkyl is selected from methyl, ethyl, propyl, and butyl.

[0796] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₂ is heterocyclyl-amino-C₁₋₄alkyl, wherein heterocyclyl is selected from tetrahydrofuranyl, oxanyl, and 8-oxabicyclo[3.2.1]octanyl, and C₁₋₄alkyl is methyl.

[0797] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is oxanylaminomethyl, tetrahydrofuranylaminomethyl, and 8-oxabicyclo[3.2.1]octanylamino.

[0798] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is heterocyclyl-amino- C_{3-10} cycloalkyl, wherein heterocyclyl is selected from azetidiny, oxetanyl, pyrrolidiny, tetrahydrofuranyl, piperidiny, oxanyl, 8-azabicyclo[3.2.1]octanyl, and 8-oxabicyclo[3.2.1]octanyl, and C_{3-10} cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0799] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is heterocyclyl-amino- C_{3-10} cycloalkyl, wherein heterocyclyl is oxanyl, and C_{3-10} cycloalkyl is cyclopropyl.

[0800] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_2 is oxanylaminocyclopropyl.

[0801] One aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_3 is halogen, hydroxyl, cyano, C_{1-4} alkyl, deuterio- C_{1-4} alkyl, halo- C_{1-4} alkyl, amino, C_{1-4} alkoxy, and halo- C_{1-4} alkoxy.

[0802] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_3 is halogen and C_{1-4} alkyl.

[0803] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_3 is halogen selected from bromo, chloro, fluoro, and iodo.

[0804] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_3 is fluoro.

[0805] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_3 is C_{1-4} alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[0806] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_3 is methyl.

[0807] One aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_4 is selected from halogen, hydroxyl, cyano, C_{1-4} alkyl, deuterio- C_{1-4} alkyl, halo- C_{1-4} alkyl, amino,

C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, C₁₋₄alkoxy, halo-C₁₋₄alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1 or 2 substituents each selected from R₅.

[0808] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₄ is selected from halogen, C₁₋₄alkoxy, heteroaryl, and phenyl.

[0809] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₄ is halogen selected from bromo, chloro, fluoro, and iodo.

[0810] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₄ is fluoro.

[0811] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₄ is C₁₋₄alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.

[0812] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₄ methoxy.

[0813] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₄ is heteroaryl,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, optionally substituted with 1 or 2 substituents each selected from R₅.

[0814] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₄ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl,

benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridin-yl, pyrazolo[1,5-a]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, pyrazolo[1,5-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrazinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, optionally substituted with 1 or 2 substituents each selected from R₅.

[0815] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₄ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 2H-tetrazolyl, pyridinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indazolyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 1,3-oxazolo[5,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, and quinolinyl, optionally substituted with 1 or 2 substituents each selected from R₅.

[0816] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_4 is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 2H-indazol-5-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, pyrazolo[1,5-a]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl, optionally substituted with 1 or 2 substituents each selected from R_5 .

[0817] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_4 is heteroaryl selected from thien-2-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-4-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indazol-5-yl, 1H-benzimidazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, and isoquinolin-6-yl, optionally substituted with 1 or 2 substituents each selected from R_5 .

[0818] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_4 is phenyl, 1 or 2 substituents each selected from R_5 .

[0819] One aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is selected from halogen, hydroxyl, cyano, nitro, C_{1-4} alkyl, deuterio- C_{1-4} alkyl, halo- C_{1-4} alkyl, amino, C_{1-4} alkyl-amino, (C_{1-4} alkyl)₂-amino, amino- C_{1-4} alkyl, hydroxyl- C_{1-4} alkyl, C_{1-4} alkyl-carbonyl, C_{1-4} alkoxy, C_{1-4} alkylthio, halo- C_{1-4} alkoxy, and C_{3-10} cycloalkyl.

[0820] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is selected from halogen, hydroxyl, cyano, nitro, C_{1-4} alkyl, deuterio- C_{1-4} alkyl, amino, C_{1-4} alkyl-amino, amino- C_{1-4} alkyl, hydroxyl- C_{1-4} alkyl, C_{1-4} alkyl-carbonyl, C_{1-4} alkoxy, C_{1-4} alkylthio, and C_{3-10} cycloalkyl.

[0821] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is halogen selected from bromo, chloro, fluoro, and iodo.

[0822] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is halogen selected from bromo, chloro and fluoro.

[0823] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is chloro.

[0824] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is fluoro.

[0825] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is hydroxy.

[0826] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is cyano.

[0827] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is nitro.

[0828] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[0829] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is methyl.

[0830] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is deuterio-C₁₋₄alkyl wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more deuterium atoms where allowed by available valences.

[0831] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is (²H₃)methyl.

[0832] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is amino.

[0833] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is C₁₋₆alkyl-amino wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 2-methylbutyl, and 3-methylpentyl.

[0834] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is C_{1-4} alkyl-amino wherein C_{1-4} alkyl is methyl.

[0835] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is methylamino.

[0836] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is amino- C_{1-4} alkyl wherein C_{1-4} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[0837] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is amino- C_{1-4} alkyl wherein C_{1-4} alkyl is methyl.

[0838] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is aminomethyl.

[0839] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is hydroxyl- C_{1-4} alkyl, wherein C_{1-4} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more hydroxyl groups where allowed by available valences.

[0840] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is hydroxyl- C_{1-4} alkyl, wherein C_{1-4} alkyl is methyl substituted with one hydroxyl group.

[0841] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is hydroxymethyl.

[0842] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is C_{1-4} alkyl-carbonyl, wherein C_{1-4} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[0843] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is C_{1-4} alkyl-carbonyl, wherein C_{1-4} alkyl is methyl.

[0844] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is $CH_3C(O)---$.

[0845] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R_5 is C_{1-4} alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.

[0846] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ methoxy.

[0847] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is C₁₋₄alkylthio selected from methylthio, ethylthio, propylthio, isopropylthio, butylthio, and tert-butylthio.

[0848] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ methylthio.

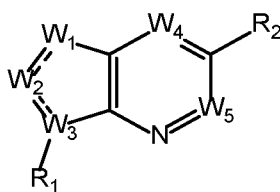
[0849] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is C₃₋₁₀cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantyl.

[0850] Another aspect includes a compound of Formula (XV) or Formula (XVI), wherein R₅ is cyclopropyl.

HD Compounds of Formula (XVII)

[0851] In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in the published International PCT Patent Application No. PCT/US2019/038889, the content of which is incorporated by reference herein in its entirety.

[0852] In one aspect, an HD compound of the disclosure can refer to a compound of Formula (XVII):



(XVII)

or a form thereof, wherein:

the dashed lines represent one or more double bonds optionally present where allowed by available valences;

W₁ is independently C-R_a, CH-R_a, N, N-R_b, O, or S where allowed by available valences;

W₂ is independently C-R_a, CH-R_a, N, or N-R_b where allowed by available valences, and;

W₃ is independently C, CH, or N where allowed by available valences;

wherein at least one of W₁, W₂, or W₃ is N or N-R_b;

W₄ and W₅ are independently C-R_a or N,

wherein when W₁ is S or O, W₂ is C-R_a, and W₃ is C;

R_a is, in each instance, independently selected from hydrogen, cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl;

R_b is selected from hydrogen and C₁₋₆alkyl;

R₁ is selected from C₃₋₁₀cycloalkyl and heterocyclyl,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

wherein, each instance of C₃₋₁₀cycloalkyl and heterocyclyl is optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent, or,

wherein, alternatively, each instance of C₃₋₁₀cycloalkyl and heterocyclyl is optionally substituted with one, two, three, or four R₃ substituents;

R₂ is selected from phenyl, heterocyclyl, and heteroaryl,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

wherein, each instance of phenyl, heterocyclyl, and heteroaryl is optionally substituted with one, two, or three R₅ substituents, and optionally, with one additional R₆ substituent;

R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl;

R₄ is selected from C₃₋₁₀cycloalkyl, phenyl, heteroaryl, and heterocyclyl,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

wherein, each instance of C₃₋₁₀cycloalkyl, phenyl, heterocyclyl, and heteroaryl is optionally substituted with one, two, or three R₇ substituents;

R₅ is, in each instance, independently selected from halogen, hydroxy, cyano, nitro, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, oxime, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, and C₁₋₆alkyl-thio;

R₆ is selected from phenyl and heteroaryl,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

wherein, each instance of phenyl and heteroaryl is optionally substituted with one, two, three or four R₈ substituents;

R₇ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and C₃₋₁₀cycloalkyl;

R₈ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, or C₃₋₁₀cycloalkyl.

[0853] One aspect includes a compound of Formula (XVII), wherein W₁ is N-R_b and W₄ is N.

[0854] Another aspect includes a compound of Formula (XVII), wherein W₁ is N-R_b, W₂ is C-R_a, W₃ is C, W₄ is N and W₅ is C-R_a.

[0855] Another aspect includes a compound of Formula (XVII), wherein W₁ is N-R_b, W₂ is CH-R_a, W₃ is CH, W₄ is N and W₅ is C-R_a.

[0856] One aspect includes a compound of Formula (XVII), wherein W₂ is N-R_b and W₄ is N.

[0857] Another aspect includes a compound of Formula (XVII), wherein W_1 is $CH-R_a$, W_2 is $N-R_b$, W_3 is CH , W_4 is N and W_5 is $C-R_a$.

[0858] One aspect includes a compound of Formula (XVII), wherein W_3 and W_4 are N .

[0859] Another aspect includes a compound of Formula (XVII), wherein W_1 is $C-R_a$, W_2 is $C-R_a$, W_3 is N , W_4 is N and W_5 is $C-R_a$.

[0860] Another aspect includes a compound of Formula (XVII), wherein W_1 is $CH-R_a$, W_2 is $CH-R_a$, W_3 is N , W_4 is N and W_5 is $C-R_a$.

[0861] One aspect includes a compound of Formula (XVII), wherein W_1 , W_2 and W_4 are N .

[0862] Another aspect includes a compound of Formula (XVII), wherein W_1 is N , W_2 is N , W_3 is CH , W_4 is N and W_5 is $C-R_a$.

[0863] One aspect includes a compound of Formula (XVII), wherein W_1 and W_2 are $N-R_b$ and W_4 is N .

[0864] Another aspect includes a compound of Formula (XVII), wherein W_1 and W_2 are $N-R_b$, W_3 is CH , W_4 is N and W_5 is $C-R_a$.

[0865] One aspect includes a compound of Formula (XVII), wherein W_1 , W_3 and W_4 are N .

[0866] Another aspect includes a compound of Formula (XVII), wherein W_1 is N , W_2 is $C-R_a$, W_3 is N , W_4 is N and W_5 is $C-R_a$.

[0867] One aspect includes a compound of Formula (XVII), wherein W_1 is $N-R_b$ and W_3 and W_4 are N .

[0868] Another aspect includes a compound of Formula (XVII), wherein W_1 is $N-R_b$, W_2 is $CH-R_a$, W_3 is N , W_4 is N and W_5 is $C-R_a$.

[0869] One aspect includes a compound of Formula (XVII), wherein W_2 , W_3 and W_4 are N .

[0870] Another aspect includes a compound of Formula (XVII), wherein W_1 is $C-R_a$, W_2 is N , W_3 is N , W_4 is N and W_5 is $C-R_a$.

[0871] One aspect includes a compound of Formula (XVII), wherein W_2 is $N-R_b$ and W_3 and W_4 are N .

[0872] Another aspect includes a compound of Formula (XVII), wherein W_1 is $CH-R_a$, W_2 is $N-R_b$, W_3 is N , W_4 is N and W_5 is $C-R_a$.

[0873] One aspect includes a compound of Formula (XVII), wherein W_1 , W_2 , W_3 and W_4 are N.

[0874] Another aspect includes a compound of Formula (XVII), wherein W_1 is N, W_2 is N, W_3 is N, W_4 is N and W_5 is C- R_a .

[0875] One aspect includes a compound of Formula (XVII), wherein W_1 is S and W_4 is N.

[0876] Another aspect includes a compound of Formula (XVII), wherein W_1 is S, W_2 is C- R_a , W_3 is C, W_4 is N and W_5 is C- R_a .

[0877] One aspect includes a compound of Formula (XVII), wherein W_1 is O and W_4 is N.

[0878] Another aspect includes a compound of Formula (XVII), wherein W_1 is O, W_2 is C- R_a , W_3 is C, W_4 is N and W_5 is C- R_a .

[0879] One aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b and W_5 is N.

[0880] Another aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b , W_2 is C- R_a , W_3 is C, W_4 is C- R_a and W_5 is N.

[0881] Another aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b , W_2 is CH- R_a , W_3 is CH, W_4 is C- R_a and W_5 is N.

[0882] One aspect includes a compound of Formula (XVII), wherein W_2 is N- R_b and W_5 is N.

[0883] Another aspect includes a compound of Formula (XVII), wherein W_1 is CH- R_a , W_2 is N- R_b , W_3 is CH, W_4 is C- R_a and W_5 is N.

[0884] One aspect includes a compound of Formula (XVII), wherein W_3 and W_5 are N.

[0885] Another aspect includes a compound of Formula (XVII), wherein W_1 is C- R_a , W_2 is C- R_a , W_3 is N, W_4 is C- R_a and W_5 is N.

[0886] Another aspect includes a compound of Formula (XVII), wherein W_1 is CH- R_a , W_2 is CH- R_a , W_3 is N, W_4 is C- R_a and W_5 is N.

[0887] One aspect includes a compound of Formula (XVII), wherein W_1 , W_2 and W_5 are N.

[0888] Another aspect includes a compound of Formula (XVII), wherein W_1 is N, W_2 is N, W_3 is CH, W_4 is C- R_a and W_5 is N.

[0889] One aspect includes a compound of Formula (XVII), wherein W_1 and W_2 are N- R_b and W_5 is N.

[0890] Another aspect includes a compound of Formula (XVII), wherein W_1 and W_2 are N- R_b , W_3 is CH, W_4 is C- R_a and W_5 is N.

[0891] One aspect includes a compound of Formula (XVII), wherein W_1 , W_3 and W_5 are N.

[0892] Another aspect includes a compound of Formula (XVII), wherein W_1 is N, W_2 is C- R_a , W_3 is N, W_4 is C- R_a and W_5 is N.

[0893] One aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b and W_3 and W_5 are N.

[0894] Another aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b , W_2 is CH- R_a , W_3 is N, W_4 is C- R_a and W_5 is N.

[0895] One aspect includes a compound of Formula (XVII), wherein W_2 , W_3 and W_5 are N.

[0896] Another aspect includes a compound of Formula (XVII), wherein W_1 is C- R_a , W_2 is N, W_3 is N, W_4 is C- R_b and W_5 is N.

[0897] One aspect includes a compound of Formula (XVII), wherein W_2 is N- R_b and W_3 and W_5 are N.

[0898] Another aspect includes a compound of Formula (XVII), wherein W_1 is CH- R_a , W_2 is N- R_b , W_3 is N, W_4 is C- R_a and W_5 is N.

[0899] One aspect includes a compound of Formula (XVII), wherein W_1 , W_2 , W_3 and W_5 are N.

[0900] Another aspect includes a compound of Formula (XVII), wherein W_1 is N, W_2 is N, W_3 is N, W_4 is C- R_a and W_5 is N.

[0901] One aspect includes a compound of Formula (XVII), wherein W_1 is S and W_5 is N.

[0902] Another aspect includes a compound of Formula (XVII), wherein W_1 is S, W_2 is C- R_a , W_3 is C, W_4 is C- R_a and W_5 is N.

[0903] One aspect includes a compound of Formula (XVII), wherein W_1 is O and W_5 is N.

[0904] Another aspect includes a compound of Formula (XVII), wherein W_1 is O, W_2 is C- R_a , W_3 is C, W_4 is C- R_a and W_5 is N.

- [0905] One aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b .
- [0906] Another aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b , W_2 is C- R_a , W_3 is C and W_4 and W_5 are C- R_a .
- [0907] Another aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b , W_2 is CH- R_a , W_3 is CH and W_4 and W_5 are C- R_a .
- [0908] One aspect includes a compound of Formula (XVII), wherein W_2 is N- R_b .
- [0909] Another aspect includes a compound of Formula (XVII), wherein W_1 is C- R_a , W_2 is N- R_b , W_3 is C and W_4 and W_5 are C- R_a .
- [0910] Another aspect includes a compound of Formula (XVII), wherein W_1 is CH- R_a , W_2 is N- R_b , W_3 is CH and W_4 and W_5 are C- R_a .
- [0911] One aspect includes a compound of Formula (XVII), wherein W_3 is N.
- [0912] Another aspect includes a compound of Formula (XVII), wherein W_1 is C- R_a , W_2 is C- R_a , W_3 is N and W_4 and W_5 are C- R_a .
- [0913] Another aspect includes a compound of Formula (XVII), wherein W_1 is CH- R_a , W_2 is CH- R_a , W_3 is N and W_4 and W_5 are C- R_a .
- [0914] One aspect includes a compound of Formula (XVII), wherein W_1 and W_2 are N.
- [0915] Another aspect includes a compound of Formula (XVII), wherein W_1 is N, W_2 is N, W_3 is CH and W_4 and W_5 are C- R_a .
- [0916] One aspect includes a compound of Formula (XVII), wherein W_1 and W_2 are N- R_b .
- [0917] Another aspect includes a compound of Formula (XVII), wherein W_1 and W_2 are N- R_b , W_3 is CH and W_4 and W_5 are C- R_a .
- [0918] One aspect includes a compound of Formula (XVII), wherein W_1 and W_3 are N.
- [0919] Another aspect includes a compound of Formula (XVII), wherein W_1 is N, W_2 is C- R_a , W_3 is N and W_4 and W_5 are C- R_a .
- [0920] One aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b and W_3 is N.
- [0921] Another aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b , W_2 is CH- R_a , W_3 is N and W_4 and W_5 are C- R_a .

- [0922] One aspect includes a compound of Formula (XVII), wherein W_2 and W_3 are N.
- [0923] Another aspect includes a compound of Formula (XVII), wherein W_1 is C- R_a , W_2 is N, W_3 is N and W_4 and W_5 are C- R_a .
- [0924] One aspect includes a compound of Formula (XVII), wherein W_2 is N- R_b and W_3 is N.
- [0925] Another aspect includes a compound of Formula (XVII), wherein W_1 is CH- R_b , W_2 is N- R_b , W_3 is N and W_4 and W_5 are C- R_a .
- [0926] One aspect includes a compound of Formula (XVII), wherein W_1 , W_2 and W_3 are N.
- [0927] Another aspect includes a compound of Formula (XVII), wherein W_1 is N, W_2 is N, W_3 is N and W_4 and W_5 are C- R_a .
- [0928] One aspect includes a compound of Formula (XVII), wherein W_1 is S.
- [0929] Another aspect includes a compound of Formula (XVII), wherein W_1 is S, W_2 is C- R_a , W_3 is C and W_4 and W_5 are C- R_a .
- [0930] One aspect includes a compound of Formula (XVII), wherein W_1 is O.
- [0931] Another aspect includes a compound of Formula (XVII), wherein W_1 is O, W_2 is C- R_a , W_3 is C and W_4 and W_5 are C- R_a .
- [0932] One aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b and W_4 and W_5 are N.
- [0933] Another aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b , W_2 is C- R_a , W_3 is C and W_4 and W_5 are N.
- [0934] Another aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b , W_2 is CH- R_a , W_3 is CH and W_4 and W_5 are N.
- [0935] One aspect includes a compound of Formula (XVII), wherein W_2 is N- R_b and W_4 and W_5 are N.
- [0936] Another aspect includes a compound of Formula (XVII), wherein W_1 is CH- R_a , W_2 is N- R_b , W_3 is CH and W_4 and W_5 are N.
- [0937] One aspect includes a compound of Formula (XVII), wherein W_3 , W_4 and W_5 are N.

[0938] Another aspect includes a compound of Formula (XVII), wherein W_1 is C- R_a , W_2 is C- R_a , W_3 is N and W_4 and W_5 are N.

[0939] Another aspect includes a compound of Formula (XVII), wherein W_1 is CH- R_a , W_2 is CH- R_a , W_3 is N and W_4 and W_5 are N.

[0940] One aspect includes a compound of Formula (XVII), wherein W_1 , W_2 , W_4 and W_5 are N.

[0941] Another aspect includes a compound of Formula (XVII), wherein W_1 is N, W_2 is N, W_3 is CH and W_4 and W_5 are N.

[0942] One aspect includes a compound of Formula (XVII), wherein W_1 and W_2 are N- R_b and W_4 and W_5 are N.

[0943] Another aspect includes a compound of Formula (XVII), wherein W_1 and W_2 are N- R_b , W_3 is CH and W_4 and W_5 are N.

[0944] One aspect includes a compound of Formula (XVII), wherein W_1 , W_3 , W_4 and W_5 are N.

[0945] Another aspect includes a compound of Formula (XVII), wherein W_1 is N, W_2 is C- R_a , W_3 is N and W_4 and W_5 are N.

[0946] One aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b and W_3 , W_4 and W_5 are N.

[0947] Another aspect includes a compound of Formula (XVII), wherein W_1 is N- R_b , W_2 is CH- R_a , W_3 is N and W_4 and W_5 are N.

[0948] One aspect includes a compound of Formula (XVII), wherein W_2 , W_3 , W_4 and W_5 are N.

[0949] Another aspect includes a compound of Formula (XVII), wherein W_1 is C- R_a , W_2 is N, W_3 is N and W_4 and W_5 are N.

[0950] One aspect includes a compound of Formula (XVII), wherein W_2 is N- R_b and W_3 , W_4 and W_5 are N.

[0951] Another aspect includes a compound of Formula (XVII), wherein W_1 is CH- R_a , W_2 is N- R_b , W_3 is N and W_4 and W_5 are N.

[0952] One aspect includes a compound of Formula (XVII), wherein W_1 , W_2 , W_3 , and W_4 and W_5 are N.

[0953] Another aspect includes a compound of Formula (XVII), wherein W_1 is N, W_2 is N, W_3 is N, and W_4 and W_5 are N.

[0954] One aspect includes a compound of Formula (XVII), wherein W_1 is S and W_4 and W_5 are N.

[0955] Another aspect includes a compound of Formula (XVII), wherein W_1 is S, W_2 is C- R_a , W_3 is C and W_4 and W_5 are N.

[0956] One aspect includes a compound of Formula (XVII), wherein W_1 is O and W_4 and W_5 are N.

[0957] Another aspect includes a compound of Formula (XVII), wherein W_1 is O, W_2 is C- R_a , W_3 is C and W_4 and W_5 are N.

[0958] One aspect includes a compound of Formula (XVII), wherein R_a is, in each instance, independently selected from hydrogen, cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[0959] Another aspect includes a compound of Formula (XVII), wherein R_a is, in each instance, independently selected from hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, and C₁₋₆alkyl-amino.

[0960] Another aspect includes a compound of Formula (XVII), wherein R_a is hydrogen.

[0961] Another aspect includes a compound of Formula (XVII), wherein R_a is hydroxy.

[0962] Another aspect includes a compound of Formula (XVII), wherein R_a is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[0963] Another aspect includes a compound of Formula (XVII), wherein R_a is methyl.

[0964] Another aspect includes a compound of Formula (XVII), wherein R_a is C₁₋₆alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, and tert-butoxy.

[0965] Another aspect includes a compound of Formula (XVII), wherein R_a is methoxy.

[0966] Another aspect includes a compound of Formula (XVII), wherein R_a is C_{1-6} alkyl-amino wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[0967] Another aspect includes a compound of Formula (XVII), wherein R_a is C_{1-6} alkyl-amino selected from methylamino and ethylamino.

[0968] One aspect includes a compound of Formula (XVII), wherein R_b is selected from hydrogen and C_{1-6} alkyl.

[0969] Another aspect includes a compound of Formula (XVII), wherein R_b is hydrogen.

[0970] One aspect includes a compound of Formula (XVII), wherein R_1 is selected from C_{3-10} cycloalkyl and heterocyclyl,

[0971] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

[0972] wherein, each instance of C_{3-10} cycloalkyl and heterocyclyl is optionally substituted with one, two or three R_3 substituents and optionally, with one additional R_4 substituent, or,

[0973] wherein, alternatively, each instance of C_{3-10} cycloalkyl and heterocyclyl is optionally substituted with one, two, three, or four R_3 substituents.

[0974] Another aspect includes a compound of Formula (XVII), wherein R_1 is C_{3-10} cycloalkyl, optionally substituted with one, two or three R_3 substituents and optionally, with one additional R_4 substituent, or alternatively, optionally substituted with one, two, three, or four R_3 substituents.

[0975] Another aspect includes a compound of Formula (XVII), wherein R_1 is C_{3-10} cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantyl, optionally substituted with one, two or three R_3 substituents and optionally, with one additional R_4 substituent, or alternatively, optionally substituted with one, two, three, or four R_3 substituents.

[0976] Another aspect includes a compound of Formula (XVII), wherein R_1 is C_{3-10} cycloalkyl selected from cyclobutyl and cyclohexyl, optionally substituted with one, two or three R_3 substituents and optionally, with one additional R_4 substituent, or alternatively, optionally substituted with one, two, three, or four R_3 substituents.

[0977] Another aspect includes a compound of Formula (XVII), wherein R₁ is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidiny, piperidiny, piperaziny, 1,4-diazepany, 1,2,5,6-tetrahydropyridiny, 1,2,3,6-tetrahydropyridiny, 3-azabicyclo[3.1.0]hexyl, (1*R*,5*S*)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-en-yl, (1*R*,5*S*)-8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonyl, (1*R*,5*S*)-9-azabicyclo[3.3.1]nonyl, 3-oxa-9-azabicyclo[3.3.1]nonyl, and 3-oxa-9-azabicyclo[3.3.1]non-6-en-yl, optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent, or, alternatively, optionally substituted with one, two, three or four R₃ substituents.

[0978] Another aspect includes a compound of Formula (XVII), wherein R₁ is heterocyclyl selected from piperidiny, piperaziny, 1,2,3,6-tetrahydropyridiny, 8-azabicyclo[3.2.1]octyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 3-oxa-9-azabicyclo[3.3.1]nonyl, and 3-oxa-9-azabicyclo[3.3.1]non-6-en-yl, optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent, or, alternatively, optionally substituted with one, two, three or four R₃ substituents.

[0979] Another aspect includes a compound of Formula (XVII), wherein R₁ is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, 8-azabicyclo[3.2.1]oct-3-yl, (1*R*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, (1*R*,5*S*)-8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]non-7-yl, (1*R*,5*S*)-9-azabicyclo[3.3.1]non-3-yl, 3-oxa-9-azabicyclo[3.3.1]non-7-yl, and 3-oxa-9-azabicyclo[3.3.1]non-6-en-7-yl, optionally substituted with one, two or three R₃ substituents and optionally, with one additional R₄ substituent, or, alternatively, optionally substituted with one, two, three or four R₃ substituents.

[0980] Another aspect includes a compound of Formula (XVII), wherein R₁ is heterocyclyl selected from piperidin-4-yl, piperazin-1-yl, 1,2,3,6-tetrahydropyridin-4-yl, 8-azabicyclo[3.2.1]oct-3-yl, (1*R*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 3-oxa-9-azabicyclo[3.3.1]non-7-yl, and 3-oxa-9-azabicyclo[3.3.1]non-6-en-7-yl, optionally substituted with one, two or three R₃ substituents

and optionally, with one additional R₄ substituent, or, alternatively, optionally substituted with one, two, three or four R₃ substituents.

[0981] One aspect includes a compound of Formula (XVII), wherein R₂ is selected from phenyl, heterocyclyl, and heteroaryl,

[0982] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S,

[0983] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

[0984] wherein, each instance of phenyl, heterocyclyl, and heteroaryl is optionally substituted with one, two, or three R₅ substituents, and optionally, with one additional R₆ substituent.

[0985] Another aspect includes a compound of Formula (XVII), wherein R₂ is phenyl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent.

[0986] Another aspect includes a compound of Formula (XVII), wherein R₂ is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,4-diazepanyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, and 2,3-dihydro-1*H*-indenyl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent.

[0987] Another aspect includes a compound of Formula (XVII), wherein R₂ is 2,3-dihydro-1*H*-indenyl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent.

[0988] Another aspect includes a compound of Formula (XVII), wherein R₂ is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, and 2,3-dihydro-1*H*-inden-5-yl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent.

[0989] Another aspect includes a compound of Formula (XVII), wherein R₂ is 2,3-dihydro-1*H*-inden-5-yl optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent.

[0990] Another aspect includes a compound of Formula (XVII), wherein R₂ is heteroaryl selected from furanyl, 1*H*-pyrrolyl, 1*H*-pyrazolyl, 1*H*-imidazolyl, 1,3-oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1*H*-indolyl, 1*H*-indazolyl, benzofuranyl, 1*H*-benzimidazolyl, 1*H*-benzotriazolyl, and quinolinyl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent.

[0991] Another aspect includes a compound of Formula (XVII), wherein R₂ is heteroaryl selected from pyridinyl, 1*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-benzotriazolyl, and quinolinyl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent.

[0992] Another aspect includes a compound of Formula (XVII), wherein R₂ is heteroaryl selected from furan-3-yl, 1*H*-pyrrol-3-yl, 1*H*-pyrazol-1-yl, 1*H*-pyrazol-3-yl, 1*H*-pyrazol-4-yl, 1*H*-imidazol-1-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, 1,3-oxazol-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-5-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, pyrazin-3-yl, 1*H*-indol-3-yl, 1*H*-indol-4-yl, 1*H*-indol-5-yl, 1*H*-indol-6-yl, 1*H*-indazol-5-yl, 1*H*-indazol-6-yl, benzofuran-2-yl, benzofuran-5-yl, 1*H*-benzimidazol-5-yl, 1*H*-benzimidazol-6-yl, 1*H*-benzotriazol-4-yl, 1*H*-benzotriazol-5-yl, 1*H*-benzotriazol-6-yl, 1*H*-benzotriazol-7-yl, and quinolin-7-yl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent.

[0993] Another aspect includes a compound of Formula (XVII), wherein R₂ is heteroaryl selected from pyridin-2-yl, 1*H*-indazol-6-yl, 1*H*-benzimidazol-6-yl, 1*H*-benzotriazol-7-yl, and quinolin-7-yl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent.

[0994] One aspect includes a compound of Formula (XVII), wherein R₃ is, in each instance, independently selected from from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[0995] Another aspect includes a compound of Formula (XVII), wherein R₃ is, in each instance, independently selected from from halogen, C₁₋₆alkyl, and C₁₋₆alkyl-amino.

[0996] Another aspect includes a compound of Formula (XVII), wherein R₃ is halogen selected from bromo, chloro, fluoro, and iodo.

[0997] Another aspect includes a compound of Formula (XVII), wherein R₃ is fluoro.

[0998] Another aspect includes a compound of Formula (XVII), wherein R₃ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[0999] Another aspect includes a compound of Formula (XVII), wherein R₃ is methyl.

[1000] Another aspect includes a compound of Formula (XVII), wherein R₃ is C₁₋₆alkyl-amino wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[1001] Another aspect includes a compound of Formula (XVII), wherein R₃ is tert-butylamino.

[1002] One aspect includes a compound of Formula (XVII), wherein R₄ is selected from C₃₋₁₀cycloalkyl, phenyl, heteroaryl, and heterocyclyl,

[1003] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S,

[1004] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

[1005] wherein, each instance of C₃₋₁₀cycloalkyl, phenyl, heterocyclyl, and heteroaryl is optionally substituted with one, two, or three R₇ substituents.

[1006] One aspect includes a compound of Formula (XVII), wherein R₅ is, in each instance, independently selected from from halogen, hydroxy, cyano, nitro, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, oxime, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, and C₁₋₆alkyl-thio.

[1007] Another aspect includes a compound of Formula (XVII), wherein R₅ is, in each instance, independently selected from from halogen, hydroxy, C₁₋₆alkyl, and oxime.

[1008] Another aspect includes a compound of Formula (XVII), wherein R₅ is halogen selected from bromo, chloro, fluoro, and iodo.

[1009] Another aspect includes a compound of Formula (XVII), wherein R₅ is halogen selected from chloro and fluoro.

[1010] Another aspect includes a compound of Formula (XVII), wherein R₅ is hydroxy.

[1011] Another aspect includes a compound of Formula (XVII), wherein R₅ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1012] Another aspect includes a compound of Formula (XVII), wherein R₅ methyl.

[1013] Another aspect includes a compound of Formula (XVII), wherein R₅ is oxime.

[1014] One aspect includes a compound of Formula (XVII), wherein R₆ is selected from phenyl and heteroaryl,

[1015] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

[1016] wherein, each instance of phenyl and heteroaryl is optionally substituted with one, two, three or four R₈ substituents.

[1017] Another aspect includes a compound of Formula (XVII), wherein R₆ is phenyl, optionally substituted with one, two, three or four R₈ substituents.

[1018] Another aspect includes a compound of Formula (XVII) wherein R₆ is heteroaryl selected from furanyl, thienyl, 1*H*-pyrrolyl, 1*H*-pyrazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 4*H*-1,2,4-triazolyl, 1,3-thiazolyl, 1,2-oxazolyl, 1,3-oxazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazol-yl, pyridinyl, pyridin-2(1*H*)-on-yl, pyridazinyl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyrazinyl, 1,3,5-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, benzofuranyl, 1*H*-benzimidazolyl, 1*H*-benzotriazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*c*]pyrimidinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,5-*a*]pyridinyl, [1,2,3]triazolo[1,5-*a*]pyridinyl, 1*H*-[1,2,3]triazolo[4,5-*b*]pyridinyl, 3*H*-[1,2,3]triazolo[4,5-*c*]pyridinyl, 3*H*-[1,2,3]triazolo[4,5-*c*]pyridazinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, and quinolinyl, optionally substituted with one, two, three or four R₈ substituents.

[1019] Another aspect includes a compound of Formula (XVII) wherein R₆ is heteroaryl selected from furanyl, thienyl, 1*H*-pyrrolyl, 1*H*-pyrazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl,

2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 4*H*-1,2,4-triazolyl, 1,3-thiazolyl, 1,2-oxazolyl, 1,3-oxazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazol-yl, pyridinyl, pyridin-2(1*H*)-on-yl, pyridazinyl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyrazinyl, 1,3,5-triazinyl, 1*H*-benzotriazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,5-*a*]pyridinyl, [1,2,3]triazolo[1,5-*a*]pyridinyl, 1*H*-[1,2,3]triazolo[4,5-*b*]pyridinyl, 3*H*-[1,2,3]triazolo[4,5-*c*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, and [1,2,4]triazolo[4,3-*b*]pyridazinyl, optionally substituted with one, two, three or four R₈ substituents.

[1020] Another aspect includes a compound of Formula (XVII), wherein R₆ is heteroaryl selected from furan-2-yl, furan-3-yl, thien-2-yl, thien-3-yl, 1*H*-pyrrol-3-yl, 1*H*-pyrazol-1-yl, 1*H*-pyrazol-3-yl, 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1*H*-imidazol-1-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, 1*H*-1,2,3-triazol-1-yl, 1*H*-1,2,3-triazol-4-yl, 2*H*-1,2,3-triazol-2-yl, 2*H*-1,2,3-triazol-4-yl, 1*H*-1,2,4-triazol-1-yl, 4*H*-1,2,4-triazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,2-oxazol-4-yl, 1,3-oxazol-2-yl, 1,3-oxazol-3-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1*H*)-on-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3*H*)-on-6-yl, pyrazin-1-yl, pyrazin-2-yl, 1,3,5-triazin-2-yl, 1*H*-indol-3-yl, 1*H*-indol-4-yl, 1*H*-indol-5-yl, 1*H*-indol-6-yl, 1*H*-indazol-5-yl, 1*H*-indazol-6-yl, benzofuran-2-yl, benzofuran-5-yl, 1*H*-benzimidazol-2-yl, 1*H*-benzimidazol-5-yl, 1*H*-benzimidazol-6-yl, 1*H*-benzotriazol-4-yl, 1*H*-benzotriazol-5-yl, 1*H*-benzotriazol-6-yl, 1*H*-benzotriazol-7-yl, 1*H*-pyrrolo[2,3-*b*]pyridin-4-yl, 1*H*-pyrrolo[2,3-*b*]pyridin-5-yl, 1*H*-pyrrolo[2,3-*c*]pyridin-4-yl, pyrrolo[1,2-*a*]pyrimidin-7-yl, pyrrolo[1,2-*a*]pyrazin-7-yl, pyrrolo[1,2-*b*]pyridazin-2-yl, pyrazolo[1,5-*a*]pyridin-2-yl, pyrazolo[1,5-*a*]pyridin-5-yl, 2*H*-pyrazolo[4,3-*b*]pyridin-5-yl, 2*H*-pyrazolo[4,3-*c*]pyridin-5-yl, pyrazolo[1,5-*a*]pyrazin-2-yl, imidazo[1,2-*a*]pyridin-2-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyridin-7-yl, imidazo[1,2-*a*]pyrimidin-2-yl, imidazo[1,2-*a*]pyrimidin-6-yl, imidazo[1,2-*c*]pyrimidin-2-yl, imidazo[1,2-*b*]pyridazin-2-yl, imidazo[1,2-*b*]pyridazin-6-yl, imidazo[1,2-*a*]pyrazin-2-yl, imidazo[1,2-*a*]pyrazin-3-yl, imidazo[1,2-*a*]pyrazin-6-yl, imidazo[1,5-*a*]pyridine-6-yl, imidazo[1,5-*a*]pyridin-7-yl, [1,2,3]triazolo[1,5-*a*]pyridin-5-yl, [1,2,3]triazolo[1,5-*a*]pyridin-7-yl, 1*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5-yl, 1*H*-[1,2,3]triazolo[4,5-*b*]pyridin-6-yl, 3*H*-[1,2,3]triazolo[4,5-*c*]pyridin-6-yl, 3*H*-[1,2,3]triazolo[4,5-*c*]pyridazin-6-yl, [1,2,4]triazolo[1,5-*a*]pyridin-7-yl, [1,2,4]triazolo[4,3-

b]pyridazin-6-yl, quinolin-6-yl, quinolin-7-yl, and quinolin-8-yl, optionally substituted with one, two, three or four R₈ substituents.

[1021] Another aspect includes a compound of Formula (XVII), wherein R₆ is heteroaryl selected from furan-3-yl, thien-3-yl, 1*H*-pyrrol-3-yl, 1*H*-pyrazol-1-yl, 1*H*-pyrazol-3-yl, 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1*H*-imidazol-1-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, 1*H*-1,2,3-triazol-1-yl, 1*H*-1,2,3-triazol-4-yl, 2*H*-1,2,3-triazol-2-yl, 2*H*-1,2,3-triazol-4-yl, 1*H*-1,2,4-triazol-1-yl, 4*H*-1,2,4-triazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,2-oxazol-4-yl, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1*H*)-on-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3*H*)-on-6-yl, pyrazin-2-yl, 1,3,5-triazin-2-yl, 1*H*-benzotriazol-6-yl, 1*H*-pyrrolo[2,3-*b*]pyridin-4-yl, 1*H*-pyrrolo[2,3-*c*]pyridin-4-yl, imidazo[1,2-*a*]pyridin-7-yl, imidazo[1,2-*a*]pyrimidin-6-yl, imidazo[1,2-*b*]pyridazin-6-yl, imidazo[1,2-*a*]pyrazin-3-yl, imidazo[1,2-*a*]pyrazin-6-yl, imidazo[1,5-*a*]pyridin-7-yl, [1,2,3]triazolo[1,5-*a*]pyridin-5-yl, [1,2,3]triazolo[1,5-*a*]pyridin-7-yl, 1*H*-[1,2,3]triazolo[4,5-*b*]pyridin-5-yl, 1*H*-[1,2,3]triazolo[4,5-*b*]pyridin-6-yl, 3*H*-[1,2,3]triazolo[4,5-*c*]pyridin-6-yl, and [1,2,4]triazolo[4,3-*b*]pyridazin-6-yl, optionally substituted with one, two, three or four R₈ substituents.

[1022] One aspect includes a compound of Formula (XVII) wherein R₇ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and C₃₋₁₀cycloalkyl.

[1023] One aspect includes a compound of Formula (XVII) wherein R₈ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and C₃₋₁₀cycloalkyl.

[1024] One aspect includes a compound of Formula (XVII) wherein R₈ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, and C₃₋₁₀cycloalkyl.

[1025] Another aspect includes a compound of Formula (XVII) wherein R₈ is cyano.

[1026] Another aspect includes a compound of Formula (XVII), wherein R₈ is halogen selected from bromo, chloro, fluoro, and iodo.

[1027] Another aspect includes a compound of Formula (XVII), wherein R₈ is halogen selected from bromo, chloro, and fluoro.

[1028] Another aspect includes a compound of Formula (XVII) wherein R₈ is hydroxy.

[1029] Another aspect includes a compound of Formula (XVII), wherein R₈ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1030] Another aspect includes a compound of Formula (XVII), wherein R₈ is C₁₋₆alkyl selected from methyl, ethyl, and propyl.

[1031] Another aspect includes a compound of Formula (XVII) wherein R₈ is deuterio-C₁₋₄alkyl wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more deuterium atoms where allowed by available valences.

[1032] Another aspect includes a compound of Formula (XVII) wherein R₈ is (²H₃)methyl.

[1033] Another aspect includes a compound of Formula (XVII), wherein R₈ is halo-C₁₋₆alkyl, wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more halogens selected from bromo, chloro, fluoro, and iodo where allowed by available valences.

[1034] Another aspect includes a compound of Formula (XVII), wherein R₈ is halo-C₁₋₆alkyl selected from trifluoromethyl and difluoromethyl.

[1035] Another aspect includes a compound of Formula (XVII), wherein R₈ is C₁₋₆alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, and tert-butoxy.

[1036] Another aspect includes a compound of Formula (XVII), wherein R₈ is C₁₋₆alkoxy selected from methoxy and ethoxy.

[1037] Another aspect includes a compound of Formula (XVII), wherein R₈ is halo-C₁₋₆alkoxy, wherein C₁₋₆alkoxy is selected from methoxy, ethoxy, propoxy, isopropoxy, and tert-butoxy partially or completely substituted with one or more halogens selected from bromo, chloro, fluoro, and iodo where allowed by available valences.

[1038] Another aspect includes a compound of Formula (XVII), wherein R₈ is difluoromethoxy.

[1039] Another aspect includes a compound of Formula (XVII) wherein R₈ is amino.

[1040] Another aspect includes a compound of Formula (XVII), wherein R₈ is C₁₋₆alkyl-amino wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[1041] Another aspect includes a compound of Formula (XVII), wherein R₈ is methylamino.

[1042] Another aspect includes a compound of Formula (XVII), wherein R₈ is (C₁₋₆alkyl)₂-amino wherein C₁₋₆alkyl is independently selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[1043] Another aspect includes a compound of Formula (XVII), wherein R₈ is dimethylamino.

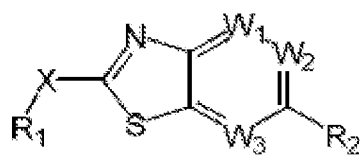
[1044] Another aspect includes a compound of Formula (XVII), wherein R₈ is C₃₋₁₀cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cyclohexyl.

[1045] Another aspect includes a compound of Formula (XVII), wherein R₈ is cyclopropyl.

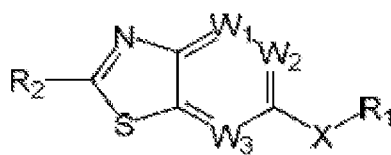
HD Compounds of Formula (XVIII) and (XIX)

[1046] In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in the published International PCT Patent Application No. PCT/US2019/038895, the content of which is incorporated by reference herein in its entirety.

[1047] In one aspect, an HD compound of the disclosure can refer to a compound of Formula (XVIII) or (XIX):



(XVIII)



(XIX)

or a form thereof, wherein:

W₁, W₂ and W₃ are independently C-R_a or N;

R_a is, in each instance, independently selected from hydrogen, cyano, halogen, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkyl-carbonyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl;

X is selected from N-R_b, O, or a bond;

R_b is selected from hydrogen and C₁₋₆alkyl;

R₁ is selected from C₃₋₁₀cycloalkyl and heterocyclyl,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

wherein, each instance of C₃₋₁₀cycloalkyl and heterocyclyl is optionally substituted with one, two, three, or four R₃ substituents and optionally, with one additional R₄ substituent, or,

wherein, alternatively, each instance of C₃₋₁₀cycloalkyl and heterocyclyl is optionally substituted with one, two, three, four, or five R₃ substituents;

R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkyl-carbonyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl,

C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl;

R₄ is selected from C₃₋₁₀cycloalkyl, phenyl, heterocyclyl, and heteroaryl;

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

wherein, each instance of C₃₋₁₀cycloalkyl, phenyl, heterocyclyl, and heteroaryl is optionally substituted with one, two or three R₇ substituents; R₂ is selected from phenyl and heteroaryl,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein, each instance of phenyl and heteroaryl is optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent, or,

wherein, alternatively, each instance of phenyl and heteroaryl is optionally substituted with one, two, three or four R₅ substituents;

R₅ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkyl-carbonyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, C₁₋₆alkoxy-carbonyl-C₁₋₆alkyl, carboxyl, C₁₋₆alkyl-carboxyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, amino-carbonyl, and hydroxy-C₁₋₆alkyl;

R₆ is selected from C₃₋₁₀cycloalkyl, phenyl, phenyl-C₁₋₆alkoxy, phenyl-oxy, heterocyclyl, and heteroaryl;

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

wherein, each instance of C₃₋₁₀cycloalkyl, phenyl, heterocyclyl, and heteroaryl is optionally substituted with one, two or three R₇ substituents; and

R₇ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkyl-carbonyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[1048] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₁, W₂ and W₃ are C-R_a.

[1049] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₁ is N.

[1050] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₁ is N, and W₂ and W₃ are C-R_a.

[1051] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₂ is N. Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₂ is N, and W₁ and W₃ are C-R_a.

[1052] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₃ is N. Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₃ is N, and W₁ and W₂ are C-R_a.

[1053] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₁ and W₂ are N.

[1054] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₁ and W₂ are N and W₃ is C-R_a.

[1055] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₁ and W₃ are N.

[1056] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₁ and W₃ are N and W₂ is C-R_a.

[1057] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₂ and W₃ are N.

[1058] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₂ and W₃ are N and W₂ is C-R_a.

[1059] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein W₁, W₂ and W₃ are N.

[1060] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_a is, in each instance, independently selected from hydrogen, cyano, halogen, hydroxy, C₁-6alkyl, halo-C₁-6alkyl, C₁-6alkyl-carbonyl, C₁-6alkoxy, halo-C₁-6alkoxy, C₁-6alkoxy-C₁-6alkyl, C₁-6alkoxy-carbonyl, amino, C₁-6alkyl-amino, (C₁-6alkyl)₂-amino, amino-C₁-6alkyl, and hydroxy-C₁-6alkyl.

[1061] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_a is, in each instance, independently selected from hydrogen, cyano, halogen, hydroxy, and C₁-6alkoxy.

[1062] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_a is, in each instance, hydrogen.

[1063] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_a is, in each instance, cyano.

[1064] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_a is, in each instance, halogen selected from bromo, chloro, fluoro, and iodo.

[1065] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_a is, in each instance, halogen selected from chloro and fluoro.

[1066] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_a is, in each instance, hydroxy.

[1067] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_a is, in each instance, C_{1-6} alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, and tert-butoxy.

[1068] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_a is, in each instance, methoxy.

[1069] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein X is selected from N- R_b , O, or a bond.

[1070] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein X is N- R_b . Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein X is O. Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein X is a bond. One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_b is selected from hydrogen and C_{1-6} alkyl.

[1071] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_b is hydrogen.

[1072] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_b is C_{1-6} alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1073] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_b is C_{1-6} alkyl selected from methyl and ethyl.

[1074] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_1 is selected from C_{3-10} cycloalkyl and heterocyclyl,

[1075] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic,

[1076] 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

[1077] wherein, each instance of C₃₋₁₀cycloalkyl and heterocyclyl is optionally substituted with one, two, three, or four R₃ substituents and optionally, with one additional R₄ substituent, or,

[1078] wherein, alternatively, each instance of C₃₋₁₀cycloalkyl and heterocyclyl is optionally substituted with one, two, three, four, or five R₃ substituents.

[1079] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₁ is C₃₋₁₀cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,

[1080] cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantyl, optionally substituted with one, two, three, or four R₃ substituents and optionally, with one additional R₄ substituent, or, alternatively, optionally substituted with one, two, three, four, or five R₃ substituents.

[1081] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₁ is

[1082] C₃₋₁₀cycloalkyl selected from cyclobutyl and cyclohexyl, optionally substituted with one, two, three, or four R₃ substituents and optionally, with one additional R₄ substituent, or, alternatively, optionally substituted with one, two, three, four, or five R₃ substituents.

[1083] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₁ is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, 1*H*-azepinyl, 2,3,6,7-tetrahydro-1*H*-azepinyl, azepanyl, 1,4-diazepanyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, octahydroindolizinyl, octahydro-1*H*-pyrrolo[3,2-*c*]pyridinyl, (3*aS*,7*aR*)-octahydro-1*H*-pyrrolo[3,2-*c*]pyridinyl, 1-azabicyclo[2.2.2]octyl, 3-azabicyclo[3.1.0]hexyl, (1*R*,5*S*)-3-azabicyclo[3.1.0]hexyl, 3-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]octyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]octyl, azabicyclo[3.2.1]oct-2-en-yl, (1*R*,5*S*)-8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonyl, (1*R*,5*S*)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptyl, 1,4-diazabicyclo[3.1.1]heptyl, 3,6-diazabicyclo[3.2.0]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 1,4-diazabicyclo[3.2.1]octyl, 3,8-diazabicyclo[3.2.1]octyl, (1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, 3,8-diazabicyclo[4.2.0]octyl, (1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octyl, (1*R*,6*S*)-3,8-diazabicyclo[4.2.0]octyl, 2-azaspiro[3.3]heptyl, 4,7-diazaspiro[2.5]octyl, 2,6-diazaspiro[3.3]heptyl, 2,6-diazaspiro[3.4]octyl, 1,6-diazaspiro[3.5]nonyl, 1,7-

diazaspiro[3.5]nonyl, 2,6-diazaspiro[3.5]nonyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 1,7-diazaspiro[4.4]nonyl, 2,7-diazaspiro[4.4]nonyl, 2,7-diazaspiro[4.5]decyl, and 6,9-diazaspiro[4.5]decyl, optionally substituted with one, two three, or four R₃ substituents and optionally, with one additional R₄ substituent, or, alternatively, optionally substituted with one, two, three, four, or five R₃ substituents.

[1084] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₁ is heterocyclyl selected from azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, 2,3,6,7-tetrahydro-1*H*-azepiny, azepanyl, 1,4-diazepanyl, 1,2,3,6-tetrahydropyridinyl, octahydroindoliziny, octahydro-1*H*-pyrrolo[3,2-*c*]pyridinyl, (3*aS*,7*aR*)-octahydro-1*H*-pyrrolo[3,2-*c*]pyridinyl, 1-azabicyclo[2.2.2]octyl, 8-azabicyclo[3.2.1]octyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]octyl, azabicyclo[3.3.1]nonyl, 3,8-diazabicyclo[4.2.0]octyl, (1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octyl, (1*R*,6*S*)-3,8-diazabicyclo[4.2.0]octyl, 2-azaspiro[3.3]heptyl, 2,6-diazaspiro[3.3]heptyl, 1,6-diazaspiro[3.5]nonyl, 1,7-diazaspiro[3.5]nonyl, 2,6-diazaspiro[3.5]nonyl, 2,7-diazaspiro[3.5]nonyl, and 2,7-diazaspiro[4.4]nonyl, optionally substituted with one, two three, or four R₃ substituents and optionally, with one additional R₄ substituent, or, alternatively, optionally substituted with one, two, three, four, or five R₃ substituents.

[1085] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₁ is heterocyclyl selected from azetidin-2-yl, azetidin-3-yl, tetrahydrofuran-3-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, 1*H*-azepin-2-yl, 1*H*-azepin-3-yl, 1*H*-azepin-4-yl, 2,3,6,7-tetrahydro-1*H*-azepin-4-yl, azepan-2-yl, azepan-3-yl, azepan-4-yl, 1,4-diazepan-1-yl, 1,4-diazepan-2-yl, 1,4-diazepan-3-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, octahydroindolizin-7-yl, octahydro-1*H*-pyrrolo[3,2-*c*]pyridin-1-yl, (3*aS*,7*aR*)-octahydro-1*H*-pyrrolo[3,2-*c*]pyridin-1-yl, 1-azabicyclo[2.2.2]oct-4-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 3-azabicyclo[3.2.1]octan-8-yl, 8-azabicyclo[3.2.1]oct-3-yl, (1*R*,5*S*)-8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, (1*R*,5*S*)-8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]non-3-yl, (1*R*,5*S*)-9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, (1*R*,5*S*)-3,8-

diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 3,8-diazabicyclo[4.2.0]oct-8-yl, (1*S*,6*R*)-3,8-diazabicyclo[4.2.0]oct-8-yl, (1*R*,6*S*)-3,8-diazabicyclo[4.2.0]oct-8-yl, 2-azaspiro[3.3]hept-2-yl, 2-azaspiro[3.3]hept-6-yl, 4,7-diazaspiro[2.5]oct-4-yl, 4,7-diazaspiro[2.5]oct-7-yl, 2,6-diazaspiro[3.3]hept-2-yl, 2,6-diazaspiro[3.4]oct-2-yl, 2,6-diazaspiro[3.4]oct-6-yl, 1,6-diazaspiro[3.5]non-1-yl, 1,7-diazaspiro[3.5]non-1-yl, 1,7-diazaspiro[4.4]non-1-yl, 1,7-diazaspiro[4.4]non-7-yl, 2,6-diazaspiro[3.5]non-2-yl, 2,6-diazaspiro[3.5]non-6-yl, 2,7-diazaspiro[3.5]non-7-yl, 5,8-diazaspiro[3.5]non-8-yl, 2,7-diazaspiro[4.4]non-2-yl, 2,7-diazaspiro[4.5]deca-2-yl, 2,7-diazaspiro[4.5]dec-7-yl, and 6,9-diazaspiro[4.5]dec-9-yl, optionally substituted with one, two three, or four R₃ substituents and optionally, with one additional R₄ substituent, or, alternatively, optionally substituted with one, two, three, four, or five R₃ substituents.

[1086] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₁ is heterocyclyl selected from azetidin-3-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2,3,6,7-tetrahydro-1*H*-azepin-4-yl, azepan-4-yl, 1,4-diazepan-1-yl, 1,2,3,6-tetrahydropyridin-4-yl, octahydroindolizin-7-yl, octahydro-1*H*-pyrrolo[3,2-*c*]pyridin-1-yl, (3*aS*,7*aR*)-octahydro-1*H*-pyrrolo[3,2-*c*]pyridin-1-yl, 1-azabicyclo[2.2.2]oct-4-yl, 3-azabicyclo[3.2.1]octan-8-yl, 8-azabicyclo[3.2.1]oct-3-yl, 9-azabicyclo[3.3.1]non-3-yl, 3,8-diazabicyclo[4.2.0]oct-8-yl, (1*S*,6*R*)-3,8-diazabicyclo[4.2.0]oct-8-yl, (1*R*,6*S*)-3,8-diazabicyclo[4.2.0]oct-8-yl, 2-azaspiro[3.3]hept-6-yl, 2,6-diazaspiro[3.3]hept-2-yl, 1,6-diazaspiro[3.5]non-1-yl, 1,7-diazaspiro[3.5]non-1-yl, 2,6-diazaspiro[3.5]non-2-yl, 2,7-diazaspiro[3.5]non-7-yl, and 2,7-diazaspiro[4.4]non-2-yl, optionally substituted with one, two, three, or four R₃ substituents and optionally, with one additional R₄ substituent, or, alternatively, each instance of heterocyclyl is optionally substituted with one, two, three, four, or five R₃ substituents.

[1087] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkyl-carbonyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[1088] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₃ is, in each instance, independently selected from halogen, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, amino,

[1089] C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, and hydroxy-C₁₋₆alkyl.

[1090] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₃ is, in each instance, halogen selected from bromo, chloro, fluoro, and iodo.

[1091] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₃ is, in each instance, fluoro.

[1092] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₃ is, in each instance, hydroxy.

[1093] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₃ is, in each instance, C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1094] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₃ is, in each instance, C₁₋₆alkyl selected from methyl and ethyl.

[1095] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₃ is, in each instance, halo-C₁₋₆alkyl, wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more halogens selected from bromo, chloro, fluoro, and iodo where allowed by available valences.

[1096] Another aspect includes a compound of Formula (XVIII), wherein R₃ is, in each instance, halo-C₁₋₆alkyl selected from fluoroethyl.

[1097] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₃ is, in each instance, amino.

[1098] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₃ is, in each instance, C₁₋₆alkyl-amino wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[1099] Another aspect includes a compound of Formula (XVIII), wherein R₃ is, in each instance, methylamino.

[1100] Another aspect includes a compound of Formula (XVIII), wherein R₃ is, in each instance, (C₁₋₆alkyl)₂-amino wherein C₁₋₆alkyl is independently selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[1101] Another aspect includes a compound of Formula (XVIII), wherein R₃ is, in each instance, dimethylamino.

[1102] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₃ is, in each instance, hydroxy-C₁₋₆alkyl, wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more hydroxy groups where allowed by available valences.

[1103] Another aspect includes a compound of Formula (XVIII), wherein R₃ is, in each instance, hydroxy-C₁₋₆alkyl selected from hydroxymethyl and hydroxyethyl.

[1104] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₄ is selected from C₃₋₁₀cycloalkyl, phenyl, heterocyclyl, and heteroaryl;

[1105] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S,

[1106] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

[1107] wherein, each instance of C₃₋₁₀cycloalkyl, phenyl, heterocyclyl, and heteroaryl is optionally substituted with one, two or three R₇ substituents.

[1108] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₄ is C₃₋₁₀cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantyl, optionally substituted with one, two or three R₇ substituents.

[1109] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₄ is cyclopropyl, optionally substituted with one, two or three R₇ substituents.

[1110] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₂ is selected from phenyl and heteroaryl,

[1111] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

[1112] wherein, each instance of phenyl and heteroaryl is optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent, or,

[1113] wherein, alternatively, each instance of phenyl and heteroaryl is optionally substituted with one, two, three or four R₅ substituents.

[1114] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₂ is phenyl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent, or, alternatively, optionally substituted with one, two, three or four R₅ substituents.

[1115] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₂ is heteroaryl selected from furanyl, 1*H*-pyrazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 4*H*-1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1*H*-indolyl, 2*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, indolizinyl, benzofuranyl, 1*H*-benzimidazolyl, 1,3-benzoxazolyl, furo[2,3-*b*]pyridinyl, furo[2,3-*c*]pyridinyl, furo[3,2-*b*]pyridinyl, furo[3,2-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, pyrrolo[1,2-*a*]pyrimidinyl, pyrrolo[1,2-*a*]pyrazinyl, pyrrolo[1,2-*b*]pyridazinyl, pyrazolo[1,5-*a*]pyridinyl, 1*H*-pyrazolo[4,3-*b*]pyridinyl, 2*H*-pyrazolo[4,3-*b*]pyridinyl, 2*H*-pyrazolo[4,3-*c*]pyridinyl, pyrazolo[1,5-*a*]pyrazinyl, pyrazolo[1,5-*a*]pyrimidinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*c*]pyrimidinyl, imidazo[1,5-*a*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, imidazo[2,1-*b*][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-*b*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[1,5-*b*]pyridazinyl, and quinolinyl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent, or, alternatively, optionally substituted with one, two, three or four R₅ substituents.

[1116] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₂ is heteroaryl selected from 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1,3-benzoxazolyl,

[1117] furo[3,2-*b*]pyridinyl, pyrrolo[1,2-*a*]pyrazinyl, 1*H*-pyrazolo[4,3-*b*]pyridinyl, 2*H*-pyrazolo[4,3-*b*]pyridinyl, pyrazolo[1,5-*a*]pyrimidinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*b*]pyridazinyl,

[1118] imidazo[2,1-*b*][1,3]thiazolyl, imidazo[2,1-*b*][1,3,4]thiadiazolyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, and [1,2,4]triazolo[1,5-*b*]pyridazinyl, optionally substituted with one, two or three R₅ substituents

[1119] and optionally, with one additional R₆ substituent, or, alternatively, optionally substituted with one, two, three or four R₅ substituents.

[1120] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₂ is heteroaryl selected from furan-2-yl, furan-3-yl, 1*H*-pyrazol-3-yl, 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1*H*-imidazol-1-yl, 1*H*-imidazol-4-yl, 1*H*-1,2,3-triazol-1-yl, 4*H*-1,2,4-triazol-4-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-5-yl, pyrimidin-4-yl, pyrazin-1-yl, 1*H*-indol-3-yl, 1*H*-indol-4-yl, 1*H*-indol-5-yl, 1*H*-indol-6-yl, 1*H*-indazol-5-yl, 1*H*-indazol-6-yl, 2*H*-indazol-5-yl, 2*H*-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, 1*H*-benzimidazol-2-yl, 1*H*-benzimidazol-5-yl, 1*H*-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, furo[2,3-*b*]pyridine-6-yl, furo[2,3-*c*]pyridin-2-yl, furo[3,2-*b*]pyridin-2-yl, furo[3,2-*c*]pyridin-2-yl, 1*H*-pyrrolo[2,3-*b*]pyridin-5-yl, 1*H*-pyrrolo[2,3-*c*]pyridin-4-yl, pyrrolo[1,2-*a*]pyrimidin-7-yl, pyrrolo[1,2-*a*]pyrazin-7-yl, pyrrolo[1,2-*b*]pyridazin-2-yl, pyrazolo[1,5-*a*]pyridin-2-yl, pyrazolo[1,5-*a*]pyridin-5-yl, 1*H*-pyrazolo[4,3-*b*]pyridin-5-yl, 2*H*-pyrazolo[4,3-*b*]pyridin-5-yl, 2*H*-pyrazolo[4,3-*c*]pyridin-5-yl, pyrazolo[1,5-*a*]pyrazin-2-yl, pyrazolo[1,5-*a*]pyrimidin-5-yl, imidazo[1,2-*a*]pyridin-2-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyrimidin-2-yl, imidazo[1,2-*a*]pyrimidin-6-yl, imidazo[1,2-*a*]pyrazin-2-yl, imidazo[1,2-*a*]pyrazin-3-yl, imidazo[1,2-*a*]pyrazin-6-yl, imidazo[1,2-*b*]pyridazin-2-yl, imidazo[1,2-*b*]pyridazin-6-yl, imidazo[1,2-*c*]pyrimidin-2-yl, imidazo[1,5-*a*]pyridin-6-yl, imidazo[1,5-*a*]pyridin-7-yl, imidazo[2,1-*b*][1,3]thiazol-6-yl, imidazo[2,1-*b*][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-*b*]pyridin-2-yl, [1,2,4]triazolo[1,5-*a*]pyridin-5-yl, [1,2,4]triazolo[1,5-*a*]pyridin-6-yl, [1,2,4]triazolo[1,5-*b*]pyridin-6-yl, [1,2,4]triazolo[1,5-*b*]pyridazin-5-yl, [1,2,4]triazolo[1,5-*b*]pyridazin-6-yl, quinolin-6-yl, quinolin-7-yl, and quinolin-8-yl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent, or, alternatively, optionally substituted with one, two, three or four R₅ substituents.

[1121] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₂ is heteroaryl selected from 1*H*-indazol-5-yl, 2*H*-indazol-5-yl, 1*H*-benzimidazol-6-yl, 1,3-benzoxazol-6-yl, furo[2,3-*b*]pyridine-6-yl, pyrrolo[1,2-*a*]pyrazin-7-yl, 1*H*-pyrazolo[4,3-*b*]pyridin-5-yl, 2*H*-pyrazolo[4,3-*b*]pyridin-5-yl, pyrazolo[1,5-*a*]pyrimidin-5-yl, imidazo[1,2-*a*]pyridin-6-yl, imidazo[1,2-*a*]pyrimidin-6-yl, imidazo[1,2-*a*]pyrazin-2-yl, imidazo[1,2-*a*]pyrazin-6-yl, imidazo[1,2-*b*]pyridazin-6-yl, imidazo[2,1-*b*][1,3]thiazol-6-yl, imidazo[2,1-

b][1,3,4]thiadiazol-6-yl, [1,2,4]triazolo[1,5-*a*]pyridin-6-yl, and [1,2,4]triazolo[1,5-*b*]pyridazin-6-yl, optionally substituted with one, two or three R₅ substituents and optionally, with one additional R₆ substituent, or, alternatively, optionally substituted with one, two, three or four R₅ substituents.

[1122] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₅ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkyl-carbonyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, C₁₋₆alkoxy-carbonyl-C₁₋₆alkyl, carboxyl, C₁₋₆alkyl-carboxyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, amino-carbonyl, and hydroxy-C₁₋₆alkyl.

[1123] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₅ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxy-carbonyl-C₁₋₆alkyl, carboxyl, C₁₋₆alkyl-carboxyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and amino-carbonyl.

[1124] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₅ is, in each instance, cyano.

[1125] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₅ is, in each instance, halogen selected from bromo, chloro, fluoro, and iodo.

[1126] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₅ is, in each instance, fluoro.

[1127] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₅ is, in each instance, hydroxy.

[1128] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₅ is, in each instance, C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1129] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₅ is, in each instance, C₁₋₆alkyl selected from methyl and ethyl.

[1130] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₅ is, in each instance, halo-C₁₋₆alkyl, wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more halogens selected from bromo, chloro, fluoro, and iodo where allowed by available valences.

[1131] Another aspect includes a compound of Formula (XVIII), wherein R_5 is, in each instance, halo- C_{1-6} alkyl selected from trifluoromethyl.

[1132] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_5 is, in each instance, C_{1-6} alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, and tert-butoxy.

[1133] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_a is, in each instance, methoxy.

[1134] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_5 is, in each instance, C_{1-6} alkoxy-carbonyl- C_{1-6} alkyl, wherein C_{1-6} alkoxy is selected from methoxy, ethoxy, propoxy, isopropoxy, and tert-butoxy, and wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1135] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_5 is, in each instance, $-CH_2CO_2CH_3$.

[1136] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_5 is, in each instance, carboxyl.

[1137] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_5 is, in each instance, C_{1-6} alkyl-carboxyl, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1138] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_5 is, in each instance, $-CH_2CO_2H$.

[1139] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_5 is, in each instance, amino.

[1140] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R_5 is, in each instance, C_{1-6} alkyl-amino wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[1141] Another aspect includes a compound of Formula (XVIII), wherein R_5 is, in each instance, methylamino.

[1142] Another aspect includes a compound of Formula (XVIII), wherein R_5 is, in each instance, $(C_{1-6}alkyl)_2$ -amino wherein $C_{1-6}alkyl$ is independently selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[1143] Another aspect includes a compound of Formula (XVIII), wherein R₅ is, in each instance, dimethylamino.

[1144] Another aspect includes a compound of Formula (XVIII), wherein R₅ is, in each instance, amino-C₁₋₆alkyl wherein C₁₋₆alkyl is independently selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

[1145] Another aspect includes a compound of Formula (XVIII), wherein R₅ is, in each instance, methanamine.

[1146] Another aspect includes a compound of Formula (XVIII), wherein R₅ is, in each instance, amino-carbonyl.

[1147] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₆ is selected from C₃₋₁₀cycloalkyl, phenyl, phenyl-C₁₋₆alkoxy, phenyl-oxy, heterocyclyl, and heteroaryl;

[1148] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and wherein, each instance of C₃₋₁₀cycloalkyl, phenyl, heterocyclyl, and heteroaryl is optionally substituted with one, two or three R₇ substituents.

[1149] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₆ is C₃₋₁₀cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantyl, optionally substituted with one, two or three R₇ substituents.

[1150] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₆ is cyclopropyl, optionally substituted with one, two or three R₇ substituents.

[1151] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₆ is phenyl-C₁₋₆alkoxy, wherein C₁₋₆alkoxy is selected from methoxy, ethoxy, propoxy, isopropoxy, and tert-butoxy, and wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, and tert-butyl, and wherein, phenyl is optionally substituted with one, two or three R₇ substituents.

[1152] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₆ is benzyloxy.

[1153] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₆ is phenyl-oxy, wherein, phenyl is optionally substituted with one, two or three R₇ substituents.

[1154] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₆ is benzyloxy.

[1155] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₆ is heteroaryl selected from furanyl, 1*H*-pyrazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 4*H*-1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl, optionally substituted with one, two or three R₇ substituents.

[1156] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₆ is heteroaryl selected from 1*H*-pyrazolyl and 1*H*-imidazolyl, optionally substituted with one, two or three R₇ substituents.

[1157] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₆ is heteroaryl selected from furan-2-yl, furan-3-yl, 1*H*-pyrazol-3-yl, 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1*H*-imidazol-1-yl, 1*H*-imidazol-4-yl, 1*H*-1,2,3-triazol-1-yl, 4*H*-1,2,4-triazol-4-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-5-yl, pyrimidin-4-yl, pyrazin-1-yl, optionally substituted with one, two or three R₇ substituents.

[1158] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₆ is heteroaryl selected from 1*H*-pyrazol-4-yl and 1*H*-imidazol-1-yl, optionally substituted with one, two or three R₇ substituents.

[1159] One aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₇ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkyl-carbonyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[1160] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₇ is, in each instance, halogen, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkyl-carbonyl, C₁₋

alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

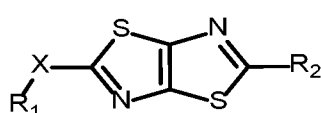
[1161] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₇ is, in each instance, halogen selected from bromo, chloro, fluoro, and iodo.

[1162] Another aspect includes a compound of Formula (XVIII) or Formula (XIX), wherein R₇ is, in each instance, fluoro.

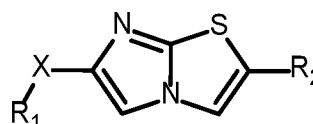
HD Compounds of Formula (XX) - (XXIII)

[1163] In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in the published International PCT Patent Application No. PCT/US2019/038900, the content of which is incorporated by reference herein in its entirety.

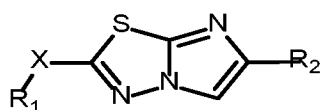
[1164] In one aspect, an HD compound of the disclosure can refer to a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII):



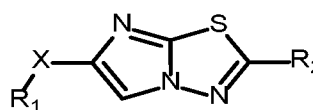
(XX)



(XXI)



(XXII)



(XXIII)

or a form thereof, wherein:

X is selected from N-R_b, O, and a bond;

R_b is selected from hydrogen and C₁₋₆alkyl;

R₁ is heterocyclyl,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

wherein each instance of heterocyclyl is optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents;

R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, hydroxy-C₁₋₆alkyl, and C₃₋₁₀cycloalkyl;

R₂ is selected from phenyl and heteroaryl,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

wherein each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or,

wherein, alternatively, each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents;

R₄ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl;

R₅ is heteroaryl;

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

wherein, each instance of heteroaryl is optionally substituted where allowed by available valences with one, two or three R₆ substituents; and

R₆ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₈alkyl, and hydroxy-C₁₋₆alkyl;

wherein a form of the compound is selected from the group consisting of a salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, and tautomer form thereof.

[1165] One aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein X is selected from N-R_b, O, and a bond.

[1166] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein X is N-R_b.

[1167] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein X is O.

[1168] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein X is a bond.

[1169] One aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R_b is selected from hydrogen and C₁₋₆alkyl.

[1170] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R_b is hydrogen.

[1171] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R_b is C₁₋₆alkyl.

[1172] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R_b is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1173] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R_b is C₁₋₆alkyl selected from methyl and ethyl.

[1174] One aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₁ is heterocyclyl,

[1175] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

[1176] wherein each instance of heterocyclyl is optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1177] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₁ is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, octahydroindolizinyl, hexahydropyrrolo[3,4-*c*] pyrrol-(1*H*)-yl, 8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, 1,6-diazaspiro [3.5]nonyl, 1,7-diazaspiro[3.5]nonyl, 2,7-

diazaspiro[3.5]nonyl, and 8'-azaspiro[azetidine-3,3'-bicyclo[3.2.1]octan]-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1178] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₁ is heterocyclyl selected from pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, 1,2,3,6-tetrahydropyridin-2-yl, 1,2,3,6-tetrahydropyridin-3-yl, 1,2,3,6-tetrahydropyridin-4-yl, octahydroindolizin-7-yl, hexahydropyrrolo[3,4-*c*]pyrrol-1(1*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-5(1*H*)-yl, 8-azabicyclo[3.2.1]oct-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 1,6-diazaspiro[3.5]non-1-yl, 1,7-diazaspiro[3.5]non-1-yl, 2,7-diazaspiro[3.5]non-2-yl, and 8'-azaspiro[azetidine-3,3'-bicyclo[3.2.1]octan]-1-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1179] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₁ is heterocyclyl selected from pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 1,2,3,6-tetrahydropyridin-4-yl, octahydroindolizin-7-yl, hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, 8-azabicyclo[3.2.1]oct-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 1,6-diazaspiro[3.5]non-1-yl, 1,7-diazaspiro[3.5]non-1-yl, 2,7-diazaspiro[3.5]non-2-yl, and 8'-azaspiro[azetidine-3,3'-bicyclo[3.2.1]octan]-1-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1180] One aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, hydroxy-C₁₋₆alkyl, and C₃₋₁₀cycloalkyl.

[1181] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₃ is, in each instance, independently selected from C₁₋₆alkyl, C₁₋₆alkyl-amino, hydroxy-C₁₋₆alkyl, and C₃₋₁₀cycloalkyl.

[1182] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₃ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1183] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₃ is C₁₋₆alkyl selected from methyl, ethyl, propyl, and isopropyl.

[1184] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₃ is C₁₋₆alkyl-amino wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 2-methylbutyl, and 3-methylpentyl.

[1185] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₃ is tert-butylamino.

[1186] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₃ is hydroxyl-C₁₋₆alkyl, wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more hydroxyl groups where allowed by available valences.

[1187] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₃ is hydroxymethyl.

[1188] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₃ is C₃₋₁₀cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantyl.

[1189] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₃ is cyclopropyl.

[1190] One aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₂ is selected from phenyl and heteroaryl,

[1191] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

[1192] wherein each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or,

[1193] wherein, alternatively, each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1194] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₂ is phenyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1195] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₂ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1196] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₂ is heteroaryl selected from 1*H*-imidazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, and imidazo[2,1-*b*][1,3]thiazolyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1197] One aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₄ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy,

C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[1198] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₄ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, and C₁₋₆alkoxy.

[1199] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₄ is cyano.

[1200] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₄ is halogen selected from bromo, chloro, fluoro, and iodo.

[1201] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₄ is halogen selected from bromo, chloro, and fluoro.

[1202] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₄ is hydroxy.

[1203] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₄ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1204] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₄ is methyl.

[1205] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₄ is C₁₋₆alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.

[1206] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₄ is methoxy.

[1207] One aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₅ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl,

imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two or three R₆ substituents.

[1208] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₅ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyridazinyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two or three R₆ substituents.

[1209] One aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₆ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[1210] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₆ is, in each instance, independently selected from halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, and C₁₋₆alkoxy.

[1211] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₆ is halogen selected from bromo, chloro, fluoro, and iodo.

[1212] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₆ is halogen selected from chloro, and fluoro.

[1213] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₆ is hydroxy.

[1214] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₆ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1215] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R₆ is C₁₋₆alkyl selected from methyl and ethyl.

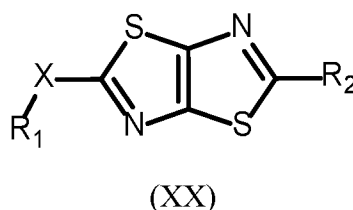
[1216] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R_6 is deuterio- C_{1-4} alkyl wherein C_{1-4} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more deuterium atoms where allowed by available valences.

[1217] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R_6 is ($^2H_3$)methyl.

[1218] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R_6 is C_{1-6} alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.

[1219] Another aspect includes a compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII), wherein R_6 is methoxy.

[1220] One aspect of the compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII) includes the compound of Formula (XX):



or a form thereof.

[1221] One aspect includes a compound of Formula (XX) wherein X is selected from N- R_b , O, and a bond.

[1222] Another aspect includes a compound of Formula (XX), wherein X is N- R_b .

[1223] Another aspect includes a compound of Formula (XX), wherein X is O.

[1224] Another aspect includes a compound of Formula (XX), wherein X is a bond.

[1225] One aspect includes a compound of Formula (XX), wherein R_b is selected from hydrogen and C_{1-6} alkyl.

[1226] Another aspect includes a compound of Formula (XX), wherein R_b is hydrogen.

[1227] Another aspect includes a compound of Formula (XX), wherein R_b is C_{1-6} alkyl.

[1228] Another aspect includes a compound of Formula (XX), wherein R_b is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1229] Another aspect includes a compound of Formula (XX), wherein R_b is C₁₋₆alkyl selected from methyl and ethyl.

[1230] One aspect includes a compound of Formula (XX), wherein R₁ is heterocyclyl,

[1231] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

[1232] wherein each instance of heterocyclyl is optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1233] Another aspect includes a compound of Formula (XX), wherein R₁ is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, octahydroindoliziny, hexahydropyrrolo[3,4-*c*]pyrrol-(1*H*)-yl, 8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, 1,6-diazaspiro[3.5]nonyl, 1,7-diazaspiro[3.5]nonyl, 2,7-diazaspiro[3.5]nonyl, and 8'-azaspiro[azetidine-3,3'-bicyclo[3.2.1]octan]-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1234] Another aspect includes a compound of Formula (XX), wherein R₁ is heterocyclyl selected from pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, 1,2,3,6-tetrahydropyridin-2-yl, 1,2,3,6-tetrahydropyridin-3-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydropyrrolo[3,4-*c*]pyrrol-1(1*H*)-yl, octahydroindolizin-7-yl, hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-5(1*H*)-yl, 8-azabicyclo[3.2.1]oct-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 1,6-diazaspiro[3.5]non-1-yl, 1,7-diazaspiro[3.5]non-1-yl, 2,7-diazaspiro[3.5]non-2-yl, and 8'-azaspiro[azetidine-3,3'-bicyclo[3.2.1]octan]-1-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1235] Another aspect includes a compound of Formula (XX), wherein R₁ is heterocyclyl selected from pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, octahydroindolizin-7-yl, 8-azabicyclo[3.2.1]oct-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 1,6-diazaspiro[3.5]non-1-yl, 1,7-diazaspiro[3.5]non-1-yl, 2,7-diazaspiro[3.5]non-2-yl, and 8'-azaspiro[azetidine-3,3'-

bicyclo[3.2.1]octan]-1-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1236] One aspect includes a compound of Formula (XX), wherein R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, hydroxy-C₁₋₆alkyl, and C₃₋₁₀cycloalkyl.

[1237] Another aspect includes a compound of Formula (XX), wherein R₃ is, in each instance, independently selected from C₁₋₆alkyl, C₁₋₆alkyl-amino, hydroxy-C₁₋₆alkyl, and C₃₋₁₀cycloalkyl.

[1238] Another aspect includes a compound of Formula (XX), wherein R₃ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1239] Another aspect includes a compound of Formula (XX), wherein R₃ is C₁₋₆alkyl selected from methyl, ethyl, propyl, and isopropyl.

[1240] Another aspect includes a compound of Formula (XX), wherein R₃ is C₁₋₆alkyl-amino wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 2-methylbutyl, and 3-methylpentyl.

[1241] Another aspect includes a compound of Formula (XX), wherein R₃ is tert-butylamino.

[1242] Another aspect includes a compound of Formula (XX), wherein R₃ is hydroxyl-C₁₋₆alkyl, wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more hydroxyl groups where allowed by available valences.

[1243] Another aspect includes a compound of Formula (XX), wherein R₃ is hydroxymethyl.

[1244] Another aspect includes a compound of Formula (XX), wherein R₃ is C₃₋₁₀cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantyl.

[1245] Another aspect includes a compound of Formula (XX), wherein R₃ is cyclopropyl.

[1246] One aspect includes a compound of Formula (XX), wherein R₂ is selected from phenyl and heteroaryl,

[1247] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

[1248] wherein each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or,

[1249] wherein, alternatively, each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1250] Another aspect includes a compound of Formula (XX), wherein R₂ is phenyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1251] Another aspect includes a compound of Formula (XX), wherein R₂ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1252] Another aspect includes a compound of Formula (XX), wherein R₂ is heteroaryl selected from 1*H*-imidazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, and imidazo[2,1-*b*][1,3]thiazolyl, optionally substituted where

allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1253] One aspect includes a compound of Formula (XX), wherein R₄ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[1254] Another aspect includes a compound of Formula (XX), wherein R₂ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, and C₁₋₆alkoxy.

[1255] Another aspect includes a compound of Formula (XX), wherein R₄ is cyano.

[1256] Another aspect includes a compound of Formula (XX), wherein R₄ is halogen selected from bromo, chloro, fluoro, and iodo.

[1257] Another aspect includes a compound of Formula (XX), wherein R₄ is halogen selected from bromo, chloro and fluoro.

[1258] Another aspect includes a compound of Formula (XX), wherein R₄ is hydroxy.

[1259] Another aspect includes a compound of Formula (XX), wherein R₄ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1260] Another aspect includes a compound of Formula (XX), wherein R₄ is methyl.

[1261] Another aspect includes a compound of Formula (XX), wherein R₄ is C₁₋₆alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.

[1262] Another aspect includes a compound of Formula (XX), wherein R₄ is methoxy.

[1263] One aspect includes a compound of Formula (XX), wherein R₅ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two or three R₆ substituents.

[1264] Another aspect includes a compound of Formula (XX), wherein R₅ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyridazinyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two or three R₆ substituents.

[1265] One aspect includes a compound of Formula (XX), wherein R₆ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[1266] Another aspect includes a compound of Formula (XX), wherein R₆ is, in each instance, independently selected from halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, and C₁₋₆alkoxy.

[1267] Another aspect includes a compound of Formula (XX), wherein R₆ is halogen selected from bromo, chloro, fluoro, and iodo.

[1268] Another aspect includes a compound of Formula (XX), wherein R₆ is halogen selected from chloro and fluoro.

[1269] Another aspect includes a compound of Formula (XX), wherein R₆ is hydroxy.

[1270] Another aspect includes a compound of Formula (XX), wherein R₆ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1271] Another aspect includes a compound of Formula (XX), wherein R₆ is C₁₋₆alkyl selected from methyl and ethyl.

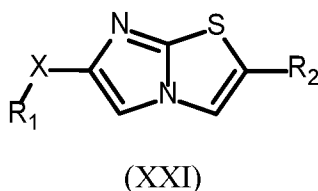
[1272] Another aspect includes a compound of Formula (XX), wherein R₆ is deuterio-C₁₋₄alkyl wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more deuterium atoms where allowed by available valences.

[1273] Another aspect includes a compound of Formula (XX), wherein R₆ is (²H₃)methyl.

[1274] Another aspect includes a compound of Formula (XX), wherein R₄ is C₁₋₆alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.

[1275] Another aspect includes a compound of Formula (XX), wherein R₆ is methoxy.

[1276] One aspect of the compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII) includes the compound of Formula (XXI):



or a form thereof.

[1277] One aspect includes a compound of Formula (XXI) wherein X is selected from N-R_b, O, and a bond.

[1278] Another aspect includes a compound of Formula (XXI), wherein X is a bond.

[1279] One aspect includes a compound of Formula (XXI), wherein R₁ is heterocyclyl,

[1280] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

[1281] wherein each instance of heterocyclyl is optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1282] Another aspect includes a compound of Formula (XXI), wherein R₁ is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, octahydroindolizinyl, hexahydropyrrolo[3,4-*c*]pyrrol-(1*H*)-yl, 8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, 1,6-diazaspiro[3.5]nonyl, 1,7-diazaspiro[3.5]nonyl, 2,7-diazaspiro[3.5]nonyl, and 8'-azaspiro[azetidine-3,3'-bicyclo[3.2.1]octan]-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1283] Another aspect includes a compound of Formula (XXI), wherein R₁ is piperidinyl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1284] Another aspect includes a compound of Formula (XXI), wherein R₁ is heterocyclyl selected from pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, 1,2,3,6-tetrahydropyridin-2-yl, 1,2,3,6-tetrahydropyridin-3-yl, 1,2,3,6-tetrahydropyridin-4-yl, octahydroindolizin-7-yl, hexahydropyrrolo[3,4-*c*]pyrrol-1(1*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-5(1*H*)-yl, 8-azabicyclo[3.2.1]oct-3-yl,

8-azabicyclo[3.2.1]oct-2-en-3-yl, 1,6-diazaspiro[3.5]non-1-yl, 1,7-diazaspiro[3.5]non-1-yl, 2,7-diazaspiro[3.5]non-2-yl, and 8'-azaspiro[azetidine-3,3'-bicyclo[3.2.1]octan]-1-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1285] Another aspect includes a compound of Formula (XXI), wherein R₁ is piperidin-4-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1286] One aspect includes a compound of Formula (XXI), wherein R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, hydroxy-C₁₋₆alkyl, and C₃₋₁₀cycloalkyl.

[1287] One aspect includes a compound of Formula (XXI), wherein R₂ is selected from phenyl and heteroaryl,

[1288] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

[1289] wherein each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or,

[1290] wherein, alternatively, each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1291] Another aspect includes a compound of Formula (XXI), wherein R₂ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or,

alternatively, is optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1292] Another aspect includes a compound of Formula (XXI), wherein R₂ is 2*H*-indazolyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1293] One aspect includes a compound of Formula (XXI), wherein R₄ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

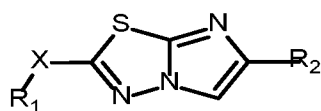
[1294] Another aspect includes a compound of Formula (XXI), wherein R₄ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1295] Another aspect includes a compound of Formula (XXI), wherein R₄ is methyl.

[1296] One aspect includes a compound of Formula (XXI), wherein R₅ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two or three R₆ substituents.

[1297] One aspect includes a compound of Formula (XXI), wherein R₆ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[1298] One aspect of the compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII) includes the compound of Formula (XXII):



(XXII)

or a form thereof.

[1299] One aspect includes a compound of Formula (XXII) wherein X is selected from N-R_b, O, and a bond.

[1300] Another aspect includes a compound of Formula (XXII), wherein X is N-R_b.

[1301] Another aspect includes a compound of Formula (XXII), wherein X is a bond.

[1302] One aspect includes a compound of Formula (XXII), wherein R_b is selected from hydrogen and C₁₋₆alkyl.

[1303] Another aspect includes a compound of Formula (XXII), wherein R_b is C₁₋₆alkyl.

[1304] Another aspect includes a compound of Formula (XXII), wherein R_b is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1305] Another aspect includes a compound of Formula (XXII), wherein R_b is methyl.

[1306] One aspect includes a compound of Formula (XXII), wherein R₁ is heterocyclyl,

[1307] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

[1308] wherein each instance of heterocyclyl is optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1309] Another aspect includes a compound of Formula (XXII), wherein R₁ is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, octahydroindoliziny, hexahydropyrrolo[3,4-*c*]pyrrol-(1*H*)-yl, 8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, 1,6-diazaspiro[3.5]nonyl, 1,7-diazaspiro[3.5]nonyl, 2,7-diazaspiro[3.5]nonyl, and 8'-azaspiro[azetidine-3,3'-bicyclo[3.2.1]octan]-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1310] Another aspect includes a compound of Formula (XXII), wherein R₁ is heterocyclyl selected from piperidinyl, 8-azabicyclo[3.2.1]octyl, and 8-azabicyclo[3.2.1]oct-2-enyl,

optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1311] Another aspect includes a compound of Formula (XXII), wherein R₁ is heterocyclyl selected from pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, 1,2,3,6-tetrahydropyridin-2-yl, 1,2,3,6-tetrahydropyridin-3-yl, 1,2,3,6-tetrahydropyridin-4-yl, octahydroindolizin-7-yl, hexahydropyrrolo[3,4-*c*]pyrrol-1(1*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-5(1*H*)-yl, 8-azabicyclo[3.2.1]oct-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 1,6-diazaspiro[3.5]non-1-yl, 1,7-diazaspiro[3.5]non-1-yl, 2,7-diazaspiro[3.5]non-2-yl, and 8'-azaspiro[azetidine-3,3'-bicyclo[3.2.1]octan]-1-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1312] Another aspect includes a compound of Formula (XXII), wherein R₁ is heterocyclyl selected from piperidin-4-yl, 8-azabicyclo[3.2.1]oct-3-yl, and 8-azabicyclo[3.2.1]oct-2-en-3-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1313] One aspect includes a compound of Formula (XXII), wherein R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, hydroxy-C₁₋₆alkyl, and C₃₋₁₄cycloalkyl.

[1314] Another aspect includes a compound of Formula (XXII), wherein R₃ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1315] Another aspect includes a compound of Formula (XXII), wherein R₃ is methyl.

[1316] One aspect includes a compound of Formula (XXII), wherein R₂ is selected from phenyl and heteroaryl,

[1317] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

[1318] wherein each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or,

[1319] wherein, alternatively, each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1320] Another aspect includes a compound of Formula (XXII), wherein R₂ is phenyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1321] Another aspect includes a compound of Formula (XXII), wherein R₂ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1322] Another aspect includes a compound of Formula (XXII), wherein R₂ is 2*H*-indazolyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1323] One aspect includes a compound of Formula (XXII), wherein R₄ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[1324] Another aspect includes a compound of Formula (XXII), wherein R₄ is, in each instance, independently selected from cyano and hydroxy.

[1325] Another aspect includes a compound of Formula (XXII), wherein R₄ is hydroxy.

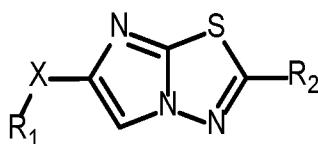
[1326] One aspect includes a compound of Formula (XXII), wherein R₅ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-

1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, wherein, optionally substituted where allowed by available valences with one, two or three R₆ substituents.

[1327] Another aspect includes a compound of Formula (XXII), wherein R₅ is 1*H*-pyrazolyl, optionally substituted where allowed by available valences with one, two or three R₆ substituents.

[1328] One aspect includes a compound of Formula (XXII), wherein R₆ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[1329] One aspect of the compound of Formula (XX), Formula (XXI), Formula (XXII), or Formula (XXIII) includes the compound of Formula (XXIII):



(XXIII)

or a form thereof.

[1330] One aspect includes a compound of Formula (XXIII) wherein X is selected from N- R_b, O, and a bond.

[1331] Another aspect includes a compound of Formula (XXIII), wherein X is a bond.

[1332] One aspect includes a compound of Formula (XXIII), wherein R₁ is heterocyclyl,

[1333] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

[1334] wherein each instance of heterocyclyl is optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1335] Another aspect includes a compound of Formula (XXIII), wherein R₁ is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, octahydroindolizinyl, hexahydropyrrolo[3,4-*c*]pyrrol-(1*H*)-yl, 8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, 1,6-diazaspiro[3.5]nonyl, 1,7-diazaspiro[3.5]nonyl, 2,7-diazaspiro[3.5]nonyl, and 8'-azaspiro[azetidine-3,3'-bicyclo[3.2.1]octan]-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1336] Another aspect includes a compound of Formula (XXIII), wherein R₁ is piperidinyl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1337] Another aspect includes a compound of Formula (XXIII), wherein R₁ is heterocyclyl selected from pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, 1,2,3,6-tetrahydropyridin-2-yl, 1,2,3,6-tetrahydropyridin-3-yl, 1,2,3,6-tetrahydropyridin-4-yl, octahydroindolizin-7-yl, hexahydropyrrolo[3,4-*c*]pyrrol-1(1*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-5(1*H*)-yl, 8-azabicyclo[3.2.1]oct-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 1,6-diazaspiro[3.5]non-1-yl, 1,7-diazaspiro[3.5]non-1-yl, 2,7-diazaspiro[3.5]non-2-yl, and 8'-azaspiro[azetidine-3,3'-bicyclo[3.2.1]octan]-1-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1338] Another aspect includes a compound of Formula (XXIII), wherein R₁ is piperidin-4-yl, optionally substituted where allowed by available valences with one, two, three, or four R₃ substituents.

[1339] One aspect includes a compound of Formula (XXIII), wherein R₃ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, hydroxy-C₁₋₆alkyl, and C₃₋₁₀cycloalkyl.

[1340] One aspect includes a compound of Formula (XXIII), wherein R₂ is selected from phenyl and heteroaryl,

[1341] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, and

[1342] wherein each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or,

[1343] wherein, alternatively, each instance of phenyl or heteroaryl is optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1344] Another aspect includes a compound of Formula (XXIII), wherein R₂ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1345] Another aspect includes a compound of Formula (XXIII), wherein R₂ is heteroaryl selected from 2*H*-indazolyl and imidazo[1,2-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two, or three R₄ substituents and optionally, with one additional R₅ substituent or, alternatively, optionally substituted where allowed by available valences with one, two, three, or four R₄ substituents.

[1346] One aspect includes a compound of Formula (XXIII), wherein R₄ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

[1347] Another aspect includes a compound of Formula (XXIII), wherein R₄ is, in each instance, independently selected from cyano, halogen, and C₁₋₆alkyl.

[1348] Another aspect includes a compound of Formula (XXIII), wherein R₄ is cyano.

[1349] Another aspect includes a compound of Formula (XXIII), wherein R₄ is halogen selected from bromo, chloro, fluoro, and iodo.

[1350] Another aspect includes a compound of Formula (XXIII), wherein R₄ is fluoro.

[1351] Another aspect includes a compound of Formula (XXIII), wherein R₄ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1352] Another aspect includes a compound of Formula (XXIII), wherein R₄ is methyl.

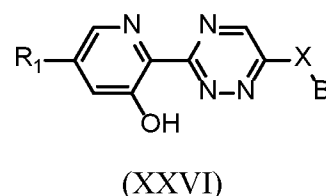
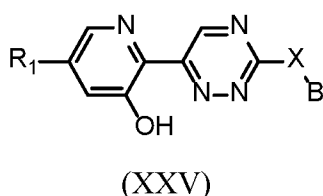
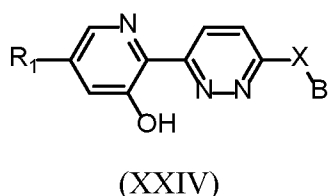
[1353] One aspect includes a compound of Formula (XXIII), wherein R₅ is heteroaryl selected from 1*H*-pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, 1*H*-imidazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, 2*H*-tetrazolyl, pyridinyl, pyridin-2(1*H*)-on-yl, pyrimidinyl, pyrimidin-4(3*H*)-on-yl, pyridazinyl, pyrazinyl, 1,2,4-triazinyl, 1*H*-indolyl, 1*H*-indazolyl, 2*H*-indazolyl, 1*H*-benzimidazolyl, 1*H*-pyrazolo[3,4-*c*]pyridinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*c*]pyrimidinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, 3*H*-imidazo[4,5-*c*]pyridinyl, imidazo[2,1-*b*][1,3]thiazolyl, and [1,2,4]triazolo[4,3-*a*]pyridinyl, optionally substituted where allowed by available valences with one, two or three R₆ substituents.

[1354] One aspect includes a compound of Formula (XXIII), wherein R₆ is, in each instance, independently selected from cyano, halogen, hydroxy, C₁₋₆alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, C₁₋₆alkoxy-C₁₋₆alkyl, C₁₋₆alkoxy-carbonyl, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, amino-C₁₋₆alkyl, and hydroxy-C₁₋₆alkyl.

HD Compounds of Formula (XXIV) - (XXVI)

[1355] In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in the published International PCT Patent Application No. PCT/US2020/032446, the content of which is incorporated by reference herein in its entirety.

[1356] In one aspect, an HD compound of the disclosure can refer to a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI):



or a form thereof, wherein:

X is O, NR_x, or a bond;

R_x is selected from hydrogen and C₁₋₄alkyl;

B is heterocyclyl,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents;

R_b is independently selected from halogen, C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, and C₃₋₆cycloalkyl;

R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents; and

R_{1a} is independently selected from halogen, hydroxyl, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, C₁₋₄alkoxy, deuterio-C₁₋₄alkoxy, and halo-C₁₋₄alkoxy.

[1357] One aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein X is selected from O, NR_x, and a bond.

[1358] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI) wherein X is O.

[1359] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI) wherein X is NR_x.

[1360] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI) wherein X is a bond.

[1361] One aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_x is selected from hydrogen and C₁₋₄alkyl.

[1362] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_x hydrogen.

[1363] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_x is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1364] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_x is methyl.

[1365] One aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1366] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is unsubstituted heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S.

[1367] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with one R_b substituent.

[1368] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, each substituted where allowed by available valences with two R_b substituents.

[1369] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with three R_b substituents.

[1370] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with four R_b substituents.

[1371] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with five R_b substituents.

[1372] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl,

1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7,-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1373] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is unsubstituted heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7,-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl.

[1374] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl,

pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with one R_b substituent.

[1375] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl,

1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7,-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with two R_b substituents.

[1376] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidiny, piperidiny, piperidin-1-olate-yl, piperaziny, 1,4-diazepanyl, 1,2-dihydropyridiny, 1,2,5,6-tetrahydropyridiny, 1,2,3,6-tetrahydropyridiny, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridiny, octahydro-5H-pyrrolo[3,2-c]pyridiny, octahydro-6H-pyrrolo[3,4-b]pyridiny, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyraziny, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7,-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl,

2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with three R_b substituents.

[1377] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with four R_b substituents.

[1378] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl,

hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with five R_b substituents.

[1379] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1380] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is unsubstituted heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl.

[1381] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl, substituted where allowed by available valences with one R_b substituent.

[1382] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl, substituted where allowed by available valences with two R_b substituents.

[1383] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl, substituted where allowed by available valences with three R_b substituents.

[1384] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1385] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is unsubstituted heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl.

[1386] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with one R_b substituent.

[1387] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl,

piperazinyl, and 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with two R_b substituents.

[1388] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with three R_b substituents.

[1389] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with four R_b substituents.

[1390] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with five R_b substituents.

[1391] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is pyrrolidinyl, substituted where allowed by available valences with one R_b substituent.

[1392] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperidinyl, substituted where allowed by available valences with four R_b substituents.

[1393] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperidinyl, substituted where allowed by available valences with five R_b substituents.

[1394] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is unsubstituted piperazinyl.

[1395] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperazinyl, substituted where allowed by available valences with one R_b substituent.

[1396] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperazinyl, substituted where allowed by available valences with two R_b substituents.

[1397] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperazinyl, substituted where allowed by available valences with three R_b substituents.

[1398] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperazinyl, substituted where allowed by available valences with four R_b substituents.

[1399] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is unsubstituted 4-azaspiro[2.5]octanyl.

[1400] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with one R_b substituent.

[1401] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with two R_b substituents.

[1402] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl,

3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1403] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is unsubstituted heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl,

8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl.

[1404] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl,

2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with one R_b substituent.

[1405] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl,

4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7,-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with two R_b substituents.

[1406] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl,

1,7,-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with three R_b substituents.

[1407] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7,-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-

7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with four R_b substituents.

[1408] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl,

2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with five R_b substituents.

[1409] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1410] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is unsubstituted heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl.

[1411] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl, substituted where allowed by available valences with one R_b substituent.

[1412] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl, substituted where allowed by available valences with two R_b substituents.

[1413] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl,

8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl, substituted where allowed by available valences with three R_b substituents.

[1414] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl, substituted where allowed by available valences with four R_b substituents.

[1415] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl, substituted where allowed by available valences with five R_b substituents.

[1416] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1417] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is unsubstituted heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl.

[1418] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with one R_b substituent.

[1419] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with two R_b substituents.

[1420] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with three R_b substituents.

[1421] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with four R_b substituents.

[1422] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with five R_b substituents.

[1423] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is pyrrolidin-1-yl, substituted where allowed by available valences with one R_b substituent.

[1424] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperidin-4-yl, substituted where allowed by available valences with 4 or 5 R_b substituents.

[1425] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperidin-4-yl, substituted where allowed by available valences with four R_b substituents.

[1426] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperidin-4-yl, substituted where allowed by available valences with five R_b substituents.

[1427] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is unsubstituted piperazin-1-yl.

[1428] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is m piperazin-1-yl, substituted where allowed by available valences with one R_b substituent.

[1429] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperazin-1-yl, substituted where allowed by available valences with two R_b substituents.

[1430] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperazin-1-yl, substituted where allowed by available valences with three R_b substituents.

[1431] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is piperazin-1-yl, substituted where allowed by available valences with four R_b substituents.

[1432] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is unsubstituted 4-azaspiro[2.5]octan-7-yl.

[1433] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with one R_b substituent.

[1434] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with two R_b substituents.

[1435] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl containing at least one chiral carbon atom having an (R) configuration.

[1436] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl containing at least one chiral carbon atom having an (S) configuration.

[1437] One aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is selected from halogen, C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, and C₃₋₆cycloalkyl.

[1438] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is selected from halogen, C₁₋₄alkyl, C₁₋₄alkyl-amino, and C₃₋₆cycloalkyl.

[1439] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is halogen selected from bromo, chloro, fluoro, and iodo.

[1440] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is fluoro.

[1441] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is C_{1-4} alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1442] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is C_{1-4} alkyl selected from methyl, ethyl, and isopropyl.

[1443] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is methyl.

[1444] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is ethyl.

[1445] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is isopropyl.

[1446] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is C_{1-4} alkyl-amino.

[1447] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is C_{1-4} alkyl-amino, wherein C_{1-4} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1448] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is selected from methylamino and tert-butylamino.

[1449] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is methylamino.

[1450] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is tert-butylamino.

[1451] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is C_{3-6} cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[1452] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_b is cyclopropyl.

[1453] One aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

[1454] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

[1455] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

[1456] wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1457] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

[1458] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

[1459] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

[1460] wherein each instance of phenyl, heteroaryl or heterocyclyl is unsubstituted.

[1461] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

[1462] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

[1463] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

[1464] wherein each instance of phenyl, heteroaryl or heterocyclyl is substituted where allowed by available valences with one R_{1a} substituent.

[1465] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

[1466] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

[1467] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

[1468] wherein each instance of phenyl, heteroaryl or heterocyclyl is substituted where allowed by available valences with two R_{1a} substituents.

[1469] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is selected from heteroaryl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

[1470] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1471] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is selected from heteroaryl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

[1472] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is unsubstituted.

[1473] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is selected from heteroaryl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and

wherein heteroaryl is substituted where allowed by available valences with one R_{1a} substituent.

[1474] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is selected from heteroaryl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is substituted where allowed by available valences with two R_{1a} substituents.

[1475] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1476] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is unsubstituted heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl.

[1477] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl,

1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, substituted where allowed by available valences with one R_{1a} substituent.

[1478] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl,

[1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, substituted where allowed by available valences with two R_{1a} substituents.

[1479] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrimidin-4(3H)-on-yl, pyridazinyl, 1H-indazolyl, 2H-indazolyl, 1,3-benzoxazolyl, pyrrolo[1,2-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, and [1,2,4]triazolo[1,5-a]pyrazinyl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1480] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is unsubstituted heteroaryl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrimidin-4(3H)-on-yl, pyridazinyl, 1H-indazolyl, 2H-indazolyl, 1,3-benzoxazolyl, pyrrolo[1,2-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, and [1,2,4]triazolo[1,5-a]pyrazinyl.

[1481] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrimidin-4(3H)-on-yl, pyridazinyl, 1H-indazolyl, 2H-indazolyl, 1,3-benzoxazolyl, pyrrolo[1,2-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, and [1,2,4]triazolo[1,5-a]pyrazinyl, substituted where allowed by available valences with one R_{1a} substituent.

[1482] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrimidin-4(3H)-on-yl, pyridazinyl, 1H-indazolyl, 2H-indazolyl, 1,3-benzoxazolyl, pyrrolo[1,2-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl,

imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, and [1,2,4]triazolo[1,5-a]pyrazinyl, substituted where allowed by available valences with two R_{1a} substituents.

[1483] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl,

imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1484] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is unsubstituted heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-

b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl.

[1485] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl,

1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl, substituted where allowed by available valences with one R_{1a} substituent.

[1486] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl,

benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl, substituted where allowed by available valences with two R_{1a} substituents.

[1487] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1,3-thiazol-2-yl, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-2-yl, 1H-1,2,4-triazol-1-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, 1H-indazol-5-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 1,3-benzoxazol-6-yl, pyrrolo[1,2-a]pyrazin-7-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-6-yl, 2H-

[1,2,3]triazolo[4,5-b]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, and [1,2,4]triazolo[1,5-a]pyrazin-2-yl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1488] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is unsubstituted heteroaryl selected from 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1,3-thiazol-2-yl, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-2-yl, 1H-1,2,4-triazol-1-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, 1H-indazol-5-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 1,3-benzoxazol-6-yl, pyrrolo[1,2-a]pyrazin-7-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-6-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, and [1,2,4]triazolo[1,5-a]pyrazin-2-yl.

[1489] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1,3-thiazol-2-yl, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-2-yl, 1H-1,2,4-triazol-1-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, 1H-indazol-5-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 1,3-benzoxazol-6-yl, pyrrolo[1,2-a]pyrazin-7-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-6-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, and [1,2,4]triazolo[1,5-a]pyrazin-2-yl, substituted where allowed by available valences with one R_{1a} substituent.

[1490] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl selected from 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1,3-thiazol-2-yl, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-2-yl, 1H-1,2,4-triazol-1-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, 1H-indazol-5-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 1,3-benzoxazol-6-yl, pyrrolo[1,2-a]pyrazin-7-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-6-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, and [1,2,4]triazolo[1,5-a]pyrazin-2-yl, substituted where allowed by available valences with two R_{1a} substituents.

[1491] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl-C₂₋₄alkenyl,

[1492] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1493] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl-C₂₋₄alkenyl, wherein heteroaryl is selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, quinolinyl, isoquinolinyl, and quinoxalinyl;

[1494] wherein C₂₋₄alkenyl is selected from ethenyl, propenyl, and butenyl; and

[1495] wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1496] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is 2-(1H-pyrazol-4-yl)ethenyl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1497] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl-amino, wherein heteroaryl is selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, quinolinyl, isoquinolinyl, and quinoxalinyl; and wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1498] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is (pyridin-3-yl)amino, (pyrazin-2-yl)amino, and (pyrimidin-5-yl)amino, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1499] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is heteroaryl-C₁₋₄alkyl-amino, wherein heteroaryl is selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, quinolinyl, isoquinolinyl, and quinoxalinyl;

wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, and butyl; and

wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1500] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R₁ is (1H-pyrazol-4-yl)methylamino, (pyridin-3-yl)methylamino, (pyridin-4-yl)methylamino, (quinolin-3-yl)methylamino, and (quinolin-8-yl)methylamino, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1501] One aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is independently selected from halogen, hydroxyl, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, C₁₋₄alkoxy, deuterio-C₁₋₄alkoxy, and halo-C₁₋₄alkoxy.

[1502] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is independently selected from halogen, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, C₁₋₄alkoxy, and deuterio-C₁₋₄alkoxy.

[1503] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1504] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is selected from methyl and ethyl.

[1505] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is methyl.

[1506] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is ethyl.

[1507] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is halogen selected from bromo, chloro, fluoro, and iodo.

[1508] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is fluoro.

[1509] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is cyano.

[1510] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is deuterio-C₁₋₄alkyl wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl, partially or completely substituted with one or more deuterium atoms where allowed by available valences.

[1511] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is (²H₃)methyl.

[1512] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is halo-C₁₋₄alkyl wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl, partially or completely substituted with one or more halogen atoms where allowed by available valences.

[1513] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is trifluoromethyl.

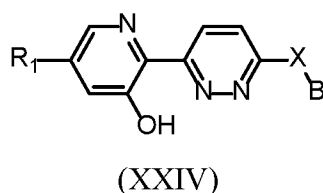
[1514] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is C₁₋₄alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

[1515] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is methoxy.

[1516] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is deuterio-C₁₋₄alkoxy wherein C₁₋₄alkoxy is selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy, partially or completely substituted with one or more deuterium atoms where allowed by available valences.

[1517] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein R_{1a} is ($^2H_3$)methoxy.

[1518] Another aspect of the present description includes a compound of Formula (XXIV):



or a form thereof, wherein:

X is O, NR_x , or a bond;

R_x is selected from hydrogen and C_{1-4} alkyl;

B is heterocyclyl,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, each optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 substituents R_b ;

R_b is independently selected from halogen, C_{1-4} alkyl, amino, C_{1-4} alkyl-amino, (C_{1-4} alkyl) $_2$ -amino, and C_{3-6} cycloalkyl;

R_1 is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl- C_{1-4} alkyl, heteroaryl- C_{2-4} alkenyl, heteroaryl-amino, heteroaryl- C_{1-4} alkyl -amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents; and

R_{1a} is independently selected from halogen, hydroxyl, cyano, C_{1-4} alkyl, deuterio- C_{1-4} alkyl, halo- C_{1-4} alkyl, amino, C_{1-4} alkyl-amino, (C_{1-4} alkyl) $_2$ -amino, C_{1-4} alkoxy, deuterio- C_{1-4} alkoxy, and halo- C_{1-4} alkoxy.

[1519] One aspect includes a compound of Formula (XXIV), wherein X is selected from O, NR_x, and a bond.

[1520] Another aspect includes a compound of Formula (XXIV) wherein X is O.

[1521] Another aspect includes a compound of Formula (XXIV) wherein X is NR_x.

[1522] Another aspect includes a compound of Formula (XXIV) wherein X is a bond.

[1523] One aspect includes a compound of Formula (XXIV), wherein R_x is selected from hydrogen and C₁₋₄alkyl.

[1524] Another aspect includes a compound of Formula (XXIV), wherein R_x hydrogen.

[1525] Another aspect includes a compound of Formula (XXIV), wherein R_x is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1526] Another aspect includes a compound of Formula (XXIV), wherein R_x is methyl.

[1527] One aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1528] Another aspect includes a compound of Formula (XXIV), wherein B is unsubstituted heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S.

[1529] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with one R_b substituent.

[1530] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, each substituted where allowed by available valences with two R_b substituents.

[1531] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with three R_b substituents.

[1532] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with four R_b substituents.

[1533] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with five R_b substituents.

[1534] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7,-diazaspiro[4.4]nonanyl,

1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1535] Another aspect includes a compound of Formula (XXIV), wherein B is unsubstituted heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl.

[1536] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-

b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with one R_b substituent.

[1537] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl,

1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with two R_b substituents.

[1538] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidiny, piperidiny, piperidin-1-olate-yl, piperaziny, 1,4-diazepany, 1,2-dihydropyridiny, 1,2,5,6-tetrahydropyridiny, 1,2,3,6-tetrahydropyridiny, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridiny, octahydro-5H-pyrrolo[3,2-c]pyridiny, octahydro-6H-pyrrolo[3,4-b]pyridiny, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyraziny, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with three R_b substituents.

[1539] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with four R_b substituents.

[1540] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl,

1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with five R_b substituents.

[1541] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1542] Another aspect includes a compound of Formula (XXIV), wherein B is unsubstituted heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl.

[1543] Another aspect includes a compound of Formula (XXIV), Formula (XXV), or Formula (XXVI), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl, substituted where allowed by available valences with one R_b substituent.

[1544] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-

azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl, substituted where allowed by available valences with two R_b substituents.

[1545] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl, substituted where allowed by available valences with three R_b substituents.

[1546] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl, substituted where allowed by available valences with four R_b substituents.

[1547] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 4-azaspiro[2.5]octanyl, 8-azabicyclo[3.2.1]octanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, and 4-azadispiro[2.1.2⁵.3³]decanyl, substituted where allowed by available valences with five R_b substituents.

[1548] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1549] Another aspect includes a compound of Formula (XXIV), wherein B is unsubstituted heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl.

[1550] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with one R_b substituent.

[1551] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with two R_b substituents.

[1552] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with three R_b substituents.

[1553] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with four R_b substituents.

[1554] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, piperazinyl, and 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with five R_b substituents.

[1555] Another aspect includes a compound of Formula (XXIV), wherein B is pyrrolidinyl, substituted where allowed by available valences with one R_b substituent.

[1556] Another aspect includes a compound of Formula (XXIV), wherein B is piperidinyl, substituted where allowed by available valences with 4 or 5 R_b substituents.

[1557] Another aspect includes a compound of Formula (XXIV), wherein B is piperidinyl, substituted where allowed by available valences with four R_b substituents.

[1558] Another aspect includes a compound of Formula (XXIV), wherein B is piperidinyl, substituted where allowed by available valences with five R_b substituents.

[1559] Another aspect includes a compound of Formula (XXIV), wherein B is unsubstituted piperazinyl.

[1560] Another aspect includes a compound of Formula (XXIV), wherein B is piperazinyl, substituted where allowed by available valences with one R_b substituent.

[1561] Another aspect includes a compound of Formula (XXIV), wherein B is piperazinyl, substituted where allowed by available valences with two R_b substituents.

[1562] Another aspect includes a compound of Formula (XXIV), wherein B is piperazinyl, substituted where allowed by available valences with three R_b substituents.

[1563] Another aspect includes a compound of Formula (XXIV), wherein B is piperazinyl, substituted where allowed by available valences with four R_b substituents.

[1564] Another aspect includes a compound of Formula (XXIV), wherein B is unsubstituted 4-azaspiro[2.5]octanyl.

[1565] Another aspect includes a compound of Formula (XXIV), wherein B is 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with one R_b substituent.

[1566] Another aspect includes a compound of Formula (XXIV), wherein B is 4-azaspiro[2.5]octanyl, substituted where allowed by available valences with two R_b substituents.

[1567] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl,

1,7,-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1568] Another aspect includes a compound of Formula (XXIV), wherein B is unsubstituted heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7,-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-

7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl.

[1569] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl,

2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with one R_b substituent.

[1570] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-

azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with two R_b substituents.

[1571] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclcyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with three R_b substituents.

[1572] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclcyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with four R_b substituents.

[1573] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclcyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl,

piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with five R_b substituents.

[1574] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and

4-azadispiro[2.1.2⁵.3³]decan-9-yl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1575] Another aspect includes a compound of Formula (XXIV), wherein B is unsubstituted heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl.

[1576] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl, substituted where allowed by available valences with one R_b substituent.

[1577] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl, substituted where allowed by available valences with two R_b substituents.

[1578] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl, substituted where allowed by available valences with three R_b substituents.

[1579] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl, substituted where allowed by available valences with four R_b substituents.

[1580] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 4-azaspiro[2.5]octan-7-yl, 8-azabicyclo[3.2.1]octan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, and 4-azadispiro[2.1.2⁵.3³]decan-9-yl, substituted where allowed by available valences with five R_b substituents.

[1581] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1582] Another aspect includes a compound of Formula (XXIV), wherein B is unsubstituted heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl.

[1583] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with one R_b substituent.

[1584] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with two R_b substituents.

[1585] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with three R_b substituents.

[1586] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with four R_b substituents.

[1587] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, piperazin-1-yl, and 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with five R_b substituents.

[1588] Another aspect includes a compound of Formula (XXIV), wherein B is pyrrolidin-1-yl, substituted where allowed by available valences with one R_b substituent.

[1589] Another aspect includes a compound of Formula (XXIV), wherein B is piperidin-4-yl, substituted where allowed by available valences with 4 or 5 R_b substituents.

[1590] Another aspect includes a compound of Formula (XXIV), wherein B is piperidin-4-yl, substituted where allowed by available valences with four R_b substituents.

[1591] Another aspect includes a compound of Formula (XXIV), wherein B is piperidin-4-yl, substituted where allowed by available valences with five R_b substituents.

[1592] Another aspect includes a compound of Formula (XXIV), wherein B is unsubstituted piperazin-1-yl.

[1593] Another aspect includes a compound of Formula (XXIV), wherein B is piperazin-1-yl, substituted where allowed by available valences with one R_b substituent.

[1594] Another aspect includes a compound of Formula (XXIV), wherein B is piperazin-1-yl, substituted where allowed by available valences with two R_b substituents.

[1595] Another aspect includes a compound of Formula (XXIV), wherein B is piperazin-1-yl, substituted where allowed by available valences with three R_b substituents.

[1596] Another aspect includes a compound of Formula (XXIV), wherein B is piperazin-1-yl, substituted where allowed by available valences with four R_b substituents.

[1597] Another aspect includes a compound of Formula (XXIV), wherein B is unsubstituted 4-azaspiro[2.5]octan-7-yl.

[1598] Another aspect includes a compound of Formula (XXIV), wherein B is 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with one R_b substituent.

[1599] Another aspect includes a compound of Formula (XXIV), wherein B is 4-azaspiro[2.5]octan-7-yl, substituted where allowed by available valences with two R_b substituents.

[1600] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl containing at least one chiral carbon atom having an (R) configuration.

[1601] Another aspect includes a compound of Formula (XXIV), wherein B is heterocyclyl containing at least one chiral carbon atom having an (S) configuration.

[1602] One aspect includes a compound of Formula (XXIV), wherein R_b is selected from halogen, C_{1-4} alkyl, amino, C_{1-4} alkyl-amino, $(C_{1-4}$ alkyl)₂-amino, and C_{3-6} cycloalkyl.

[1603] Another aspect includes a compound of Formula (XXIV), wherein R_b is selected from halogen, C_{1-4} alkyl, C_{1-4} alkyl-amino, and C_{3-6} cycloalkyl.

[1604] Another aspect includes a compound of Formula (XXIV), wherein R_b is halogen selected from bromo, chloro, fluoro, and iodo.

[1605] Another aspect includes a compound of Formula (XXIV), wherein R_b is fluoro.

[1606] Another aspect includes a compound of Formula (XXIV), wherein R_b is C_{1-4} alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1607] Another aspect includes a compound of Formula (XXIV), wherein R_b is C_{1-4} alkyl selected from methyl, ethyl, and isopropyl.

[1608] Another aspect includes a compound of Formula (XXIV), wherein R_b is methyl.

[1609] Another aspect includes a compound of Formula (XXIV), wherein R_b is ethyl.

[1610] Another aspect includes a compound of Formula (XXIV), wherein R_b is isopropyl.

[1611] Another aspect includes a compound of Formula (XXIV), wherein R_b is C_{1-4} alkyl-amino.

[1612] Another aspect includes a compound of Formula (XXIV), wherein R_b is C_{1-4} alkyl-amino, wherein C_{1-4} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1613] Another aspect includes a compound of Formula (XXIV), wherein R_b is selected from methylamino and tert-butylamino.

[1614] Another aspect includes a compound of Formula (XXIV), wherein R_b is methylamino.

[1615] Another aspect includes a compound of Formula (XXIV), wherein R_b is tert-butylamino.

[1616] Another aspect includes a compound of Formula (XXIV), wherein R_b is C_{3-6} cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[1617] Another aspect includes a compound of Formula (XXIV), wherein R_b is cyclopropyl.

[1618] One aspect includes a compound of Formula (XXIV), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1619] Another aspect includes a compound of Formula (XXIV), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

wherein each instance of phenyl, heteroaryl or heterocyclyl is unsubstituted.

[1620] Another aspect includes a compound of Formula (XXIV), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

wherein each instance of phenyl, heteroaryl or heterocyclyl is substituted where allowed by available valences with one R_{1a} substituent.

[1621] Another aspect includes a compound of Formula (XXIV), wherein R_1 is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl- C_{1-4} alkyl, heteroaryl- C_{2-4} alkenyl, heteroaryl-amino, and heteroaryl- C_{1-4} alkyl-amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

wherein each instance of phenyl, heteroaryl or heterocyclyl is substituted where allowed by available valences with two R_{1a} substituents.

[1622] Another aspect includes a compound of Formula (XXIV), wherein R_1 is selected from heteroaryl, heteroaryl- C_{2-4} alkenyl, heteroaryl-amino, and heteroaryl- C_{1-4} alkyl-amino, wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1623] Another aspect includes a compound of Formula (XXIV), wherein R_1 is independently selected from heteroaryl, heteroaryl- C_{2-4} alkenyl, heteroaryl-amino, and heteroaryl- C_{1-4} alkyl-amino,

[1624] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is unsubstituted.

[1625] Another aspect includes a compound of Formula (XXIV), wherein R_1 is selected from heteroaryl, heteroaryl- C_{2-4} alkenyl, heteroaryl-amino, and heteroaryl- C_{1-4} alkyl-amino, wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is substituted where allowed by available valences with one R_{1a} substituent.

[1626] Another aspect includes a compound of Formula (XXIV), wherein R_1 is selected from heteroaryl, heteroaryl- C_{2-4} alkenyl, heteroaryl-amino, and heteroaryl- C_{1-4} alkyl-amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is substituted where allowed by available valences with two R_{1a} substituents.

[1627] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1628] Another aspect includes a compound of Formula (XXIV), wherein R₁ is unsubstituted heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-

triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl.

[1629] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl,

imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, substituted where allowed by available valences with one R_{1a} substituent.

[1630] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, substituted where allowed by available valences with two R_{1a} substituents.

[1631] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1H-1,2,3-triazolyl, 2H-

1,2,3-triazolyl, 1H-1,2,4-triazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrimidin-4(3H)-on-yl, pyridazinyl, 1H-indazolyl, 2H-indazolyl, 1,3-benzoxazolyl, pyrrolo[1,2-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, [1,2,4]triazolo[1,5-a]pyridinyl, and [1,2,4]triazolo[1,5-a]pyrazinyl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1632] Another aspect includes a compound of Formula (XXIV), wherein R₁ is unsubstituted heteroaryl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrimidin-4(3H)-on-yl, pyridazinyl, 1H-indazolyl, 2H-indazolyl, 1,3-benzoxazolyl, pyrrolo[1,2-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, [1,2,4]triazolo[1,5-a]pyridinyl, and [1,2,4]triazolo[1,5-a]pyrazinyl.

[1633] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrimidin-4(3H)-on-yl, pyridazinyl, 1H-indazolyl, 2H-indazolyl, 1,3-benzoxazolyl, pyrrolo[1,2-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, [1,2,4]triazolo[1,5-a]pyridinyl, and [1,2,4]triazolo[1,5-a]pyrazinyl, substituted where allowed by available valences with one R_{1a} substituent.

[1634] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrimidin-4(3H)-on-yl, pyridazinyl, 1H-indazolyl, 2H-indazolyl, 1,3-benzoxazolyl, pyrrolo[1,2-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, [1,2,4]triazolo[1,5-a]pyridinyl, and [1,2,4]triazolo[1,5-a]pyrazinyl, substituted where allowed by available valences with two R_{1a} substituents.

[1635] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl,

2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl,

and quinoxalin-2-yl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1636] Another aspect includes a compound of Formula (XXIV), wherein R₁ is unsubstituted heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl,

[1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl.

[1637] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl,

imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl, substituted where allowed by available valences with one R_{1a} substituent.

[1638] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl,

pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl, substituted where allowed by available valences with two R_{1a} substituents.

[1639] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1,3-thiazol-2-yl, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-2-yl, 1H-1,2,4-triazol-1-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, 1H-indazol-5-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 1,3-benzoxazol-6-yl, pyrrolo[1,2-a]pyrazin-7-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, and [1,2,4]triazolo[1,5-a]pyrazin-2-yl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1640] Another aspect includes a compound of Formula (XXIV), wherein R₁ is unsubstituted heteroaryl selected from 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1,3-thiazol-2-yl, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-2-yl, 1H-1,2,4-triazol-1-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyrimidin-4(3H)-on-6-yl,

pyridazin-3-yl, 1H-indazol-5-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 1,3-benzoxazol-6-yl, pyrrolo[1,2-a]pyrazin-7-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, and [1,2,4]triazolo[1,5-a]pyrazin-2-yl.

[1641] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1,3-thiazol-2-yl, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-2-yl, 1H-1,2,4-triazol-1-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, 1H-indazol-5-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 1,3-benzoxazol-6-yl, pyrrolo[1,2-a]pyrazin-7-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, and [1,2,4]triazolo[1,5-a]pyrazin-2-yl, substituted where allowed by available valences with one R_{1a} substituent.

[1642] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl selected from 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1,3-thiazol-2-yl, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, 1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-2-yl, 1H-1,2,4-triazol-1-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, 1H-indazol-5-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 1,3-benzoxazol-6-yl, pyrrolo[1,2-a]pyrazin-7-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, and [1,2,4]triazolo[1,5-a]pyrazin-2-yl, substituted where allowed by available valences with two R_{1a} substituents.

[1643] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl-C₂₋₄alkenyl,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1644] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl-C₂₋₄alkenyl,

wherein heteroaryl is selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, quinolinyl, isoquinolinyl, and quinoxalinyl;

wherein C₂₋₄alkenyl is selected from ethenyl, propenyl, and butenyl; and

wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1645] Another aspect includes a compound of Formula (XXIV), wherein R₁ is 2-(1H-pyrazol-4-yl)ethenyl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1646] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl-amino, wherein heteroaryl is selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, quinolinyl, isoquinolinyl, and quinoxalinyl; and wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1647] Another aspect includes a compound of Formula (XXIV), wherein R₁ is (pyridin-3-yl)amino, (pyrazin-2-yl)amino, and (pyrimidin-5-yl)amino, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1648] Another aspect includes a compound of Formula (XXIV), wherein R₁ is heteroaryl-C₁₋₄alkyl-amino, wherein heteroaryl is selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl,

1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, quinolinyl, isoquinolinyl, and quinoxalinyl;

wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, and butyl; and

wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1649] Another aspect includes a compound of Formula (XXIV), wherein R₁ is (1H-pyrazol-4-yl)methylamino, (pyridin-3-yl)methylamino, (pyridin-4-yl)methylamino, (quinolin-3-yl)methylamino, and (quinolin-8-yl)methylamino, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1650] One aspect includes a compound of Formula (XXIV), wherein R_{1a} is independently selected from halogen, hydroxyl, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, C₁₋₄alkoxy, deuterio-C₁₋₄alkoxy, and halo-C₁₋₄alkoxy.

[1651] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is independently selected from halogen, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, C₁₋₄alkoxy, and deuterio-C₁₋₄alkoxy.

[1652] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1653] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is selected from methyl and ethyl.

[1654] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is methyl.

[1655] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is ethyl.

[1656] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is halogen selected from bromo, chloro, fluoro, and iodo.

[1657] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is fluoro.

[1658] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is cyano.

[1659] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is deuterio-C₁₋₄alkyl wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl, partially or completely substituted with one or more deuterium atoms where allowed by available valences.

[1660] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is ($^2H_3$)methyl.

[1661] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is halo- C_{1-4} alkyl wherein C_{1-4} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl, partially or completely substituted with one or more halogen atoms where allowed by available valences.

[1662] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is trifluoromethyl.

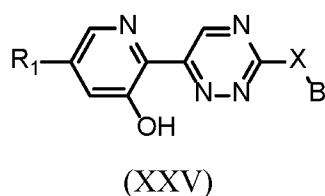
[1663] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is C_{1-4} alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

[1664] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is methoxy.

[1665] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is deuterio- C_{1-4} alkoxy wherein C_{1-4} alkoxy is selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy partially or completely substituted with one or more deuterium atoms where allowed by available valences.

[1666] Another aspect includes a compound of Formula (XXIV), wherein R_{1a} is ($^2H_3$)methoxy.

[1667] Another aspect of the present description includes a compound of Formula (XXV):



or a form thereof, wherein:

X is O, NR_x , or a bond;

R_x is selected from hydrogen and C_{1-4} alkyl;

B is heterocyclyl,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, each optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 substituents R_b ;

R_b is independently selected from halogen, C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, and C₃₋₆cycloalkyl;

R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, heteroaryl-C₁₋₄alkyl -amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents; and

R_{1a} is independently selected from halogen, hydroxyl, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, C₁₋₄alkoxy, deuterio-C₁₋₄alkoxy, and halo-C₁₋₄alkoxy.

[1668] One aspect includes a compound of Formula (XXV), wherein X is selected from O, NR_x, and a bond.

[1669] Another aspect includes a compound of Formula (XXV) wherein X is O.

[1670] Another aspect includes a compound of Formula (XXV) wherein X is NR_x.

[1671] Another aspect includes a compound of Formula (XXV) wherein X is a bond.

[1672] One aspect includes a compound of Formula (XXV), wherein R_x is selected from hydrogen and C₁₋₄alkyl.

[1673] Another aspect includes a compound of Formula (XXV), wherein R_x hydrogen.

[1674] Another aspect includes a compound of Formula (XXV), wherein R_x is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1675] Another aspect includes a compound of Formula (XXV), wherein R_x is methyl.

[1676] One aspect includes a compound of Formula (XXV), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3

heteroatom ring members independently selected from N, O, or S, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1677] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with one R_b substituent.

[1678] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with four R_b substituents.

[1679] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with five R_b substituents.

[1680] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl,

1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7,-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1681] Another aspect includes a compound of Formula (XXV), wherein B is unsubstituted heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7,-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl.

[1682] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl,

piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with one R_b substituent.

[1683] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl,

9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7,-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with two R_b substituents.

[1684] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperaziny, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7,-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and

7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with three R_b substituents.

[1685] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with four R_b substituents.

[1686] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl,

hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl,
 octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl,
 hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl,
 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl,
 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl,
 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-
 diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl,
 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl,
 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl,
 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7,-diazaspiro[4.4]nonanyl,
 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl,
 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl,
 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-
 diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and
 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with five
 R_b substituents.

[1687] Another aspect includes a compound of Formula (XXV), wherein B is unsubstituted heterocyclyl selected from pyrrolidinyl, piperidinyl, and piperazinyl.

[1688] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, and piperazinyl, substituted where allowed by available valences with one R_b substituent.

[1689] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, and piperazinyl, substituted where allowed by available valences with two R_b substituents.

[1690] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, and piperazinyl, substituted where allowed by available valences with three R_b substituents.

[1691] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, and piperazinyl, substituted where allowed by available valences with four R_b substituents.

[1692] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from pyrrolidinyl, piperidinyl, and piperazinyl, substituted where allowed by available valences with five R_b substituents.

[1693] Another aspect includes a compound of Formula (XXV), wherein B is pyrrolidinyl, substituted where allowed by available valences with one R_b substituent.

[1694] Another aspect includes a compound of Formula (XXV), wherein B is piperidinyl, substituted where allowed by available valences with 4 or 5 R_b substituents.

[1695] Another aspect includes a compound of Formula (XXV), wherein B is piperidinyl, substituted where allowed by available valences with four R_b substituents.

[1696] Another aspect includes a compound of Formula (XXV), wherein B is piperidinyl, substituted where allowed by available valences with five R_b substituents.

[1697] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from piperazinyl, substituted where allowed by available valences with one R_b substituent.

[1698] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl,

3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7,-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1699] Another aspect includes a compound of Formula (XXV), wherein B is unsubstituted heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl,

3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl.

[1700] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl,

1,7,-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with one R_b substituent.

[1701] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7,-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-

7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with two R_b substituents.

[1702] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl,

2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with three R_b substituents.

[1703] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclcyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-

yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with four R_b substituents.

[1704] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7,-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-

azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with five R_b substituents.

[1705] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, and piperazin-1-yl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1706] Another aspect includes a compound of Formula (XXV), wherein B is unsubstituted heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, and piperazin-1-yl.

[1707] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, and piperazin-1-yl, substituted where allowed by available valences with one R_b substituent.

[1708] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, and piperazin-1-yl, substituted where allowed by available valences with two R_b substituents.

[1709] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, and piperazin-1-yl, substituted where allowed by available valences with three R_b substituents.

[1710] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, and piperazin-1-yl, substituted where allowed by available valences with four R_b substituents.

[1711] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from pyrrolidin-1-yl, piperidin-4-yl, and piperazin-1-yl, substituted where allowed by available valences with five R_b substituents.

[1712] Another aspect includes a compound of Formula (XXV), wherein B is pyrrolidin-1-yl, substituted where allowed by available valences with one R_b substituent.

[1713] Another aspect includes a compound of Formula (XXV), wherein B is piperidin-4-yl, substituted where allowed by available valences with 4 or 5 R_b substituents.

[1714] Another aspect includes a compound of Formula (XXV), wherein B is piperidin-4-yl, substituted where allowed by available valences with four R_b substituents.

[1715] Another aspect includes a compound of Formula (XXV), wherein B is piperidin-4-yl, substituted where allowed by available valences with five R_b substituents.

[1716] Another aspect includes a compound of Formula (XXV), wherein B is piperazin-1-yl, substituted where allowed by available valences with one R_b substituent.

[1717] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl containing at least one chiral carbon atom having an (R) configuration.

[1718] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl containing at least one chiral carbon atom having an (S) configuration.

[1719] One aspect includes a compound of Formula (XXV), wherein R_b is selected from halogen, C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, and C₃₋₆cycloalkyl.

[1720] Another aspect includes a compound of Formula (XXV), wherein R_b is selected from halogen, C₁₋₄alkyl, C₁₋₄alkyl-amino, and C₃₋₆cycloalkyl.

[1721] Another aspect includes a compound of Formula (XXV), wherein R_b is halogen selected from bromo, chloro, fluoro, and iodo.

[1722] Another aspect includes a compound of Formula (XXV), wherein R_b is fluoro.

[1723] Another aspect includes a compound of Formula (XXV), wherein R_b is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1724] Another aspect includes a compound of Formula (XXV), wherein R_b is C₁₋₄alkyl selected from methyl and isopropyl.

[1725] Another aspect includes a compound of Formula (XXV), wherein R_b is methyl.

[1726] Another aspect includes a compound of Formula (XXV), wherein R_b is isopropyl.

[1727] Another aspect includes a compound of Formula (XXV), wherein R_b is C₁₋₄alkyl-amino.

[1728] Another aspect includes a compound of Formula (XXV), wherein R_b is C₁₋₄alkyl-amino, wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1729] Another aspect includes a compound of Formula (XXV), wherein R_b is tert-butylamino.

[1730] Another aspect includes a compound of Formula (XXV), wherein R_b is C₃₋₆cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[1731] Another aspect includes a compound of Formula (XXV), wherein R_b is cyclopropyl.

[1732] One aspect includes a compound of Formula (XXV), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

[1733] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

[1734] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

[1735] wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1736] Another aspect includes a compound of Formula (XXV), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

[1737] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

[1738] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

[1739] wherein each instance of phenyl, heteroaryl or heterocyclyl is unsubstituted.

[1740] Another aspect includes a compound of Formula (XXV), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

[1741] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

[1742] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

[1743] wherein each instance of phenyl, heteroaryl or heterocyclyl is substituted where allowed by available valences with one R_{1a} substituent.

[1744] Another aspect includes a compound of Formula (XXV), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

[1745] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

[1746] wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

[1747] wherein each instance of phenyl, heteroaryl or heterocyclyl is substituted where allowed by available valences with two R_{1a} substituents.

[1748] Another aspect includes a compound of Formula (XXV), wherein R₁ is selected from heteroaryl, and heteroaryl-amino,

[1749] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1750] Another aspect includes a compound of Formula (XXV), wherein R₁ is selected from heteroaryl, and heteroaryl-amino,

[1751] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is unsubstituted.

[1752] Another aspect includes a compound of Formula (XXV), wherein R₁ is selected from heteroaryl, and heteroaryl-amino,

[1753] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is substituted where allowed by available valences with one R_{1a} substituent.

[1754] Another aspect includes a compound of Formula (XXV), wherein R₁ is selected from heteroaryl, and heteroaryl-amino,

[1755] wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is substituted where allowed by available valences with two R_{1a} substituents.

[1756] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1757] Another aspect includes a compound of Formula (XXV), wherein R₁ is unsubstituted heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl,

1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl.

[1758] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl,

imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, substituted where allowed by available valences with one R_{1a} substituent.

[1759] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, substituted where allowed by available valences with two R_{1a} substituents.

[1760] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from 1H-pyrazolyl, 2H-1,2,3-triazolyl, 2H-indazolyl, imidazo[1,2-a]pyridinyl,

imidazo[1,2-b]pyridazinyl, and 2H-[1,2,3]triazolo[4,5-b]pyridinyl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1761] Another aspect includes a compound of Formula (XXV), wherein R₁ is unsubstituted heteroaryl selected from 1H-pyrazolyl, 2H-1,2,3-triazolyl, 2H-indazolyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-b]pyridazinyl, and 2H-[1,2,3]triazolo[4,5-b]pyridinyl.

[1762] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from 1H-pyrazolyl, 2H-1,2,3-triazolyl, 2H-indazolyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-b]pyridazinyl, and 2H-[1,2,3]triazolo[4,5-b]pyridinyl, substituted where allowed by available valences with one R_{1a} substituent.

[1763] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from 1H-pyrazolyl, 2H-1,2,3-triazolyl, 2H-indazolyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-b]pyridazinyl, and 2H-[1,2,3]triazolo[4,5-b]pyridinyl, substituted where allowed by available valences with two R_{1a} substituents.

[1764] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl,

pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1765] Another aspect includes a compound of Formula (XXV), wherein R₁ is unsubstituted heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl,

benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl.

[1766] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl,

pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl, substituted where allowed by available valences with one R_{1a} substituent.

[1767] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl,

1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl,

[1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl, substituted where allowed by available valences with two R_{1a} substituents.

[1768] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from 1H-pyrazol-4-yl, 2H-1,2,3-triazol-2-yl, 2H-indazol-5-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-b]pyridazin-6-yl, and 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1769] Another aspect includes a compound of Formula (XXV), wherein R₁ is unsubstituted heteroaryl selected from 1H-pyrazol-4-yl, 2H-1,2,3-triazol-2-yl, 2H-indazol-5-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-b]pyridazin-6-yl, and 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl.

[1770] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from 1H-pyrazol-4-yl, 2H-1,2,3-triazol-2-yl, 2H-indazol-5-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-b]pyridazin-6-yl, and 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, substituted where allowed by available valences with 1 R_{1a} substituent.

[1771] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl selected from 1H-pyrazol-4-yl, 2H-1,2,3-triazol-2-yl, 2H-indazol-5-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-b]pyridazin-6-yl, and 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, substituted where allowed by available valences with 2 R_{1a} substituents.

[1772] Another aspect includes a compound of Formula (XXV), wherein R₁ is heteroaryl-amino, wherein heteroaryl is selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, quinolinyl, isoquinolinyl, and quinoxalinyl; and

[1773] wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1774] Another aspect includes a compound of Formula (XXV), wherein R₁ is (pyrazin-2-yl)amino, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1775] One aspect includes a compound of Formula (XXV), wherein R_{1a} is independently selected from halogen, hydroxyl, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, C₁₋₄alkoxy, deuterio-C₁₋₄alkoxy, and halo-C₁₋₄alkoxy.

[1776] Another aspect includes a compound of Formula (XXV), wherein R_{1a} is independently selected from halogen, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, and C₁₋₄alkoxy.

[1777] Another aspect includes a compound of Formula (XXV), wherein R_{1a} is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1778] Another aspect includes a compound of Formula (XXV), wherein R_{1a} is methyl.

[1779] Another aspect includes a compound of Formula (XXV), wherein R_{1a} is halogen selected from bromo, chloro, fluoro, and iodo.

[1780] Another aspect includes a compound of Formula (XXV), wherein R_{1a} is fluoro.

[1781] Another aspect includes a compound of Formula (XXV), wherein R_{1a} is cyano.

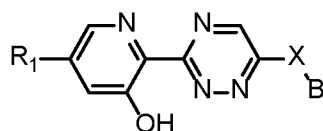
[1782] Another aspect includes a compound of Formula (XXV), wherein R_{1a} is deuterio-C₁₋₄alkyl wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl, partially or completely substituted with one or more deuterium atoms where allowed by available valences.

[1783] Another aspect includes a compound of Formula (XXV), wherein R_{1a} is (²H₃)methyl.

[1784] Another aspect includes a compound of Formula (XXV), wherein R_{1a} is C₁₋₄alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

[1785] Another aspect includes a compound of Formula (XXV), wherein R_{1a} is methoxy.

[1786] Another aspect of the present description includes a compound of Formula (XXVI):



(XXVI)

or a form thereof, wherein:

X is O, NR_x, or a bond;

R_x is selected from hydrogen and C₁₋₄alkyl;

B is heterocyclyl,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, each optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 substituents R_b;

R_b is independently selected from halogen, C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, and C₃₋₆cycloalkyl;

R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, heteroaryl-C₁₋₄alkyl -amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents; and

R_{1a} is independently selected from halogen, hydroxyl, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, C₁₋₄alkoxy, deuterio-C₁₋₄alkoxy, and halo-C₁₋₄alkoxy.

[1787] One aspect includes a compound of Formula (XXVI), wherein X is selected from O, NR_x, and a bond.

[1788] Another aspect includes a compound of Formula (XXVI) wherein X is NR_x.

[1789] Another aspect includes a compound of Formula (XXVI) wherein X is a bond.

[1790] One aspect includes a compound of Formula (XXVI), wherein R_x is selected from hydrogen and C₁₋₄alkyl.

[1791] Another aspect includes a compound of Formula (XXVI), wherein R_x hydrogen.

[1792] Another aspect includes a compound of Formula (XXVI), wherein R_x is C_{1-4} alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1793] Another aspect includes a compound of Formula (XXVI), wherein R_x is methyl.

[1794] One aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1795] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with two R_b substituents.

[1796] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S, substituted where allowed by available valences with four R_b substituents.

[1797] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-

diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1798] Another aspect includes a compound of Formula (XXVI), wherein B is unsubstituted heterocyclyl selected from azetidynyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl.

[1799] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with one R_b substituent.

[1800] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl,

1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with two R_b substituents.

[1801] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidiny, piperidiny, piperidin-1-olate-yl, piperaziny, 1,4-diazepany, 1,2-dihydropyridiny, 1,2,5,6-tetrahydropyridiny, 1,2,3,6-tetrahydropyridiny, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridiny, octahydro-5H-pyrrolo[3,2-c]pyridiny, octahydro-6H-pyrrolo[3,4-b]pyridiny, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyraziny, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-

diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with three R_b substituents.

[1802] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl, hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with four R_b substituents.

[1803] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidiny, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperidin-1-olate-yl, piperazinyl, 1,4-diazepanyl, 1,2-dihydropyridinyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, hexahydrocyclopentapyrrol-(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-(2H)-yl, octahydro-2H-pyrrolo[3,4-c]pyridinyl, octahydro-5H-pyrrolo[3,2-c]pyridinyl, octahydro-6H-pyrrolo[3,4-b]pyridinyl,

hexahydropyrrolo[1,2-a]pyrazin-(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-b][1,4]oxazin-(2H)-yl, 5-azaspiro[2.4]heptanyl, 1-azaspiro[3.3]heptanyl, 4-azaspiro[2.5]octanyl, 2-oxa-6-azaspiro[3.4]octanyl, 3-azabicyclo[3.1.0]hexanyl, 8-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]oct-2-en-yl, 9-azabicyclo[3.3.1]nonanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 1,4-diazabicyclo[3.1.1]heptanyl, 3,6-diazabicyclo[3.2.0]heptanyl, 2,5-diazabicyclo[2.2.2]octanyl, 1,4-diazabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl, 1,4-diazabicyclo[3.2.2]nonanyl, 4,7-diazaspiro[2.5]octanyl, 2,6-diazaspiro[3.3]heptanyl, 1,6-diazaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1,7-diazaspiro[4.4]nonanyl, 1,7-diazaspiro[3.5]nonanyl, 2,6-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[3.5]nonanyl, 5,8-diazaspiro[3.5]nonanyl, 2-oxa-5,8-diazaspiro[3.5]nonanyl, 2,7-diazaspiro[4.4]nonanyl, 2,7-diazaspiro[4.5]decanyl, 2,8-diazaspiro[4.5]decanyl, 6,9-diazaspiro[4.5]decyl, 6-oxa-2,9-diazaspiro[4.5]decanyl, 2,9-diazaspiro[5.5]undecanyl, 4-azadispiro[2.1.2⁵.3³]decanyl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecanyl, substituted where allowed by available valences with five R_b substituents.

[1804] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from piperidinyl and piperazinyl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1805] Another aspect includes a compound of Formula (XXVI), wherein B is unsubstituted heterocyclyl selected from piperidinyl and piperazinyl.

[1806] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from piperidinyl and piperazinyl, substituted where allowed by available valences with one R_b substituent.

[1807] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from piperidinyl and piperazinyl, substituted where allowed by available valences with two R_b substituents.

[1808] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from piperidinyl and piperazinyl, substituted where allowed by available valences with three R_b substituents.

[1809] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclcyl selected from piperidinyl and piperazinyl, substituted where allowed by available valences with four R_b substituents.

[1810] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclcyl selected from piperidinyl and piperazinyl, substituted where allowed by available valences with five R_b substituents.

[1811] Another aspect includes a compound of Formula (XXVI), wherein B is piperidinyl, substituted where allowed by available valences with four R_b substituents.

[1812] Another aspect includes a compound of Formula (XXVI), wherein B is piperazinyl, substituted where allowed by available valences with two R_b substituents.

[1813] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclcyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl,

1,7,-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1814] Another aspect includes a compound of Formula (XXVI), wherein B is unsubstituted heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7,-diazaspiro[4.4]nonan-1-yl, 1,7,-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-

7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl.

[1815] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl,

2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with one R_b substituent.

[1816] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-

azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with two R_b substituents.

[1817] Another aspect includes a compound of Formula (XXV), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with three R_b substituents.

[1818] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with four R_b substituents.

[1819] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from azetidin-1-yl, tetrahydrofuran-3-yl, pyrrolidin-1-yl, pyrrolidin-3-yl,

piperidin-1-yl, piperidin-3-yl, piperidin-4-yl, piperidin-1-olate-4-yl, piperazin-1-yl, 1,4-diazepan-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-4-yl, hexahydrocyclopentapyrrol-2(1H)-yl, hexahydropyrrolo[3,2-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-b]pyrrol-1(2H)-yl, hexahydropyrrolo[3,4-c]pyrrol-1(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, hexahydropyrrolo[3,4-c]pyrrol-5(1H)-yl, octahydro-5H-pyrrolo[3,2-c]pyridin-5-yl, octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl, hexahydropyrrolo[1,2-a]pyrazin-6(2H)-one, hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, hexahydro-1H-cyclobuta[1.2-c:1,4-c']dipyrrol-2(3H)-yl, octahydropyrrolo[1,2-a]pyrazin-2(1H)-yl, octahydro-2H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-b][1,4]oxazin-6(2H)-yl, 5-azaspiro[2.4]heptan-5-yl, 1-azaspiro[3.3]heptan-2-yl, 4-azaspiro[2.5]octan-7-yl, 2-oxa-6-azaspiro[3.4]octan-6-yl, 3-azabicyclo[3.1.0]hexan-3-yl, 8-azabicyclo[3.2.1]octan-3-yl, 8-azabicyclo[3.2.1]oct-2-en-3-yl, 9-azabicyclo[3.3.1]nonan-3-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 1,4-diazabicyclo[3.1.1]heptan-4-yl, 3,6-diazabicyclo[3.2.0]heptan-3-yl, 3,6-diazabicyclo[3.2.0]heptan-6-yl, 2,5-diazabicyclo[2.2.2]octan-2-yl, 1,4-diazabicyclo[3.2.1]octan-4-yl, 3,8-diazabicyclo[3.2.1]octan-3-yl, 1,4-diazabicyclo[3.2.2]nonan-4-yl, 4,7-diazaspiro[2.5]octan-4-yl, 4,7-diazaspiro[2.5]octan-7-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 1,6-diazaspiro[3.4]octan-6-yl, 2,6-diazaspiro[3.4]octan-2-yl, 2,6-diazaspiro[3.4]octan-6-yl, 1,7-diazaspiro[4.4]nonan-1-yl, 1,7-diazaspiro[4.4]nonan-7-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,6-diazaspiro[3.5]nonan-2-yl, 2,6-diazaspiro[3.5]nonan-6-yl, 1,7-diazaspiro[3.5]nonan-7-yl, 2,7-diazaspiro[3.5]nonan-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl, 5,8-diazaspiro[3.5]nonan-8-yl, 2-oxa-5,8-diazaspiro[3.5]nonan-8-yl, 2,7-diazaspiro[4.4]nonan-2-yl, 2,7-diazaspiro[4.5]decan-2-yl, 2,7-diazaspiro[4.5]decan-7-yl, 2,8-diazaspiro[4.5]decan-8-yl, 6,9-diazaspiro[4.5]dec-9-yl, 6-oxa-2,9-diazaspiro[4.5]decan-2-yl, 2,9-diazaspiro[5.5]undecan-9-yl, 4-azadispiro[2.1.2⁵.3³]decan-9-yl, and 7-azadispiro[5.1.5⁸.3⁶]hexadecan-15-yl, substituted where allowed by available valences with five R_b substituents.

[1820] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from piperidin-4-yl and piperazin-1-yl, optionally substituted where allowed by available valences with 1, 2, 3, 4, or 5 R_b substituents.

[1821] Another aspect includes a compound of Formula (XXVI), wherein B is unsubstituted heterocyclyl selected from piperidin-4-yl and piperazin-1-yl.

[1822] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from piperidin-4-yl and piperazin-1-yl, substituted where allowed by available valences with one R_b substituent.

[1823] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from piperidin-4-yl and piperazin-1-yl, substituted where allowed by available valences with two R_b substituents.

[1824] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from piperidin-4-yl and piperazin-1-yl, substituted where allowed by available valences with three R_b substituents.

[1825] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from piperidin-4-yl and piperazin-1-yl, substituted where allowed by available valences with four R_b substituents.

[1826] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from piperidin-4-yl and piperazin-1-yl, substituted where allowed by available valences with five R_b substituents.

[1827] Another aspect includes a compound of Formula (XXVI), wherein B is piperidin-4-yl, substituted where allowed by available valences with four R_b substituents.

[1828] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl selected from piperazin-4-yl, substituted where allowed by available valences with two R_b substituents.

[1829] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl containing at least one chiral carbon atom having an (R) configuration.

[1830] Another aspect includes a compound of Formula (XXVI), wherein B is heterocyclyl containing at least one chiral carbon atom having an (S) configuration.

[1831] One aspect includes a compound of Formula (XXVI), wherein R_b is selected from halogen, C₁₋₄alkyl, amino, C₁₋₄alkyl-amino, (C₁₋₄alkyl)₂-amino, and C₃₋₆cycloalkyl.

[1832] Another aspect includes a compound of Formula (XXVI), wherein R_b is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1833] Another aspect includes a compound of Formula (XXVI), wherein R_b is methyl.

[1834] One aspect includes a compound of Formula (XXVI), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1835] Another aspect includes a compound of Formula (XXVI), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

wherein each instance of phenyl, heteroaryl or heterocyclyl is unsubstituted.

[1836] Another aspect includes a compound of Formula (XXVI), wherein R₁ is selected from heteroaryl, heterocyclyl, phenyl, heteroaryl-C₁₋₄alkyl, heteroaryl-C₂₋₄alkenyl, heteroaryl-amino, and heteroaryl-C₁₋₄alkyl-amino,

wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, or S; and

wherein each instance of phenyl, heteroaryl or heterocyclyl is substituted where allowed by available valences with one R_{1a} substituent.

[1837] Another aspect includes a compound of Formula (XXVI), wherein R₁ is heteroaryl, wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1838] Another aspect includes a compound of Formula (XXVI), wherein R₁ is heteroaryl, wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is unsubstituted.

[1839] Another aspect includes a compound of Formula (XXVI), wherein R₁ is heteroaryl, wherein heteroaryl is a 3-7 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S; and wherein heteroaryl is substituted where allowed by available valences with one R_{1a} substituent.

[1840] Another aspect includes a compound of Formula (XXVI), wherein R₁ is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl,

imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1841] Another aspect includes a compound of Formula (XXVI), wherein R₁ is unsubstituted heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl.

[1842] Another aspect includes a compound of Formula (XXVI), wherein R_1 is heteroaryl selected from thienyl, 1H-pyrazolyl, 1H-imidazolyl, 1,3-thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, pyridinyl, pyridin-2(1H)-on-yl, pyrazinyl, pyrimidinyl, pyrimidin-4(3H)-on-yl, pyridazinyl, pyridazin-3(2H)-on-yl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1H-indolyl, 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, 1H-pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[2,3-c]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, 1H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridin-yl, 5H-pyrrolo[2,3-b]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidinyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 2H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, substituted where allowed by available valences with one R_{1a} substituent.

[1843] Another aspect includes a compound of Formula (XXVI), wherein R_1 is heteroaryl selected from 1H-pyrazolyl, 2H-1,2,3-triazolyl, and 2H-indazolyl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1844] Another aspect includes a compound of Formula (XXVI), wherein R_1 is unsubstituted heteroaryl selected from 1H-pyrazolyl, 2H-1,2,3-triazolyl, and 2H-indazolyl.

[1845] Another aspect includes a compound of Formula (XXVI), wherein R_1 is heteroaryl selected from 1H-pyrazolyl, 2H-1,2,3-triazolyl, and 2H-indazolyl, substituted where allowed by available valences with one R_{1a} substituent.

[1846] Another aspect includes a compound of Formula (XXVI), wherein R₁ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-

a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1847] Another aspect includes a compound of Formula (XXVI), wherein R₁ is unsubstituted heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl,

imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl.

[1848] Another aspect includes a compound of Formula (XXVI), wherein R₁ is heteroaryl selected from thien-2-yl, thien-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-4-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, 2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridin-2(1H)-on-4-yl, pyridin-2(1H)-on-5-yl, pyridin-2(1H)-on-6-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-4(3H)-on-6-yl, pyridazin-3-yl, pyridazin-4-yl, pyridazin-3(2H)-on-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothien-2-yl, benzothien-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 9H-purin-8-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-

c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-2-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-7-yl, [1,2,4]triazolo[1,5-a]pyrazin-2-yl, [1,2,4]triazolo[1,5-a]pyrazin-5-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, isoquinolin-6-yl, and quinoxalin-2-yl, substituted where allowed by available valences with one R_{1a} substituent.

[1849] Another aspect includes a compound of Formula (XXVI), wherein R₁ is heteroaryl selected from 1H-pyrazol-4-yl, 2H-1,2,3-triazol-2-yl, and 2H-indazol-5-yl, optionally substituted where allowed by available valences with 1 or 2 R_{1a} substituents.

[1850] Another aspect includes a compound of Formula (XXVI), wherein R₁ is unsubstituted heteroaryl selected from 1H-pyrazol-4-yl, 2H-1,2,3-triazol-2-yl, and 2H-indazol-5-yl.

[1851] Another aspect includes a compound of Formula (XXVI), wherein R₁ is heteroaryl selected from 1H-pyrazol-4-yl, 2H-1,2,3-triazol-2-yl, and 2H-indazol-5-yl, substituted where allowed by available valences with one R_{1a} substituent.

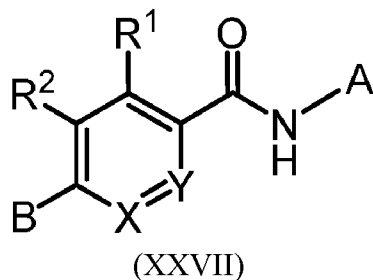
[1852] Another aspect includes a compound of Formula (XXVI), wherein R_{1a} is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1853] Another aspect includes a compound of Formula (XXVI), wherein R_{1a} is methyl.

HD Compounds of Formula (XXVII)

[1854] In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in the published International PCT Patent Application No. PCT/US2020/041300, the content of which is incorporated by reference herein in its entirety.

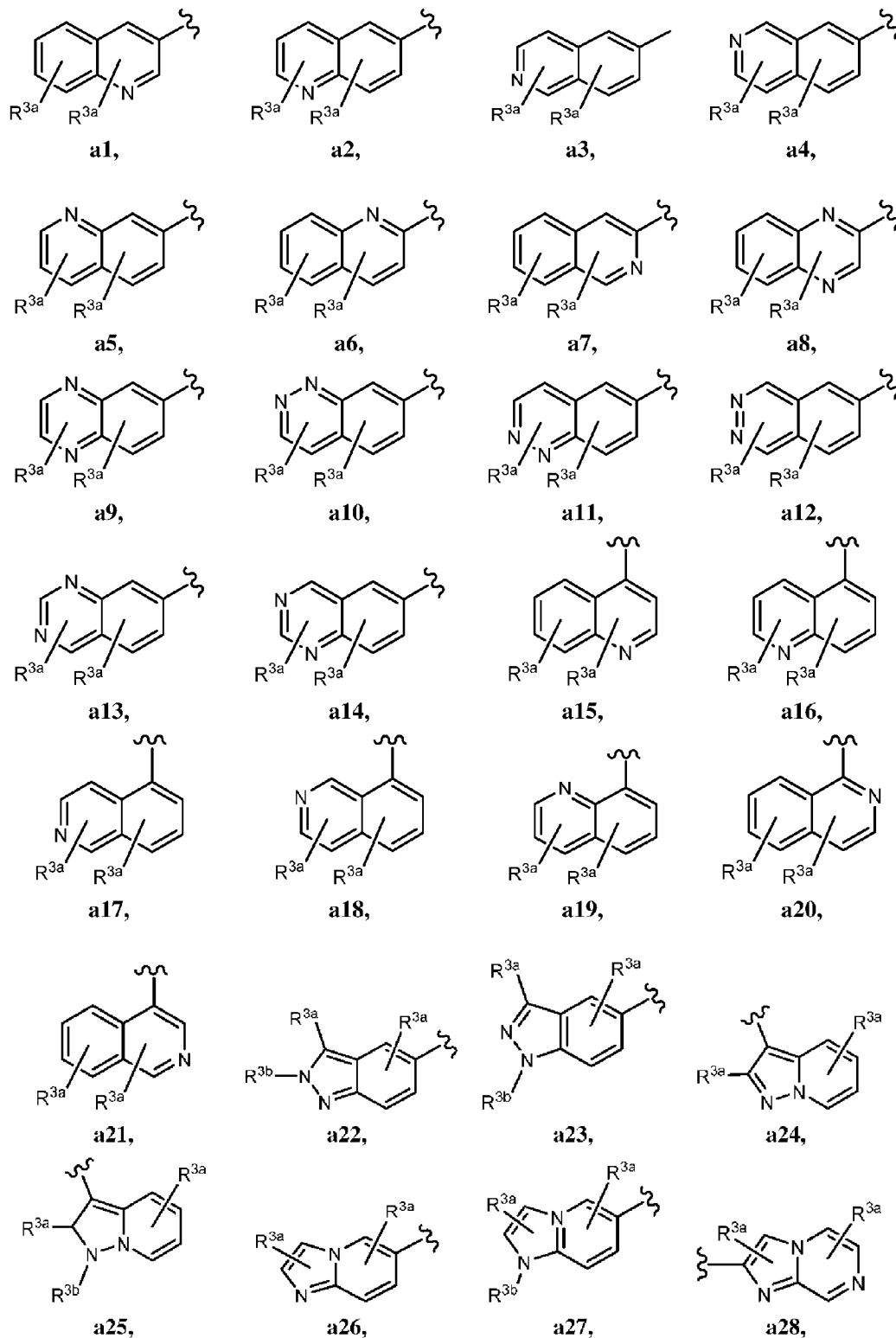
[1855] In one aspect, an HD compound of the disclosure can refer to a compound of Formula (XXVII):



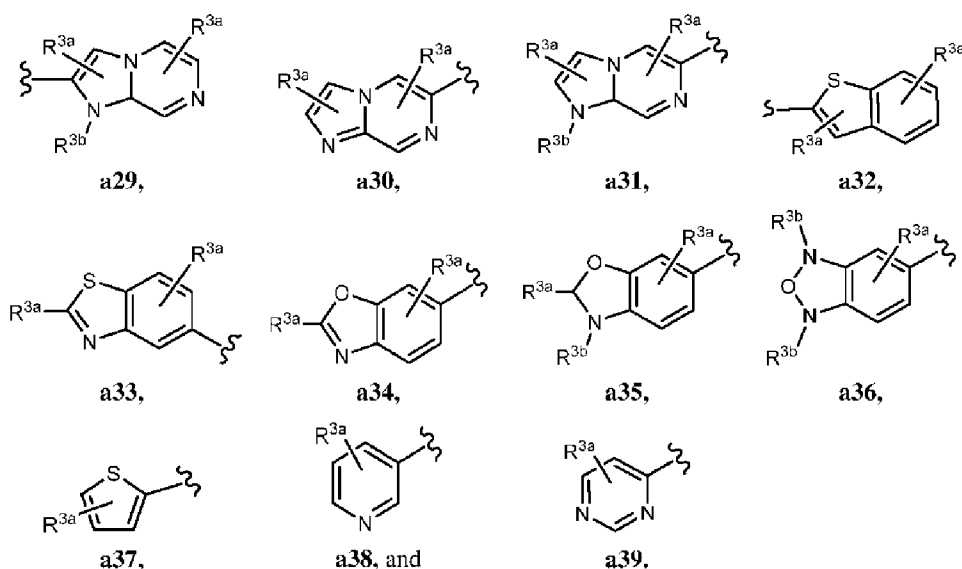
or a form or composition thereof, wherein X and Y are each independently selected from CR⁵ or N, wherein X and Y are not simultaneously N; A is heteroaryl or heterocyclyl, wherein heteroaryl is an unsaturated monocyclic ring system having 5 or 6 ring members or an unsaturated bicyclic ring system having 9 or 10 ring members, wherein 1, 2, or 3 ring members are heteroatoms independently selected from N, O, or S and the remainder are carbon atoms, and wherein heteroaryl is optionally substituted, where allowed by available valences, with 1, 2, 3, 4, or 5 substituents each independently selected from R³, wherein heterocyclyl is a saturated or partially unsaturated monocyclic ring system having 4, 5, 6 or 7 ring members or a saturated or partially unsaturated bicyclic ring system having 9 or 10 ring members, wherein one or more ring members are heteroatoms independently selected from N, O, or S and the remainder are carbon atoms, and wherein heterocyclyl is optionally substituted, where allowed by available valences, with 1, 2, 3, 4, or 5 substituents each independently selected from R³; B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated monocyclic ring system having 4, 5, 6 or 7 ring members or a saturated or partially unsaturated bicyclic ring system having 9 or 10 ring members, wherein one or more ring members are heteroatoms independently selected from N, O, or S and the remainder are carbon atoms, and wherein heterocyclyl is optionally substituted, where allowed by available valences, with 1, 2, 3, 4, or 5 substituents each independently selected from R⁴; R¹ and R² are each independently selected from hydrogen, halogen, C₁₋₄alkyl, C₁₋₄alkoxy, or halo-C₁₋₄alkoxy; R³ is selected from halogen, C₁₋₄alkyl, halo-C₁₋₄alkyl, C₁₋₄alkoxy, or C₃₋₇cycloalkyl; R⁴ is selected from halogen, C₁₋₄alkyl, halo-C₁₋₄alkyl, C₃₋₇cycloalkyl, or heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated monocyclic ring system having 4, 5, 6 or 7 ring members or a saturated or partially unsaturated bicyclic ring system having 9 or 10 ring members, wherein one or more ring members are heteroatoms independently selected from N, O, or S and the remainder are

carbon atoms, and wherein heterocyclyl is optionally substituted, where allowed by available valences, with 1, 2, 3, 4, or 5 substituents each independently selected from R⁶; R⁵ is selected from hydrogen, halogen, C₁₋₄alkyl, C₁₋₄alkoxy, or halo-C₁₋₄alkoxy; R⁶ is selected from halogen, C₁₋₄alkyl, C₁₋₄alkoxy, or halo-C₁₋₄alkoxy; and, wherein a form of the compound is selected from the group consisting of a prodrug, salt, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

[1856] In another aspect described herein, A is heteroaryl or heterocyclyl selected from the



group consisting of:

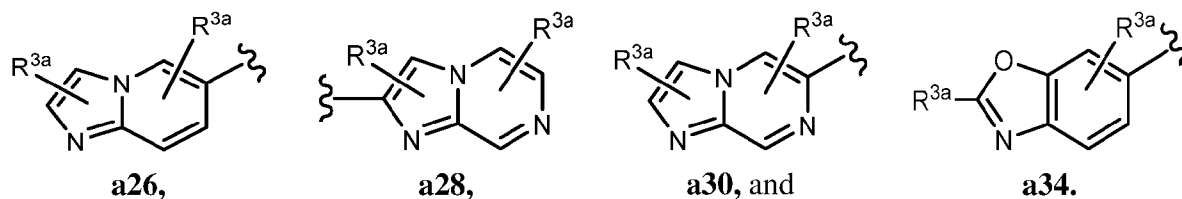


[1857] In another aspect described herein, R^{3a} and R^{3b} are each, where allowed by available valences, independently selected from hydrogen, halogen, C_{1-4} alkyl, halo- C_{1-4} alkyl, or C_{3-7} cycloalkyl.

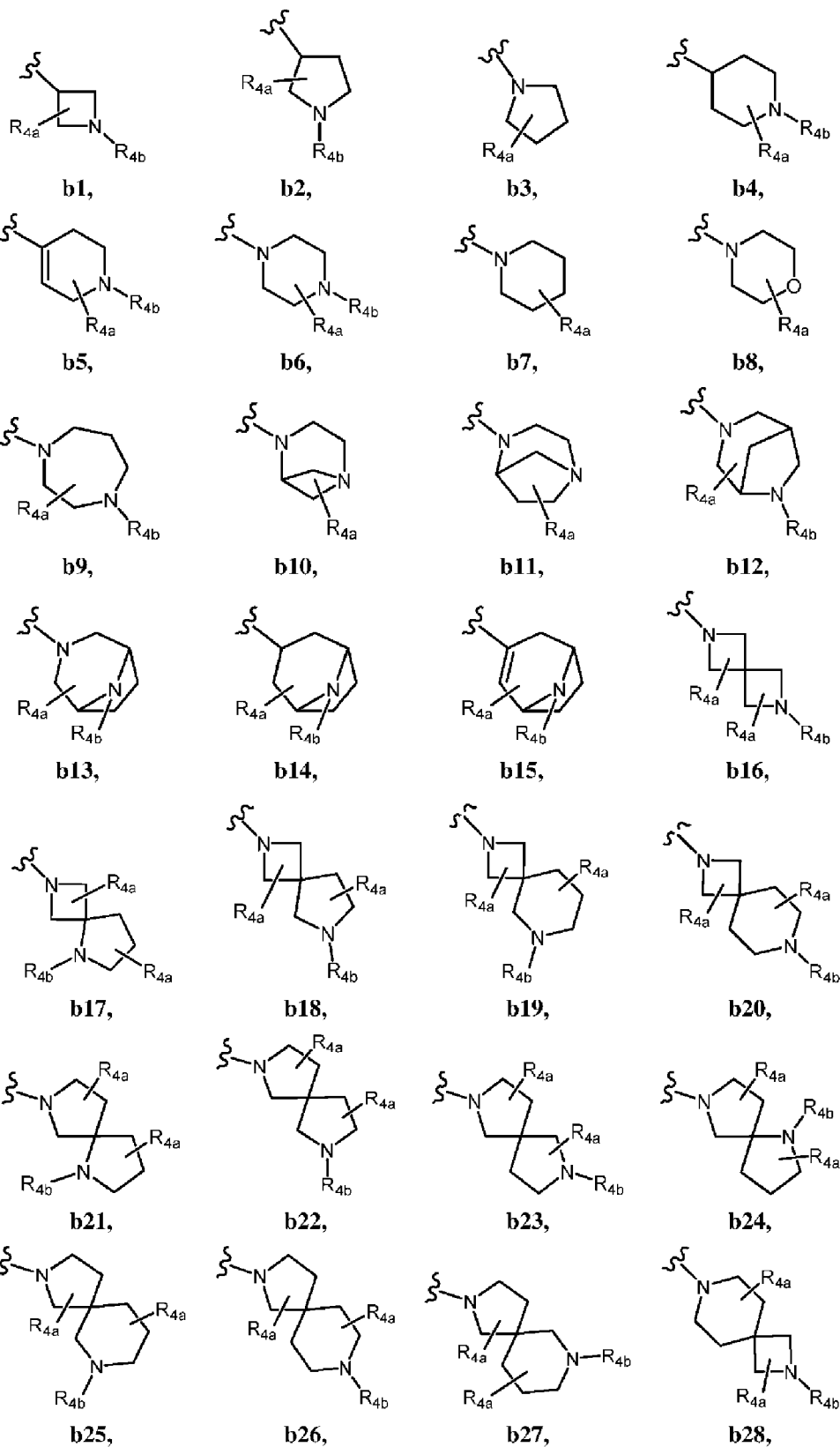
[1858] In another aspect described herein, R^{3a} is selected from hydrogen, halogen, C_{1-4} alkyl, halo- C_{1-4} alkyl, or C_{3-7} cycloalkyl.

[1859] In another aspect described herein, R^{3b} is selected from hydrogen, C_{1-4} alkyl, halo- C_{1-4} alkyl, or C_{3-7} cycloalkyl.

[1860] In another aspect described herein, A is heteroaryl, wherein heteroaryl is an unsaturated monocyclic ring system having 5 or 6 ring members or an unsaturated bicyclic ring system having 9 or 10 ring members, wherein 1, 2, or 3 ring members are heteroatoms independently selected from N, O, or S and the remainder are carbon atoms, and wherein heteroaryl is optionally substituted, where allowed by available valences, with 1, 2, 3, 4, or 5 substituents each independently selected from R^3 . In another aspect described herein, A is heteroaryl selected from the group consisting of:



[1861] In another aspect described herein, B is heterocyclyl selected from the group consisting of:



[1862] In another aspect described herein, R^{4a} and R^{4b} are each, where allowed by available valences, independently selected from hydrogen, C₁₋₄alkyl, or heterocyclyl, wherein

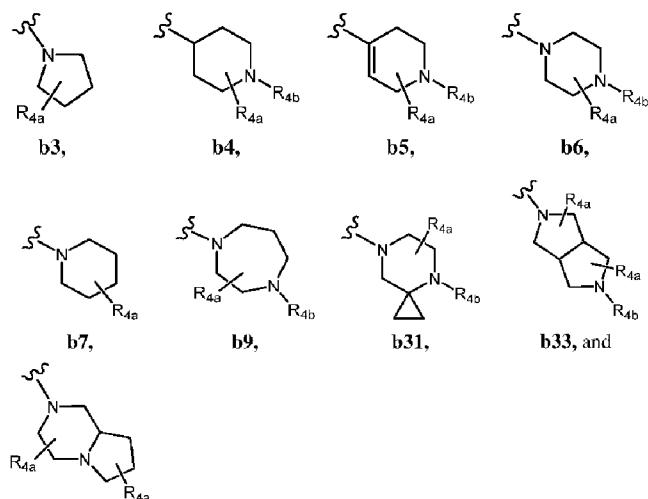
heterocyclyl is a saturated or partially unsaturated monocyclic ring system having 4, 5, 6 or 7 ring members or a saturated or partially unsaturated bicyclic ring system having 9 or 10 ring members, wherein one or more ring members are heteroatoms independently selected from N, O, or S and the remainder are carbon atoms, and wherein heterocyclyl is optionally substituted [1863], where allowed by available valences, with 1, 2, 3, 4, or 5 substituents each independently selected from R⁶.

[1864] In another aspect described herein, R^{4a} is selected from hydrogen, C₁₋₄alkyl, or heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated monocyclic ring system having 4, 5, 6 or 7 ring members or a saturated or partially unsaturated bicyclic ring system having 9 or 10 ring members, wherein one or more ring members are heteroatoms independently selected from N, O, or S and the remainder are carbon atoms, and wherein heterocyclyl is optionally substituted, where allowed by available valences, with 1, 2, 3, 4, or 5 substituents each independently selected from R⁶.

[1865] In another aspect described herein, R^{4b} is C₁₋₄alkyl.

[1866] In another aspect described herein, B is heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated monocyclic ring system having 4, 5, 6 or 7 ring members or a saturated or partially unsaturated bicyclic ring system having 9 or 10 ring members, wherein one or more ring members are heteroatoms independently selected from N, O, or S and the remainder are carbon atoms, and wherein heterocyclyl is optionally substituted, where allowed by available valences, with 1, 2, 3, 4, or 5 substituents each independently selected from R⁴.

[1867] In another aspect described herein, B is heterocyclyl selected from the group consisting of:

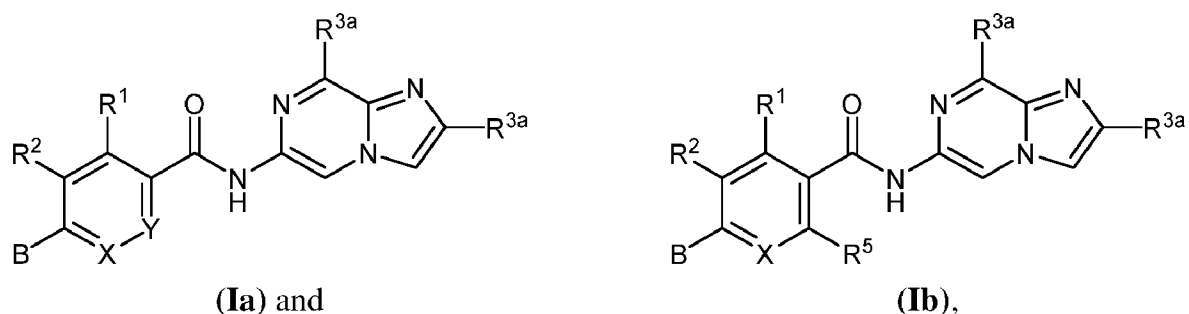


b34.

[1868] In another aspect described herein, R^5 is selected from hydrogen, halogen, C_{1-4} alkoxy, or halo- C_{1-4} alkoxy.

[1869] In another aspect described herein, R^6 is C_{1-4} alkoxy.

[1870] In another aspect described herein, the compound of Formula (XXVII) or a form or composition thereof is selected from a compound of Formula (Ia) or Formula (Ib) or a form or composition thereof:

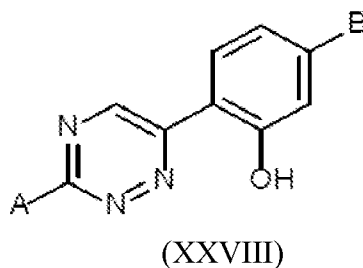


wherein B, X, Y, R^1 , R^2 , R^{3a} , and R^5 are as defined herein, or forms and compositions thereof.

HD Compounds of Formula (XXVIII)

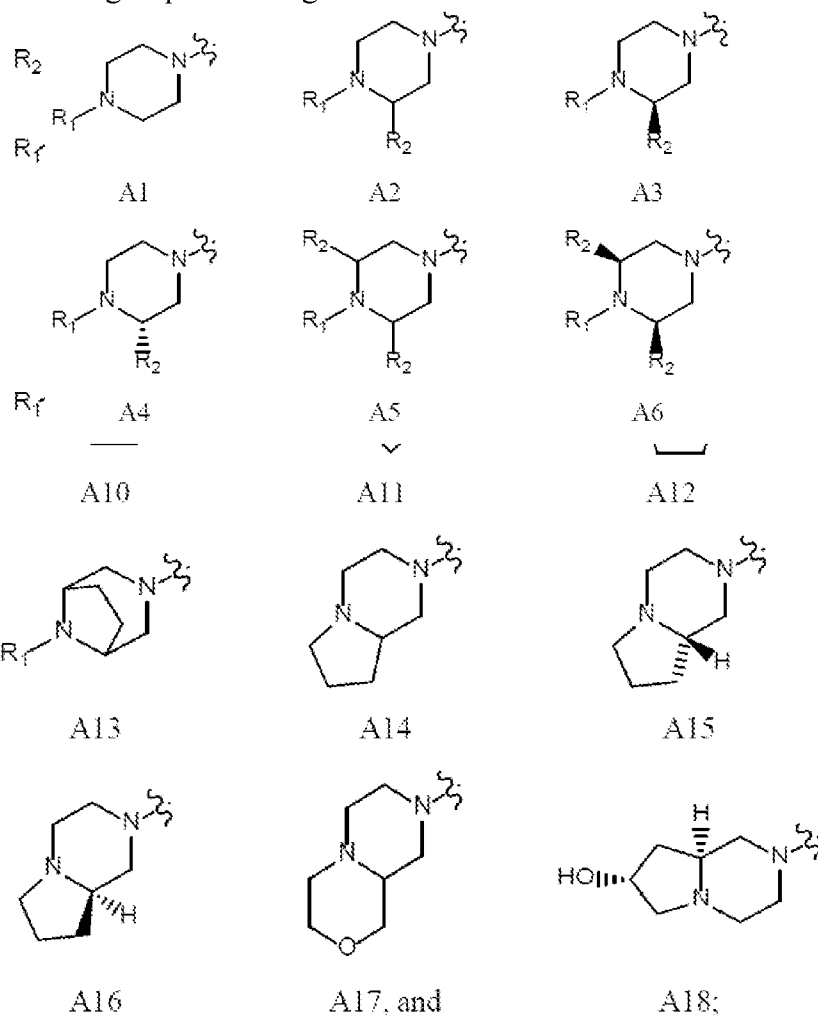
[1871] In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in the Provisional Patent Application No. 63/007650, the content of which is incorporated by reference herein in its entirety.

[1872] In one aspect, an HD compound of the disclosure can refer to a compound of Formula (XXVIII):



or a form thereof, wherein:

A is selected from the group consisting of



R₁ is selected from the group consisting of hydrogen, C₁₋₄alkyl, and C₃₋₆cycloalkyl;

R₂ is independently selected from the group consisting of C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkoxy-C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₆cycloalkyl, phenyl, and pyridinyl, and

wherein each instance of C₃₋₆cycloalkyl, phenyl, and pyridinyl, is optionally substituted with one or two R₃ substituents;

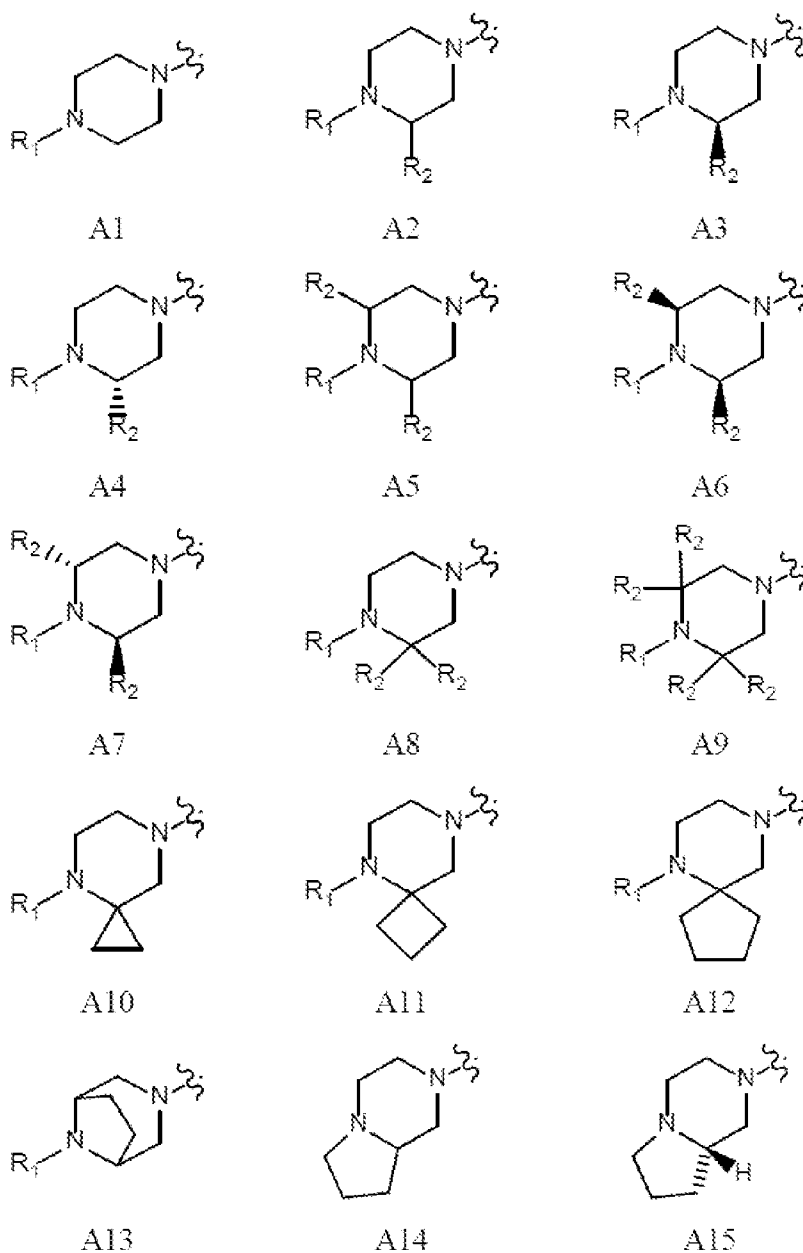
R₃ is independently selected from the group consisting of halogen, hydroxyl, C₁₋₄alkyl, and C₁₋₄alkoxy;

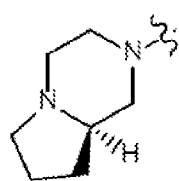
B is heteroaryl, wherein heteroaryl is a 5- or 6- membered monocyclic aromatic carbon atom ring structure radical containing 1, 2 or 3 heteroatoms selected from N, O, and S, optionally substituted with one R₄ substituent; and

R₄ is selected from the group consisting of halogen, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, C₁₋₄alkoxy, deuterio-C₁₋₄alkoxy, and C₃₋₆cycloalkyl;

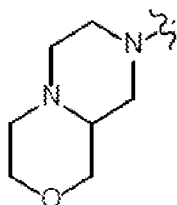
wherein a form of the compound is selected from the group consisting of a salt, hydrate, solvate, and tautomer form thereof.

[1873] One aspect includes a compound of Formula (XXVIII), wherein A is selected from the group consisting of

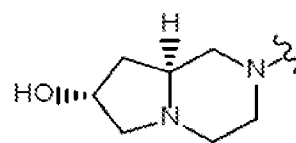




A16

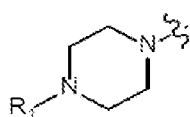


A17, and

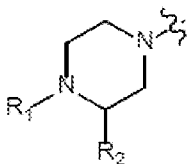


A18.

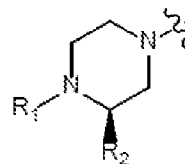
[1874] Another aspect includes a compound of Formula (XXVIII), wherein A is selected from the group consisting of



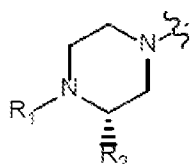
A1



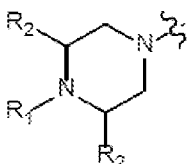
A2



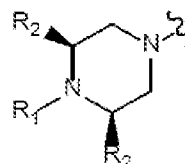
A3



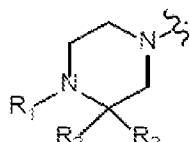
A4



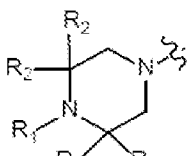
A5



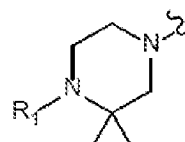
A6



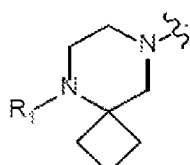
A8



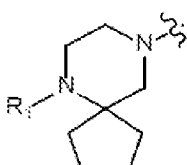
A9



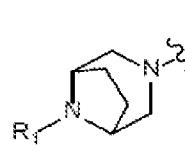
A10



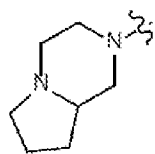
A11



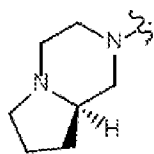
A12



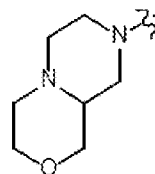
A13



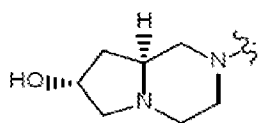
A14



A16

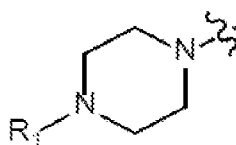


A17, and



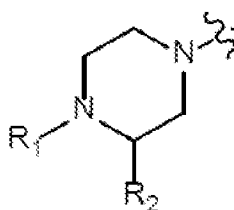
A18;

[1875] Another aspect includes a compound of Formula (XXVIII), wherein A is



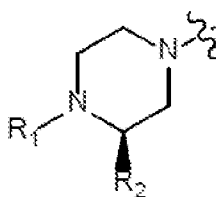
A1.

[1876] Another aspect includes a compound of Formula (XXVIII), wherein A is



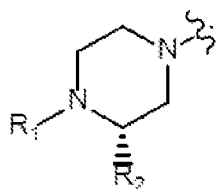
A2.

[1877] Another aspect includes a compound of Formula (XXVIII), wherein A is



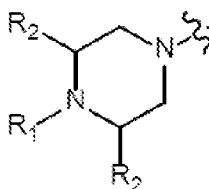
A3.

[1878] Another aspect includes a compound of Formula (XXVIII), wherein A is



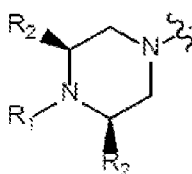
A4.

[1879] Another aspect includes a compound of Formula (XXVIII), wherein A is



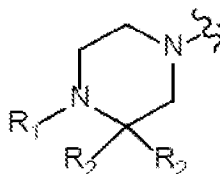
A5.

[1880] Another aspect includes a compound of Formula (XXII), wherein A is



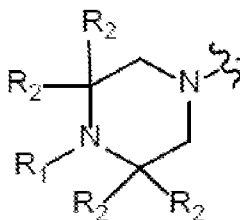
A6.

[1881] Another aspect includes a compound of Formula (XXVIII), wherein A is



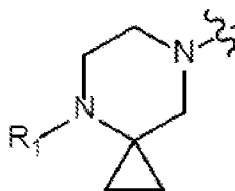
A8.

[1882] Another aspect includes a compound of Formula (XXVIII), wherein A is



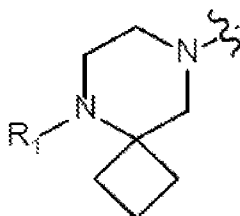
A9.

[1883] Another aspect includes a compound of Formula (XXVIII), wherein A is



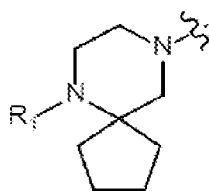
A10.

[1884] Another aspect includes a compound of Formula (XXVIII), wherein A is



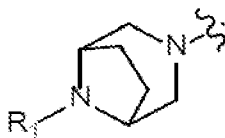
A11.

[1885] Another aspect includes a compound of Formula (XXVIII), wherein A is



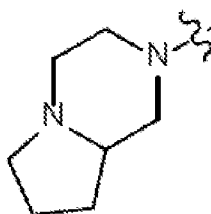
A12.

[1886] Another aspect includes a compound of Formula (XXVIII), wherein A is



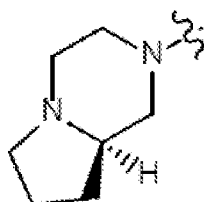
A13.

[1887] Another aspect includes a compound of Formula (XXVIII), wherein A is



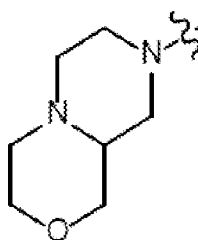
A14.

[1888] Another aspect includes a compound of Formula (XXVIII), wherein A is



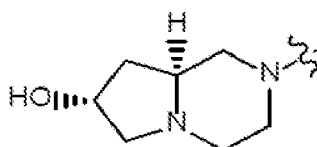
A16.

[1889] Another aspect includes a compound of Formula (XXVIII), wherein A is



A17.

[1890] Another aspect includes a compound of Formula (XXVIII), wherein A is



A18.

[1891] One aspect includes a compound of Formula (XXVIII) wherein R₁ is selected from the group consisting of hydrogen, C₁₋₄alkyl, and C₃₋₆cycloalkyl.

[1892] Another aspect includes a compound of Formula (XXVIII) wherein R₁ is hydrogen.

[1893] Another aspect includes a compound of Formula (XXVIII) wherein R₁ is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1894] Another aspect includes a compound of Formula (XXVIII) wherein R₁ is methyl.

[1895] Another aspect includes a compound of Formula (XXVIII) wherein R₁ is C₃₋₆cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[1896] Another aspect includes a compound of Formula (XXVIII) wherein R₁ is cyclopropyl.

[1897] One aspect includes a compound of Formula (XXVIII) wherein R₂ is independently selected from the group consisting of C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkoxy-C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₆cycloalkyl, phenyl, and pyridinyl, and wherein each instance of C₃₋₆cycloalkyl, phenyl, and pyridinyl, is optionally substituted with one or two R₃ substituents.

[1898] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is independently selected from the group consisting of C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₆cycloalkyl, phenyl, and pyridinyl, and wherein each instance of C₃₋₆cycloalkyl, phenyl, and pyridinyl, is optionally substituted with one or two R₃ substituents.

[1899] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1900] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, and tert-butyl.

[1901] Another aspect includes a compound of Formula (XXVIII), wherein R₂ is hydroxyl-C₁₋₄alkyl, wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, and butyl, partially or completely substituted with one or more hydroxyl groups where allowed by available valences

[1902] Another aspect includes a compound of Formula (XXVIII), wherein R₂ is isopropyl substituted with one hydroxyl group.

[1903] Another aspect includes a compound of Formula (XXVIII), wherein R₂ is 2-hydroxypropan-2-yl.

[1904] Another aspect includes a compound of Formula (XXVIII), wherein R₂ is C₁₋₄alkoxy-C₁₋₄alkyl, wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, and butyl, partially or completely substituted with one or more C₁₋₄alkoxy groups selected from methoxy, ethoxy, propoxy, and butoxy where allowed by available valences.

[1905] Another aspect includes a compound of Formula (XXVIII), wherein R₂ is methoxymethyl.

[1906] Another aspect includes a compound of Formula (XXVIII), wherein R₂ is C₂₋₄alkenyl selected from ethenyl, propenyl, and butenyl.

[1907] Another aspect includes a compound of Formula (XXVIII), wherein R₂ from ethenyl.

[1908] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is C₃₋₆cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl optionally substituted with one or two R₃ substituents.

[1909] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is C₃₋₆cycloalkyl selected from cyclopropyl and cyclobutyl optionally substituted with one or two R₃ substituents.

[1910] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is from unsubstituted cyclopropyl.

[1911] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is cyclopropyl substituted with one or two R₃ substituents.

[1912] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is cyclopropyl substituted with one R₃ substituent.

[1913] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is cyclopropyl substituted with two R₃ substituents.

[1914] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is cyclobutyl optionally substituted with one or two R₃ substituents.

[1915] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is unsubstituted cyclobutyl.

[1916] One aspect includes a compound of Formula (XXVIII) wherein R₂ is phenyl optionally substituted with one or two R₃ substituents.

[1917] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is unsubstituted phenyl.

[1918] One aspect includes a compound of Formula (XXVIII) wherein R₂ is pyridinyl optionally substituted with one or two R₃ substituents.

[1919] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is unsubstituted pyridinyl.

[1920] Another aspect includes a compound of Formula (XXVIII) wherein R₂ is unsubstituted pyridine-4-yl.

[1921] One aspect includes a compound of Formula (XXVIII) wherein R₃ is independently selected from the group consisting of halogen, hydroxyl, C₁₋₄alkyl, and C₁₋₄alkoxy.

[1922] Another aspect includes a compound of Formula (XXVIII) wherein R₃ is independently selected from the group consisting of halogen, hydroxyl, and C₁₋₄alkoxy.

[1923] Another aspect includes a compound of Formula (XXVIII), wherein R₃ is halogen selected from bromo, chloro, fluoro, and iodo.

[1924] Another aspect includes a compound of Formula (XXVIII), wherein R₃ is fluoro.

[1925] Another aspect includes a compound of Formula (XXVIII), wherein R₃ is hydroxyl.

[1926] Another aspect includes a compound of Formula (XXVIII), wherein R₃ is C₁₋₄alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

[1927] Another aspect includes a compound of Formula (XXVIII), wherein R₃ is from methoxy.

[1928] One aspect includes a compound of Formula (XXVIII) wherein B is heteroaryl, wherein heteroaryl is a 5- or 6- membered monocyclic aromatic carbon atom ring structure radical containing 1, 2 or 3 heteroatoms selected from N, O, and S, optionally substituted with one R₄ substituent.

[1929] Another aspect includes a compound of Formula (XXVIII) wherein B is heteroaryl selected from, furanyl, thiophenyl, 1H-pyrazolyl, 1H-imidazolyl, isoxazolyl, 1,3-thiazolyl, 1,3-oxazolyl, tetrazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl, optionally substituted with one R₄ substituent.

[1930] Another aspect includes a compound of Formula (XXVIII) wherein B is heteroaryl selected from, 1H-pyrazolyl, 2H-1,2,3-triazolyl, pyridinyl, and pyrimidinyl, optionally substituted with one R₄ substituent.

[1931] Another aspect includes a compound of Formula (XXVIII) wherein B is heteroaryl selected from, 1H-pyrazolyl, 2H-1,2,3-triazolyl, pyridinyl, and pyrimidinyl, substituted with one R₄ substituent.

[1932] Another aspect includes a compound of Formula (XXVIII) wherein B is unsubstituted heteroaryl selected from, 1H-pyrazolyl, 2H-1,2,3-triazolyl, pyridinyl, and pyrimidinyl.

[1933] Another aspect includes a compound of Formula (XXVIII), wherein B is heteroaryl selected from furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-1-yl, 1H-imidazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, tetrazol-5-yl, 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-5-yl, 2H-1,2,3-triazol-2-yl, 2H-1,2,3-triazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-4-yl, pyrazin-2-yl, pyridazin-3-yl, and pyridazin-4-yl, optionally substituted with one R₄ substituents.

[1934] Another aspect includes a compound of Formula (XXVIII), wherein B is heteroaryl selected from 1H-pyrazol-4-yl, 2H-1,2,3-triazol-2-yl, pyridin-4-yl, and pyrimidin-4-yl, optionally substituted with one R₄ substituents.

[1935] Another aspect includes a compound of Formula (XXVIII), wherein B is heteroaryl selected from 1H-pyrazol-4-yl, 2H-1,2,3-triazol-2-yl, pyridin-4-yl, and pyrimidin-4-yl, substituted with one R₄ substituents.

[1936] Another aspect includes a compound of Formula (XXVIII), wherein B is unsubstituted heteroaryl selected from 1H-pyrazol-4-yl, 2H-1,2,3-triazol-2-yl, pyridin-4-yl, and pyrimidin-4-yl.

[1937] One aspect includes a compound of Formula (XXVIII) wherein R₄ is selected from the group consisting of halogen, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, C₁₋₄alkoxy, deuterio-C₁₋₄alkoxy, and C₃₋₆cycloalkyl.

[1938] Another aspect includes a compound of Formula (XXVIII) wherein R₄ is selected from the group consisting of halogen, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, C₁₋₄alkoxy, and deuterio-C₁₋₄alkoxy.

[1939] Another aspect includes a compound of Formula (XXVIII), wherein R₄ is halogen selected from bromo, chloro, fluoro, and iodo.

[1940] Another aspect includes a compound of Formula (XXVIII), wherein R₄ is fluoro.

[1941] Another aspect includes a compound of Formula (XXVIII) wherein R₄ is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1942] Another aspect includes a compound of Formula (XXVIII) wherein R₄ is methyl.

[1943] Another aspect includes a compound of Formula (XXVIII), wherein R₄ is deuterio-C₁₋₄alkyl wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl partially or completely substituted with one or more deuterium atoms where allowed by available valences.

[1944] Another aspect includes a compound of Formula (XXVIII), wherein R₄ is (2H₃)methyl.

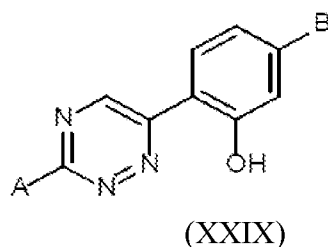
[1945] Another aspect includes a compound of Formula (XXVIII), wherein R₅ is C₁₋₄alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

[1946] Another aspect includes a compound of Formula (XXVIII), wherein R₄ is from methoxy.

HD Compounds of Formula (XXIX)

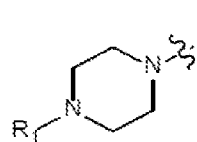
[1947] In one aspect, an HD compound of the disclosure can refer to a compound as disclosed in the Provisional Patent Application No. 63/007660, the content of which is incorporated by reference herein in its entirety.

[1948] In one aspect, an HD compound of the disclosure can refer to a compound of Formula (XXIX):

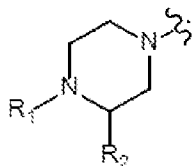


or a form thereof, wherein:

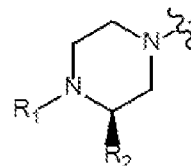
A is selected from the group consisting of



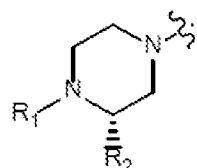
A1



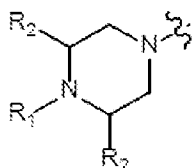
A2



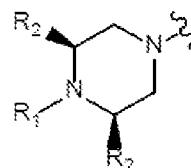
A3



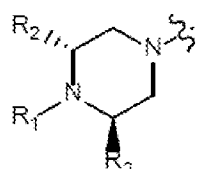
A4



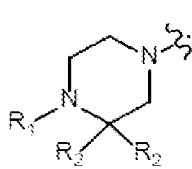
A5



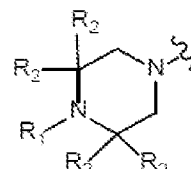
A6



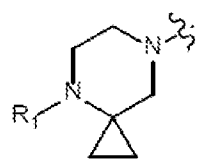
A7



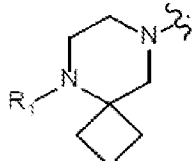
A8



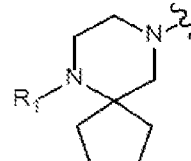
A9



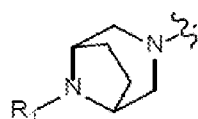
A10



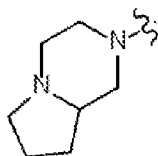
A11



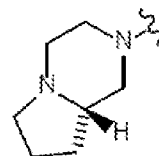
A12



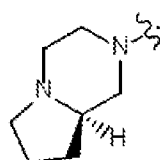
A13



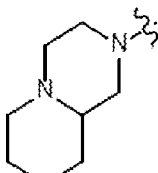
A14,



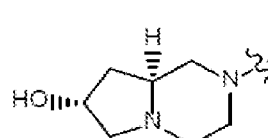
A15,



A16



A17, and



A18;

[1949] R₁ is selected from the group consisting of hydrogen, C₁₋₄alkyl, and C₃₋₆cycloalkyl;

[1950] R₂ is independently selected from the group consisting of C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkoxy-C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₆cycloalkyl, phenyl, and pyridinyl, and

wherein each instance of C₃₋₆cycloalkyl, phenyl, and pyridinyl, is optionally substituted with one or two R₃ substituents;

R₃ is independently selected from the group consisting of halogen, hydroxyl, C₁₋₄alkyl, and C₁₋₄alkoxy;

B is heteroaryl, wherein heteroaryl is a 9- or 10- membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, optionally substituted with one or two independently selected R₄ substituents; and

R₄ is selected from the group consisting of halogen, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, C₁₋₄alkoxy, deuterio-C₁₋₄alkoxy, and C₃₋₆cycloalkyl;

wherein a form of the compound is selected from the group consisting of a salt, hydrate, solvate, and tautomer form thereof.

[1951] One aspect includes a compound of Formula (XXIX) wherein R₁ is selected from the group consisting of hydrogen, C₁₋₄alkyl, and C₃₋₆cycloalkyl.

[1952] Another aspect includes a compound of Formula (XXIX) wherein R₁ is hydrogen.

[1953] Another aspect includes a compound of Formula (XXIX) wherein R₁ is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1954] Another aspect includes a compound of Formula (XXIX) wherein R₁ is selected from methyl and ethyl.

[1955] Another aspect includes a compound of Formula (XXIX) wherein R₁ is methyl. Another aspect includes a compound of Formula (XXIX) wherein R₁ is ethyl.

[1956] Another aspect includes a compound of Formula (XXIX) wherein R₁ is C₃₋₆cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[1957] One aspect includes a compound of Formula (XXIX) wherein R₂ is independently selected from the group consisting of C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, C₁₋₄alkoxy-C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₆cycloalkyl, phenyl, and pyridinyl, and wherein each instance of C₃₋₆cycloalkyl, phenyl, and pyridinyl, is optionally substituted with one or two R₃ substituents.

[1958] Another aspect includes a compound of Formula (XXIX) wherein R₂ is independently selected from the group consisting of C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl, and C₃₋₆cycloalkyl, and

wherein each instance of C₃₋₆cycloalkyl is optionally substituted with one or two R₃ substituents.

[1959] Another aspect includes a compound of Formula (XXIX) wherein R₂ is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[1960] Another aspect includes a compound of Formula (XXIX) wherein R₂ is C₁₋₄alkyl selected from methyl, ethyl, and isopropyl.

[1961] Another aspect includes a compound of Formula (XXIX), wherein R₂ is hydroxyl-C₁₋₄alkyl,

[1962] wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, and butyl, partially or completely substituted with one or more hydroxyl groups where allowed by available valences.

[1963] Another aspect includes a compound of Formula (XXIX), wherein R₂ is isopropyl substituted with one hydroxyl group.

[1964] Another aspect includes a compound of Formula (XXIX), wherein R₂ is hydroxymethyl.

[1965] Another aspect includes a compound of Formula (XXIX) wherein R₂ is C₃₋₆cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl optionally substituted with one or two R₃ substituents.

[1966] Another aspect includes a compound of Formula (XXIX) wherein R₂ is cyclopropyl optionally substituted with one or two R₃ substituents.

[1967] Another aspect includes a compound of Formula (XXIX) wherein R₂ is from unsubstituted cyclopropyl.

[1968] One aspect includes a compound of Formula (XXIX) wherein R₃ is independently selected from the group consisting of halogen, hydroxyl, C₁₋₄alkyl, and C₁₋₄alkoxy.

[1969] One aspect includes a compound of Formula (XXIX) wherein B is heteroaryl, wherein heteroaryl is a 9- or 10- membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, optionally substituted with one or two independently selected R₄ substituents.

[1970] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 1H-indazolyl, 2H-indazolyl, indoliziny, benzofuranyl, benzothiophenyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 7H-puriny, furo[3,2-b]pyridiny, furo[3,2-c]pyridiny, 1,3-oxazolo[5,4-b]pyridiny, thieno[3,2-c]pyridiny, thieno[2,3-d]pyrimidiny, pyrrolo[1,2-a]pyrimidiny, pyrrolo[1,2-a]pyraziny, pyrrolo[1,2-b]pyridaziny, pyrazolo[1,5-a]pyridiny, 1H-pyrrolo[2,3-b]pyridiny, 5H-pyrrolo[2,3-b]pyraziny, 1H-pyrrolo[2,3-c]pyridiny, 1H-pyrazolo[3,4-b]pyridiny, 2H-pyrazolo[3,4-b]pyridiny, 1H-pyrazolo[3,4-b]pyraziny, 1H-pyrazolo[3,4-c]pyridiny, 1H-pyrazolo[4,3-b]pyridiny, 2H-pyrazolo[4,3-b]pyridiny, 2H-pyrazolo[4,3-c]pyridiny, 1H-pyrazolo[4,3-d]pyrimidiny, pyrazolo[1,5-a]pyraziny, imidazo[1,2-a]pyridiny, imidazo[1,2-a]pyrimidiny, imidazo[1,2-a]pyraziny, imidazo[1,2-b]pyridaziny, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridiny, 3H-imidazo[4,5-b]pyridiny, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridiny, [1,2,3]triazolo[1,5-a]pyridiny, 1H-[1,2,3]triazolo[4,5-b]pyridiny, 3H-[1,2,3]triazolo[4,5-b]pyridiny, [1,2,4]triazolo[1,5-a]pyridiny, [1,2,4]triazolo[1,5-a]pyrimidiny, [1,2,4]triazolo[1,5-a]pyraziny, [1,2,4]triazolo[1,5-b]pyridaziny, [1,2,4]triazolo[4,3-a]pyridiny, tetrazolo[1,5-a]pyridiny, tetrazolo[1,5-b]pyridaziny, thiazolo[4,5-b]pyraziny, thiazolo[5,4-c]pyridiny, quinoliny, and isoquinoliny, optionally substituted with one or two independently selected R₄ substituents.

[1971] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2H-indazolyl, 7H-puriny, furo[3,2-b]pyridiny, 2H-pyrazolo[3,4-b]pyridiny, imidazo[1,2-a]pyridiny, imidazo[1,2-a]pyraziny, imidazo[1,2-b]pyridaziny, [1,2,4]triazolo[1,5-a]pyridiny, [1,2,4]triazolo[1,5-a]pyrimidiny, [1,2,4]triazolo[1,5-a]pyraziny, [1,2,4]triazolo[1,5-b]pyridaziny, [1,2,4]triazolo[4,3-a]pyridiny, thiazolo[4,5-b]pyraziny, and thiazolo[5,4-c]pyridiny, optionally substituted with one or two independently selected R₄ substituents.

[1972] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl, wherein heteroaryl is a 9- or 10- membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, substituted with one or two independently selected R₄ substituents.

[1973] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 1H-indazolyl, 2H-indazolyl, indoliziny, benzofuranyl, benzothiophenyl, 1H-

benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 7H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, 1H-pyrrolo[2,3-b]pyridinyl, 5H-pyrrolo[2,3-b]pyrazinyl, 1H-pyrrolo[2,3-c]pyridinyl, 1H-pyrazolo[3,4-b]pyridinyl, 2H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, thiazolo[4,5-b]pyrazinyl, thiazolo[5,4-c]pyridinyl, quinolinyl, and isoquinolinyl, substituted with one or two independently selected R₄ substituents.

[1974] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2H-indazolyl, 7H-purinyl, furo[3,2-b]pyridinyl, 2H-pyrazolo[3,4-b]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-b]pyridazinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, thiazolo[4,5-b]pyrazinyl, and thiazolo[5,4-c]pyridinyl, substituted with one or two independently selected R₄ substituents.

[1975] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl, wherein heteroaryl is a 9- or 10- membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, substituted with one R₄ substituent.

[1976] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothiophenyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 7H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, 1,3-oxazolo[5,4-

b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, 1H-pyrrolo[2,3-b]pyridinyl, 5H-pyrrolo[2,3-b]pyrazinyl, 1H-pyrrolo[2,3-c]pyridinyl, 1H-pyrazolo[3,4-b]pyridinyl, 2H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-c]pyridinyl, 1H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3-c]pyridinyl, 1H-pyrazolo[4,3-d]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5-b]pyridinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5-b]pyridazinyl, thiazolo[4,5-b]pyrazinyl, thiazolo[5,4-c]pyridinyl, quinolinyl, and isoquinolinyl, substituted with one R₄ substituent.

[1977] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2H-indazolyl, 7H-purinyl, furo[3,2-b]pyridinyl, 2H-pyrazolo[3,4-b]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-b]pyridazinyl, [1,2,4]triazolo[1,5-a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, thiazolo[4,5-b]pyrazinyl, and thiazolo[5,4-c]pyridinyl, substituted with one R₄ substituent.

[1978] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl, wherein heteroaryl is a 9- or 10- membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S, substituted with two independently selected R₄ substituents.

[1979] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 1H-indazolyl, 2H-indazolyl, indolizinyl, benzofuranyl, benzothiophenyl, 1H-benzimidazolyl, 1,3-benzoxazolyl, 1,3-benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 7H-purinyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, 1,3-oxazolo[5,4-b]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-d]pyrimidinyl, pyrrolo[1,2-a]pyrimidinyl, pyrrolo[1,2-a]pyrazinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridinyl, 1H-pyrrolo[2,3-b]pyridinyl, 5H-pyrrolo[2,3-b]pyrazinyl, 1H-pyrrolo[2,3-c]pyridinyl, 1H-pyrazolo[3,4-b]pyridinyl, 2H-pyrazolo[3,4-b]pyridinyl, 1H-pyrazolo[3,4-b]pyrazinyl, 1H-pyrazolo[3,4-

c]pyridinyl, 1H-pyrazolo[4,3- b]pyridinyl, 2H-pyrazolo[4,3-b]pyridinyl, 2H-pyrazolo[4,3- c]pyridinyl, 1H-pyrazolo[4,3- d]pyrimidinyl, pyrazolo[1,5-a]pyrazinyl, imidazo[1,2- a]pyridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, [1,3]oxazolo[4,5-b]pyridinyl, [1,2,3]triazolo[1,5-a]pyridinyl, 1H-[1,2,3]triazolo[4,5-b]pyridinyl, 3H-[1,2,3]triazolo[4,5- b]pyridinyl, [1,2,4]triazolo[1,5- a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, 1,2,4]triazolo[1,5-a]pyrazinyl, [1,2,4]triazolo[1,5-b]pyridazinyl, [1,2,4]triazolo[4,3- a]pyridinyl, tetrazolo[1,5-a]pyridinyl, tetrazolo[1,5- b]pyridazinyl, thiazolo[4,5-b]pyrazinyl, thiazolo[5,4-c]pyridinyl, quinolinyl, and isoquinolinyl, substituted with two independently selected R₄ substituents.

[1980] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2H-indazolyl, 7H-purinyl, furo[3,2-b]pyridinyl, 2H-pyrazolo[3,4-b]pyridinyl, imidazo[1,2-a]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-b]pyridazinyl, [1,2,4]triazolo[1,5- a]pyridinyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, 1,2,4]triazolo[1,5- a]pyrazinyl, [1,2,4]triazolo[1,5- b]pyridazinyl, [1,2,4]triazolo[4,3-a]pyridinyl, thiazolo[4,5- b]pyrazinyl, and thiazolo[5,4- c]pyridinyl, substituted with two independently selected R₄ substituents.

[1981] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 1H-indazol-5-yl, 2H-indazol-5-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothiophen-2-yl, benzothiophen-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3- benzotriazol-5-yl, 7H-purin-2-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3- c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3- d]pyrimidin-6-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2- b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, 1H-pyrrolo[2,3- b]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, 1H pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 2H-pyrazolo[3,4-b]pyridine-5- yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4- c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 2H- pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-

yl, pyrazolo[1,5-a]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyrimidin-2-yl, [1,2,4]triazolo[1,5-a]pyrimidin-6-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[1,5-b]pyridazine-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, thiazolo[4,5-b]pyrazin-2-yl, thiazolo[5,4-c]pyridine-2-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, and isoquinolin-6-yl, optionally substituted with one or two independently selected R₄ substituents.

[1982] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2H-indazol-5-yl, 7H-purin-2-yl, furo[3,2-b]pyridine-2-yl, 2H-pyrazolo[3,4-b]pyridin-5-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-b]pyridazin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyrimidin-2-yl, [1,2,4]triazolo[1,5-a]pyrimidin-6-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[1,5-b]pyridazine-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, thiazolo[4,5-b]pyrazin-2-yl, and thiazolo[5,4-c]pyridine-2-yl, optionally substituted with one or two independently selected R₄ substituents.

[1983] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 1H-indazol-5-yl, 2H-indazol-5-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothiophen-2-yl, benzothiophen-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 7H-purin-2-yl, furo[3,2-b]pyridine-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 2H-pyrazolo[3,4-b]pyridine-5-

yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyrimidin-2-yl, [1,2,4]triazolo[1,5-a]pyrimidin-6-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[1,5-b]pyridazine-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, thiazolo[4,5-b]pyrazin-2-yl, thiazolo[5,4-c]pyridine-2-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, and isoquinolin-6-yl, substituted with one R₄ substituent.

[1984] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2H-indazol-5-yl, 7H-purin-2-yl, furo[3,2-b]pyridine-2-yl, 2H-pyrazolo[3,4-b]pyridine-5-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-b]pyridazin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyrimidin-2-yl, [1,2,4]triazolo[1,5-a]pyrimidin-6-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[1,5-b]pyridazine-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, thiazolo[4,5-b]pyrazin-2-yl, and thiazolo[5,4-c]pyridine-2-yl, substituted with one R₄ substituent.

[1985] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 1H-indazol-5-yl, 2H-indazol-5-yl, indolizin-2-yl, benzofuran-2-yl, benzofuran-5-yl, benzothiophen-2-yl, benzothiophen-3-yl, 1H-benzimidazol-2-yl, 1H-benzimidazol-5-yl, 1H-benzimidazol-6-yl, 1,3-benzoxazol-2-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 1,3-benzothiazol-2-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl, 1,3-benzodioxol-5-yl, 1,2,3-benzotriazol-5-yl, 7H-purin-2-yl, furo[3,2-b]pyridin-2-yl, furo[3,2-c]pyridin-2-yl, furo[2,3-c]pyridin-2-yl, 1,3-oxazolo[5,4-b]pyridine-5-yl, thieno[3,2-c]pyridin-2-yl, thieno[2,3-d]pyrimidin-6-yl, pyrrolo[1,2-a]pyrimidin-7-yl, pyrrolo[1,2-a]pyrazin-7-yl, pyrrolo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-5-yl, 1H-pyrrolo[2,3-b]pyridin-5-yl, 5H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-c]pyridin-4-yl, 1H

pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-6-yl, 2H-pyrazolo[3,4-b]pyridine-5-yl, 1H-pyrazolo[3,4-b]pyrazin-5-yl, 1H-pyrazolo[3,4-c]pyridin-1-yl, 1H-pyrazolo[3,4-c]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-5-yl, 1H-pyrazolo[4,3-b]pyridin-6-yl, 2H-pyrazolo[4,3-b]pyridin-5-yl, 2H-pyrazolo[4,3-c]pyridin-5-yl, 1H-pyrazolo[4,3-d]pyrimidin-5-yl, pyrazolo[1,5-a]pyrazin-2-yl, imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrimidin-2-yl, imidazo[1,2-a]pyrimidin-6-yl, imidazo[1,2-a]pyrazin-2-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-b]pyridazin-2-yl, imidazo[1,2-b]pyridazin-6-yl, imidazo[1,2-c]pyrimidin-2-yl, 1H-imidazo[4,5-b]pyridin-5-yl, 3H-imidazo[4,5-b]pyridin-5-yl, imidazo[2,1-b][1,3]thiazol-6-yl, imidazo[2,1-b][1,3,4]thiadiazol-6-yl, [1,3]oxazol[4,5-b]pyridin-2-yl, [1,2,3]triazolo[1,5-a]pyridin-5-yl, [1,2,3]triazolo[1,5-a]pyridin-6-yl, 1H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyrimidin-2-yl, [1,2,4]triazolo[1,5-a]pyrimidin-6-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[1,5-b]pyridazine-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, thiazolo[4,5-b]pyrazin-2-yl, thiazolo[5,4-c]pyridine-2-yl, tetrazolo[1,5-a]pyridin-7-yl, tetrazolo[1,5-b]pyridazin-7-yl, quinolin-6-yl, and isoquinolin-6-yl, substituted with two independently selected R₄ substituents.

[1986] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2H-indazol-5-yl, 7H-purin-2-yl, furo[3,2-b]pyridin-2-yl, 2H-pyrazolo[3,4-b]pyridin-5-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyrazin-6-yl, imidazo[1,2-b]pyridazin-6-yl, [1,2,4]triazolo[1,5-a]pyridin-6-yl, [1,2,4]triazolo[1,5-a]pyrimidin-2-yl, [1,2,4]triazolo[1,5-a]pyrimidin-6-yl, [1,2,4]triazolo[1,5-a]pyrazin-6-yl, [1,2,4]triazolo[1,5-b]pyridazine-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, thiazolo[4,5-b]pyrazin-2-yl, and thiazolo[5,4-c]pyridin-2-yl, substituted with two independently selected R₄ substituents.

[1987] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2-methyl-2H-indazol-5-yl, 8-methyl-7H-purin-2-yl, 2-methyl-2H-pyrazolo[3,4-b]pyridin-5-yl, 2-methylimidazo[1,2-a]pyridin-6-yl, 2-methylimidazo[1,2-a]pyrazin-6-yl, 2-methylimidazo[1,2-b]pyridazin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyridin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyrazin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyrazin-6-yl, and 2-methyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl, optionally substituted with one R₄ substituent.

[1988] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2H-indazol-5-yl, 8-methyl-7H-purin-2-yl, 2-methylimidazo[1,2-a]pyridin-6-yl,

2-methylimidazo[1,2-a]pyrazin-6-yl, 2-methylimidazo[1,2-b]pyridazin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyrazin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyridin-6-yl, and 2-methyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl substituted with one R₄ substituent.

[1989] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2-methyl-2H-indazol-5-yl, 2-methyl-2H-pyrazolo[3,4-b]pyridin-5-yl, 2-methylimidazo[1,2-a]pyrazin-6-yl, 2-methylimidazo[1,2-b]pyridazin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyridin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyrazin-6-yl, and 2-methyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl.

[1990] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2-methyl-2H-indazol-5-yl, 7-cyano-2-methyl-2H-indazol-5-yl, 7-fluoro-2-methyl-2H-indazol-5-yl, 6,8-dimethyl-7H-purin-2-yl, 2-methyl-2H-pyrazolo[3,4-b]pyridin-5-yl, 8-cyano-2-methylimidazo[1,2-a]pyridin-6-yl, 8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl, 2-methylimidazo[1,2-a]pyrazin-6-yl, 2,8-dimethylimidazo[1,2-a]pyrazin-6-yl, 2-methylimidazo[1,2-b]pyridazin-6-yl, 2,8-dimethylimidazo[1,2-b]pyridazin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyridin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyrazin-6-yl, 2,8-dimethyl[1,2,4]triazolo[1,5-a]pyrazin-6-yl, 8-methoxy-2-methyl[1,2,4]triazolo[1,5-a]pyrazin-6-yl, 2-methyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl, 2,8-dimethyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl, and 8-methoxy-2-methyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl.

[1991] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2H-indazol-5-yl, 8-methyl-7H-purin-2-yl, 2-methylimidazo[1,2-a]pyrazin-6-yl, 2-methylimidazo[1,2-b]pyridazin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyrazin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyridin-6-yl, 2-methyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl, and 2-methyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl, optionally substituted with one R₄ substituent.

[1992] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2H-indazol-5-yl, 8-methyl-7H-purin-2-yl, 2-dimethylimidazo[1,2-a]pyrazin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyrazin-6-yl, 2-methyl[1,2,4]triazolo[1,5-a]pyridin-6-yl, 2-methyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl, and 2-methyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl substituted with one R₄ substituent.

[1993] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2-methylimidazo[1,2-a]pyrazin-6-yl and 2-methylimidazo[1,2-b]pyridazin-6-yl.

[1994] Another aspect includes a compound of Formula (XXIX) wherein B is heteroaryl selected from 2-methyl-2H-indazol-5-yl, 7-cyano-2-methyl-2H-indazol-5-yl, 6,8-dimethyl-7H-purin-2-yl, 2-methylimidazo[1,2-a]pyrazin-6-yl, 2,8-dimethylimidazo[1,2-a]pyrazin-6-yl, 2-methylimidazo[1,2-b]pyridazin-6-yl, 2,8-dimethyl[1,2,4]triazolo[1,5-a]pyrazin-6-yl, 8-methoxy-2-methyl[1,2,4]triazolo[1,5-a]pyrazin-6-yl, 2,8-dimethyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl, and 8-methoxy-2-methyl[1,2,4]triazolo[1,5-b]pyridazin-6-yl.

[1995] One aspect includes a compound of Formula (XXIX) wherein R₄ is selected from the group consisting of halogen, cyano, C₁₋₄alkyl, deuterio-C₁₋₄alkyl, halo-C₁₋₄alkyl, C₁₋₄alkoxy, deuterio-C₁₋₄alkoxy, and C₃₋₆cycloalkyl.

[1996] Another aspect includes a compound of Formula (XXIX) wherein R₄ is selected from the group consisting of halogen, cyano, C₁₋₄alkyl, halo-C₁₋₄alkyl, C₁₋₄alkoxy, and C₃₋₆cycloalkyl.

[1997] Another aspect includes a compound of Formula (XXIX), wherein R₄ is halogen selected from bromo, chloro, fluoro, and iodo.

[1998] Another aspect includes a compound of Formula (XXIX), wherein R₄ is fluoro.

[1999] Another aspect includes a compound of Formula (XXIX), wherein R₄ is cyano.

[2000] Another aspect includes a compound of Formula (XXIX) wherein R₄ is C₁₋₄alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

[2001] Another aspect includes a compound of Formula (XXIX) wherein R₄ is methyl.

[2002] Another aspect includes a compound of Formula (XXIX), wherein R₄ is halo-C₁₋₄alkyl wherein C₁₋₄alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl, partially or completely substituted with one or more halogen atoms where allowed by available valences.

[2003] Another aspect includes a compound of Formula (XXIX), wherein R₄ is wherein methyl substituted with two fluorine atoms.

[2004] Another aspect includes a compound of Formula (XXIX), wherein R₄ is C₁₋₄alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

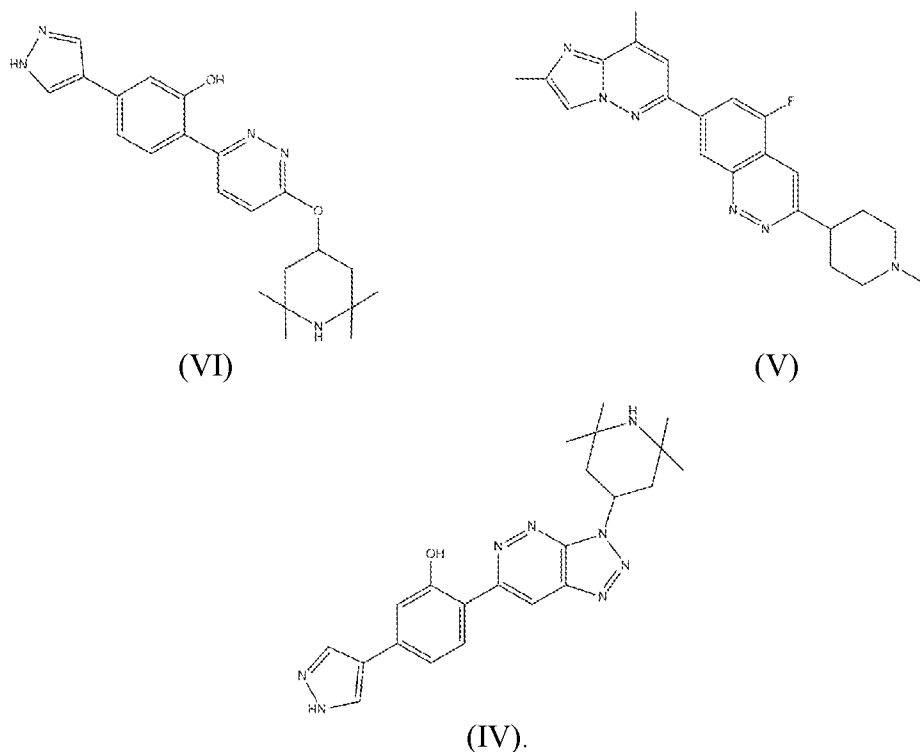
[2005] Another aspect includes a compound of Formula (XXIX), wherein R₄ is from methoxy.

[2006] Another aspect includes a compound of Formula (XXIX) wherein R₄ is C₃₋₆cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[2007] Another aspect includes a compound of Formula (XXIX) wherein R₄ is cyclopropyl.

[2008] In certain aspects, the small molecule splicing modifier (SMSM) composition is not branaplam (LMI070).

[2009] In one aspect, the HD compounds may have the structure of:



Exemplary FD compounds

[2010] Familial dysautonomia (FD, OMIM #223900), also known as Riley–Day syndrome, is an autosomal recessive congenital neuropathy that affects the development and survival of sensory and autonomic neurons. FD is caused by mutations in the IκB kinase complex-associated protein IKBKAP or ELP1 gene in which at least one allele has a T to C transition mutation present at position +6 of the 5' splice donor site in intron 20 resulting in exon 20 exclusion and exon skipping.

[2011] In one aspect, as disclosed herein, FD SMSM compounds, also referred to herein simply as “FD compounds,” can induce splicing at 5' splice sites having the nucleotide sequence of:

5'-NCAA/gtnnnn-3' (SEQ ID NO: 66), or

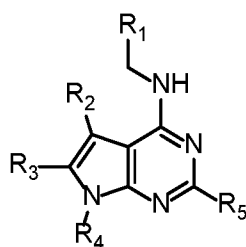
5'-NNNT/gtnnnn-3' (SEQ ID NO: 67),

where N is A, G, C or T and "/" is the splice site (see FIG. 1Ai-ii).

FD compounds of Formula (XLIII)

[2012] In one aspect, an FD compound can refer to a compound as disclosed in the published International PCT Patent No. PCT/US2020/017423, the content of which is incorporated by reference herein in its entirety.

[2013] In one aspect, an FD compound of the disclosure can refer to a compound of Formula (XLIII):



(XLIII)

or a form thereof, wherein:

R₁ is phenyl or heteroaryl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents,

wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S;

R_{1a} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, deuterio-C₁₋₆alkyl, or C₁₋₆alkoxy;

R₂ is hydrogen, halo, or C₁₋₆alkyl;

R₃ is C₂₋₆alkyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents,

wherein C₂₋₆alkyl may optionally contain a chiral carbon having an (*R*) or (*S*) configuration;

R_{3a} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, deuterio-C₁₋₆alkyl, C₁₋₆alkoxy, amino, C₁₋₆alkyl-amino, deuterio-C₁₋₆alkyl-amino, and (C₁₋₆alkyl)₂-amino;

R₄ is hydrogen, C₁₋₆alkyl, or phenyl,

wherein each instance of C₁₋₆alkyl or phenyl are optionally substituted with one, two, three, or four independently selected R_{4a} substituents; and

R_{4a} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, or C₁₋₆alkoxy;

R₅ is hydrogen, halo, or C₁₋₆alkyl;

wherein the form of the compound is selected from the group consisting of a salt, hydrate, solvate, and tautomer form thereof.

[2014] One aspect includes a compound of Formula (XLIII), wherein R₁ is phenyl or heteroaryl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents, wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S.

[2015] Another aspect includes a compound of Formula (XLIII), wherein R₁ is phenyl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents.

[2016] Another aspect includes a compound of Formula (XLIII), wherein R₁ is phenyl, optionally substituted with one R_{1a} substituent.

[2017] Another aspect includes a compound of Formula (XLIII), wherein R₁ is heteroaryl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents, wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S.

[2018] Another aspect includes a compound of Formula (XLIII), wherein R₁ is heteroaryl, optionally substituted with one R_{1a} substituent, wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S.

[2019] Another aspect of includes a compound of Formula (XLIII), wherein R₁ is heteroaryl selected from furanyl, thiophenyl, 1*H*-pyrazolyl, 1*H*-imidazolyl, isoxazolyl, 1,3-thiazolyl, 1,3-oxazolyl, tetrazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzofuranyl, and quinolinyl, wherein heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2020] Another aspect of includes a compound of Formula (XLIII), wherein R₁ is heteroaryl selected from furanyl, thiophenyl, 1,3-thiazolyl, 1,3-oxazolyl, and pyridinyl, wherein heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2021] Another aspect includes a compound of Formula (XLIII), wherein R_1 is heteroaryl selected from furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, 1*H*-pyrazol-3-yl, 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1*H*-imidazol-1-yl, 1*H*-imidazol-4-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, tetrazol-5-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-4-yl, pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, benzofuran-2-yl, benzofuran-5-yl, and quinoline-4-yl, wherein heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2022] Another aspect includes a compound of Formula (XLIII), wherein R_1 is heteroaryl selected from furan-2-yl, furan-3-yl, thiophen-2-yl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl, wherein heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2023] One aspect includes a compound of Formula (XLIII), wherein R_{1a} is cyano, halo, hydroxy, C_{1-6} alkyl, halo- C_{1-6} alkyl, deuterio- C_{1-6} alkyl, or C_{1-6} alkoxy.

[2024] Another aspect includes a compound of Formula (XLIII), wherein R_{1a} is halo.

[2025] Another aspect includes a compound of Formula (XLIII), wherein R_{1a} is halo selected from fluoro, chloro, bromo, and iodo.

[2026] Another aspect includes a compound of Formula (XLIII), wherein R_{1a} is fluoro.

[2027] One aspect includes a compound of Formula (XLIII), wherein R_2 is hydrogen, halo, or C_{1-6} alkyl.

[2028] Another aspect includes a compound of Formula (XLIII), wherein R_2 is hydrogen.

[2029] Another aspect includes a compound of Formula (XLIII), wherein R_2 is halo.

[2030] Another aspect includes a compound of Formula (XLIII), wherein R_2 is halo selected from fluoro, chloro, bromo, and iodo.

[2031] Another aspect includes a compound of Formula (XLIII), wherein R_2 is halo selected from fluoro, chloro, and bromo.

[2032] Another aspect includes a compound of Formula (XLIII), wherein R_2 is C_{1-6} alkyl.

[2033] Another aspect includes a compound of Formula (XLIII), wherein R₂ is C₁₋₆alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl, or isohexyl.

[2034] Another aspect includes a compound of Formula (XLIII), wherein R₂ is C₁₋₆alkyl selected from methyl and butyl.

[2035] One aspect includes a compound of Formula (XLIII), wherein R₃ is C₂₋₆alkyl, optionally containing a chiral carbon having an (*R*) or (*S*) configuration.

[2036] Another aspect includes a compound of Formula (XLIII), wherein R₃ is C₂₋₆alkyl, optionally substituted with one, two, three, or four, independently selected R_{3a} substituents.

[2037] Another aspect includes a compound of Formula (XLIII), wherein R₃ is C₂₋₆alkyl selected from ethyl, propyl, butyl, pentyl, and hexyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2038] Another aspect includes a compound of Formula (XLIII), wherein R₃ is C₂₋₆alkyl selected from ethyl, propyl, butyl, and pentyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2039] Another aspect includes a compound of Formula (XLIII), wherein R₃ is C₂₋₆alkyl selected from ethyl, propyl, butyl, pentyl, and hexyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C₂₋₆alkyl contains a chiral carbon having an (*R*) configuration.

[2040] Another aspect includes a compound of Formula (XLIII), wherein R₃ is C₂₋₆alkyl selected from ethyl, propyl, butyl, and pentyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C₂₋₆alkyl contains a chiral carbon having an (*R*) configuration.

[2041] Another aspect includes a compound of Formula (XLIII), wherein R₃ is C₂₋₆alkyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein, C₂₋₆alkyl contains a chiral carbon having an (*S*) configuration.

[2042] Another aspect includes a compound of Formula (XLIII), wherein R₃ is C₂₋₆alkyl selected from ethyl, propyl, butyl, pentyl, and hexyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C₂₋₆alkyl contains a chiral carbon having an (*S*) configuration.

[2043] Another aspect includes a compound of Formula (XLIII), wherein R_3 is C_{2-6} alkyl selected from ethyl, propyl, butyl, and pentyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{2-6} alkyl optionally contains a chiral carbon having an (*S*) configuration.

[2044] One aspect includes a compound of Formula (XLIII), wherein R_{3a} is cyano, halo, hydroxy, C_{1-6} alkyl, halo- C_{1-6} alkyl, deuterio- C_{1-6} alkyl, C_{1-6} alkoxy, amino, C_{1-6} alkyl-amino, deuterio- C_{1-6} alkyl-amino, and $(C_{1-6}alkyl)_2$ -amino.

[2045] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, C_{1-6} alkyl-amino, deuterio- C_{1-6} alkyl-amino, and $(C_{1-6}alkyl)_2$ -amino.

[2046] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is hydroxy.

[2047] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is C_{1-6} alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl, and isohexyl.

[2048] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is C_{1-6} alkyl selected from methyl, ethyl, isopropyl, and tert-butyl.

[2049] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is C_{1-6} alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, iso-butoxy, tert-butoxy, pentoxy, and hexyloxy.

[2050] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} methoxy.

[2051] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is amino.

[2052] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, and tert-butyl.

[2053] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is methyl.

[2054] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is deuterio- C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, and tert-butyl partially or completely substituted with one or more deuterium atoms where allowed by available valences.

[2055] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is deuterio- C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is methyl substituted three deuterium atoms.

[2056] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is $(C_{1-6}alkyl)_2$ -amino, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, and tert-butyl.

[2057] Another aspect includes a compound of Formula (XLIII), wherein R_{3a} is $(C_{1-6}alkyl)_2$ -amino, wherein C_{1-6} alkyl is methyl.

[2058] One aspect includes a compound of Formula (XLIII), wherein R_4 is hydrogen, C_{1-6} alkyl, or phenyl, wherein C_{1-6} alkyl or phenyl are optionally substituted with one, two, three, or four independently selected R_{4a} substituents.

[2059] Another aspect includes a compound of Formula (XLIII), wherein R_4 is hydrogen.

[2060] Another aspect includes a compound of Formula (XLIII), wherein R_4 is C_{1-6} alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl, and isohexyl, optionally substituted with one, two, three, or four independently selected R_{4a} substituents.

[2061] Another aspect includes a compound of Formula (XLIII), wherein R_4 is C_{1-6} alkyl selected from methyl and ethyl, optionally substituted with one, two, three, or four independently selected R_{4a} substituents.

[2062] Another aspect includes a compound of Formula (XLIII), wherein R_4 is phenyl, optionally substituted with one, two, three, or four independently selected R_{4a} substituents.

[2063] One aspect includes a compound of Formula (XLIII), wherein R_{4a} is cyano, halo, hydroxy, C_{1-6} alkyl, halo- C_{1-6} alkyl, or C_{1-6} alkoxy.

[2064] Another aspect includes a compound of Formula (XLIII), wherein R_{4a} is C_{1-6} alkoxy.

[2065] Another aspect includes a compound of Formula (XLIII), wherein R_{4a} is C_{1-6} alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, iso-butoxy, tert-butoxy, pentoxy, and hexyloxy.

[2066] Another aspect includes a compound of Formula (XLIII), wherein R_{4a} is methoxy.

[2067] One aspect includes a compound of Formula (XLIII), wherein R_5 is hydrogen, halo, or C_{1-6} alkyl.

[2068] One aspect includes a compound of Formula (XLIII), wherein R₅ is hydrogen, halo, or C₁₋₆alkyl.

[2069] Another aspect includes a compound of Formula (XLIII), wherein R₅ is halo.

[2070] Another aspect includes a compound of Formula (XLIII), wherein R₅ is halo selected from fluoro, chloro, bromo, and iodo.

[2071] Another aspect includes a compound of Formula (XLIII), wherein R₅ is chloro or bromo.

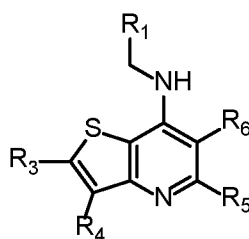
[2072] Another aspect includes a compound of Formula (XLIII), wherein R₅ is chloro.

[2073] Another aspect includes a compound of Formula (XLIII), wherein R₅ is bromo.

FD compounds of Formula (XLIV)

[2074] In one aspect, an FD compound can refer to a compound as disclosed in the published International PCT Patent No. PCT/US2020/017430, the content of which is incorporated by reference herein in its entirety.

[2075] In one aspect, an FD compound of the disclosure can refer to a compound of Formula (XLIV):



(XLIV)

or a form thereof, wherein:

R₁ is phenyl or heteroaryl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents,

wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S;

R_{1a} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, or C₁₋₆alkoxy;

R₃ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, and C₁₋₆alkyl-amino,

wherein C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl is optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and

wherein each instance of C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl may optionally contain a chiral carbon having an (*R*) or (*S*) configuration;

R_{3a} is cyano, halo, hydroxy, oxo, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, carboxyl, amino, C₁₋₆alkoxy-carbonyl, C₁₋₆alkyl-amino, halo-C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, phenyl-amino, heterocyclyl-amino, heteroaryl-amino, phenyl-(C₁₋₆alkyl)-amino, heterocyclyl-(C₁₋₆alkyl)-amino, heteroaryl-(C₁₋₆alkyl)-amino, C₁₋₆alkyl-thio, C₁₋₆alkyl-sulfoxyl, and C₁₋₆alkyl-sulfonyl,

wherein heterocyclyl is a 3-7 membered monocyclic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S,

wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S;

wherein each instance of phenyl, heterocyclyl, and heteroaryl is optionally substituted with one, two, three or four independently selected R_{3a'} substituents;

R_{3a'} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, or amino;

R₄ is hydrogen, cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, C₃₋₁₀cycloalkyl, phenyl, heterocyclyl, or heteroaryl,

wherein heterocyclyl is a 3-7 membered monocyclic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S,

wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S, and

wherein each instance of C₁₋₆alkyl, C₃₋₁₀cycloalkyl, phenyl, heterocyclyl, or heteroaryl are optionally substituted with one, two, three, or four independently selected R_{4a} substituents;

R_{4a} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, or C₁₋₆alkoxy;

R₅ is hydrogen, cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, carbamoyl, C₃₋₁₀cycloalkyl, or heterocyclyl,

wherein heterocyclyl is a 3-7 membered monocyclic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S; and

R₆ is hydrogen, halo, or C₁₋₆alkyl;

wherein the form of the compound is selected from the group consisting of a salt, hydrate, solvate, and tautomer form thereof.

[2076] One aspect includes a compound of Formula (XLIV), wherein R₁ is phenyl or heteroaryl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents, wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S.

[2077] Another aspect includes a compound of Formula (XLIV), wherein R₁ is phenyl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents.

[2078] Another aspect includes a compound of Formula (XLIV), wherein R₁ is phenyl, optionally substituted with one R_{1a} substituent.

[2079] Another aspect includes a compound of Formula (XLIV), wherein R₁ is heteroaryl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents, wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S.

[2080] Another aspect includes a compound of Formula (XLIV), wherein R₁ is heteroaryl, optionally substituted with one R_{1a} substituent, wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S.

[2081] Another aspect of includes a compound of Formula (XLIV), wherein R₁ is heteroaryl selected from furanyl, thiophenyl, 1*H*-pyrazolyl, 1*H*-imidazolyl, isoxazolyl, 1,3-thiazolyl, 1,3-oxazolyl, tetrazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzofuranyl, and quinolinyl, wherein heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2082] Another aspect of includes a compound of Formula (XLIV), wherein R₁ is heteroaryl selected from furanyl, thiophenyl, 1,3-thiazolyl, and pyridinyl, wherein heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2083] Another aspect includes a compound of Formula (XLIV), wherein R₁ is heteroaryl selected from furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, 1*H*-pyrazol-1-yl, 1*H*-pyrazol-3-yl, 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1*H*-imidazol-1-yl, 1*H*-imidazol-4-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, tetrazol-5-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-4-yl, pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, benzofuran-2-yl, benzofuran-5-yl, and quinoline-4-yl, wherein, heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2084] Another aspect includes a compound of Formula (XLIV), wherein R₁ is heteroaryl selected from furan-2-yl, thiophen-2-yl, 1,3-thiazol-2-yl, and pyridin-4-yl, wherein heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2085] One aspect includes a compound of Formula (XLIV), wherein R_{1a} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, or C₁₋₆alkoxy.

[2086] Another aspect includes a compound of Formula (XLIV), wherein R_{1a} is halo.

[2087] Another aspect includes a compound of Formula (XLIV), wherein R_{1a} is halo selected from fluoro, chloro, bromo, and iodo.

[2088] Another aspect includes a compound of Formula (XLIV), wherein R_{1a} is fluoro.

[2089] One aspect includes a compound of Formula (XLIV), wherein R₃ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, or C₁₋₆alkyl-amino,

[2090] wherein each instance of C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl is optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and

[2091] wherein each instance of C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl may optionally contain a chiral carbon having an (*R*) or (*S*) configuration.

[2092] Another aspect includes a compound of Formula (XLIV), wherein R₃ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, or C₂₋₆alkynyl, optionally substituted with one, two, three, or four, independently selected R_{3a} substituents, wherein C₁₋₆alkyl, C₂₋₆alkenyl, or C₂₋₆alkynyl may optionally contain a chiral carbon having an (*R*) or (*S*) configuration.

[2093] Another aspect includes a compound of Formula (XLIV), wherein R₃ is hydrogen.

[2094] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl, optionally substituted with one, two, three, or four, independently selected R_{3a} substituents, and wherein, C_{1-6} alkyl optionally contains a chiral carbon having an (*R*) or (*S*) configuration.

[2095] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2096] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2097] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl selected from methyl, ethyl, propyl, butyl, and pentyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2098] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{1-6} alkyl optionally contains a chiral carbon having an (*R*) configuration.

[2099] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{1-6} alkyl optionally contains a chiral carbon having an (*R*) configuration.

[2100] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl selected from methyl, ethyl, propyl, butyl, and pentyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{1-6} alkyl optionally contains a chiral carbon having an (*R*) configuration.

[2101] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{1-6} alkyl optionally contains a chiral carbon having an (*S*) configuration.

[2102] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{1-6} alkyl optionally contains a chiral carbon having an (*S*) configuration.

[2103] Another aspect includes a compound of Formula (XLIV), wherein R₃ is C₁₋₆alkyl selected from methyl, ethyl, propyl, butyl, and pentyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C₁₋₆alkyl optionally contains a chiral carbon having an (*S*) configuration.

[2104] Another aspect includes a compound of Formula (XLIV), wherein R₃ is C₂₋₆alkenyl, optionally substituted with one, two, three, or four, independently selected R_{3a} substituents, and wherein, C₂₋₆alkenyl optionally contains a chiral carbon having an (*R*) or (*S*) configuration.

[2105] Another aspect includes a compound of Formula (XLIV), wherein R₃ is C₂₋₆alkenyl selected from ethenyl, propenyl, butenyl, pentenyl, hexenyl, and heptenyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2106] Another aspect includes a compound of Formula (XLIV), wherein R₃ is butenyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2107] Another aspect includes a compound of Formula (XLIV), wherein R₃ is C₂₋₆alkenyl selected from ethenyl, propenyl, butenyl, pentenyl, hexenyl, and heptenyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C₂₋₆alkenyl optionally contains a chiral carbon having an (*R*) configuration.

[2108] Another aspect includes a compound of Formula (XLIV), wherein R₃ is butenyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C₂₋₆alkenyl optionally contains a chiral carbon having an (*R*) configuration.

[2109] Another aspect includes a compound of Formula (XLIV), wherein R₃ is C₂₋₆alkynyl, optionally substituted with one, two, three, or four, independently selected R_{3a} substituents, and wherein, C₂₋₆alkynyl optionally contains a chiral carbon having an (*R*) or (*S*) configuration.

[2110] Another aspect includes a compound of Formula (XLIV), wherein R₃ is C₂₋₆alkenyl selected from ethenyl, propenyl, butenyl, pentenyl, hexenyl, and heptenyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C₂₋₆alkenyl optionally contains a chiral carbon having an (*S*) configuration.

[2111] Another aspect includes a compound of Formula (XLIV), wherein R₃ is butenyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C₂₋₆alkenyl optionally contains a chiral carbon having an (*S*) configuration.

[2112] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{2-6} alkynyl selected from ethynyl, propynyl, butynyl, pentynyl, hexynyl, and heptynyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2113] Another aspect includes a compound of Formula (XLIV), wherein R_3 is butynyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2114] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{2-6} alkynyl selected from ethynyl, propynyl, butynyl, pentynyl, hexynyl, and heptynyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{2-6} alkynyl optionally contains a chiral carbon having an (*R*) configuration.

[2115] Another aspect includes a compound of Formula (XLIV), wherein R_3 is butynyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{2-6} alkynyl optionally contains a chiral carbon having an (*R*) configuration.

[2116] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{2-6} alkynyl selected from ethynyl, propynyl, butynyl, pentynyl, hexynyl, and heptynyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{2-6} alkynyl optionally contains a chiral carbon having an (*S*) configuration.

[2117] Another aspect includes a compound of Formula (XLIV), wherein R_3 is butynyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{2-6} alkynyl optionally contains a chiral carbon having an (*S*) configuration.

[2118] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl-amino, optionally substituted with one, two, three, or four, independently selected R_{3a} substituents, and wherein, C_{1-6} alkyl optionally contains a chiral carbon having an (*R*) or (*S*) configuration.

[2119] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl-amino, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2120] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, and tert-butyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2121] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is propyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2122] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl-amino, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{1-6} alkyl optionally contains a chiral carbon having an (*R*) configuration.

[2123] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, and tert-butyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{1-6} alkyl optionally contains a chiral carbon having an (*R*) configuration.

[2124] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is propyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{1-6} alkyl optionally contains a chiral carbon having an (*R*) configuration.

[2125] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl-amino, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{1-6} alkyl optionally contains a chiral carbon having an (*S*) configuration.

[2126] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, and tert-butyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{1-6} alkyl optionally contains a chiral carbon having an (*S*) configuration.

[2127] Another aspect includes a compound of Formula (XLIV), wherein R_3 is C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is propyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents, and wherein C_{1-6} alkyl optionally contains a chiral carbon having an (*S*) configuration.

[2128] Another aspect includes a compound of Formula (XLIV), wherein R₃ is C₃₋₁₀cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, optionally substituted with one, two, three or four independently selected R_{3a} substituents.

[2129] Another aspect includes a compound of Formula (XLIV), wherein R₃ is cyclopropyl or cyclopentyl, optionally substituted with one, two, three or four independently selected R_{3a} substituents.

[2130] Another aspect includes a compound of Formula (XLIV), wherein R₃ is heterocyclyl, optionally substituted with one, two, three, or four, independently selected R_{3a} substituents, wherein heterocyclyl is a 3-7 membered monocyclic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S, and wherein heterocyclyl optionally contains a chiral carbon having an (*R*) or (*S*) configuration.

[2131] Another aspect includes a compound of Formula (XLIV), wherein R₃ is heterocyclyl selected from azetidiny, oxetanyl, pyrazolidiny, tetrahydrofuranyl, oxazolidiny, thiazolidiny, isothiazolidiny, pyrrolidiny, piperidiny, piperaziny, 2H-pyranyl, tetrahydropyranyl, morpholinyl, 1,3-oxazinanyl, and azepanyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2132] Another aspect includes a compound of Formula (XLIV), wherein R₃ is azetidiny, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2133] Another aspect includes a compound of Formula (XLIV), wherein R₃ is heterocyclyl selected from azetidin-2-yl, azetidin-3-yl, oxetan-2-yl, oxetan-3-yl, pyrazolidine-1-yl, pyrazolidine-2-yl, pyrazolidine-3-yl, pyrazolidine-4-yl, pyrazolidine-5-yl, tetrahydrofuran-1-yl, tetrahydrofuran-2-yl, oxazolidin-2-yl, oxazolidin-4-yl, oxazolidine-5-yl, thiazolidin-2-yl, thiazolidin-4-yl, thiazolidin-5-yl, isothiazolidin-3-yl, isothiazolidin-4-yl, isothiazolidin-5-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, 2H-pyran-2-yl, 2H-pyran-3-yl, 2H-pyran-4-yl, 2H-pyran-5-yl, 2H-pyran-6-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, 1,3-oxazinan-2-yl, 1,3-oxazinan-3-yl, 1,3-oxazinan-4-yl, azepan-1-yl, azepan-2-yl, azepan-3-yl, and azepan-4-yl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2134] Another aspect includes a compound of Formula (XLIV), wherein R₃ is azetidin-3-yl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2135] One aspect includes a compound of Formula (XLIV), wherein R_{3a} is cyano, halo, hydroxy, oxo, C_{1-6} alkyl, halo- C_{1-6} alkyl, C_{1-6} alkoxy, halo- C_{1-6} alkoxy, carboxyl, amino, C_{1-6} alkoxy-carbonyl, C_{1-6} alkyl-amino, halo- C_{1-6} alkyl-amino, $(C_{1-6}alkyl)_2$ -amino, phenyl-amino, heterocyclyl-amino, heteroaryl-amino, phenyl- $(C_{1-6}alkyl)$ -amino, heterocyclyl- $(C_{1-6}alkyl)$ -amino, heteroaryl- $(C_{1-6}alkyl)$ -amino, C_{1-6} alkyl-thio, C_{1-6} alkyl-sulfoxyl, or C_{1-6} alkyl-sulfonyl wherein each instance of C_{3-10} cycloalkyl, phenyl, heterocyclyl and heteroaryl is optionally substituted with one, two, three or four independently selected $R_{3a'}$ substituents.

[2136] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is cyano, halo, hydroxy, oxo, C_{1-6} alkyl, C_{1-6} alkoxy, halo- C_{1-6} alkoxy, carboxyl, amino, C_{1-6} alkoxy-carbonyl, C_{1-6} alkyl-amino, halo- C_{1-6} alkyl-amino, $(C_{1-6}alkyl)_2$ -amino, phenyl-amino, heteroaryl-amino, phenyl- $(C_{1-6}alkyl)$ -amino, heterocyclyl- $(C_{1-6}alkyl)$ -amino, heteroaryl- $(C_{1-6}alkyl)$ -amino, C_{1-6} alkyl-thio, C_{1-6} alkyl-sulfoxyl, or C_{1-6} alkyl-sulfonyl, wherein heterocyclyl is a 3-7 membered monocyclic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S, wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S, and wherein each instance of C_{3-10} cycloalkyl, phenyl, heterocyclyl and heteroaryl is optionally substituted with one, two, three or four independently selected $R_{3a'}$ substituents.

[2137] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is cyano.

[2138] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is halo selected from fluoro, chloro, bromo, and iodo.

[2139] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is fluoro.

[2140] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is hydroxy.

[2141] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is oxo.

[2142] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkyl selected from C_{1-6} alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl.

[2143] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkyl selected from methyl and isopropyl.

[2144] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, iso-butoxy, tert-butoxy, pentoxy, and hexyloxy.

[2145] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is methoxy.

[2146] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is halo- C_{1-6} alkoxy wherein C_{1-6} alkoxy is selected from methoxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, iso-butoxy, tert-butoxy, pentoxy, and hexyloxy partially or completely substituted with one or more halogen atoms where allowed by available valences.

[2147] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is halo- C_{1-6} alkoxy, wherein C_{1-6} alkoxy is methoxy substituted with three fluorine atoms.

[2148] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is carboxyl.

[2149] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is amino.

[2150] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkoxy-carbonyl wherein C_{1-6} alkoxy is selected from methoxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, iso-butoxy, tert-butoxy, pentoxy, and hexyloxy.

[2151] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkoxy-carbonyl wherein C_{1-6} alkoxy is methoxy.

[2152] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, and hexyl.

[2153] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is methyl.

[2154] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is halo- C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, and hexyl partially or completely substituted with one or more halogen atoms where allowed by available valences.

[2155] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is halo- C_{1-6} alkyl-amino, wherein C_{1-6} alkyl is methyl substituted with three fluorine atoms.

[2156] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is $(C_{1-6}alkyl)_2$ -amino, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, and hexyl.

[2157] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is (C₁₋₆alkyl)₂-amino, wherein C₁₋₆alkyl is methyl.

[2158] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is phenyl-amino, wherein phenyl is optionally substituted with one, two, three or four independently selected R_{3a'} substituents.

[2159] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is phenyl-amino wherein phenyl is optionally substituted with one independently selected R_{3a'} substituents.

[2160] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is heteroaryl-amino, wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S, wherein heteroaryl is optionally substituted with one, two, three or four independently selected R_{3a'} substituents.

[2161] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is heteroaryl-amino, wherein heteroaryl is selected from furanyl, thiophenyl, 1*H*-pyrazolyl, 1*H*-imidazolyl, isoxazolyl, 1,3-thiazolyl, 1,3-oxazolyl, tetrazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzofuranyl, and quinolinyl, wherein heteroaryl is optionally substituted with one, two, three or four independently selected R_{3a'} substituents.

[2162] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is heteroaryl-amino, wherein heteroaryl is selected 1*H*-pyrazolyl, pyridinyl, and pyrazinyl, wherein each instance is optionally substituted with one, two, three or four independently selected R_{3a'} substituents.

[2163] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is phenyl-(C₁₋₆alkyl)-amino, wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl, wherein phenyl is optionally substituted with one, two, three, or four independently selected R_{3a'} substituents.

[2164] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is phenyl-(C₁₋₆alkyl)-amino, wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl, wherein phenyl is optionally substituted with one independently selected R_{3a'} substituents.

[2165] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is phenyl-(C₁₋₆alkyl)-amino, wherein C₁₋₆alkyl is methyl.

[2166] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkyl-thio, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, and hexyl.

[2167] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkyl-thio, wherein C_{1-6} alkyl is methyl.

[2168] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkyl-sulfoxyl, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, and hexyl.

[2169] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkyl-sulfoxyl, wherein C_{1-6} alkyl is methyl.

[2170] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkyl-sulfonyl, wherein C_{1-6} alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, and hexyl.

[2171] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is C_{1-6} alkyl-sulfonyl, wherein C_{1-6} alkyl is methyl.

[2172] One aspect includes a compound of Formula (XLIV), wherein $R_{3a'}$ is cyano, halo, hydroxy, C_{1-6} alkyl, halo- C_{1-6} alkyl, C_{1-6} alkoxy, or amino.

[2173] Another aspect includes a compound of Formula (XLIV), wherein $R_{3a'}$ is halo or C_{1-6} alkyl.

[2174] Another aspect includes a compound of Formula (XLIV), wherein $R_{3a'}$ is cyano.

[2175] Another aspect includes a compound of Formula (XLIV), wherein $R_{3a'}$ is halo selected from fluoro, chloro, bromo, and iodo.

[2176] Another aspect includes a compound of Formula (XLIV), wherein $R_{3a'}$ is fluoro or chloro.

[2177] Another aspect includes a compound of Formula (XLIV), wherein $R_{3a'}$ is C_{1-6} alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl.

[2178] Another aspect includes a compound of Formula (XLIV), wherein $R_{3a'}$ is from methyl.

[2179] Another aspect includes a compound of Formula (XLIV), wherein $R_{3a'}$ is C_{1-6} alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, iso-butoxy, tert-butoxy, pentoxy, and hexyloxy.

[2180] Another aspect includes a compound of Formula (XLIV), wherein $R_{3a'}$ is methoxy.

[2181] Another aspect includes a compound of Formula (XLIV), wherein $R_{3a'}$ is amino.

[2182] One aspect includes a compound of Formula (XLIV), wherein R_4 is hydrogen, cyano, halo, hydroxy, C_{1-6} alkyl, halo- C_{1-6} alkyl, C_{1-6} alkoxy, halo- C_{1-6} alkoxy, amino, C_{1-6} alkyl-amino, $(C_{1-6}alkyl)_2$ -amino, C_{3-10} cycloalkyl, phenyl, heterocyclyl, or heteroaryl, wherein heterocyclyl is a 3-7 membered monocyclic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S, wherein heteroaryl is a 5-8 membered monocyclic or bicyclic aromatic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S, and wherein each instance of C_{1-6} alkyl, C_{3-10} cycloalkyl, phenyl, heterocyclyl, or heteroaryl are optionally substituted with one, two, three, or four independently selected R_{4a} substituents.

[2183] Another aspect includes a compound of Formula (XLIV), wherein R_4 is hydrogen, cyano, halo, hydroxy, C_{1-6} alkyl, halo- C_{1-6} alkoxy, or C_{3-10} cycloalkyl, wherein C_{1-6} alkyl or C_{3-10} cycloalkyl are optionally substituted with one, two, three, or four independently selected R_{4a} substituents.

[2184] Another aspect includes a compound of Formula (XLIV), wherein R_4 is hydrogen.

[2185] Another aspect includes a compound of Formula (XLIV), wherein R_4 is cyano.

[2186] Another aspect includes a compound of Formula (XLIV), wherein R_4 is halo selected from fluoro, chloro, bromo, and iodo.

[2187] Another aspect includes a compound of Formula (XLIV), wherein R_4 is halo selected from chloro and bromo.

[2188] Another aspect includes a compound of Formula (XLIV), wherein R_4 is hydroxy.

[2189] Another aspect includes a compound of Formula (XLIV), wherein R_4 is C_{1-6} alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl, wherein C_{1-6} alkyl is optionally substituted with one, two, three, or four independently selected R_{4a} substituents.

[2190] Another aspect includes a compound of Formula (XLIV), wherein R_4 is methyl optionally substituted with one, two, three, or four independently selected R_{4a} substituents.

[2191] Another aspect includes a compound of Formula (XLIV), wherein R₄ is halo-C₁₋₆alkoxy wherein C₁₋₆alkoxy is selected from methoxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, iso-butoxy, tert-butoxy, pentoxy, and hexyloxy partially or completely substituted with one or more halogen atoms where allowed by available valences.

[2192] Another aspect includes a compound of Formula (XLIV), wherein R_{3a} is halo-C₁₋₆alkoxy, wherein C₁₋₆alkoxy is methoxy substituted with two fluorine atoms.

[2193] Another aspect includes a compound of Formula (XLIV), wherein R₄ is C₃₋₁₀cycloalkyl, wherein C₃₋₁₀cycloalkyl is optionally substituted with one, two, three, or four independently selected R_{4a} substituents.

[2194] Another aspect includes a compound of Formula (XLIV), wherein R₄ is C₃₋₁₀cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, optionally substituted with one, two, three, or four independently selected R_{4a} substituents.

[2195] Another aspect includes a compound of Formula (XLIV), wherein R₄ is cyclopropyl, optionally substituted with one, two, three, or four independently selected R_{4a} substituents.

[2196] One aspect includes a compound of Formula (XLIV), wherein R_{4a} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, or C₁₋₆alkoxy.

[2197] One aspect includes a compound of Formula (XLIV), wherein R₅ is hydrogen, cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, carbamoyl, C₃₋₁₀cycloalkyl, or heterocyclyl, wherein heterocyclyl is a 3-7 membered monocyclic carbon atom ring structure radical containing 1-3 heteroatoms selected from N, O, and S.

[2198] Another aspect includes a compound of Formula (XLIV), wherein R₅ is hydrogen, cyano, halo, or C₁₋₆alkyl.

[2199] Another aspect includes a compound of Formula (XLIV), wherein R₅ is hydrogen.

[2200] Another aspect includes a compound of Formula (XLIV), wherein R₅ is cyano.

[2201] Another aspect includes a compound of Formula (XLIV), wherein R₅ is halo selected from fluoro, chloro, bromo, and iodo.

[2202] Another aspect includes a compound of Formula (XLIV), wherein R₅ is chloro.

[2203] Another aspect includes a compound of Formula (XLIV), wherein R₅ is C₁₋₆alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl.

[2204] Another aspect includes a compound of Formula (XLIV), wherein R₅ is methyl.

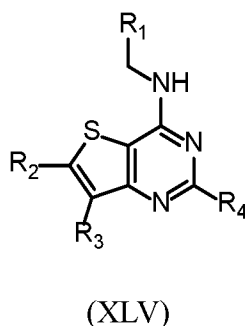
[2205] One aspect includes a compound of Formula (XLIV), wherein R₆ is hydrogen, halo, or C₁₋₆alkyl.

[2206] Another aspect includes a compound of Formula (XLIV), wherein R₆ is hydrogen.

FD compounds of Formula (XLV)

[2207] In one aspect, an FD compound can refer to a compound as disclosed in the published International PCT Patent No. PCT/US2020/063612, the content of which is incorporated by reference herein in its entirety.

[2208] In one aspect, an FD compound of the disclosure can refer to a compound of Formula (XLV):



or a form thereof, wherein:

R₁ is aryl or heteroaryl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents;

R_{1a} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, deuterio-C₁₋₆alkyl, or C₁₋₆alkoxy;

R₂ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, aryl, heterocyclyl, or heteroaryl,

wherein each instance of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, aryl, heterocyclyl, and heteroaryl is optionally substituted with one, two, three, or four independently selected R_{2a} substituents, and

wherein each instance of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and heterocyclyl optionally contains a chiral carbon having an (*R*) or (*S*) configuration;

R_{2a} is cyano, halo, hydroxy, oxo, C₁₋₆alkyl, halo-C₁₋₆alkyl, deuterio-C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, carboxyl, amino, C₁₋₆alkyl-amino,

halo-C₁₋₆alkyl-amino, deuterio-C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, C₃₋₁₀cycloalkyl-amino, aryl-amino, heterocyclyl-amino, heteroaryl-amino, C₁₋₆alkyl-thio, C₁₋₆alkyl-sulfonyl, C₃₋₁₀cycloalkyl, aryl, heterocyclyl, or heteroaryl,

wherein each instance of C₃₋₁₀cycloalkyl, aryl, heterocyclyl and heteroaryl is optionally substituted with one, two, three or four independently selected R_{2a'} substituents;

R_{2a'} is cyano, halo, hydroxy, oxo, C₁₋₆alkyl, halo-C₁₋₆alkyl, deuterio-C₁₋₆alkyl, or C₁₋₆alkoxy;

R₃ is hydrogen, cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, C₃₋₁₀cycloalkyl, aryl, heterocyclyl, or heteroaryl,

wherein each instance of C₁₋₆alkyl, C₃₋₁₀cycloalkyl, aryl, heterocyclyl, or heteroaryl are optionally substituted with one, two, three, or four independently selected R_{3a} substituents;

R_{3a} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, or C₁₋₆alkoxy; and

R₄ is hydrogen, cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, carbamoyl, C₃₋₁₀cycloalkyl, aryl, or heterocyclyl,

wherein the form of the compound is selected from the group consisting of a salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, and tautomer form thereof.

[2209] One aspect includes a compound of Formula (XLV), wherein R₁ is aryl or heteroaryl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents.

[2210] Another aspect includes a compound of Formula (XLV), wherein R₁ is aryl or heteroaryl, optionally substituted with one or two, independently selected R_{1a} substituents.

[2211] Another aspect includes a compound of Formula (XLV), wherein R₁ is aryl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents.

[2212] Another aspect includes a compound of Formula (XLV), wherein R₁ is aryl, optionally substituted with one R_{1a} substituent.

[2213] Another aspect of includes a compound of Formula (XLV), wherein R₁ is aryl selected from phenyl and naphthyl, optionally substituted with one, two, three, or four independently selected R_{1a} substituents.

[2214] Another aspect includes a compound of Formula (XLV), wherein R₁ is phenyl, wherein phenyl is optionally substituted with one, two, three, or four independently selected R_{1a} substituents.

[2215] Another aspect includes a compound of Formula (XLV), wherein R₁ is heteroaryl, optionally substituted with one, two, three, or four, independently selected R_{1a} substituents.

[2216] Another aspect includes a compound of Formula (XLV), wherein R₁ is heteroaryl, optionally substituted with one or two, independently selected R_{1a} substituents.

[2217] Another aspect includes a compound of Formula (XLV), wherein R₁ is heteroaryl selected from furanyl, thienyl, 1*H*-pyrazolyl, 1*H*-imidazolyl, isoxazolyl, 1,2-thiazolyl, 1,3-thiazolyl, 1,2-oxazolyl, 1,3-oxazolyl, tetrazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzofuranyl, and quinolinyl, wherein each instance of heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2218] Another aspect includes a compound of Formula (XLV), wherein R₁ is heteroaryl selected from furanyl, thienyl, 1*H*-pyrazolyl, 1*H*-imidazolyl, 1,2-thiazolyl, 1,3-thiazolyl, 1,2-oxazolyl, 1,3-oxazolyl, pyridinyl, pyrimidinyl, and pyrazinyl, wherein each instance of heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2219] Another aspect includes a compound of Formula (XLV), wherein R₁ is heteroaryl selected from furan-2-yl, furan-3-yl, thien-2-yl, thien-3-yl, 1*H*-pyrazol-1-yl, 1*H*-pyrazol-3-yl, 1*H*-pyrazol-4-yl, 1*H*-pyrazol-5-yl, 1*H*-imidazol-1-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,2-thiazol-3-yl, 1,2-thiazol-4-yl, 1,2-thiazol-5-yl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1,2-oxazol-3-yl, 1,2-oxazol-4-yl, 1,2-oxazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, tetrazol-5-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrazin-2-yl, pyridazin-3-yl, pyridazin-4-yl, benzofuran-2-yl, benzofuran-5-yl, and quinoline-4-yl wherein, each instance of heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2220] Another aspect includes a compound of Formula (XLV), wherein R₁ is heteroaryl selected from furan-2-yl, thien-2-yl, 1*H*-pyrazol-5-yl, 1*H*-imidazol-2-yl, 1,2-thiazol-5-yl, 1,3-thiazol-2-yl, 1,3-thiazol-5-yl, 1,2-oxazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, and pyrazin-2-yl, wherein each instance of heteroaryl is optionally substituted with one, two, three, or four, independently R_{1a} substituents.

[2221] One aspect includes a compound of Formula (XLV), wherein R_{1a} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, deuterio-C₁₋₆alkyl, or C₁₋₆alkoxy.

[2222] Another aspect includes a compound of Formula (XLV), wherein R_{1a} is halo or C₁₋₆alkyl.

[2223] Another aspect includes a compound of Formula (XLV), wherein R_{1a} is halo selected from fluoro, chloro, bromo, and iodo.

[2224] Another aspect includes a compound of Formula (XLV), wherein R_{1a} is fluoro.

[2225] Another aspect includes a compound of Formula (XLV), wherein R_{1a} is C₁₋₆alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl.

[2226] Another aspect includes a compound of Formula (XLV), wherein R_{1a} is methyl.

[2227] One aspect includes a compound of Formula (XLV), wherein R₂ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, aryl, heterocyclyl, or heteroaryl,

[2228] wherein each instance of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, aryl, heterocyclyl, and heteroaryl is optionally substituted with one, two, three, or four independently selected R_{2a} substituents, and

[2229] wherein each instance of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and heterocyclyl may optionally contain a chiral carbon having an (*R*) or (*S*) configuration.

[2230] Another aspect includes a compound of Formula (XLV), wherein R₂ is hydrogen.

[2231] Another aspect includes a compound of Formula (XLV), wherein R₂ is C₁₋₆alkyl, optionally substituted with one, two, three, or four, independently selected R_{2a} substituents, and wherein, C₁₋₆alkyl optionally contains a chiral carbon having an (*R*) or (*S*) configuration.

[2232] Another aspect includes a compound of Formula (XLV), wherein R₂ is C₁₋₆alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl optionally substituted with one, two, three, or four, independently selected R_{2a} substituents, and wherein, C₁₋₆alkyl optionally contains a chiral carbon having an (*R*) or (*S*) configuration.

[2233] Another aspect includes a compound of Formula (XLV), wherein R₂ is heterocyclyl, optionally substituted with one, two, three, or four, independently selected R_{2a} substituents, and wherein heterocyclyl optionally contains a chiral carbon having an (*R*) or (*S*) configuration.

[2234] Another aspect includes a compound of Formula (XLV), wherein R₂ is heterocyclcyl selected from azetidiny, oxetanyl, pyrazolidiny, tetrahydrofuranyl, oxazolidiny, thiazolidiny, isothiazolidiny, pyrrolidiny, piperidiny, piperaziny, 2H-pyranyl, tetrahydropyranyl, morpholiny, 1,3-oxazinanyl, 1,3-oxazinan-2-on-yl, and azepanyl, optionally substituted with one, two, three, or four independently selected R_{2a} substituents.

[2235] Another aspect includes a compound of Formula (XLV), wherein R₂ is heterocyclcyl selected from azetidiny and pyrrolidiny, optionally substituted with one, two, three, or four independently selected R_{2a} substituents.

[2236] Another aspect includes a compound of Formula (XLV), wherein R₂ is heterocyclcyl selected from azetidin-2-yl, azetidin-3-yl, oxetan-2-yl, oxetan-3-yl, pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl, pyrazolidin-5-yl, tetrahydrofuran-1-yl, tetrahydrofuran-2-yl, oxazolidin-2-yl, oxazolidin-4-yl, oxazolidin-5-yl, thiazolidin-2-yl, thiazolidin-4-yl, thiazolidin-5-yl, isothiazolidin-3-yl, isothiazolidin-4-yl, isothiazolidin-5-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, 2H-pyran-2-yl, 2H-pyran-3-yl, 2H-pyran-4-yl, 2H-pyran-5-yl, 2H-pyran-6-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, 1,3-oxazinan-2-yl, 1,3-oxazinan-3-yl, 1,3-oxazinan-4-yl, 1,3-oxazinan-2-on-6-yl, azepan-1-yl, azepan-2-yl, azepan-3-yl, and azepan-4-yl, optionally substituted with one, two, three, or four independently selected R_{2a} substituents.

[2237] Another aspect includes a compound of Formula (XLV), wherein R₂ is heterocyclcyl selected from azetidin-3-yl and pyrrolidin-3-yl, optionally substituted with one, two, three, or four independently selected R_{2a} substituents.

[2238] One aspect includes a compound of Formula (XLV), wherein R_{2a} is cyano, halo, hydroxy, oxo, C₁₋₆alkyl, halo-C₁₋₆alkyl, deuterio-C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, halo-C₁₋₆alkoxy, carboxyl, amino, C₁₋₆alkyl-amino, halo-C₁₋₆alkyl-amino, deuterio-C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, C₃₋₁₀cycloalkyl-amino, aryl-amino, heterocyclcyl-amino, heteroaryl-amino, C₁₋₆alkyl-thio, C₁₋₆alkyl-sulfonyl, C₃₋₁₀cycloalkyl, aryl, heterocyclcyl, or heteroaryl,

[2239] wherein each instance of C₃₋₁₀cycloalkyl, aryl, heterocyclcyl and heteroaryl is optionally substituted with one, two, three or four independently selected R_{2a'} substituents.

[2240] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, amino, C₁₋₆alkyl-amino, C₃₋₁₀cycloalkyl-amino, or heterocyclyl,

wherein each instance of heterocyclyl is optionally substituted with one, two, three or four independently selected R_{2a'} substituents.

[2241] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is halo selected from fluoro, chloro, bromo, and iodo.

[2242] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is fluoro.

[2243] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is hydroxy.

[2244] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is C₁₋₆alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl.

[2245] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is methyl.

[2246] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is C₁₋₆alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.

[2247] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is methoxy.

[2248] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is amino.

[2249] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is C₁₋₆alkyl-amino, wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, and tert-butyl.

[2250] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is methyl-amino.

[2251] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is C₃₋₁₀cycloalkyl-amino, wherein C₃₋₁₀cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, wherein each instance of C₃₋₁₀cycloalkyl is optionally substituted with one, two, three or four independently selected R_{2a'} substituents.

[2252] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is cyclobutyl-amino.

[2253] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is heterocyclyl selected from heterocyclyl selected from azetidiny, oxetanyl, pyrazolidiny, tetrahydrofuranyl, oxazolidiny, thiazolidiny, isothiazolidiny, pyrrolidiny, piperidiny, piperaziny, 2H-pyranyl, tetrahydropyranyl, morpholinyl, 1,3-oxazinanyl, 1,3-oxazinan-2-on-yl, and azepanyl, wherein

each instance of heterocyclyl is optionally substituted with one, two, three or four independently selected R_{2a'} substituents.

[2254] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is 1,3-oxazinan-2-on-yl.

[2255] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is heterocyclyl selected from heterocyclyl selected from azetidin-2-yl, azetidin-3-yl, oxetan-2-yl, oxetan-3-yl, pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl, pyrazolidin-5-yl, tetrahydrofuran-1-yl, tetrahydrofuran-2-yl, oxazolidin-2-yl, oxazolidin-4-yl, oxazolidin-5-yl, thiazolidin-2-yl, thiazolidin-4-yl, thiazolidin-5-yl, isothiazolidin-3-yl, isothiazolidin-4-yl, isothiazolidin-5-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, 2H-pyran-2-yl, 2H-pyran-3-yl, 2H-pyran-4-yl, 2H-pyran-5-yl, 2H-pyran-6-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, 1,3-oxazinan-2-yl, 1,3-oxazinan-3-yl, 1,3-oxazinan-4-yl, 1,3-oxazinan-2-on-6-yl, azepan-1-yl, azepan-2-yl, azepan-3-yl, and azepan-4-yl, wherein each instance of heterocyclyl is optionally substituted with one, two, three or four independently selected R_{2a'} substituents.

[2256] Another aspect includes a compound of Formula (XLV), wherein R_{2a} is 1,3-oxazinan-2-on-6-yl.

[2257] One aspect includes a compound of Formula (XLV), wherein R₃ is hydrogen, cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, amino, C₁₋₆alkyl-amino, (C₁₋₆alkyl)₂-amino, C₃₋₁₀cycloalkyl, aryl, heterocyclyl, or heteroaryl,

[2258] wherein each instance of C₁₋₆alkyl, C₃₋₁₀cycloalkyl, aryl, heterocyclyl, or heteroaryl are optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2259] Another aspect includes a compound of Formula (XLV), wherein R₃ is hydrogen, cyano, halo, C₁₋₆alkyl, C₁₋₆alkoxy, C₃₋₁₀cycloalkyl, or aryl,

[2260] wherein each instance of C₁₋₆alkyl, C₃₋₁₀cycloalkyl, or aryl, are optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2261] Another aspect includes a compound of Formula (XLV), wherein R₃ is hydrogen.

[2262] Another aspect includes a compound of Formula (XLV), wherein R₃ is cyano.

[2263] Another aspect includes a compound of Formula (XLV), wherein R₃ is halo selected from fluoro, chloro, bromo, and iodo.

[2264] Another aspect includes a compound of Formula (XLV), wherein R₃ is bromo.

[2265] Another aspect includes a compound of Formula (XLV), wherein R₃ is hydroxy.

[2266] Another aspect includes a compound of Formula (XLV), wherein R₃ is C₁₋₆alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl, optionally substituted with one, two, three, or four, independently selected R_{3a} substituents.

[2267] Another aspect includes a compound of Formula (XLV), wherein R₃ is C₁₋₆alkyl selected from methyl and ethyl, optionally substituted with one, two, three, or four, independently selected R_{3a} substituents.

[2268] Another aspect includes a compound of Formula (XLV), wherein R₃ is C₁₋₆alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.

[2269] Another aspect includes a compound of Formula (XLV), wherein R₃ is methoxy.

[2270] Another aspect includes a compound of Formula (XLV), wherein R₃ is C₃₋₁₀cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2271] Another aspect includes a compound of Formula (XLV), wherein R₃ is cyclopropyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2272] Another aspect includes a compound of Formula (XLV), wherein R₃ is aryl selected from phenyl and naphthyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2273] Another aspect includes a compound of Formula (XLV), wherein R₃ is phenyl, optionally substituted with one, two, three, or four independently selected R_{3a} substituents.

[2274] One aspect includes a compound of Formula (XLV), wherein R_{3a} is cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, or C₁₋₆alkoxy.

[2275] Another aspect includes a compound of Formula (XLV), wherein R_{3a} is halo or C₁₋₆alkoxy.

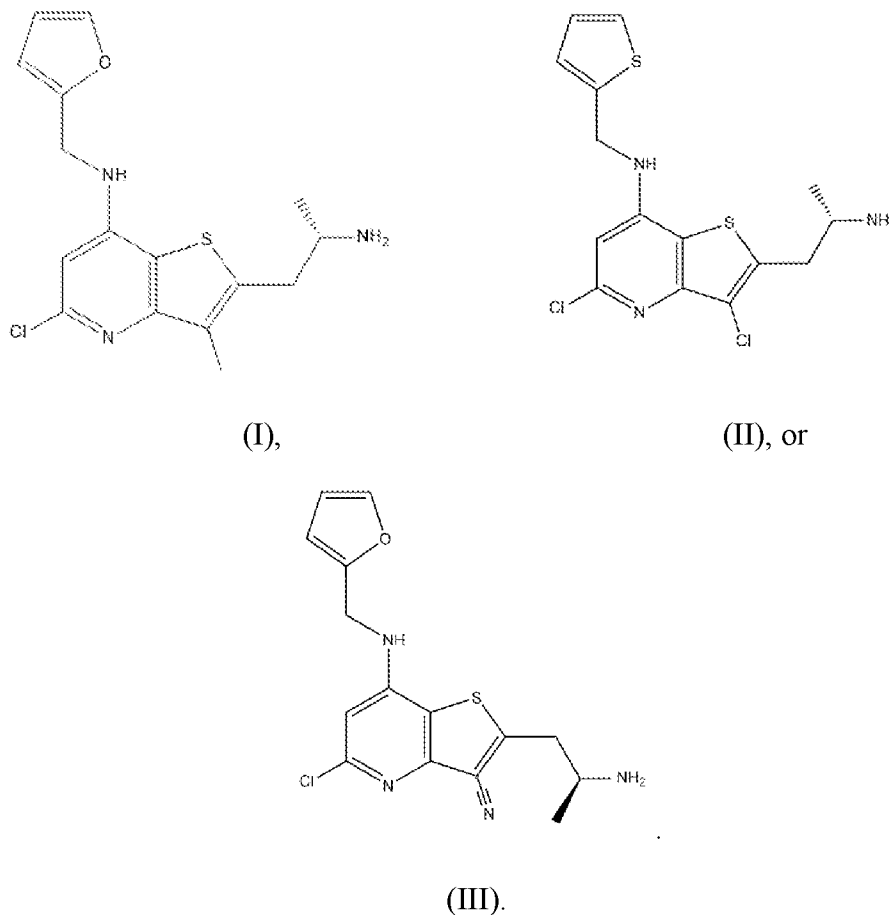
[2276] Another aspect includes a compound of Formula (XLV), wherein R_{3a} is halo selected from fluoro, chloro, bromo, and iodo.

- [2277] Another aspect includes a compound of Formula (XLV), wherein R_{3a} is chloro.
- [2278] Another aspect includes a compound of Formula (XLV), wherein R_{3a} is C₁₋₆alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.
- [2279] Another aspect includes a compound of Formula (XLV), wherein R_{3a} is methoxy.
- [2280] One aspect includes a compound of Formula (XLV), wherein R₄ is hydrogen, cyano, halo, hydroxy, C₁₋₆alkyl, halo-C₁₋₆alkyl, C₁₋₆alkoxy, carbamoyl, C₃₋₁₀cycloalkyl, aryl, or heterocyclyl.
- [2281] Another aspect includes a compound of Formula (XLV), wherein R₄ is hydrogen, cyano, halo, C₁₋₆alkyl, halo-C₁₋₆alkyl, carbamoyl, C₃₋₁₀cycloalkyl, or aryl.
- [2282] Another aspect includes a compound of Formula (XLV), wherein R₄ is hydrogen.
- [2283] Another aspect includes a compound of Formula (XLV), wherein R₄ is cyano.
- [2284] Another aspect includes a compound of Formula (XLV), wherein R₄ is halo selected from fluoro, chloro, bromo, and iodo.
- [2285] Another aspect includes a compound of Formula (XLV), wherein R₄ is halo selected from chloro and bromo.
- [2286] Another aspect includes a compound of Formula (XLV), wherein R₄ is C₁₋₆alkyl selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl.
- [2287] Another aspect includes a compound of Formula (XLV), wherein R₄ is C₁₋₆alkyl selected from methyl and ethyl.
- [2288] Another aspect includes a compound of Formula (XLV), wherein R₄ is halo-C₁₋₆alkyl wherein C₁₋₆alkyl is selected from methyl, ethyl, propyl, butyl, pentyl, and hexyl partially or completely substituted with one or more halogen atoms where allowed by available valences.
- [2289] Another aspect includes a compound of Formula (XLV), wherein R₄ is halo-C₁₋₆alkyl, wherein C₁₋₆alkyl is methyl substituted with three fluorine atoms.
- [2290] Another aspect includes a compound of Formula (XLV), wherein R₄ is carbamoyl.
- [2291] Another aspect includes a compound of Formula (XLV), wherein R₄ is C₃₋₁₀cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.
- [2292] Another aspect includes a compound of Formula (XLV), wherein R₄ is cyclopropyl.

[2293] Another aspect includes a compound of Formula (XLV), wherein R₄ is aryl selected from phenyl and naphthyl.

[2294] Another aspect includes a compound of Formula (XLV), wherein R₄ is phenyl.

[2295] In one aspect, an FD compound may have the structure of



[2296] In one aspect, as described herein, an FD compound or a pharmaceutically acceptable salt thereof, may be prepared by those skilled in the art, such as, by the synthetic methods set forth in International Application Number PCT/US2016/013553, filed January 15, 2016 and published as International Publication Number WO2016115434 on July 21, 2016 and International Application Number PCT/US2020/017430, filed February 10, 2020 and published as International Publication Number WO2020167628 on August 20, 2020. All these references are incorporated by reference herein in their entireties as if fully set forth herein.

III. SMALL MOLECULE SPLICING MODIFIER (SMSM) COMPOUND FORMS

[2297] As used herein, the term “form” means an SMSM compound, as disclosed herein, can have a form selected from the group consisting of a free acid, free base, prodrug, salt, hydrate,

solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph, and tautomer form thereof.

[2298] In certain aspects described herein, the form of the SMSM compound, as disclosed herein, can have a free acid, free base, or salt thereof.

[2299] In certain aspects described herein, the form of the SMSM compound, as disclosed herein, can have a salt thereof.

[2300] In certain aspects described herein, the form of the SMSM compound, as disclosed herein, can have an isotopologue thereof.

[2301] In certain aspects described herein, the form of the SMSM compound, as disclosed herein, can have a stereoisomer, racemate, enantiomer or diastereomer thereof.

[2302] In certain aspects described herein, the form of the SMSM compound, as disclosed herein, can have a tautomer thereof.

[2303] In certain aspects described herein, the form of the SMSM compound, as disclosed herein, can have a pharmaceutically acceptable form.

[2304] In certain aspects described herein, the SMSM compound, as disclosed herein, or a form thereof, can be isolated for use.

[2305] As used herein, the term “isolated” means the physical state of an SMSM compound, as disclosed herein, or a form thereof, after being isolated and/or purified from a synthetic process (*e.g.*, from a reaction mixture) or natural source or combination thereof according to an isolation or purification process or processes described herein or which are well known to the skilled artisan (*e.g.*, chromatography, recrystallization and the like) in sufficient purity to be characterized by standard analytical techniques described herein or well known to the skilled artisan.

[2306] As used herein, the term “protected” means that a functional group in an SMSM compound, as disclosed herein, or a form thereof, is in a form modified to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T.W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York. Such functional groups include hydroxy, phenol, amino and carboxylic acid. Suitable protecting groups for hydroxy or phenol include

trialkylsilyl or diarylalkylsilyl (e.g., t-butyl dimethylsilyl, t-butyl diphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, substituted benzyl, methyl, methoxymethanol, and the like. Suitable protecting groups for amino, amidino and guanidino include t-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or arylalkyl esters. In certain instances, the protecting group may also be a polymer resin, such as a Wang resin or a 2-chlorotrityl-chloride resin. Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. It will also be appreciated by those skilled in the art, although such protected derivatives of compounds described herein may not possess pharmacological activity as such, they may be administered to a subject and thereafter metabolized in the body to form compounds described herein which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All prodrugs of compounds described herein are included within the scope of the use described herein.

[2307] As used herein, the term "prodrug" means a form of an instant compound (e.g., a drug precursor) that is transformed *in vivo* to yield an active SMSM compound or a form thereof. The transformation may occur by various mechanisms (e.g., by metabolic and/or non-metabolic chemical processes), such as, for example, by hydrolysis and/or metabolism in blood, liver and/or other organs and tissues. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

[2308] In one example, when an SMSM compound, as disclosed herein, or a form thereof, contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a functional group such as alkyl and the like. In another example, when an SMSM compound, as disclosed herein, or a form thereof, contains a hydroxyl functional group, a prodrug form can be prepared by replacing the hydrogen atom of the hydroxyl with another functional group such as alkyl, alkylcarbonyl or a phosphonate ester and the like. In another example, when an SMSM compound, as disclosed herein, or a form thereof, contains an amine functional group, a prodrug form can be prepared by replacing one or more amine hydrogen atoms with a functional group such as alkyl or substituted carbonyl. Pharmaceutically acceptable prodrugs of SMSM compounds, as disclosed herein, or a form thereof, include those compounds substituted with one or more of

the following groups: carboxylic acid esters, sulfonate esters, amino acid esters, phosphonate esters and mono-, di- or triphosphate esters or alkyl substituents, where appropriate. As described herein, it is understood by a person of ordinary skill in the art that one or more of such substituents may be used to provide an SMSM compound, as disclosed herein, or a form thereof, as a prodrug.

[2309] One or more compounds described herein may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and the description herein is intended to embrace both solvated and unsolvated forms.

[2310] As used herein, the term "solvate" means a physical association of a compound described herein with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. As used herein, "solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanulates, methanulates, and the like.

[2311] As used herein, the term "hydrate" means a solvate wherein the solvent molecule is water.

[2312] The SMSM compounds, as disclosed herein, can form salts, which are intended to be included within the scope of this description. Reference to an SMSM compound, as disclosed herein, or a form thereof, herein is understood to include reference to salt forms thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when an SMSM compound, as disclosed herein, or a form thereof, contains both a basic moiety, such as, without limitation an amine moiety, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein.

[2313] The term "pharmaceutically acceptable salt(s)", as used herein, means those salts of compounds described herein that are safe and effective (*i.e.*, non-toxic, physiologically acceptable) for use in mammals and that possess biological activity, although other salts are also useful. Salts of the SMSM compounds may be formed, for example, by reacting an SMSM compound, as disclosed herein, or a form thereof, with an amount of acid or base, such as an

equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[2314] Pharmaceutically acceptable salts include one or more salts of acidic or basic groups present in compounds described herein. Certain aspects of acid addition salts include, and are not limited to, acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, bitartrate, borate, bromide, butyrate, chloride, citrate, camphorate, camphorsulfonate, ethanesulfonate, formate, fumarate, gentisinate, gluconate, glucaronate, glutamate, iodide, isonicotinate, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, pamoate, pantothenate, phosphate, propionate, saccharate, salicylate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate (also known as tosylate), trifluoroacetate salts and the like. Certain aspects of acid addition salts include chloride, dichloride, trichloride, bromide, acetate, formate or trifluoroacetate salts.

[2315] Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33, 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

[2316] Suitable basic salts include, but are not limited to, aluminum, ammonium, calcium, lithium, magnesium, potassium, sodium, and zinc salts.

[2317] All such acid salts and base salts are intended to be included within the scope of pharmaceutically acceptable salts as described herein. In addition, all such acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of this description.

[2318] SMSM compounds, as disclosed herein, and forms thereof, may further exist in a tautomeric form. All such tautomeric forms are contemplated and intended to be included within the scope of the SMSM compounds, or a form thereof, as described herein.

[2319] The SMSM compounds, as disclosed herein, or a form thereof, may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. The present description

is intended to include all stereoisomeric forms of the SMSM compounds, as disclosed herein, as well as mixtures thereof, including racemic mixtures.

[2320] The compounds described herein may include one or more chiral centers, and as such may exist as racemic mixtures (*R/S*) or as substantially pure enantiomers and diastereomers. The compounds may also exist as substantially pure (*R*) or (*S*) enantiomers (when one chiral center is present). In one aspect, the compounds described herein are (*S*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*S*) isomer. In another aspect, the compounds described herein are (*R*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*R*) isomer. As one of skill in the art will recognize, when more than one chiral center is present, the compounds described herein may also exist as a (*R,R*), (*R,S*), (*S,R*) or (*S,S*) isomer, as defined by *IUPAC* Nomenclature Recommendations.

[2321] As used herein, the term “substantially pure” refers to compounds consisting substantially of a single isomer in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100% of the single isomer.

[2322] In one aspect of the description, an SMSM compound, as disclosed herein, or a form thereof, is a substantially pure (*S*) enantiomer form present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

[2323] In one aspect of the description, an SMSM compound, as disclosed herein, or a form thereof, is a substantially pure (*R*) enantiomer form present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

[2324] As used herein, a “racemate” is any mixture of isometric forms that are not “enantiomerically pure”, including mixtures such as, without limitation, in a ratio of about 50/50, about 60/40, about 70/30, or about 80/20.

[2325] In addition, the present description embraces all geometric and positional isomers. For example, if an SMSM compound, as disclosed herein, or a form thereof, incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the description. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by use of chiral HPLC column or other chromatographic methods known to those skilled in the art. Enantiomers can also be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the SMSM compounds, as disclosed herein, may be atropisomers (*e.g.*, substituted biaryls) and are considered as part of this description.

[2326] All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this description, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds described herein may, for example, be substantially free of other isomers, or may be present in a racemic mixture, as described supra.

[2327] The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or isotopologues of the instant compounds.

[2328] The term "isotopologue" refers to isotopically-enriched compounds described herein which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine

and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{35}Cl and ^{36}Cl , respectively, each of which are also within the scope of this description.

[2329] Certain isotopically-enriched compounds described herein (*e.g.*, those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^3H) and carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances.

[2330] Polymorphic crystalline and amorphous forms of the SMSM compounds, as disclosed herein, and of the salts, solvates, hydrates, esters and prodrugs of the SMSM compounds, as disclosed herein, are further intended to be included in the present description.

[2331] Another aspect, described herein includes a compound, as disclosed herein, selected from a polymorphic crystalline and amorphous form of the compound, and a salt, solvate, hydrate or ester of the compound.

[2332] Nomenclature for a compound, as disclosed herein, may differ slightly from other chemical names known to those skilled in the art; however, such differences will be recognized by one skilled in the art as equivalents for the structure of the compound provided herein.

IV. SMSM COMPOUND INDUCIBLE SPLICING AMONGST HUMAN GENES

[2333] To identify genes responsive to SMSM compound inducible splicing, RNA-seq analysis of transcriptome changes can be analyzed in human tissue culture cells (*e.g.* HEK293 or SH-SY5Y cells) treated an SMSM compound. Total RNA is then extracted, and RNA sequencing reads are mapped to the human genome.

[2334] For gene expression analysis, the number of reads in a coding sequence (CDS) region of protein-coding genes and exonic regions of non-coding genes can be counted and analyzed (Love et al., (2014) *Genome Biology*, 15:550).

[2335] For splicing analysis, reads can be counted for different exons or exonic regions. For each exon, a change in Percent Spliced In (ΔPSI) can be calculated using read data from RNAseq (or any other method that can distinguish mRNA splice isoforms) to calculate the ratio (percentage) between reads that either demonstrate inclusion (junctions between the upstream exon and the exon of interest) or exclusion (junction between the upstream and downstream

exons, excluding the exon of interest), to determine if the presence of a SMSM compound can alter the amount of exon inclusion relative to the amount of inclusion in the absence of the SMSM compound or the presence of a negative control.

[2336] The Δ PSI value is derived from the formula:

$$\Delta\text{PSI (\%)} = C - U \times 100$$

where “U” represents the value for probability of exon inclusion $(a+b)/2/[(a+b)/2+c]$ in the absence of an SMSM compound; and, where “C” represents the value for probability of exon inclusion $(a+b)/2/[(a+b)/2 + c]$ in the presence of the SMSM compound. The values for “a” and “b” represent the number of reads supporting exon inclusion in an RNA transcript. In other words, the “a” value is derived from the amount of reads for a first intronic nucleotide sequence comprising, in 5’ to 3’ order: a first exon 5’ splice site operably linked and upstream from a first intronic nucleotide sequence comprising a first branch point further operably linked and upstream from a first intronic 3’ splice site. The “b” value is derived from the amount of reads for a second intronic nucleotide sequence comprising, in 5’ to 3’ order: a second exon’s non-canonical 5’ splice site that when present in an intron can be recognized by U1 snRNP and/or other components of the pre-mRNA splicing machinery only in the presence of an SMSM compound, wherein gene expression can have modulated by inducing alternative splicing at the non-canonical 5’ splice site in the transcribed RNA operably linked and upstream from a second intronic nucleotide sequence comprising a second branch point operably linked and upstream from a second intronic 3’ splice site. The value for “C” represents the number of reads supporting exon exclusion. Accordingly, when an SMSM compound enables the splicing machinery to recognize the non-canonical 5’ splice site, the value for “C” in the presence of the SMSM compound will differ from the value for “U” in the absence of the SMSM compound. The statistically significant value for the likelihood of exon 2 inclusion may be obtained according to statistical analysis methods or other probability analysis methods known to those of ordinary skill in the art.

[2337] For comparing sequence difference of a particular region for two groups of exons (e.g., UP vs. NC), the k-mer (k=4 to 6) frequencies of the two groups can be compared by Fisher’s Exact Test (one k-mer vs. all other k-mers, group 1 vs. group 2). The resulting P-value can be converted to a significance score ($SS = -S \times \log_{10} P\text{-value}$), in which S is the sign indicating enrichment (1) or depletion (-1) of the k-mer in group 1.

[2338] Potential SMSM compound-responsive exons can be selected having at least one of the following criteria: (1) a length between 6-200 nt, 3' splice site (ss) MAXENT score >2.3 and a 5' splice site (ss) MAXENT score >-2.1 ; (2) within intron region of another Refseq annotated gene; and (3) a SMSM compound inducible non-canonical 5' splice site (ss) as described herein.

[2339] [0190] Methods of determining a 5' or 3' splice site's Maxent score are described in Yeo, G. & Burge, C. B. (2004) *Journal of computational biology* 11, 377-394, the content of which is incorporated by reference herein in its entirety.

[2340] In one aspect, a putative SMSM compound-responsive exon can be 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199 or 200 nucleotides in length.

[2341] In one aspect, a 3' splice site (ss) of an SMSM compound-responsive exon can have a MAXENT score greater than about 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 5, 6, 7, 8 or 9 or more. In one aspect, a 3' splice site (ss) of an SMSM compound-responsive exon can have a MAXENT score of about 2.3 to about 9.

[2342] In one aspect, a 3' splice site (ss) of an SMSM compound-responsive exon can have a MAXENT score of about 2.3 to about 3.

[2343] In one aspect, a 5' splice site (ss) of an SMSM compound-responsive exon can have a MAXENT score greater than about -2.1, -2.0, -1.9, -1.8, -1.7, -1.6, -1.5, -1.4, -1.3, -1.2, -1.1, -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, -0.1, 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 5, 6, 7, 8 or 9 or more.

[2344] In one aspect, a 5' splice site (ss) of an SMSM compound-responsive exon can have a MAXENT score of about -2.1 to about 9.

[2345] In one aspect, the 5' splice site (ss) of an SMSM compound-responsive exon can have a MAXENT score of about -2.1 to about 3.

[2346] To test if a small molecule-induced spliced transcript is unstable due to nonsense-mediated decay (NMD), human tissue culture cells can be treated with or without an SMSM compound, followed by addition of DMSO or cycloheximide (CHX). RNA can then be analyzed by RT-qPCR. Compound treatment resulting in a ~80% reduction gene expression can be indicative of SMSM compound induced NMD.

A. Exemplary HD/SMA compound-inducible splicing of human genes

[2347] In one aspect, HD/SMA compounds may modify the alternative splicing of pre-mRNAs to enhance the abundance of exon inclusion in spliced mRNAs transcribed from one or more of the following HD/SMA compound inducible genes including, but not limited to, ABCA1, ABCA10, ABCB7, ABCB8, ABCC1, ABCC3, ABHD10, ABL2, ABLIM3, ACACA, ACADVL, ACAT2, ACTA2, ADAL, ADAM12, ADAM15, ADAM17, ADAM23, ADAM33, ADAMTS1, ADAMTS19, ADCY3, ADD1, ADGRG6, ADH6, ADHFE1, AFF2, AFF3, AGK, AGPAT3, AGPAT4, AGPS, AHCYL2, AHDC1, AHRR, AJUBA, AK021888, AK310472, AKAP1, AKAP3, AKAP8L, AKAP9, AKNA, AKT1, ALCAM, ALDH4A1, AMPD2, ANK1, ANK2, ANK3, ANKFY1, ANKHD1-EIF4EBP3, ANKRA2, ANKRD13C, ANKRD17, ANKRD33B, ANKRD36, ANKS6, ANP32A, ANXA11, ANXA6, AP2B1, AP4B1-AS1, APAF1, APIP, APLP2, APOA2, APP, APPL2, APTX, ARHGAP1, ARHGAP12, ARHGAP22, ARHGAP5, ARHGEF16, ARID1A, ARID2, ARID5B, ARL9, ARL15, ARL5B, ARMCX3, ARMCX6, ARSJ, ASAP1, ASIC1, ASL, ASNS, ASPH, ATAD2B, ATF6, ATF7IP, ATG5, ATG9A, ATMIN, ATP2A3, ATP2C1, ATXN1, ATXN3, AURKA, AXIN1, B3GALT2, B3GNT6, B4GALT2, BACE1, BAG2, BASP1, BC033281, BCAR3, BCL2L15, BCYRN1, BECN1, BEND6, BHMT2, BICD1, BIN1, BIN3, BIN3-IT1, BIRC3, BIRC6, BNC1, BNC2, BRCA1, BRCA2, BRD2, BRPF1, BSCL2, BTBD10, BTG2, BTN3A1, BZW1, C1QTNF9B-AS1, C1orf27, C1orf86, C10orf54, C11orf30, C11orf70, C11orf73, C11orf76, C11orf94, C12orf4, C12orf56, C14orf132, C17orf76-AS1, C19orf47, C2orf47, C3, C4orf27, C5orf24, C6orf48, C7orf31, C8orf34, C8orf44, C8orf44-SGK3, C8orf88, C9orf69, CA13, CA3, CAB39, CACNA2D2, CACNB1, CACNB4, CADM1, CADM2, CALU, CAMKK1, CAND2, CAPNS1, CASC3, CASP7, CASP8AP2, CAV1, CCAR1, CCDC77, CCDC79, CCDC88A, CCDC92, CCDC122, CCER2, CCNF, CCNL2, CCT6A, CD276, CD46, CDC25B, CDC40, CDC42BPA, CDCA7, CDH11, CDH13, CDH18, CDK11B, CDK16, CDKAL1, CDKN1C,

CECR7, CELSR1, CEMIP, CENPI, CEP112, CEP162, CEP170, CEP192, CEP57, CEP68, CFH, CFLAR, CHD8, CHEK1, CHRM2, CIITA, CIZ1, CLDN23, CLIC1, CLK4, CLTA, CMAHP, CNGA4, CNOT1, CNRIP1, CNTD1, CMSS1, CNOT7, CNRIP1, CNTN1, COG1, COL1A1, COL11A1, COL12A1, COL14A1, COL15A1, COL5A1, COL5A3, COL6A1, COL6A6, COL8A1, COLEC12, COMP, COPS7B, CPA4, CPEB2, CPQ, CPSF4, CREB5, CRISPLD2, CRLF1, CRLS1, CRTAP, CRX, CRYBG3, CRYL1, CSDE1, CSNK1A1, CSNK1E, CSNK1G1, CTDSP2, CTNND1, CTRC, CUL2, CUL4A, CUX1, CYB5B, CYB5R2, CYBRD1, CYGB, CYP1B1, CYP51A1, DAAM1, DAB2, DACT1, DAGLB, DARS, DAXX, DCAF10, DCAF11, DCAF17, DCBLD2, DCLK1, DCN, DCUN1D4, DDAH1, DDAH2, DDHD2, DDIT4L, DDR1, DDX39B, DDX42, DDX50, DEGS1, DENND1A, DENND1B, DENND4A, DENND5A, DEPTOR, DET1, DFN59, DGCR2, DGK1, DGKA, DHCR24, DHCR7, DHFR, DHX9, DIAPH1, DIAPH3, DIRAS3, DIS3L, DKFZp434M1735, DKK3, DLC1, DLG5, DLGAP4, DMD, DMXL1, DNAH8, DNAH11, DNAJA4, DNAJC13, DNAJC27, DNM2, DNMBP, DOCK1, DOCK11, DPP8, DSEL, DST, DSTN, DYNC1I1, DYRK1A, DZIP1L, EBF1, EEA1, EEF1A1, EFCAB14, EFEMP1, EGR1, EGR3, EHMT2, EIF2B3, EIF4G1, EIF4G2, EIF4G3, ELF2, ELMO2, ELN, ELP4, EMX2OS, ENAH, ENG, ENOX1, ENPP1, ENPP2, ENSA, EP300, EPN1, EPT1, ERC1, ERC2, ERCC1, ERCC8, ERGIC3, ERLIN2, ERFF1, ESM1, ETV5, EVC, EVC2, EXO1, EXOC3, EXOC6B, EXTL2, EYA3, F2R, FADS1, FADS2, FAF1, FAIM, FAM111A, FAM126A, FAM13A, FAM160A1, FAM162A, FAM174A, FAM195B, FAM198B, FAM20A, FAM208B, FAM219A, FAM219B, FAM3C, FAM46B, FAM49B, FAM65A, FAM65B, FAM69B, FAP, FARP1, FBLN2, FBN2, FBXL16, FBXL6, FBXO9, FBXO10, FBXO18, FBXO31, FBXO34, FBXO9, FCHO1, FDFT1, FDPS, FER, FEZ1, FGD4, FGD5-AS1, FGFR2, FGFR1, FGL2, FHOD3, FLII, FLNB, FLT1, FN1, FNBP1, FOCAD, FOS, FOSB, FOSL1, FOXK1, FOXM1, FRAS1, FSCN2, FUS, FYN, GABPB1, GAL3ST4, GALC, GALNT1, GALNT15, GAS7, GATA6, GBA2, GBGT1, GBP1, GCFC2, GLCE, GCNT1, GDF6, GGACT, GGCT, GHDC, GIGYF2, GJC1, GLCE, GMIP, GNA13, GNAQ, GNAS, GNG12, GNL3L, GOLGA2, GOLGA4, GOLGB1, GORASP1, GPR1, GPR183, GPR50, GPR89A, GPRC5A, GPRC5B, GPSM2, GREM1, GRK6, GRTP1, GSE1, GTF2H2B, GTSF1, GUCA1B, GULP1, GXYLT1, HAPLN1, HAPLN2, HAS2, HAS3, HAT1, HAUS3, HAUS6, HAVCR2, HDAC5, HDAC7, HDX, HECTD2-AS1, HEG1, HEPH, HEY1, HLA-A, HLA-E, HLTF, HMGA1, HMGA2, HMGB1, HMGCR, HMGN3-AS1, HMGCS1, HMGXB4, HOOK3, HOXB3, HMOX1, HNMT, HNRNP, HNRNPUL1, HP1BP3, HPS1, HRH1, HSD17B12, HSD17B4, HSPA1L,

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[2348] In another aspect, HD/SMA compounds can modify the alternative splicing of pre-mRNAs to enhance the abundance of exon inclusion in spliced mRNAs transcribed from one or more of the following HD/SMA compound inducible genes including, but not limited to, ABCA1, ABCB7, ABCC1, ABHD10, ABL2, ABLIM3, ACACA, ACADVL, ACAT2, ADAM12, ADAM15, ADAM17, ADAM33, AFF2, AGK, AGPAT3, AGPS, AHCYL2, AHDC1, AHRR, AJUBA, AK021888, AK310472, AKAP1, AKAP9, AKNA, ALCAM, ALDH4A1, AMPD2, ANK2, ANKFY1, ANKHD1-EIF4EBP3, ANKRD17, ANKS6, ANP32A, ANXA11, ANXA6, AP2B1, APAF1, APLP2, APP, APPL2, APTX, ARHGAP22, ARID1A, ARID2, ARMCX3, ASAP1, ASL, ASNS, ASPH, ATAD2B, ATF7IP, ATG9A, ATMIN, ATP2C1, ATXN3, AURKA, AXIN1, B4GALT2, BACE1, BAG2, BASP1, BC033281, BCAR3, BEND6, BICD1, BIN1, BNC1, BRD2, BRPF1, BSCL2, BTBD10, BZW1, C11orf30, C11orf73, C17orf76-AS1, C4orf27, C5orf24, C6orf48, C9orf69, CAB39, CALU, CAMKK1, CAPNS1, CASC3, CASP8AP2, CAV1, CCAR1, CCDC77, CCDC88A, CCDC92, CCT6A, CD276, CD46, CDC25B, CDC40, CDC42BPA, CDCA7, CDH11, CDH13,

CDK11B, CDK16, CDKAL1, CEP68, CFLAR, CHD8, CIZ1, CLIC1, CLK4, CNOT1, COG1, COL12A1, COL1A1, COL6A1, COPS7B, CPEB2, CREB5, CRLS1, CRTAP, CSDE1, CSNK1A1, CTDSP2, CTNND1, CUL2, CUL4A, CUX1, CYB5B, CYBRD1, CYP51A1, DAB2, DACT1, DAKS, DAXX, DCAF10, DCAF11, DCBLD2, DCUN1D4, DDAH1, DDAH2, DDHD2, DDR1, DDX39B, DDX42, DENND1A, DENND1B, DENND5A, DGCR2, DGKA, DHCR24, DHCR7, DHFR, DHX9, DIAPH1, DIAPH3, DIS3L, DKFZp434M1735, DKK3, DLC1, DNM2, DOCK1, DPP8, DSEL, DST, DSTN, EBF1, EEA1, EEF1A1, EFCAB14, EGR1, EHMT2, EIF2B3, EIF4G1, EIF4G2, EIF4G3, ELF2, ENG, ENPP2, ENSA, EPN1, EPT1, ERC1, ERGIC3, ETV5, EXO1, EXTL2, EYA3, FADS1, FADS2, FAF1, FAM111A, FAM198B, FAM219A, FAM219B, FAM3C, FAM65A, FBXO10, FBXO18, FBXO31, FBXO34, FBXO9, FDFT1, FDPS, PER, FEZ1, FGD5-AS1, FGFRL1, FHOD3, FLII, FLNB, FN1, FNBP1, FOCAD, FOS, FOSB, FOSL1, FOXK1, FOXM1, FUS, FYN, GABPB1, GALC, GALNT1, GAS7, GBA2, GCFC2, GGCT, GHDC, GIGYF2, GJC1, GMIP, GNA13, GNAS, GNL3L, GOLGA2, GOLGA4, GOLGB1, GORASP1, GPR1, GPR89A, GPSM2, GREM1, GRK6, GSE1, GTF2H2B, HAS2, HAT1, HAUS3, HAUS6, HDAC7, HEG1, HLA-A, HLA-E, HLTF, HMGA1, HMGB1, HMGCR, HMGCS1, HMOX1, HNRNPR, HNRNPUL1, HP1BP3, HRH1, HSD17B12, HSD17B4, HTT, IARS, IDH1, IDI1, IGF2BP2, IL6ST, INHBA, INSIG1, IQCE, ITGAV, ITGB5, ITM2C, ITSN1, KANSL3, KCNK2, KIAA1033, KIAA1143, KIAA1199, KIAA1522, KIAA1524, KIAA1549, KIAA1715, KIF14, KIF2A, KIF3A, KLC1, KLC2, KLF6, KLHL7, KRT18, KRT19, KRT34, KRTAP2-3, LAMA2, LAMB1, LARP4, LARP7, LATS2, LDLR, LEMD3, LGALS8, LIMS1, LINC00341, LINC00657, LMAN2L, LMO7, LONP1, LOX, LRCH4, LRIG1, LRP8, LRRC8A, LSS, LTBR, LUC7L2, LZTS2, MADD, MAGED4, MAGED4B, MAN1A2, MAP4K4, MBD1, MBOAT7, MDM2, MED1, MEDAG, MEF2D, MEIS2, MEMO1, MEPCE, MFGE8, MICAL2, MINPP1, MKL1, MKLN1, MKNK2, MLLT4, MLST8, MMAB, MMS19, MMS22L, MPPE1, MPZL1, MRPL3, MSANTD3, MSC, MSH2, MSH6, MSL3, MEMO1, MSRB3, MTAP, MTERFD1, MTHFD1L, MTMR9, MTRR, MUM1, MVD, MVK, MYADM, MYLK, MYOID, MYO9B, MYOF, NAA35, NADK, NASP, NAV1, NAV2, NCOA1, NCOA3, NCOA4, NCSTN, NELFA, NEO1, NEURL1B, NF2, NFE2L1, NFX1, NID1, NID2, NIPA1, NKX3-1, NOL10, NOMO3, NPEPPS, NRD1, NREP, NRG1, NSUN4, NT5C2, NT5E, NTNG1, NUDT4, NUP153, NUP35, NUP50, NUPL1, NUSAP1, ODF2, OS9, OSBPL6, OSMR, P4HA1, P4HB, PABPC1, PAK4, PAPD4, PARD3, PARN, PARP14, PARP4, PARVB, PCBP2, PCBP4, PCDHGB3, PCGF3, PCM1, PCMTD2, PCNXL2, PCSK9, PDE4A, PDE7A,

PDLIM7, PDXDC1, PEPD, PEX5, PFKP, PHF19, PHF8, PHRF1, PHTF2, PI4K2A, PIEZO1, PIGU, PIK3C2B, PITPNA, PITPNB, PITPNM1, PLAUI, PLEC, PLEKHB2, PLSCR3, PLXNB2, PLXNC1, PMS1, POLE3, POLR3D, POSTN, POU2F1, PPAPDC1A, PPARA, PPHLN1, PPIP5K1, PPP1R12A, PPP6R1, PPP6R2, PRKACB, PRKDC, PRMT1, PRNP, PRSS23, PSMA4, PSMC1, PSMD6, PTK2B, PTPN14, PUF60, PUS7, PVR, PXN, QKI, RAB23, RAB2B, RAB34, RAD1, RAD23B, RALB, RAP1A, RAP1GDS1, RARG, RASSF8, RBCK1, RBFOX2, RBM10, RCC1, RFTN1, RFWD2, RGS10, RGS3, RIF1, RNF14, RNF19A, RNF38, RNFT1, RPL10, RPS6KC1, RRBP1, RWDD4, SAMD9, SAMD9L, SAR1A, SART3, SCAF4, SCAF8, SCD, SCLT1, SCO1, SDCBP, SEC14L1, SEC22A, SEC24B, SEC61A1, SEPT9, SERPINE2, SF1, SGOL2, SH3RF1, SKIL, SLC25A17, SLC39A3, SLC41A1, SLC4A4, SLC7A6, SLC7A8, SMARCA4, SMARCC2, SMC4, SMC6, SMCHD1, SMG1, SMN2, SMPD4, SMYD3, SMYD5, SNAP23, SNHG16, SNX14, SOCS2, SON, SOS2, SPATA20, SPATS2, SPG20, SPRED2, SQLE, SQRDL, SQSTM1, SRCAP, SREBF1, SREK1, SRSF3, STARD4, STAT1, STAT3, STAU1, STC2, STEAP2, STRIP1, STRN3, STX16, SUPT20H, SYNE1, SYNE2, SYT15, SYTL2, TACC1, TAF2, TANC2, TARBP1, TARS, TBC1D15, TBL2, TCF7L2, TENC1, TENM2, TEP1, TET3, TFCEP2, TGFBI, TGFBR1, TGFBRAP1, THADA, THAP4, THRB, TIMP2, TJP2, TLE3, TLK1, TMEM154, TMEM47, TMEM63A, TNC, TNFAIP3, TNFRSF12A, TNIP1, TNKS1BP1, TNPO3, TNS1, TNS3, TOE1, TOMM40, TOMM5, TOPORS, TP53INP1, TRAF3, TRAK1, TRAPPC12, TRIB1, TRIM2, TRIM23, TRIM26, TRIM28, TRIM65, TRMT1L, TRPS1, TSC2, TSHZ1, TSPAN2, TTC7A, TUBB2C, TUBB3, TXNL1, TXNRD1, U2SURP, UBAP2L, UBE2G2, UBE2V1, UBQLN4, UCHL5, UHMK1, UHRF1BP1L, UNC5B, USP19, USP7, VANGL1, VARS2, VCL, VIPAS39, VPS13A, VPS29, VPS51, VWA8, WDR19, WDR37, WDR48, WIPF1, WNT5B, WSB1, WWTR1, XIAP, XRN2, YAP1, YES1, YPEL5, YTHDF3, Z24749, ZAK, ZBTB10, ZBTB24, ZBTB7A, ZC3H12C, ZC3H14, ZC3H18, ZCCHC11, ZEB1, ZEB2, ZFAND1, ZFAND5, ZHX3, ZMIZ1, ZMYM2, ZNF12, ZNF148, ZNF219, ZNF227, ZNF24, ZNF268, ZNF28, ZNF281, ZNF335, ZNF37A, ZNF37BP, ZNF395, ZNF583, ZNF621, ZNF652, ZNF655, ZNF674, ZNF74, ZNF764, ZNF778, ZNF780A, ZNF827, ZNF839 and ZNF91.

[2349] In another aspect, HD/SMA compounds can modify the alternative splicing of pre-mRNAs to enhance the abundance of exon inclusion in spliced mRNAs transcribed from one or more of the following HD/SMA compound inducible genes including, but not limited to, ABCA1, ABCC1, ABL2, ACACA, ACAT2, AFF2, AHRR, AK021888, AK310472, AKAP1,

ANK2, ANKHD1-EIF4EBP3, AP2B1, APAF1, APLP2, ARID1A, ARMCX3, ASAP1, ASPH, ATAD2B, ATF7IP, ATG9A, AXIN1, BACE1, BIN1, BNC1, BRPF1, BZW1, C11orf30, C11orf73, C17orf76-AS1, C4orf27, C6orf48, CAB39, CAMKK1, CCDC88A, CCDC92, CDC25B, CDC42BPA, CDCA7, CDH11, CDH13, CEP68, CFLAR, COPS7B, CREB5, CUL2, CUL4A, CUX1, CYP51A1, DCUN1D4, DDR1, DDX39B, DDX42, DENND1A, DENND5A, DGKA, DHCR24, DHCR7, DIAPH1, DIAPH3, DNM2, DOCK1, EFCAB14, EIF2B3, EPN1, EPT1, ERC1, ETV5, FADS1, FADS2, FAF1, FAM198B, FAM219B, FBXO10, FBXO9, FDFT1, FDPS, FER, FEZ1, FHOD3, FLII, FLNB, FNBP1, FOS, FOSB, FOXM1, FYN, GABPB1, GALC, GAS7, GGCT, GJC1, GPSM2, GRK6, HAS2, HAT1, HLTF, HMGA1, HMGB1, HMGCR, HMGCS1, HMOX1, HP1BP3, HSD17B12, HTT, IDI1, INHBA, INSIG1, KANSL3, KIAA1199, KIAA1524, KIAA1715, KIF3A, KLF6, KRT19, KRT34, KRTAP2-3, LAMA2, LARP7, LDLR, LEMD3, LMAN2L, LRCH4, LRP8, LSS, MAGED4, MAGED4B, MAN1A2, MEDAG, MEF2D, MEMO1, MFGE8, MICAL2, MMAB, MMS19, MMS22L, MSL3, MSMO1, MTAP, MTERFD1, MVD, MVK, NASP, NAV2, NEURL1B, NFE2L1, NID1, NPEPPS, NREP, NRG1, NSUN4, NT5C2, NUP153, P4HA1, PABPC1, PAPD4, PCBP2, PCM1, PCSK9, PDXDC1, PEPD, PHF19, PHF8, PHTF2, PIK3C2B, PITPNB, PLEC, PMS1, POU2F1, PPHLN1, PRKDC, PRSS23, PSMC1, PTPN14, PUF60, PVR, RAB23, RAD23B, RAP1A, RASSF8, RBM10, RCC1, RFWD2, RNFT1, RWDD4, SAMD9L, SART3, SCAF4, SCD, SEC22A, SEC61A1, SERPINE2, SF1, SLC25A17, SLC7A6, SLC7A8, SMN2, SMYD3, SMYD5, SNAP23, SNHG16, SQLE, SQRD, SQSTM1, SRCAP, SREBF1, STARD4, STAT1, STAU1, STEAP2, STRN3, SYNE1, TACC1, TAF2, TANC2, TARBP1, TBC1D15, TEP1, TFCP2, TGFBRAP1, THADA, TIMP2, TLK1, TMEM154, TNS3, TOMM5, TRAF3, TRAK1, TRAPPC12, TRIM2, TRIM26, TRIM65, TSPAN2, U2SURP, UBAP2L, UBE2V1, UCHL5, UHRF1BP1L, VANGL1, VARS2, VPS13A, VPS29, VWA8, WSB1, XIAP, XRN2, YPEL5, ZAK, ZC3H18, ZFAND5, ZMIZ1, ZMYM2, ZNF219, ZNF227, ZNF24, ZNF37A, ZNF37BP, ZNF395, ZNF652, ZNF674, ZNF74 and ZNF778.

[2350] In another aspect, HD/SMA compounds can be expected to modify the alternative splicing of pre-mRNAs to enhance the abundance of exon inclusion in spliced mRNAs transcribed from one or more of the following HD/SMA compound inducible genes including, but not limited to, ABCC1, ACADVL, ADAM15, AGPAT3, AHRR, AJUBA, AKAP1, AKAP9, ALCAM, ALDH4A1, ANKFY1, AP2B1, APLP2, APP, ARID1A, ARID2, ASPH, ATMIN, BASP1, BC033281, BCAR3, C11orf73, C17orf76-AS1, C5orf24, C6orf48, CAB39,

CASP8AP2, CAV1, CCAR1, CCT6A, CD276, CD46, CDC25B, CDK16, CEP68, CHD8, CLIC1, COL12A1, CPEB2, CREB5, CRLS1, CRTAP, CTNND1, CUX1, CYBRD1, DACT1, DCAF10, DCAF11, DDHD2, DDX39B, DIAPH3, DKK3, DLC1, DSTN, EBF1, EGR1, EIF4G1, EIF4G3, ENG, ERC1, ETV5, FAM198B, FAM219A, FAM3C, FEZ1, FGD5-AS1, FLII, FN1, FNBP1, FOS, FOSB, FOXK1, FOXM1, FYN, GABPB1, GALC, GALNT1, GBA2, GGCT, GHDC, GMIP, GNA13, GNAS, GNL3L, GOLGA2, GORASP1, GREM1, GSE1, HAUS6, HDAC7, HEG1, HLA-A, HLA-E, HMGA1, HP1BP3, IL6ST, ITGAV, KIAA1549, KIF14, KLC1, KLF6, KLHL7, KRT18, LAMA2, LAMB1, LARP7, LATS2, LGALS8, LIMS1, LINC00341, LONP1, LOX, MDM2, MEPCE, MINPP1, MLLT4, MPPE1, MRPL3, MSH2, MSH6, MSL3, MTMR9, MTRR, MUM1, MYADM, MYLK, NADK, NAV2, NCSTN, NFE2L1, NID1, NIPA1, NPEPPS, NRD1, NUDT4, NUSAP1, P4HB, PABPC1, PAK4, PAPD4, PCNXL2, PDE4A, PDXDC1, PHRF1, PHTF2, PI4K2A, PIK3C2B, PLAU, PLEKHB2, PLSCR3, PLXNB2, POSTN, POU2F1, PPARA, PPP1R12A, PRKACB, PSMD6, PTPN14, PUS7, QKI, RAB34, RAD1, RAD23B, RASSF8, RBCK1, RBFOX2, RFTN1, RNF19A, RNF38, RPS6KC1, RWDD4, SEC14L1, SEC24B, SERPINE2, SF1, SLC39A3, SLC41A1, SLC4A4, SLC7A6, SMARCA4, SMN2, SNHG16, SNX14, SON, SPRED2, STAU1, STEAP2, STRIP1, STRN3, TBL2, TGFB1, TGFB1R1, THAP4, TLE3, TMEM47, TNKS1BP1, TOMM40, TOPORS, TRAK1, TRAPPC12, TRIB1, TRIM2, TRIM23, TRIM65, TRMT1L, TRPS1, TXNL1, TXNRD1, U2SURP, UBE2G2, UBE2V1, UHMK1, USP7, VPS29, VWA8, WDR19, WDR37, WIPF1, YPEL5, YTHDF3, Z24749, ZBTB10, ZBTB7A, ZFAND5, ZMIZ1, ZNF12, ZNF148, ZNF335, ZNF395, ZNF583, ZNF621, ZNF655, ZNF74 and ZNF780A.

[2351] In another aspect, HD/SMA compounds may modify the alternative splicing of pre-mRNAs to enhance the abundance of exon inclusion in spliced mRNAs transcribed from one or more of the following HD/SMA compound inducible genes including, but not limited to, ABCB7, ABHD10, ABLIM3, ACACA, ADAM12, ADAM17, ADAM33, AGK, AGPS, AHCYL2, AHDC1, AHRR, AK021888, AK310472, AKAP1, AKAP9, AKNA, AMPD2, ANKRD17, ANKS6, ANP32A, ANXA11, ANXA6, APLP2, APP, APPL2, APTX, ARHGAP22, ARMCX3, ASAP1, ASNS, ASPH, ATG9A, ATP2C1, AURKA, AXIN1, B4GALT2, BACE1, BASP1, BEND6, BICD1, BIN1, BRD2, BRPF1, BTBD10, C11orf30, C11orf73, C17orf76-AS1, C4orf27, C6orf48, CAB39, CAPNS1, CASC3, CCDC77, CCDC88A, CD46, CDC40, CDC42BPA, CDCA7, CDH13, CDK11B, CEP68, CIZ1, CLK4, CNOT1, COG1, COL12A1, COL1A1, COL6A1, COPS7B, CSDE1, CSNK1A1, CUX1,

CYB5B, CYBRD1, DAB2, DARS, DCBLD2, DCUN1D4, DDAH2, DDR1, DDX39B, DDX42, DENND1A, DENND1B, DENND5A, DGKA, DHFR, DHX9, DIAPH1, DIAPH3, DIS3L, DNM2, DOCK1, DPP8, DSEL, EEA1, EFCAB14, EIF2B3, EIF4G1, EIF4G3, ELF2, ENG, ENPP2, EPN1, EXTL2, EYA3, FAF1, FAM198B, FAM3C, FBXO10, FBXO18, FBXO31, FBXO9, FER, FEZ1, FHOD3, FLII, FN1, FNBP1, FOCAD, FOSL1, FOXM1, GABPB1, GALC, GALNT1, GCFC2, GGCT, GIGYF2, GMIP, GNAS, GNL3L, GOLGB1, GPR89A, GPSM2, GREM1, GRK6, GTF2H2B, HAT1, HAUS3, HEG1, HLA-A, HLTF, HP1BP3, HRH1, HSD17B12, HSD17B4, HTT, IARS, IDH1, IGF2BP2, ITM2C, KCNK2, KIAA1033, KIAA1143, KIAA1522, KIAA1524, KIAA1715, KIF3A, KLHL7, LAMA2, LARP4, LARP7, LATS2, LIMS1, LINC00341, LINC00657, LMAN2L, LMO7, LRCH4, LRIG1, LRRC8A, LTBR, LUC7L2, LZTS2, MADD, MAGED4B, MAN1A2, MAP4K4, MED1, MEDAG, MEF2D, MEIS2, MEMO1, MICAL2, MKLN1, MLLT4, MMS19, MPZL1, MSANTD3, MSC, MSL3, MTAP, MTERFD1, MTHFD1L, MYADM, MYLK, MYO9B, MYOF, NASP, NAV2, NCOA3, NCOA4, NELFA, NEO1, NEURL1B, NF2, NID2, NOL10, NPEPPS, NRG1, NSUN4, NT5C2, NT5E, NTNG1, NUP153, NUP35, NUP50, NUSAP1, ODF2, OS9, OSBPL6, P4HA1, P4HB, PABPC1, PAPD4, PARN, PARP4, PCBP2, PCBP4, PCDHGB3, PCGF3, PCM1, PCMTD2, PDE7A, PDXDC1, PEPD, PFKP, PHF19, PHRF1, PHTF2, PIEZO1, PIGU, PITPNA, PITPNB, PITPNM1, PLAUI, PLSCR3, PLXNC1, PMS1, POU2F1, PPAPDC1A, PPHLN1, PPIP5K1, PPP1R12A, PRKDC, PRMT1, PRSS23, PSMA4, PTK2B, PUF60, PVR, RAB23, RAB2B, RAD1, RAD23B, RAP1A, RAP1GDS1, RARG, RASSF8, RBCK1, RCC1, RFWD2, RGS3, RNF14, RNFT1, RPL10, RRBP1, RWDD4, SAR1A, SCAF4, SCAF8, SCLT1, SCO1, SDCBP, SEC22A, SEPT9, SF1, SGOL2, SLC25A17, SLC4A4, SLC7A6, SMARCC2, SMC4, SMC6, SMCHD1, SMN2, SMPD4, SMYD3, SNAP23, SNHG16, SOCS2, SOS2, SPATA20, SPATS2, SPG20, SQRDL, SREBF1, SREK1, SRSF3, STAT1, STAU1, STEAP2, STRN3, STX16, SUPT20H, SYNE1, SYNE2, SYT15, SYTL2, TAF2, TARBP1, TARS, TBL2, TCF7L2, TENC1, TENM2, TEP1, TET3, TGFB1, THADA, THRB, TJP2, TLE3, TMEM47, TMEM63A, TNFAIP3, TNIP1, TNPO3, TNS1, TNS3, TOE1, TOMM5, TP53INP1, TRAF3, TRAPPC12, TRIM2, TRIM23, TRIM65, TSC2, TSPAN2, TUBB2C, TXNRD1, UBAP2L, UBE2V1, UCHL5, USP19, VANGL1, VIPAS39, VPS29, VPS51, VWA8, WDR48, WNT5B, WSB1, WWTR1, XRN2, YAP1, YES1, YPEL5, YTHDF3, Z24749, ZBTB24, ZC3H14, ZFAND1, ZFAND5, ZHX3, ZMIZ1, ZMYM2, ZNF219, ZNF268, ZNF395, ZNF827 and ZNF91.

[2352] In another aspect, HD/SMA compounds may modify the alternative splicing of pre-mRNAs to enhance the abundance of exon inclusion in spliced mRNAs transcribed from one or more of the following HD/SMA compound inducible genes including, but not limited to, ACACA, ACADVL, AFF2, AHCYL2, AHRR, AKAP1, ALDH4A1, ANKRD17, AP2B1, APLP2, ASL, ASPH, ATG9A, ATMIN, ATXN3, BAG2, BASP1, BRPF1, BSCL2, C11orf30, C11orf73, C17orf76-AS1, C6orf48, C9orf69, CAB39, CALU, CDC25B, CDC42BPA, CDKAL1, CLIC1, COL12A1, COL1A1, COL6A1, CSNK1A1, CTDSP2, CUL2, CUL4A, DAXX, DCAF10, DDAH1, DDR1, DDX39B, DENND1A, DGCR2, DKFZp434M1735, DKK3, DNM2, DST, EEF1A1, EFCAB14, EHMT2, EIF4G1, EIF4G2, EIF4G3, ENSA, EXO1, FAM111A, FAM198B, FAM65A, FBXO34, FEZ1, FGD5-AS1, FGFRL1, FLII, FN1, FOXK1, FOXM1, FUS, GALC, GALNT1, GAS7, GCFC2, GGCT, GJC1, GNA13, GNL3L, GOLGA4, GPR1, GREM1, HEG1, HLA-A, HLA-E, HLTF, HNRNPR, HNRNPUL1, IQCE, ITGB5, ITSN1, KIAA1033, KIF2A, KIF3A, KLC2, LATS2, LIMS1, LINC00341, LINC00657, LONP1, LOX, LUC7L2, MBD1, MBOAT7, MEF2D, MEIS2, MICAL2, MKL1, MKNK2, MLST8, MPPE1, MSL3, MSRB3, MTRR, MYADM, MYLK, MYO1D, NAA35, NAV1, NAV2, NCOA1, NFX1, NKX3-1, NOMO3, NRG1, NUDT4, NUPL1, NUSAP1, OSMR, P4HA1, P4HB, PAPD4, PARD3, PARN, PARP14, PARVB, PCBP2, PCBP4, PCGF3, PDLIM7, PDXDC1, PEX5, PFKP, PHRF1, PI4K2A, POLE3, POLR3D, POSTN, PPARA, PPP6R1, PPP6R2, PRNP, PXN, RAB34, RAD23B, RALB, RAP1A, RASSF8, RBCK1, RBFOX2, RGS10, RIF1, RNF14, RNF19A, SAMD9, SCAF4, SDCBP, SERPINE2, SF1, SH3RF1, SKIL, SLC25A17, SLC4A4, SMG1, SMN2, SNHG16, SREBF1, STATS, STC2, STEAP2, STRN3, SYNE1, SYNE2, TACC1, TARS, TGFB1, TMEM47, TNC, TNFRSF12A, TNS1, TRAF3, TRIM28, TSC2, TSHZ1, TTC7A, TUBB2C, TUBBS, TXNL1, TXNRD1, UBE2G2, UBE2V1, UBQLN4, UNC5B, USP19, VARS2, VCL, VPS29, WDR37, WIPF1, WWTR1, ZC3H12C, ZCCHC11, ZEB1, ZEB2, ZFAND1, ZFAND5, ZMIZ1, ZNF28, ZNF281, ZNF655, ZNF764 and ZNF839.

[2353] In another aspect, HD/SMA compounds can be expected to modify the alternative splicing of pre-mRNAs to enhance the abundance of exon inclusion in spliced mRNAs transcribed from one or more of the following HD/SMA compound inducible genes including, but not limited to, ABCB8, ABCC3, ADAM17, ADCY3, AGPAT4, ANKRA2, ANXA11, APIP, APLP2, ARHGAP1, ARL15, ASAP1, ASPH, ATAD2B, ATXN1, AXIN1, BECN1, BHMT2, BICD1, BTN3A1, C11orf30, C11orf73, C12orf4, C14orf132, C8orf44, C8orf44-SGK3, C8orf88, CASC3, CASP7, CCDC122, CDH13, CECR7, CENPI, CEP112, CEP192, CHEK1,

CMAHP, CNRIP1, COPS7B, CPSF4, CRISPLD2, CRYBG3, CSNK1E, CSNK1G1, DAGLB, DCAF17, DCUN1D4, DDX42, DENND1A, DENND5A, DGKA, DHFR, DIAPH3, DLGAP4, DNAJC13, DNMBP, DOCK1, DYRK1A, EIF2B3, ENAH, ENOX1, EP300, ERC1, ERCC1, ERGIC3, ERLIN2, ERFFI1, EVC, FAF1, FAIM, FAM126A, FAM13A, FAM162A, FAM174A, FAM198B, FBN2, FER, FHOD3, FOCAD, GALC, GCFC2, GGACT, GGCT, GLCE, GOLGA4, GOLGB1, GPSM2, GULP1, GXYLT1, HAT1, HDX, HLTF, HMGA2, HNMT, HPS1, HSD17B12, HSD17B4, HTT, IFT57, INPP5K, IVD, KDM6A, KIAA1524, KIAA1715, LETM2, LOC400927, LRRC42, LUC7L3, LYRM1, MADD, MB21D2, MCM10, MED13L, MEDAG, MEMO1, MFN2, MMS19, MRPL45, MRPS28, MTERF3, MYCBP2, MYLK, MYOF, NGF, NREP, NSUN4, NT5C2, OSMR, OXCT1, PAPD4, PCM1, PDE7A, PDS5B, PDXDC1, PIGN, PIK3CD, PIK3R1, PIKFYVE, PITPNB, PLEKHA1, PLSCR1, PMS1, POMT2, PPARG, PPHLN1, PPIP5K2, PPP1R26, PRPF31, PRSS23, PRUNE2, PSMA4, PXX, RAFI, RAP1A, RAPGEF1, RARS2, RBKS, RERE, RFWD2, RNFT1, RPA1, RPS10, RPS6KB2, SAMD4A, SAR1A, SCO1, SEC24A, SENP6, SERGEF, SGK3, SH3YL1, SKA2, SLC12A2, SLC25A17, SLC44A2, SMYD3, SNAP23, SNHG16, SNX7, SOS2, SPATA18, SPATA5, SPIDR, SPRYD7, SRGAP1, SRRM1, STAT1, STRN3, STXBP6, SUPT20H, TAF2, TASP1, TBC1D15, TCF12, TCF4, TIAM1, TJP2, TMC3, TMEM189, UBE2V1, TMEM214, TNRC6A, TNS3, TOE1, TRAF3, TRIM65, TSPAN2, TTC7B, TUBE1, TYW5, UBAP2L, UBE2V1, URGCP, VAV2, VPS29, WDR27, WDR37, WDR91, WNK1, XRN2, ZCCHC8, ZFP82, ZNF138, ZNF232, ZNF37BP and ZNF680

[2354] In another aspect, HD/SMA compounds may modify the alternative splicing of pre-mRNAs to enhance the abundance of exon inclusion in spliced mRNAs transcribed from one or more of the following HD/SMA compound inducible genes including, but not limited to, ABHD10, ADAL, ADAM17, ADAM23, ADAMTS19, AGPAT4, AGPS, AKAP8L, AKT1, ANKRD13C, ANXA11, APIP, APOA2, APPL2, ARHGAP1, ARHGAP5, ARL15, ARL5B, ARSJ, ASAP1, ATF6, BECN1, BHMT2, BIN3, BNC2, BRCA1, BRCA2, BTBD10, C1QTNF9B-AS1, C1ORF27, C11ORF30, C11ORF73, C11ORF76, C12ORF4, C2ORF47, CACNB1, CACNB4, CADM2, CCNL2, CDH18, CDKN1C, CENPI, CEP162, CEP170, CEP192, CEP57, CHEK1, CHRM2, CMAHP, CMSS1, CNOT7, CNRIP1, CNTN1, COPS7B, CRISPLD2, CRX, CRYBG3, CTCR, CUX1, DAAM1, DCAF17, DCUN1D4, DDX42, DENND1A, DENND4A, DENND5A, DET1, DGK1, DHFR, DIAPH3, DLG5, DMXL1, DMD, DNAH11, DNAJA4, DNMBP, DYRK1A, DZIP1L, EIF2B3, ELMO2, ENAH, ENOX1, EP300, ERC1, ERC2, EVC, EXOC3, EXOC6B, FAM162A, FAM174A, FAM195B,

FAM208B, FAM49B, FAM69B, FBN2, FBXL16, FBXO9, FGD4, FHOD3, GALC, GBP1, GLCE, GNG12, GOLGB1, GTSF1, GXYLT1, HDAC5, HDX, HMGXB4, HOXB3, HPS1,, HSD17B4, HTT, IFT57, IKBKAP, INO80, IPP4B, INVS, ITCH, IVD, KDM6A, KDSR, KIAA1524, KIAA1715, KIDINS220, KIF21A, L3MBTL2, LGALS3, LINCR-0002, LINGO2, LMNA, LOC400927, LPHN1, LRRC1, LRRC42, LYRM1, MACROD2, MANEA, MAPK10, MARCH7, MARCH8, MDN1, MEAF6, MECP2, MEMO1, MFN2, MLLT10, MMS19, MORF4L1, MRPL39, MRPL45, MRPS28, MTMR3, MYB, MYCBP2, MYLK, NEDD4, NFASC, NGF, NIPA1, NLGN1, NLN, NREP, NSUN4, NUPL1, OSBPL3, PAPD4, PAX6, PBX3, PCCB, PCDH10, PDE3A, PDE7A, PDXDC1, PDXDC2P, PELI1, PIGN, PITPNB, PMS1, PNISR, POMT2, PPARG, PPFIBP1, PRPF31, PSMA4, PTCH1, PXK, RAB23, RAF1, RAPGEF1, RASIP1, RBBP8, RCOR3, RERE, RGL1, RNF130, RNF144A, RNF213, RPF2, RPS10, SAMD4A, SCO1, SENP6, SF3B3, SGIP1, SGMS1, SGPL1, SH2B3, SKP1, SLC12A2, SLC25A16, SLC25A17, SLC34A3, SMN2, SMOX, SNAP23, SNX24, SNX7, SOCS6, SOGA2, SORCS1, SPIDR, SPINK5, SPRYD7, SREK1, SSBP1, STRAD8, STXBP4, STXBP6, SUPT20H, TAF2, TARBP1, TASP1, TBCA, TBL1XR1, TCF4, TEKT4P2, TET1, TIAM1, TJAP1, TJP2, TMEM67, TMEM214, TMX3, TNRC6A TRAF3, TRIM65, TSPAN7, TXNL4B, UBE2D3, UBE2L3, UBN2, UNC13B, URGCP-MRPS24, UVRAG, VDAC2, VWF, WDR27, WDR90, WHSC2, WNK1, XDH, XRN2, ZFP82, ZMIZ2, ZNF138, ZNF208, ZNF212, ZNF280D, ZNF350, ZNF37BP, ZNF426, ZNF618, ZNF680, ZNF730, ZNF777, ZNF7804A, ZNF836 and ZSCAN25.

[2355] In another aspect, HD/SMA compounds may modify the alternative splicing of pre-mRNAs to enhance the abundance of exon inclusion in spliced mRNAs transcribed from one or more of the following genes including, but not limited to, APOA2, ASAP1, BRCA1, BRCA2, CDKN1C, CRX, CTRC, DENND5A, DIAPH3, DMD, DNAH11, EIF2B3, GALC, HPS1, HTT, IKBKAP, KIAA1524, LMNA, MECP2, PAPD4, PAX6, PCCB, PITPNB, PTCH1, SLC34A3, SMN2, SPINK5, SREK1, TMEM67, VWF, XDH and XRN2.

[2356] In another aspect, HD/SMA compounds may modify the alternative splicing of pre-mRNAs to enhance the abundance of exon inclusion in spliced mRNAs transcribed from one or more of the following HD/SMA compound inducible genes including, but not limited to, ABCA1, ABCA10, ABCB7, ABCB8, ABCC1, ABCC3, ABL2, ABLIM3, ACACA, ACADVL, ACAT2, ACTA2, ADAL, ADAM15, ADAM17, ADAM23, ADAM33, ADAMTS1, ADAMTS19, ADCY3, ADD1, ADGRG6, ADH6, ADHFE1, AFF2, AFF3, AGK, AGPAT3,

AGPAT4, AGPS, AHCYL2, AHDC1, AHRR, AJUBA, AK021888, AK310472, AKAP1, AKAP3, AKAP8L, AKAP9, AKNA, ALCAM, ALDH4A1, AMPD2, ANK1, ANK2, ANK3, ANKFY1, ANKHD1-EIF4EBP3, ANKRA2, ANKRD13C, ANKRD17, ANKRD33B, ANKRD36, ANKS6, ANP32A, ANXA6, AP2B1, AP4B1-AS1, APAF1, APIP, APOA2, APP, APTX, ARHGAP1, ARHGAP12, ARHGAP22, ARHGAP5, ARHGEF16, ARID1A, ARID2, ARID5B, ARL9, ARL15, ARL5B, ARMCX3, ARSJ, ASAP1, ASIC1, ASL, ASNS, ASPH, ATAD2B, ATF6, ATF7IP, ATG9A, ATMIN, ATP2A3, ATP2C1, ATXN1, ATXN3, AURKA, B3GALT2, B3GNT6, B4GALT2, BACE1, BAG2, BASP1, BC033281, BCAR3, BCL2L15, BCYRN1, BECN1, BEND6, BHMT2, BICD1, BIN1, BIN3, BIN3-IT1, BIRC3, BIRC6, BNC1, BNC2, BRCA1, BRCA2, BRD2, BRPF1, BSCL2, BTBD10, BTG2, BTN3A1, BZW1, C1QTNF9B-AS1, C1orf27, C1orf86, C10orf54, C11orf30, C11orf70, C11orf73, C11orf76, C11orf94, C12orf4, C12orf56, C14orf132, C17orf76-AS1, C19orf47, C2orf47, C3, C4orf27, C5orf24, C6orf48, C7orf31, C8orf34, C8orf44, C8orf44-SGK3, C8orf88, C9orf69, CA13, CA3, CAB39, CACNA2D2, CACNB1, CACNB4, CADM1, CADM2, CALU, CAMKK1, CAND2, CAPNS1, CASC3, CASP7, CASP8AP2, CAV1, CCAR1, CCDC77, CCDC79, CCDC88A, CCDC92, CCDC122, CCER2, CCNF, CCNL2, CCT6A, CD276, CD46, CDC25B, CDC40, CDC42BPA, CDCA7, CDH11, CDH13, CDH18, CDK11B, CDK16, CDKAL1, CDKN1C, CECR7, CELSR1, CEMIP, CENPI, CEP112, CEP162, CEP170, CEP192, CEP68, CFH, CFLAR, CHD8, CHEK1, CHRM2, CIITA, CIZ1, CLDN23, CLIC1, CLK4, CLTA, CMAHP, CNGA4, CNOT1, CNRIP1, CNTD1, CMSS1, CNOT7, CNRIP1, CNTN1, COG1, COL1A1, COL11A1, COL12A1, COL14A1, COL15A1, COL5A1, COL5A3, COL6A1, COL6A6, COL8A1, COLEC12, COMP, COPS7B, CPA4, CPEB2, CPQ, CPSF4, CREB5, CRISPLD2, CRLF1, CRLS1, CRTAP, CRX, CRYBG3, CRYL1, CSDE1, CSNK1A1, CSNK1E, CSNK1G1, CTDSP2, CTNND1, CTRC, CUL2, CUL4A, CUX1, CYB5B, CYB5R2, CYBRD1, CYGB, CYP1B1, CYP51A1, DAAM1, DAB2, DACT1, DAGLB, DARS, DAXX, DCAF10, DCAF11, DCAF17, DCBLD2, DCLK1, DCN, DCUN1D4, DDAH1, DDAH2, DDHD2, DDIT4L, DDR1, DDX39B, DDX42, DDX50, DEGS1, DENND1A, DENND1B, DENND4A, DENND5A, DEBTOR, DET1, DFNB59, DGCR2, DGK1, DGKA, DHCR24, DHCR7, DHFR, DHX9, DIAPH1, DIAPH3, DIRAS3, DIS3L, DKFZp434M1735, DKK3, DLC1, DLG5, DMD, DMXL1, DNAH8, DNAH11, DNAJA4, DNAJC13, DNAJC27, DNM2, DNMBP, DOCK1, DOCK11, DPP8, DSEL, DST, DSTN, DYNC1I1, DYRK1A, DZIP1L, EBF1, EEA1, EEF1A1, EFCAB14, EFEMP1, EGR1, EGR3, EHMT2, EIF2B3, EIF4G1, EIF4G2, EIF4G3, ELF2, ELMO2, ELN, ELP4, EMX2OS, ENAH,

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[2357] In another specific aspect, HD/SMA compounds may modify the alternative splicing of pre-mRNAs transcribed from one or more of the following HD/SMA compound inducible genes including, but not limited to, ABHD10, ADAM12, AKT1, ANXA11, APLP2, APPL2, ARMCX6, ATG5, AXIN1, BAIAP2, CCNB1IP1, CCT7, CEP57, CSF1, DLGAP4, EPN1, ERGIC3, FOXM1, GGCT, GRAMD3, HSD17B4, LARP7, LRRC42, MADD, MAN1B1, MRPL39, PCBP4, PPHLN1, PRKACB, RAB23, RAP1A, RCC1, SREK1, STRN3 and TNRC6A.

[2358] In another specific aspect, HD/SMA compounds may modify the alternative splicing of pre-mRNAs transcribed from one or more of the following genes including, but not limited to, ABHD10, ADAM2, AKT1, ANXA11, APLP2, APPL2, ARMCX6, ATG5, AXIN1, BAIAP2, CCNB1IP1, CCT7, CEP57, CSF1, DLGAP4, EPN1, ERGIC3, FOXM1, GGCT, GRAMD3, HSD17B4, LARP7, LRRC42, MADD, MAN1B1, MRPL39, PCBP4, PPHLN1, PRKACB, RAB23, RAP1A, RCC1, SMN2, SREK1, STRN3 and TNRC6A.

[2359] In another specific aspect, HD/SMA compounds may modify the alternative splicing of pre-mRNAs transcribed from SMN2.

[2360] In another specific aspect, HD/SMA compounds may modify the alternative splicing of pre-mRNAs transcribed from one or more genes including ABHD10, ADAM12, AKT1, ANXA11, APLP2, APPL2, ARMCX6, ATG5, AXIN1, BAIAP2, CCNB1IP1, CCT7, CEP57, CSF1, DLGAP4, EPN1, ERGIC3, FOXM1, GGCT, GRAMD3, HSD17B4, LARP7, LRRC42, MADD, MAN1B1, MRPL39, PCBP4, PPHLN1, PRKACB, RAB23, RAP1A, RCC1, SREK1, STRN3 and TNRC6A.

[2361] In another specific aspect, HD/SMA compounds may modify the alternative splicing of pre-mRNAs transcribed from one or more genes including ABHD10, ADAM12, AKT1, ANXA11, APLP2, APPL2, ARMCX6, ATG5, AXIN1, BAIAP2, CCNB1IP1, CCT7, CEP57, CSF1, DLGAP4, EPN1, ERGIC3, FOXM1, GGCT, GRAMD3, HSD17B4, LARP7, LRRC42, MADD, MAN1B1, MRPL39, PCBP4, PPHLN1, PRKACB, RAB23, RAP1A, RCC1, SMN2, SREK1, STRN3 and TNRC6A.

B. Exemplary FD compound-inducible splicing of human genes

[2362] Table 1 lists wildtype genes identified by RNA sequencing and mutated genes predicted by SpliceAI scores and the CNN model, as described herein, which may be modulated by FD compound toward either or both exon inclusion and exon exclusion.

TABLE 1

A1BG-AS1, AAAS, ABCA1, ABCA4, ABCA6, ABCA9, ABCB6, ABCC3, ABCC9, ABHD14A-ACY1, ABI1, ABI2, ABI3BP, AC024560.3, AC027612.6, AC037459.4, ACAA1, ACACA, ACAD10, ACADSB, ACBD4, ACBD5, ACIN1, ACLY, ACOX1, ACSL3, ACSL4, ACTN1, ACY1, AD000671.6, ADA, ADAM10, ADAM33, ADAMTSL4, ADARB1, ADK, AFMID, AGK, AHI1, AKAP11, AKAP13, AKIP1, AKR1A1, AL163636.6, ALDH3A2, ALDH3B1, ALDH4A1, ALKBH1, ALKBH3, ALMS1, AMMECR1L, AMPD2, ANK2, ANKRD10, ANKRD11, ANKRD36, ANO6, ANTXR2, ANXA2, AP1G1, AP2M1, APBB2, APC, APOL1, APP, ARHGAP12, ARHGAP23, ARHGEF10, ARHGEF10L, ARHGEF12, ARHGEF25, ARID4B, ARIH2, ARMC9, ARSK, ASAH1, ASAP2, ASCC2, ASL, ASPH, ASPM, ASUN, ASXL1, ATG10, ATG16L1, ATG7, ATG9A, ATM, ATP2C1, ATP5SL, ATPAF1, ATRX, ATXN1, ATXN3, AUP1, AUTS2, AVL9, B3GALNT1, BAG6, BANP, BAX, BAZ1A, BBS4, BBS5, BBX, BCAR1, BCOR, BFSP1, BIN1, BIRC6, BLOC1S6, BMP2K, BMPR2, BOK, BPTF, BRCA1, BRCA2, BRD8, BRIP1, BROX, BTBD19, C11orf30, C11orf70, C12orf29, C16orf13, C1orf85, C1RL, C2CD5, C3orf18, C5orf42, C5orf45, C8orf59, C9orf156, C9orf85, CA5A, CA5BP1, CALU, CAMK2D, CAMTA1, CAPN3, CAPN7, CAPRN2, CARD8, CARKD, CASP3, CAST, CCBL2, CCDC25, CCDC90B, CCNDBP1, CCNL1, CD3D, CD44, CD46, CD55, CD99P1, CDAN1, CDC14B, CDC16, CDH1, CDH23, CDK16, CEP290, CERKL, CFTR, CHD3, CHD7, CHEK2, CHKB, CKLF, CLASP1, CLCN1, CLCN6, CLK1, CLMP, CLN3, CMC1, CNGB3, CNOT10, COG6, COL11A1, COL12A1, COL16A1, COL3A1, COL4A3, COL4A5, COL5A2, COL6A1, COL6A3, COL7A1, COPB2, COPS7A, COPS8, COQ6, COX20, CPEB2, CPSF7, CPT1C, CRAT, CREBBP, CRLS1, CRNDE, CRYZ, CSAD, CSTB, CTDSPL, CTNS, CTSK, CTU2, CUBN, CUTC, CWC25, CWC27, CYB561D2, CYBB, CYLD, CYP20A1, DAB2, DBT, DCAF10, DCAF11, DCAF17, DCAF8, DCP1A, DCUN1D5, DCX, DCX, DDB2, DGKA, DGKE, DGUOK, DHRSX, DMT1, DIS3, DLG1, DMD, DMTF1, DNAH5, DNAH9, DNAJC19, DNAJC2, DNMT1, DNMT1, DOCK5, DOCK7, DPH3, DPY19L4, DRAM2, DSCR3, DTNBP1, DUSP11, DUSP22, DYNC2H1, DYNC2LI1, EBF3, EBP, EBPL, EDC3, EDEM2, EDRF1, EFEMP1, EHBP1, EHMT2, EIF4A2, EIF4E2, EIF4H, ELK1, ELN, ELOVL1, ENC1, ENOSF1, EP300, EPB41L1, EPB41L2, ERBB2IP, ERCC6, ERLEC1, ERMAP, ETHE1, EVC, EVI5L, F10, F13A1, F8, FAM104A, FAM111A, FAM134C, FAM149B1, FAM172A, FAM204A, FAM211A-AS1, FAM21C, FAP, FBN1, FBXL12, FBXL3, FBXO25, FBXW11, FGF5, FGFR1OP, FHL2, FIG4, FIP1L1, FLAD1, FLNA, FLT3, FN1, FNBP4, FNIP2, FOXN3, FRYL, FUT8, FXR2, FYN, G6PC, GAA, GAB1, GABPB2, GABRE, GABRG2, GALNS, GCK, GFPT2, GGCT, GIT2, GK, GLA, GLS, GNB5, GNPTAB, GOLGA4, GOLGB1, GOLT1B, GPR133, GPR143, GPR180, GPX4, GRHPR, GRIPAP1, GRN, GTF2I, GTF3A, GUCY2C, GUF1, GUSB, GYPA, HACL1, HAUS7, HBB, HCFC1R1, HDAC10, HDAC7, HECTD3, HERC3, HFE, HIPK3, HMGXB4, HNRNPA2B1, HNRNPD, HNRNPDL, HPS1, HSD17B4, HSF2, HUWE1, IDH1, IFT57, IFT88, IGF2BP2, IL15RA, IL36RN, INF2, ING4, INO80E, INPP1, IP6K2, IPO8, IQCB1, IRAK4, ISOC2, IST1, ITGB1BP1, KATNBL1, KDM4C, KDM5A, KDSR, KIAA0100, KIAA0586, KIAA1109, KIF14, KIF3A, KIT, KITLG, KLC1, KMT2D, KRIT1, KTN1, L3HYPDH, LACC1, LAMB3, LAMTOR3, LAS1L, LDLR, LENG8, LETMD1, LGALS8, LHCGR, LINC00963, LIPA, LMAN2L, LMNA, LMO7, LONRF1, LOXL3, LPHN2, LPIN1, LRCH3, LRRC28, LRRC32, LSM1, LTA4H, LTBP1, LTBP3, LTBP4, LUC7L, LYPLAL1, LYRM7, LZTFL1, MACF1, MADD, MAGOHB, MAN2C1, MAP3K3, MAP4K4, MAPK11, MAPK12, MAPKAP1, MAPT, MARK3, MBD5, MBNL1, MBOAT2,

TABLE 1

MCFD2, ME3, MED13, MED15, MEG3, MEGF6, METAP1, METTL14, MFF, MFSD12, MGEA5, MGST2, MINK1, MIR22HG, MKS1, MLF1, MLH1, MLLT6, MLST8, MMAB, MMP19, MORF4L2, MOSPD1, MPC1, MPDZ, MPI, MPV17, MRPL33, MSH2, MSRB3, MTCH2, MTM1, MTMR2, MTMR3, MTMR6, MTRR, MTSS1L, MYBL1, MYBPC3, MYCBP2, MYEF2, MYLK, MYNN, MYO18A, MYO19, MYO1B, MYO5A, MYO7A, NABP1, NADK2, NAE1, NBN, NEK1, NEO1, NEXN, NF1, NF2, NFE2L1, NIPA2, NIPBL, NLRC5, NLRX1, NPEPPS, NPHP1, NPR2, NPRL3, NR3C2, NRG1, NSD1, NSFL1C, NSMCE2, NSUN4, NT5C2, NUB1, NUP43, NUP62, NUPL2, NUTM2A-AS1, OARD1, OCA2, OCRL, ODF2, ODF2L, OFD1, OGT, OPTN, ORC6, ORMDL1, OS9, OSBPL8, OTC, OTOGL, PACRGL, PAFAH1B1, PAH, PAM, PARD3, PARL, PARN, PARP11, PARP6, PATL1, PCBP2, PCID2, PCM1, PCNXL2, PCNXL4, PCYT2, PDCD10, PDE4DIP, PDLIM2, PDZD11, PEAK1, PEX1, PEX11A, PEX5, PFDN1, PFDN6, PFKM, PHC3, PHKG2, PHLDB1, PI4KB, PIGG, PIGN, PIGT, PIK3C2A, PIKFYVE, PILRB, PIN1, PKIG, PLA2G12A, PLA2R1, PLAGL1, PLBD2, PMS2, PMS2P3, PNPLA8, PODNL1, POLG, POLR3GL, POMGNT1, PPAP2A, PPFIBP1, PPIL3, PPIP5K2, PPM1M, PPP1R12A, PPP1R21, PPP2R3C, PPP3CB, PPP3CC, PPP4C, PPP6R2, PPRC1, PPT1, PREB, PREPL, PRKAG1, PRMT2, PRMT7, PRPF39, PRPF40B, PRR16, PRR4, PRRX1, PRUNE, PSME4, PTEN, PTPN13, PTPN21, PTPN23, PTPN4, PTPRA, PVR, PXDN, QTRTD1, R3HCC1L, R3HDM4, RAB11FIP2, RABEPK, RAD1, RAD51B, RAD51C, RALGPS2, RALY, RB1, RBBP9, RBCK1, RBM41, RCOR3, REPS1, REV3L, RFWD2, RGL2, RGN, RHAG, RHBDD2, RHOTBTB1, RHOT1, RIF1, RIPK2, RNASE4, RNF146, RNF170, RNF214, RNF216, RNF34, RNFT1, ROBO1, RP11-1055B8.7, RP11-14N7.2, RP11-274B21.1, RP11-33B1.1, RP11-383H13.1, RP11-773D16.1, RP13-279N23.2, RPAIN, RPL7L1, RPP14, RPS6KB2, RRBP1, RSU1, RTEL1, RTEL1-TNFRSF6B, RTTN, RUFY2, RWDD1, RWDD2B, RWDD4, SBF1, SCM1H1, SCN1A, SCN5A, SDCCAG8, SDHD, SEC31B, SECISBP2L, SEMA4F, SENP1, SENP6, SERAC1, SETD5, SETX, SFXN4, SGSM3, SH3D19, SHMT2, SIPA1L1, SLC10A7, SLC12A1, SLC15A4, SLC22A17, SLC25A17, SLC25A32, SLC25A36, SLC35A1, SLC35A3, SLC35D2, SLC37A3, SLC38A2, SLC38A6, SLC4A11, SLC4A7, SLC5A6, SLC7A6, SLC9B2, SLIT2, SLMAP, SLMO1, SLTM, SMAD5, SMARCA1, SMARCD1, SMC5, SMEK2, SMPDL3A, SMS, SMURF2, SNAPC5, SNED1, SNHG14, SNHG15, SNRNP70, SNRPA1, SNRPG, SNX10, SNX14, SNX21, SPAST, SPATA20, SPATA7, SPDL1, SPG11, SPPL2A, SPTA1, SPTAN1, SPTB, SRD5A2, ST6GALNAC6, ST7, STARD3NL, STARD5, STAT6, STK11, STK16, STK19, STK40, STRA13, STRADA, STRN3, STX16, STX16-NPEPL1, STX3, STXBP1, STXBP3, STYXL1, SUCO, SUGP2, SUGT1, SULF1, SUN2, SUPT20H, SYNGAP1, SYNRG, TAF1, TAF2, TANGO2, TARBP2, TAS2R14, TAZ, TBC1D14, TBC1D17, TBC1D25, TBC1D5, TBCK, TBPL1, TBX15, TCERG1, TCIRG1, TEAD2, TECTA, TEP1, TFDP1, TFDP2, TFPI, TFR2, TGFBR2, THAP6, THAP9-AS1, THBS3, THOC2, TIA1, TIAL1, TIMM17B, TIMM21, TJP2, TM7SF3, TMCO4, TMEM11, TMEM120A, TMEM126B, TMEM138, TMEM18, TMEM194A, TMEM234, TMEM260, TMEM39B, TMEM62, TMOD2, TMPRSS6, TMUB2, TMX3, TOM1, TP53, TP53INP1, TP53TG1, TPD52L1, TPD52L2, TPO, TPRA1, TPT1-AS1, TRAPPC12, TRAPPC2, TREX2, TRIM16, TRIM37, TRIM65, TRIO, TRIP10, TRIP12, TROVE2, TRPC1, TRPM4, TRPT1, TSEN15, TSR1, TSTD3, TUBG2, TULP3, TXNDC11, TXNL4A, TYR, U2AF1L4, UACA, UBA7, UBE2A, UBE2D1, UBN2, UBP1, UBQLN1, UFD1L, UNC5B, URGCP, UROD, USMG5, USP24, USP25, USP33, USP53, USP8, VAMP7, VCAN, VEZT, VMA21, VPS13B, VPS29, WBP1, WDFY2, WDR35, WDR73, XDTP53, XPC, YEATS2, YIPF1, YME1L1, YY1AP1, ZBTB8OS, ZC2HC1A, ZC3H11A, ZCCHC6, ZCCHC8, ZDHHC16,

TABLE 1

ZDHHC20, ZDHHC7, ZFAND1, ZFAND5, ZFAS1, ZMIZ1, ZMYM4, ZMYM5, ZNF160, ZNF207, ZNF248, ZNF280D, ZNF384, ZNF512, ZNF516, ZNF532, ZNF720, and ZZZ3.

[00209] Table 2 lists wildtype genes identified by RNA sequencing, as described herein, that may be modulated by an FD toward either or both exon inclusion and exon exclusion.

TABLE 2

A1BG-AS1, AAAS, ABCA1, ABCA6, ABCA9, ABCB6, ABCC3, ABHD14A-ACY1, ABI1, ABI2, ABI3BP, AC024560.3, AC027612.6, AC037459.4, ACAA1, ACACA, ACAD10, ACBD4, ACBD5, ACIN1, ACLY, ACOX1, ACSL3, ACSL4, ACTN1, ACY1, AD000671.6, ADA, ADAM33, ADAMTSL4, ADARB1, ADK, AFMID, AHI1, AKAP11, AKAP13, AKIP1, AKR1A1, AL163636.6, ALDH3B1, ALDH4A1, ALKBH1, ALKBH3, AMMECR1L, AMPD2, ANK2, ANKRD10, ANKRD11, ANKRD36, ANO6, ANXA2, AP1G1, AP2M1, APBB2, APOL1, APP, ARHGAP12, ARHGAP23, ARHGEF10, ARHGEF10L, ARHGEF12, ARHGEF25, ARID4B, ARIH2, ARSK, ASAP2, ASCC2, ASL, ASPH, ASUN, ASXL1, ATG10, ATG16L1, ATG7, ATG9A, ATP2C1, ATP5SL, ATPAF1, ATXN1, ATXN3, AUP1, AUTS2, AVL9, B3GALNT1, BAG6, BANP, BAX, BAZ1A, BBS4, BBS5, BBX, BCAR1, BCOR, BIN1, BIRC6, BLOC1S6, BMP2K, BOK, BPTF, BRD8, BROX, BTBD19, C11orf30, C11orf70, C12orf29, C16orf13, C1orf85, C1RL, C2CD5, C3orf18, C5orf42, C5orf45, C8orf59, C9orf156, C9orf85, CA5BP1, CALU, CAMK2D, CAMTA1, CAPN7, CAPRN2, CARD8, CARKD, CASP3, CAST, CCBL2, CCDC25, CCDC90B, CCNDBP1, CCNL1, CD44, CD46, CD55, CD99P1, CDC14B, CDC16, CDK16, CEP290, CHD3, CHEK2, CHKB, CKLF, CLASP1, CLCN6, CLK1, CMC1, CNOT10, COL12A1, COL16A1, COL6A3, COPB2, COPS7A, COPS8, COQ6, COX20, CPEB2, CPSF7, CPT1C, CRAT, CREBBP, CRLS1, CRNDE, CRYZ, CSAD, CTDSPL, CUTC, CWC25, CYB561D2, CYLD, CYP20A1, DAB2, DBT, DCAF10, DCAF11, DCAF17, DCAF8, DCP1A, DCUN1D5, DDB2, DGKA, DHRSX, DMT1, DIS3, DLG1, DMD, DMTF1, DNAJC19, DNAJC2, DNMT1, DNMT1, DOCK5, DOCK7, DPH3, DPY19L4, DRAM2, DSCR3, DTNBP1, DUSP11, DUSP22, DYNC2H1, EBPL, EDC3, EDEM2, EDRF1, EFEMP1, EHBP1, EHMT2, EIF4A2, EIF4E2, EIF4H, ELK1, ELN, ELOVL1, ENC1, ENOSF1, EPB41L1, EPB41L2, ERBB2IP, ERLEC1, ERMAD, ETHE1, EVC, EVI5L, FAM104A, FAM111A, FAM134C, FAM149B1, FAM172A, FAM204A, FAM211A-AS1, FAM21C, FAP, FBXL12, FBXL3, FBXO25, FBXW11, FGF5, FGFR1OP, FHL2, FIP1L1, FLAD1, FLNA, FN1, FNBP4, FNIP2, FOXN3, FRYL, FUT8, FXR2, FYN, GAB1, GABPB2, GABRE, GALNS, GFPT2, GGCT, GIT2, GK, GLS, GOLGA4, GOLGB1, GOLT1B, GPR133, GPR180, GRIPAP1, GTF2I, GTF3A, GUF1, GUSB, HACL1, HAUS7, HCFC1R1, HDAC10, HDAC7, HECTD3, HERC3, HIPK3, HMGXB4, HNRNPA2B1, HNRNPD, HNRNPDL, HPS1, HSD17B4, HSF2, HUWE1, IFT88, IGF2BP2, IL15RA, INF2, ING4, INO80E, INPP1, IP6K2, IPO8, IQCB1, IRAK4, ISOC2, IST1, ITGB1BP1, KATNBL1, KDM4C, KDM5A, KIAA0100, KIF3A, KITLG, KLC1, KTN1, L3HYDPH, LACC1, LAMTOR3, LAS1L, LENG8, LETMD1, LGALS8, LINC00963, LMAN2L, LMO7, LONRF1, LOXL3, LPHN2, LPIN1, LRCH3, LRRC28, LRRC32, LSM1, LTA4H, LTBP1, LTBP3, LTBP4, LUC7L, LYPLAL1, LYRM7, LZTFL1, MACF1, MADD, MAGOHB, MAN2C1, MAP3K3, MAP4K4, MAPK11, MAPK12, MAPKAP1, MARK3, MBD5, MBNL1, MBOAT2, ME3, MED13, MED15, MEG3, MEG3, MEGF6, METAP1, METTL14, MFF, MFSD12, MGEA5, MGST2, MINK1, MIR22HG, MKS1, MLF1, MLH1, MLLT6, MLST8, MMP19, MORF4L2,

TABLE 2

MOSPD1, MPDZ, MPI, MPV17, MRPL33, MSRB3, MSRB3, MTCH2, MTMR2, MTMR3, MTMR6, MTRR, MTSS1L, MYBL1, MYCBP2, MYEF2, MYLK, MYNN, MYO18A, MYO19, MYO1B, MYO5A, NABP1, NADK2, NAE1, NBN, NEK1, NEO1, NEXN, NF2, NFE2L1, NIPA2, NLRC5, NLRX1, NPEPPS, NPR2, NPRL3, NRG1, NSFL1C, NSMCE2, NSUN4, NT5C2, NUB1, NUP43, NUP62, NUPL2, NUTM2A-AS1, OARD1, OCRL, ODF2, ODF2L, OFD1, OPTN, ORMDL1, OS9, OSBPL8, PACRGL, PAM, PARD3, PARL, PARP11, PARP6, PATL1, PCBP2, PCID2, PCM1, PCNXL2, PCNXL4, PCYT2, PDE4DIP, PDLIM2, PDZD11, PEAK1, PEX1, PEX11A, PEX5, PFDN1, PFDN6, PFKM, PHC3, PHKG2, PHLDB1, PI4KB, PIGG, PIGN, PIGT, PIK3C2A, PIKFYVE, PILRB, PIN1, PKIG, PLA2G12A, PLA2R1, PLAGL1, PLBD2, PMS2P3, PNPLA8, PODNL1, POLR3GL, PPAP2A, PPFIBP1, PPIL3, PPIP5K2, PPM1M, PPP1R12A, PPP1R21, PPP2R3C, PPP3CB, PPP3CC, PPP4C, PPP6R2, PPRC1, PREB, PREPL, PRKAG1, PRMT2, PRPF39, PRPF40B, PRR16, PRR4, PRRX1, PRUNE, PSME4, PTPN13, PTPN21, PTPN23, PTPN4, PTPRA, PVR, PXDN, QTRTD1, R3HCC1L, R3HDM4, RAB11FIP2, RABEPK, RAD1, RALGPS2, RALY, RBBP9, RBCK1, RBM41, RCOR3, REPS1, REV3L, RFWD2, RGL2, RGN, RHBDD2, RHOBTB1, RHOT1, RIF1, RIPK2, RNASE4, RNF146, RNF170, RNF214, RNF34, RNFT1, ROBO1, RP11-1055B8.7, RP11-14N7.2, RP11-274B21.1, RP11-33B1.1, RP11-383H13.1, RP11-773D16.1, RP13-279N23.2, RPAIN, RPL7L1, RPP14, RPS6KB2, RRBP1, RSU1, RTEL1, RTEL1-TNFRSF6B, RUFY2, RWDD1, RWDD2B, RWDD4, SBF1, SCM1H1, SDCCAG8, SEC31B, SECISBP2L, SEMA4F, SENP1, SENP6, SERAC1, SETD5, SETX, SFXN4, SGSM3, SH3D19, SHMT2, SIPA1L1, SLC15A4, SLC22A17, SLC25A17, SLC25A32, SLC25A36, SLC35A1, SLC35A3, SLC35D2, SLC37A3, SLC38A2, SLC38A6, SLC4A7, SLC5A6, SLC7A6, SLC9B2, SLIT2, SLMAP, SLMO1, SLTM, SMAD5, SMARCA1, SMARCD1, SMC5, SMEK2, SMPDL3A, SMURF2, SNAPC5, SNED1, SNHG14, SNHG15, SNRNP70, SNRPA1, SNRPG, SNX14, SNX21, SPATA20, SPATA7, SPDL1, SPPL2A, SPTAN1, ST6GALNAC6, ST7, STARD3NL, STARD5, STAT6, STK16, STK19, STK40, STRA13, STRADA, STRN3, STX16, STX16-NPEPL1, STX3, STXBP3, STYXL1, SUCO, SUGP2, SUGT1, SULF1, SUN2, SUPT20H, SYNRG, TAF1, TAF2, TANGO2, TARBP2, TAS2R14, TAZ, TBC1D14, TBC1D17, TBC1D25, TBC1D5, TBCK, TBPL1, TBX15, TCERG1, TEAD2, TEP1, TFDP1, TFDP2, TFPI, TGFB2, THAP6, THAP9-AS1, THBS3, THOC2, TIA1, TIAL1, TIMM17B, TIMM21, TM7SF3, TMCO4, TMEM11, TMEM120A, TMEM126B, TMEM18, TMEM194A, TMEM234, TMEM260, TMEM39B, TMEM62, TMOD2, TMUB2, TMX3, TOM1, TP53INP1, TP53TG1, TPD52L1, TPD52L2, TPRA1, TPT1-AS1, TRAPPC12, TREX2, TRIM16, TRIM65, TRIO, TRIP10, TRIP12, TROVE2, TRPC1, TRPM4, TRPT1, TSEN15, TSR1, TSTD3, TUBG2, TULP3, TXNDC11, TXNL4A, U2AF1L4, UACA, UBA7, UBE2A, UBE2D1, UBN2, UBP1, UBQLN1, UFD1L, UNC5B, URGCP, USMG5, USP24, USP25, USP33, USP53, USP8, VAMP7, VCAN, VEZT, VPS29, WBP1, WDFY2, YEATS2, YIPF1, YME1L1, YY1AP1, ZBTB80S, ZC2HC1A, ZC3H11A, ZCCHC6, ZCCHC8, ZDHHC16, ZDHHC20, ZDHHC7, ZFAND1, ZFAND5, ZFAS1, ZMIZ1, ZMYM4, ZMYM5, ZNF160, ZNF207, ZNF248, ZNF280D, ZNF384, ZNF512, ZNF516, ZNF532, ZNF720, and ZZZ3.

[2363] Table 3 lists wildtype genes identified by RNA sequencing, as described herein, that may be modulated by an FD compound toward exon inclusion.

TABLE 3

ABII, ABI2, AC027612.6, ACBD5, ACIN1, ACLY, ACOX1, ACSL3, AFMID, AHI1, AKAP13, AL163636.6, ANKRD11, ANXA2, APIG1, ARHGAP12, ARHGEF10, ARSK, ASAP2, ASPH, ATG10, ATP2C1, ATP5SL, B3GALNT1, BANP, BBX, BPTF, BROX, C11orf30, C12orf29, C2CD5, C3orf18, C5orf45, C8orf59, C9orf156, CA5BP1, CALU, CAMTA1, CASP3, CCBL2, CD44, CD46, CDC14B, CDK16, CEP290, CLASP1, CLK1, CMC1, COL12A1, COL6A3, COPB2, COPS8, CPSF7, CREBBP, CYLD, DAB2, DCAF8, DCP1A, DCUN1D5, DIS3, DNAJC19, DNMI1, DOCK5, DPH3, DRAM2, EDEM2, EFEMP1, EIF4H, ENC1, EPB41L2, FAM172A, FAM21C, FBXL3, FGFR1OP, FIP1L1, FNBP4, FRYL, FUT8, FXR2, GGCT, GIT2, GLS, GTF2I, HNRNPA2B1, HNRNPDL, HSD17B4, HSF2, IL15RA, INF2, INO80E, INPP1, IP6K2, IQCB1, ITGB1BP1, KATNBL1, KDM5A, KLC1, KTN1, L3HYPDH, LGALS8, LMAN2L, LONRF1, LPHN2, LPIN1, LRCH3, LSM1, MACF1, MAGOHB, MAPKAP1, MARK3, MBNL1, ME3, MEG3, METAP1, MFF, MOSPD1, MSRB3, MTMR2, MYEF2, MYLK, MYNN, MYO18A, MYO1B, MYO5A, NABP1, NEO1, NF2, NPEPPS, NRG1, NSMCE2, NUP62, OCRL, OFD1, OPTN, OSBPL8, PARP6, PDE4DIP, PDZD11, PHC3, PHLDB1, PIGN, PIN1, PNPLA8, PPP3CB, PPP3CC, PREPL, PRPF39, PRRX1, PRUNE, QTRTD1, R3HCC1L, RALY, RBBP9, RBM41, REV3L, RFWD2, RNASE4, RNF34, RP11-14N7.2, RP11-274B21.1, RPAIN, RRBPI, RWDD1, SDCCAG8, SETX, SH3D19, SIPA1L1, SLC15A4, SLC35A3, SLC38A6, SLTM, SMARCA1, SNRNP70, SPATA7, SPDL1, SPPL2A, ST6GALNAC6, STARD3NL, STK40, STRN3, SUCO, SUGP2, SUPT20H, SYNRG, TAF2, TBCK, TBPL1, TGFB2, THAP9-AS1, TIA1, TIAL1, TIMM17B, TM7SF3, TMEM126B, TMEM18, TMEM234, TPD52L1, TPT1-AS1, TRIM16, TRIM65, TRIP12, TROVE2, TSEN15, TXNL4A, UBP1, USP33, USP8, VEZT, VPS29, ZC2HC1A, ZC3H11A, ZDHHC20, ZNF207, ZNF516, and ZNF532.

[2364] Table 4 lists wildtype genes identified by RNA sequencing, as described herein, that may be modulated by an FD compound toward exon exclusion.

TABLE 4

A1BG-AS1, AAAS, ABCA1, ABCA6, ABCA9, ABCB6, ABCC3, ABHD14A-ACY1, ABI3BP, AC024560.3, AC037459.4, ACAA1, ACACA, ACAD10, ACBD4, ACSL4, ACTN1, ACY1, AD000671.6, ADA, ADAM33, ADAMTSL4, ADARB1, ADK, AKAP11, AKIP1, AKR1A1, ALDH3B1, ALDH4A1, ALKBH1, ALKBH3, AMMECR1L, AMPD2, ANK2, ANKRD10, ANKRD36, ANO6, AP2M1, APBB2, APOL1, APP, ARHGAP23, ARHGEF10L, ARHGEF12, ARHGEF25, ARID4B, ARIH2, ASCC2, ASL, ASPH, ASUN, ASXL1, ATG16L1, ATG7, ATG9A, ATPAF1, ATXN1, ATXN3, AUP1, AUTS2, AVL9, BAG6, BAX, BAZ1A, BBS4, BBS5, BCAR1, BCOR, BIN1, BIRC6, BLOC1S6, BMP2K, BOK, BPTF, BRD8, BTBD19, C11orf70, C16orf13, C1orf85, C1RL, C5orf42, C9orf85, CAMK2D, CAPN7, CAPRN2, CARD8, CARKD, CAST, CCDC25, CCDC90B, CCNDBP1, CCNL1, CD46, CD55, CD99P1, CDC14B, CDC16, CHD3, CHEK2, CHKB, CKLF, CLCN6, CNOT10, COL16A1, COL6A3, COPS7A, COQ6, COX20, CPEB2, CPT1C, CRAT, CRLS1, CRNDE, CRYZ, CSAD, CTDSPL, CUTC, CWC25, CYB561D2, CYP20A1, DBT, DCAF10, DCAF11, DCAF17, DDB2, DGKA, DHRSX, DIMT1, DIS3, DLG1, DMD, DMTF1, DNAJC2, DNMI1, DNMT1, DOCK7, DPY19L4, DRAM2, DSCR3, DTNBP1, DUSP11, DUSP22, DYNC2H1, EBPL, EDC3, EDRF1, EHBP1, EHMT2, EIF4A2, EIF4E2, ELK1, ELN, ELOVL1, ENOSF1, EPB41L1, ERBB2IP, ERLEC1, ERMAP, ETHE1, EVC, EVI5L, FAM104A, FAM111A, FAM134C, FAM149B1,

TABLE 4

FAM172A, FAM204A, FAM211A-AS1, FAP, FBXL12, FBXO25, FBXW11, FGF5, FHL2, FIP1L1, FLAD1, FLNA, FN1, FNIP2, FOXN3, FYN, GAB1, GABPB2, GABRE, GALNS, GFPT2, GIT2, GK, GLS, GOLGA4, GOLGB1, GOLT1B, GPR133, GPR180, GRIPAP1, GTF3A, GUF1, GUSB, HACL1, HAUS7, HCFC1R1, HDAC10, HDAC7, HECTD3, HERC3, HIPK3, HMGXB4, HNRNPD, HPS1, HUWE1, IFT88, IGF2BP2, ING4, IPO8, IRAK4, ISOC2, IST1, KDM4C, KIAA0100, KIF3A, KITLG, KLC1, LACC1, LAMTOR3, LAS1L, LENG8, LETMD1, LINC00963, LMAN2L, LMO7, LOXL3, LPHN2, LRRC28, LRRC32, LTA4H, LTBP1, LTBP3, LTBP4, LUC7L, LYPLAL1, LYRM7, LZTFL1, MACF1, MADD, MAN2C1, MAP3K3, MAP4K4, MAPK11, MAPK12, MBD5, MBOAT2, MED13, MED15, MEG3, MEGF6, METTL14, MFF, MFSD12, MGEA5, MGST2, MINK1, MIR22HG, MKS1, MLF1, MLH1, MLLT6, MLST8, MMP19, MORF4L2, MOSPD1, MPDZ, MPI, MPV17, MRPL33, MSRB3, MTCH2, MTMR2, MTMR3, MTMR6, MTRR, MTSS1L, MYBL1, MYCBP2, MYLK, MYNN, MYO19, MYO5A, NADK2, NAE1, NBN, NEK1, NEXN, NFE2L1, NIPA2, NLRC5, NLRX1, NPR2, NPRL3, NSFL1C, NSUN4, NT5C2, NUB1, NUP43, NUPL2, NUTM2A-AS1, OARD1, ODF2, ODF2L, OPTN, ORMDL1, OS9, PACRGL, PAM, PARD3, PARL, PARP11, PATL1, PCBP2, PCID2, PCM1, PCNXL2, PCNXL4, PCYT2, PDLIM2, PEAK1, PEX1, PEX11A, PEX5, PFDN1, PFDN6, PFKM, PHKG2, PI4KB, PIGG, PIGT, PIK3C2A, PIKFYVE, PILRB, PKIG, PLA2G12A, PLA2R1, PLAGL1, PLBD2, PMS2P3, PODNL1, POLR3GL, PPAP2A, PPFIBP1, PPIL3, PPIP5K2, PPM1M, PPP1R12A, PPP1R21, PPP2R3C, PPP4C, PPP6R2, PPRC1, PREB, PRKAG1, PRMT2, PRPF40B, PRR16, PRR4, PSME4, PTPN13, PTPN21, PTPN23, PTPN4, PTPRA, PVR, PXDN, R3HDM4, RAB11FIP2, RABEPK, RAD1, RALGPS2, RBCK1, RCOR3, REPS1, RGL2, RGN, RHBDD2, RHOBTB1, RHOT1, RIF1, RIPK2, RNF146, RNF170, RNF214, RNFT1, ROBO1, RP11-1055B8.7, RP11-33B1.1, RP11-383H13.1, RP11-773D16.1, RP13-279N23.2, RPAIN, RPL7L1, RPP14, RPS6KB2, RSU1, RTEL1, RTEL1-TNFRSF6B, RUFY2, RWDD2B, RWDD4, SBF1, SCMH1, SEC31B, SECISBP2L, SEMA4F, SENP1, SENP6, SERAC1, SETD5, SFXN4, SGSM3, SHMT2, SIPA1L1, SLC22A17, SLC25A17, SLC25A32, SLC25A36, SLC35A1, SLC35D2, SLC37A3, SLC38A2, SLC38A6, SLC4A7, SLC5A6, SLC7A6, SLC9B2, SLIT2, SLMAP, SLMO1, SMAD5, SMARCD1, SMC5, SMEK2, SMPDL3A, SMURF2, SNAPC5, SNED1, SNHG14, SNHG15, SNRPA1, SNRPG, SNX14, SNX21, SPATA20, SPTAN1, ST7, STARD5, STAT6, STK16, STK19, STRA13, STRADA, STX16, STX16-NPEPL1, STX3, STXBP3, STYXL1, SUGT1, SULF1, SUN2, SUPT20H, TAF1, TANGO2, TARBP2, TAS2R14, TAZ, TBC1D14, TBC1D17, TBC1D25, TBC1D5, TBCK, TBX15, TCERG1, TEAD2, TEPI1, TFDP1, TFDP2, TFPI, THAP6, THBS3, THOC2, TIMM21, TMCO4, TMEM11, TMEM120A, TMEM194A, TMEM260, TMEM39B, TMEM62, TMOD2, TMUB2, TMX3, TOM1, TP53INP1, TP53TG1, TPD52L2, TPRA1, TRAPPC12, TREX2, TRIO, TRIP10, TRPC1, TRPM4, TRPT1, TSEN15, TSR1, TSTD3, TUBG2, TULP3, TXNDC11, U2AF1L4, UACA, UBA7, UBE2A, UBE2D1, UBN2, UBQLN1, UFD1L, UNC5B, URGCP, USMG5, USP24, USP25, USP53, VAMP7, VCAN, WBP1, WDFY2, YEATS2, YIPF1, YME1L1, YY1AP1, ZBTB8OS, ZCCHC6, ZCCHC8, ZDHHC16, ZDHHC7, ZFAND1, ZFAND5, ZFAS1, ZMIZ1, ZMYM4, ZMYM5, ZNF160, ZNF207, ZNF248, ZNF280D, ZNF384, ZNF512, ZNF720, and ZZZ3.

[2365] Table 5 lists mutated genes predicted by SpliceAI scores and the CNN Model, as described herein, that may be modulated by an FD compound toward exon inclusion.

TABLE 5

ABCA4, ABCC9, ACADSB, ADAM10, AGK, ALDH3A2, ALMS1, ANTXR2, APC, ARMC9, ASAH1, ASPM, ATM, ATRX, BBS4, BFSP1, BMPR2, BRCA1, BRCA2, CA5A, CAPN3, CD3D, CDH1, CDH23, CERKL, CFTR, CHD7, CLCN1, CLMP, CLN3, CNGB3, COG6, COL11A1, COL3A1, COL4A3, COL4A5, COL5A2, CSTB, CTNS, CTU2, CUBN, CWC27, CYBB, DCX, DGKE, DGUOK, DMD, DNAH5, DNAH9, DYNC2H1, DYNC2LI1, EBF3, EP300, F10, F13A1, FBN1, FUT8, G6PC, GAA, GABRG2, GCK, GLA, GNB5, GNPTAB, GPR143, GPX4, GRHPR, GRN, GUCY2C, GYPA, HBB, IDH1, IFT57, IL36RN, KDSR, KIAA0586, KIAA1109, KIF14, KIT, KMT2D, KRIT1, LAMB3, LDLR, LIPA, LMNA, MCFD2, MLH1, MMAB, MPC1, MSH2, MTM1, MYBPC3, MYO7A, NF1, NIPBL, NPHP1, NR3C2, NSD1, OCA2, OFD1, OGT, ORC6, OTC, OTOGL, PAFAH1B1, PAH, PARN, PDCD10, PIGN, PMS2, POLG, POMGNT1, PPT1, PRMT7, PTEN, RAD51B, RAD51C, RB1, RHAG, RNF216, RTTN, SCN1A, SLC10A7, SLC12A1, SLC4A11, SMS, SPAST, SPG11, SPTA1, SPTB, SRD5A2, STXBP1, SYNGAP1, TGFB2, TJP2, TMEM138, TMPRSS6, TP53, TPO, TRAPPC2, TRIM37, TYR, UROD, VMA21, VPS13B, WDR35, WDR73, and XPC.

[2366] Table 6 lists mutated genes predicted by SpliceAI scores and the CNN Model, as described herein, that may be modulated by Compound (I) toward exon exclusion.

TABLE 6

BRCA1, BRIP1, CDAN1, CLN3, COL6A1, COL7A1, CTSK, EBP, ERCC6, F8, FBN1, FIG4, FLT3, GLA, HFE, LHCGR, MAPT, OTC, SCN5A, SDCCAG8, SDHD, SNX10, STK11, TCIRG1, TECTA, TFR2, and TP53.

[2367] Table 7 lists wildtype genes identified by RNA sequencing, as described herein, that may be unchanged by an FD compound toward either or both exon inclusion and exon exclusion.

TABLE 7

AAMDC, ABCA2, ABCC3, ABCD4, ABHD16A, ABI3BP, ACAD10, ACAP3, ACCS, ACOT9, ACTN1, ADAM15, AFTPH, AK4, AMBRA1, AMDHD2, AMIGO2, AMOTL1, AMZ2P1, ANAPC11, ANKRD17, ANO6, AOX1, ARHGEF10, ARID5A, ARIH2, ARMC10, ARSJ, ASCC2, ATG12, ATG13, ATG4B, ATP5C1, ATP6C, B3GALNT1, BAZ2A, BCL2L2, BEND6, BIRC6, BLOC1S6, BRD8, BTBD3, BTF3L4, C10orf118, C11orf30, C11orf57, C14orf159, C2orf76, C9orf156, CACNA1C, CAMK2G, CAMSAP1, CAPN10, CARF, CCDC126, CCDC136, CCDC25, CCNL2, CCNT1, CCNYL1, CD27-AS1, CDC42BPA, CDCA7L, CDK5RAP2, CEP164, CIRBP, CLASP2, CPNE1, CSDE1, CSNK1A1, CTIF, CTSB, DCAF8, DCTD, DGUOK, DLGAP1-AS1, DMKN, DMWD, DNAAF2, DNAJC14, DNAJC24, DPH7, DPM1, DUS2, ECHDC2, EHBP1L1, EIF4G2, ELMOD3, EMC4, ENC1, EP400, EPS15L1, ERMARD, EVA1A, FAM114A1, FAM13B, FAM160B2, FAM173A, FAM175A, FAM208B, FAM35A, FAM45A, FDPS, FGFR1, FHOD3, FLNB, FNBP1, FOSL1, FOXRED2, FRS2, GAS7, GBP3, GEMIN8, GLIS3, GLRB, GLT8D1, GNAS, GPATCH8, GPBP1, GRB10, HDAC9, HMCN1, HNRNPK, HSCB, IL17RA, IL17RC, IL6, INTS9, IP6K2, KANSL3, KAT6A, KCTD20, KIAA0232, KIAA0368, KIAA0753, KIAA1551, KIAA1586, KIAA1731, KIFC3, KLHL12, KTN1,

TABLE 7

LBR, LDB2, LRP12, MADD, MAP2K5, MAP7D1, MAPK9, MAZ, MBD1, MCCC2, MECP, MED23, MEGF6, MEIS1, METTL10, METTL21A, MGLL, MICU3, MKNK2, MLLT10, MPPE1, MRI1, MRPL55, MTIF2, MXI1, MXRA7, MYCBP2, MYO18A, MYO5A, N6AMT2, NCK2, NCOR2, NEDD1, NIN, NPRL3, NTMT1, NTPCR, NUBP2, NUMB, NUP98, NUTF2, OPN3, OSER1-AS1, P4HA2, PARD3, PCNXL2, PDGFC, PDP1, PDPR, PDXDC2P, PEAK1, PFDN5, PHLPP2, PIGF, PIGP, PIGQ, PINX1, PLD3, PLSCR4, PPP1R18, PPP6R3, PRDM5, PRRC2B, PRUNE, PTAR1, PTPRG, PTPRS, PUF60, PUM2, R3HDM1, RAD51D, RAF1, RAPH1, RBM10, RBM27, RBM4, RBM5, RCC1, RFC2, RGL1, RIF1, RILP, RILPL2, RNF14, RNF8, RNGTT, RP11-705C15.2, RP1-178F15.4, RPAIN, RPP38, RPS24, RPUSD1, RRNAD1, RTN2, RUNX1, SCRNB3, SEC13, SEC31A, SETD2, SEZ6L2, SGSM2, SIKE1, SLAIN2, SLC30A6, SLC38A9, SLC39A9, SLFN11, SLMAP, SLTM, SMEK2, SMG7, SMURF2, SNHG14, SPEN, SPIDR, SRSF2, STAG1, STAG2, STARD3, STARD4, STK38L, STOML1, STXBP5, SUOX, SYNE1, SYNJ2BP, TAMM41, TBC1D32, TBCE, TBCEL, TCF20, TCF7L2, TENM2, TET2, TFB2M, TFDP2, TGIF1, THADA, THTPA, THTPA, TJAP1, TJP1, TLK2, TMEM119, TMEM161B, TMEM175, TMEM230, TMUB2, TOR1AIP2, TOR3A, TP53BP2, TRA2A, TRIM37, TRMU, TROVE2, TSPAN5, TULP3, U2AF1, UCHL5, UPF3A, UPP1, USP3, VDR, VEGFA, VIPAS39, VPS13D, WARS, WDR27, WHSC1, WNK1, XIAP, XPNPEP3, YTHDF2, YWHAB, ZBTB38, ZCCHC6, ZEB1, ZFAT, ZFX, ZMYM1, ZNF140, ZNF217, ZNF260, ZNF266, ZNF3, ZNF346, ZNF37A, ZNF419, ZNF426, ZNF529, ZNF585B, ZNF638, ZNF655, ZNF75A, ZNF767, and ZSCAN32.

[2368] Table 8 lists wildtype genes identified by RNA sequencing and mutated genes predicted by SpliceAI scores and the CNN model, as described herein, which may be modulated by an FD compound toward either or both exon inclusion or exon exclusion and toward remaining unchanged.

TABLE 8

ABCC3, ABI3BP, ACAD10, ACTN1, ANO6, ARHGEF10, ARIH2, ASCC2, B3GALNT1, BIRC6, BLOC1S6, BRD8, C11orf30, C9orf156, CCDC25, DCAF8, DGUOK, ENC1, IP6K2, KTN1, MADD, MEGF6, MYO18A, MYO5A, NPRL3, PARD3, PCNXL2, PEAK1, PRUNE, RIF1, RPAIN, SLMAP, SLTM, SMEK2, SMURF2, SNHG14, TFDP2, TMUB2, TRIM37, TROVE2, TULP3, and ZCCHC6.

[2369] Table 9 lists wildtype genes identified by RNA sequencing, as described in International Application No. PCT/US2016/013553, filed on January 15, 2016, and published as International Publication No. WO2016/115434 on July 21, 2016, the entire contents which are incorporated herein by reference, that may be modulated by an FD compound toward exon inclusion.

TABLE 9

ABI2, ARFGEF2, ARHGEF6, BMP2K, C19orf12, CACNA1S, CC2D2A, CDKL5, CHD2, CHD7, CHD8, CHRNA4, COL6A3, CUL4B, DEPDC5, DES, DMD, DNAJC6, DYNC2H1,

TABLE 9

FBN1, FIG4, FKTN, FMR1, GOSR2, GRIN2A, HDAC8, IGHMBP2, IKBKAP, KDM5C, LAMA2, LRRK2, LRSAM1, MBD5, MECP2, MICU1, MTM1, NEB, OPHN1, PGAP1, PLEC, RB1, RYR1, SBF2, SCN1A, SCN9A, SLC35A3, SLC6A8, SLC9A9, SMCHD1, STXBP1, SYNGAP1, SZT2, TSC1, TSC2, and WDR45.

V. DESIGN OF SMSM COMPOUND INDUCIBLE SPLICING MINIGENE CASSETTES

SMSM Compound Inducible Non-canonical 5' Splice Sites

[2370] As used herein, a “minigene,” otherwise called “an inducible splicing cassette,” “minigene cassette” or simply “cassette,” can be designed to contain an exon having a non-canonical 5' splice site at its 3' end, the splicing of which is contingent on the presence of an SMSM compound. Thus, depending on the nucleotide sequence at positions -4 to -1 of the non-canonical 5' splice site, the splicing of the minigene cassette pre-mRNA may be FD, HD or SMA compound inducible as described herein (see FIGs. 1Ai-iv and 1Bi-iii).

[2371] In one aspect, a minigene cassette may comprise an FD compound inducible exonic sequence of any one of the genes described herein (see section IV, paragraph B), the splicing of which is responsive to an FD compound. Accordingly, the transgene operably linked to the minigene cassette does not comprise the FD compound inducible exonic sequence of any one of the genes described herein (see section IV, paragraph B), the splicing of which is responsive to an FD compound.

[2372] Thus, in one aspect, the expression of a transgene incorporating a minigene cassette comprising a non-canonical 5' splice site can have the nucleotide sequence of:

5'-NCAA/gtnnnn-3' (SEQ ID NO: 66), or

5'-NNNT/gtnnnn-3' (SEQ ID NO: 67),

where N is A, G, C or T and “/” is the splice site, can be inducible in the presence of an FD compound as described herein (see FIG. 1Ai-ii).

[2373] In one aspect, a minigene cassette may comprise an SMA/HD compound inducible exonic sequence of any one of the genes described herein (see section IV, paragraph A), the splicing of which is responsive to an SMA/HD compound. Accordingly, the transgene operably linked to the minigene cassette does not comprise the SMA/HD compound inducible exonic

sequence of any one of the genes described herein (see section IV, paragraph A), the splicing of which is responsive to an SMA/HD compound.

[2374] In second aspect, the expression of a transgene incorporating a minigene cassette comprising a non-canonical 5' splice site can have the nucleotide sequence of:

5'-NAGA/gtnnnn-3' (SEQ ID NO: 69),

where N is A, G, C or T and "/" is the splice site can be inducible in the presence of an HD compound as described herein (see FIG. 1Aiii). Accordingly, the transgene operably linked to the minigene cassette does not comprise the HD compound inducible exonic sequence of any one of the genes described herein (see section IV, paragraph A), the splicing of which is responsive to an HD compound.

[2375] In a third aspect, the expression of a transgene incorporating a minigene cassette comprising a non-canonical 5' splice sites can have the nucleotide sequence of:

5'-ANGAgtnnnn-3' (SEQ ID NO: 70),

where N is A, G, C or T and "/" is the splice site, can be inducible in the presence of an SMA compound as described herein (see FIG. 1Aiv). Accordingly, the transgene operably linked to the minigene cassette does not comprise the SMA compound inducible exonic sequence of any one of the genes described herein (see section IV, paragraph A), the splicing of which is responsive to an SMA compound.

[2376] In one aspect, the nucleotides -4 to -1 of a 5' non-canonical splice site may be in exon 1, 2 or 3.

[2377] In one aspect, the nucleotides -4 to -1 of a 5' non-canonical splice site may be at the 3' end of exon 1, 2 or 3.

[2378] In another aspect, nucleotides -4 to -1 of a 5' non-canonical splice site may be located at the 3' end of exon 2.

[2379] In certain aspects, the spliced mature minigene cassette-containing mRNA comprises exon 1.

[2380] In certain aspects, the spliced mature minigene cassette-containing mRNA comprises exon 2.

[2381] In certain aspects, the spliced mature minigene cassette-containing mRNA comprises exon 3.

[2382] In certain aspects, the spliced mature minigene cassette-containing mRNA comprises exon 1 and 3.

[2383] In certain aspects, the spliced mature minigene cassette-containing mRNA does not comprise exon 2.

[2384] In certain aspects, the spliced minigene cassette mRNA comprises intron 1 or intron 2.

[2385] In certain aspects, the spliced minigene cassette mRNA comprises intron 1 and intron 2.

[2386] In certain aspects, the spliced minigene cassette mRNA does not comprise intron 1 or intron 2.

[2387] In certain aspects, the spliced minigene cassette mRNA does not comprise intron 1 and intron 2.

[2388] In certain aspects, only in the presence of an SMSM compound, is exon 2 included in the spliced minigene cassette-containing mRNA.

[2389] In certain aspects, in the absence of an SMSM compound, exon 2 is not included in the spliced minigene cassette-containing mRNA.

[2390] In another aspect, the minigene cassette described herein includes an SMSM compound inducible non-canonical 5' splice site.

[2391] In one aspect, the minigene cassette described herein includes an exon comprising an HD/SMA inducible non-canonical 5' splice site.

[2392] In one aspect, the minigene cassette described herein includes an exon comprising an FD inducible non-canonical 5' splice site.

[2393] In one aspect, the minigene cassette described herein comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129,

130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, or 200 nucleotides of an exon having an HD/SMA compound inducible non-canonical 5' splice site at its 3' end.

Configuration of SMSM compound inducible minigene cassettes

[2394] As shown in FIG. 1Bi-iii, a minigene, otherwise called “an inducible splicing cassette,” “minigene cassette” or simply “cassette,” may comprise a plurality of exons interspersed with intron. For example, a minigene cassette may comprise 3 exons (exon 1, exon 2 and exon 3) interspersed with introns (e.g., intron 1, and intron 2). Exon 2 may include a SMSM compound inducible non-canonical 5' splice site at its 3' end. According to the configuration of the minigene cassette, there can be exon 2 inclusion or exon 2 skipping (see, for example, FIGs. 1Ci-ii, 1D, 1E, 1F, 1G, 1H, and 1I).

[2395] In certain aspects, the sequence elements required for SMSM compound induced splicing to occur can be, for example: a 5' exonic splice site, a first intronic branch point, an intronic 3' splice site, a pseudo-Exonic Splicing Enhancer (pseudo-ESE), an Exonic Splicing silencer (ESS), a non-canonical 5' intronic splice site, a second intronic branch point, and a 3' exonic splice site.

[2396] In one aspect, the minigene's exon 1, exon 2 or exon 3 can each be about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199 or 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, about 600, about 650, about 700, about 750, about 800 nucleotides, about 850, about 900, about 950, or about 1000 nucleotides in length.

[2397] In one aspect, minigene's intron 1 or intron 2 can each be 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199 or 200, about 250, about 300, about 350, about 400, about 450 or about 500 nucleotides in length.

[2398] In one aspect, the minigene cassette can be 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449,

450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, or about 1000 nucleotides or more in length.

[2399] In certain aspects, the minigene cassette can be between about 50 and about 1000 nucleotides, e.g., between about 100 and about 1000 nucleotides, e.g., between about 200 and about 1000 nucleotides, e.g., between about 300 and about 1000 nucleotides, e.g., between about 400 and about 1000 nucleotides, between about 500 and about 1000 nucleotides, between about 600 and about 1000 nucleotides, e.g., between about 700 and about 1000 nucleotides, e.g., between about 800 and about 1000 nucleotides, e.g., between about 900 and about 1000 nucleotides in length.

[2400] In certain aspects, the minigene cassette can be between about 50 and about 1000 nucleotides, e.g., between about 50 and about 900 nucleotides, e.g., between about 50 and about 800 nucleotides, e.g., between about 50 and about 700 nucleotides, e.g., between about 50 and about 600 nucleotides, between about 50 and about 500 nucleotides, between about 50 and about 400 nucleotides, e.g., between about 50 and about 300 nucleotides, e.g., between about 50 and about 200 nucleotides, e.g., between about 50 and about 100 nucleotides in length.

[2401] In one aspect, minigene cassette's middle exon 2 can be about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199 or 200 nucleotides in length.

[2402] In one aspect, minigene cassette's middle exon 2 can be about 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123,

124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, or 150 nucleotides in length.

[2403] In one aspect, the minigene cassette's middle exon 2 can be 50-200, 51-200, 52-200, 53-200, 54-200, 55-200, 56-200, 57-200, 58-200, 59-200, 60-200, 61-200, 62-200, 63-200, 64-200, 65-200, 66-200, 67-200, 68-200, 69-200, 70-200, 71-200, 72-200, 73-200, 74-200, 75-200, 76-200, 77-200, 78-200, 79-200, 80-200, 81-200, 82-200, 83-200, 84-200, 85-200, 86-200, 87-200, 88-200, 89-200, 90-200, 91-200, 92-200, 93-200, 94-200, 95-200, 96-200, 97-200, 98-200, 99-200, 100-200, 101-200, 102-200, 103-200, 104-200, 105-200, 106-200, 107-200, 108-200, 109-200, 110-200, 111-200, 112-200, 113-200, 114-200, 115-200, 116-200, 117-200, 118-200, 119-200, 120-200, 121-200, 122-200, 123-200, 124-200, 125-200, 126-200, 127-200, 128-200, 129-200, 130-200, 131-200, 132-200, 133-200, 134-200, 135-200, 136-200, 137-200, 138-200, 139-200, 140-200, 141-200, 142-200, 143-200, 144-200, 145-200, 146-200, 147-200, 148-200, 149-200, 150-200, 151-200, 152-200, 153-200, 154-200, 155-200, 156-200, 157-200, 158-200, 159-200, 160-200, 161-200, 162-200, 163-200, 164-200, 165-200, 166-200, 167-200, 168-200, 169-200, 170-200, 171-200, 172-200, 173-200, 174-200, 175-200, 176-200, 177-200, 178-200, 179-200, 180-200, 181-200, 182-200, 183-200, 184-200, 185-200, 186-200, 187-200, 188-200, 189-200, 190-200, 191-200, 192-200, 193-200, 194-200, 195-200, 196-200, 197-200, 198-200, 199 or 200 nucleotides in length.

[2404] In one aspect, exon 2 can be between 50-51, 50-52, 50-53, 50-54, 50-55, 50-56, 50-57, 50-58, 50-59, 50-60, 50-61, 50-62, 50-63, 50-64, 50-65, 50-66, 50-67, 50-68, 50-69, 50-70, 50-71, 50-72, 50-73, 50-74, 50-75, 50-76, 50-77, 50-78, 50-79, 50-80, 50-81, 50-82, 50-83, 50-84, 50-85, 50-86, 50-87, 50-88, 50-89, 50-90, 50-91, 50-92, 50-93, 50-94, 50-95, 50-96, 50-97, 50-98, 50-99, 50-100, 50-101, 50-102, 50-103, 50-104, 50-105, 50-106, 50-107, 50-108, 50-109, 50-110, 50-111, 50-112, 50-113, 50-114, 50-115, 50-116, 50-117, 50-118, 50-119, 50-120, 50-121, 50-122, 50-123, 50-124, 50-125, 50-126, 50-127, 50-128, 50-129, 50-130, 50-131, 50-132, 50-133, 50-134, 50-135, 50-136, 50-137, 50-138, 50-139, 50-140, 50-141, 50-142, 50-143, 50-144, 50-145, 50-146, 50-147, 50-148, 50-149, 50-150, 50-151, 50-152, 50-153, 50-154, 50-155, 50-156, 50-157, 50-158, 50-159, 50-160, 50-161, 50-162, 50-163, 50-164, 50-165, 50-166, 50-167, 50-168, 50-169, 50-170, 50-171, 50-172, 50-173, 50-174, 50-175, 50-176, 50-177, 50-178, 50-179, 50-180, 50-181, 50-182, 50-183, 50-184, 50-185, 50-186, 50-187, 50-188, 50-189, 50-190, 50-191, 50-192, 50-193, 50-194, 50-195, 50-196, 50-197, 50-198, 50-199 or 50-200 nucleotides in length.

[2405] In certain aspects, the minigene cassette may include fewer than 2000, fewer than 1900, fewer than 1800, fewer than 1700, fewer than 1600, fewer than 1500, fewer than 1400, fewer than 1300, fewer than 1200, fewer than 1100, or fewer than 1000, fewer than 900, fewer than 800, fewer than 700, fewer than 600, fewer than 500 nucleotides, fewer than 400 nucleotides, fewer than 300 nucleotides, fewer than 200 nucleotides or fewer than 100 nucleotides.

[2406] In certain aspects, the minigene cassette may include between about 2500 and about 500 nucleotides, e.g., between about 2000 and about 600 nucleotides, e.g., between about 1500 and about 700 nucleotides, e.g., between about 1200 and about 800 nucleotides, between about 1100 and about 900 nucleotides, between about 800 and about 500 nucleotides, between about 800 and about 600 nucleotides.

[2407] In certain aspects, the minigene cassette may comprise the nucleotide sequence of SEQ ID Nos: 1-10 or a fragment thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% at least 96%, at least 97%, at least 98% or at least 99% identity thereto (see FIG. 2Bi-vi).

[2408] In certain aspects, the minigene cassette may comprise the nucleotide sequence of SEQ ID Nos: 47-55 or a fragment thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% at least 96%, at least 97%, at least 98% or at least 99% identity thereto (see FIG. 9A-9D).

[2409] In certain aspects, the minigene cassette may comprise the nucleotide sequences of SEQ ID Nos: 64-65 or a fragment thereof having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% at least 96%, at least 97%, at least 98% or at least 99% identity thereto (see FIG. 12Ci-ii).

[2410] In certain aspects, a fragment of the aforementioned nucleotide sequences (e.g. the nucleotide sequences of SEQ ID Nos: 1-10, 47-55 and 64-65) can be between about 50 and about 1000 nucleotides, e.g., between about 100 and about 1000 nucleotides, e.g., between about 200 and about 1000 nucleotides, e.g., between about 300 and about 1000 nucleotides, e.g., between about 400 and about 1000 nucleotides, between about 500 and about 1000 nucleotides, between about 600 and about 1000 nucleotides, e.g., between about 700 and about 1000 nucleotides, e.g., between about 800 and about 1000 nucleotides, e.g., between about 900 and about 1000 nucleotides in length.

[0005] In other aspects, a fragment of the aforementioned nucleotide sequences (e.g. the nucleotide sequences of SEQ ID Nos: 1-10, 47-55 and 64-65) can be between about 50 and about 1000 nucleotides, e.g., between about 50 and about 900 nucleotides, e.g., between about 50 and about 800 nucleotides, e.g., between about 50 and about 700 nucleotides, e.g., between about 50 and about 600 nucleotides, between about 50 and about 500 nucleotides, between about 50 and about 400 nucleotides, e.g., between about 50 and about 300 nucleotides, e.g., between about 50 and about 200 nucleotides, e.g., between about 50 and about 100 nucleotides in length.

[2411] In one aspect, a minigene cassette's exon 2 may comprise those exonic nucleotide sequences upstream of a SMSM compound inducible non-canonical 5' splice site having a nucleotide of SEQ ID Nos: 66, 67, 69 and 70, or a fragment of those exonic nucleotide sequences having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% at least 96%, at least 97%, at least 98% or at least 99% identity thereto (see FIG. 9A-9D).

[2412] In some aspects, the minigene DNA sequence does not comprise a regulatory element as defined herein.

[2413] In some aspects, a regulatory element is not present in either exon 1, exon 2 or exon 3.

[2414] In some aspects, a regulatory element is not present in exon 1, exon 2 and exon 3.

[2415] In some aspects, a regulatory element is not present in intron 1 or intron 2.

[2416] In some aspects, a regulatory element is not present in intron 1 and intron 3.

[2417] In some aspects, a transgene coding region's AUG start codon is not present in either exon 1, exon 2, or exon 3.

[2418] In some aspects, a transgene coding region's AUG start codon is not present in exon 1, exon 2, and exon 3.

Splicing-induced-on (SION) and splicing-induced-off (SIOFF) systems

[2419] Splicing-induced-on (SION) and splicing-induced-off (SIOFF) systems were devised in which the modulation of the splicing of a minigene cassette controls the expression of an operably linked transgene.

[2420] Depending on the configuration design for regulating transgene expression, a minigene cassette, as defined herein, can be placed anywhere within a transgene's transcription unit that

is transcribed into the pre-mRNA nucleotide sequence. For example, a minigene cassette can be placed within the 5' or 3' untranslated regions of a transgene. In another example, a minigene cassette, as defined herein, may be inserted into a transgene's intron if present. In another example, a minigene cassette, as defined herein, may be inserted into a transgene's exon. In another example, a minigene cassette, as defined herein, may be inserted into a transgene's coding region.

[2421] In one aspect, a minigene cassette, as defined herein, may be inserted 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, or about

1000 nucleotides downstream from the transcription initiation site corresponding to the 5' end of the pre-mRNA.

[2422] In one aspect, a minigene cassette, as defined herein, may be inserted 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, or about 1000 nucleotides from the polyadenylation site corresponding to the 3' end of the pre-mRNA.

[2423] In one aspect, a minigene cassette as disclosed herein may comprise 1, 2, 3, 4, 5 or more introns.

[2424] In one aspect, a minigene cassette as disclosed herein may comprise 1, 2, 3, 4, 5 or more exons.

[2425] In one aspect, a minigene cassette as disclosed herein may not have any introns.

[2426] As shown in FIG. 1Bi-iii, an exemplary minigene cassette comprises three exons (exon 1, exon 2 and exon 3) interspersed with two introns (intron 1 between exons 1 and 2 and intron 2 between exons 2 and 3). An SMSM compound-inducible non-canonical 5' splice site can be located at the 3' end of exon 2. Depending on the splicing design, the minigene cassette can be inserted either upstream (FIG. 1Bi) or downstream (FIG. 1Bii) of an operably linked transgene. In either scenario, a cis-acting regulatory element (RE), for example, an AUG start codon or a polyadenylation site, is split between exons 2 and 3 with a non-functional first portion of the regulatory element (RE(1)) located at the 3' end of exon 2 (for example, the adenosine nucleotide of the transgene's AUG start codon) and a non-functional second portion of the regulatory element (RE(2)) located at the 5' end of exon 3 (for example, the "UG" dinucleotide of the transgene's AUG start codon). SMSM compound induced splicing between exons 2 and 3 reunites RE(1) and RE(2) to form a functional regulatory element (for example, the transgene's AUG start codon) that permits expression of the operably linked transgene.

[2427] In one example of a SION system, as illustrated in FIG. 1Ci, the splicing of the minigene cassette is in an OFF state in the absence of an SMSM compound. In the presence of an SMSM compound, compound-induced splicing, and subsequent exon inclusion, restores the transgene's AUG start codon allowing the translation of the transgene's spliced mRNA.

[2428] In a SIOFF system, the splicing of a minigene cassette is in the ON state in the absence of an SMSM compound. According to this scenario, the compound-induced splicing and subsequent exon inclusion disrupts the transgene's mRNA open reading frame (ORF), for example, through the insertion of an in frame stop codon, to turn off translation of the transgene mRNA (FIG. 1C(II)).

[2429] In another SION system, as illustrated in FIG. 1D, the splicing of a minigene cassette is in the OFF state in the absence of an SMSM compound. Compound-induced splicing and subsequent exon inclusion restores the transgene's AAUAAA polyadenylation sequence thereby stabilizing the transgene's spliced mRNA to allow translation of the transgene's mRNA.

[2430] In certain aspects, the transcription unit may comprise more than one SMSM compound inducible minigene cassettes. For example, an SMSM compound inducible minigene cassette can be inserted into a transgene's 5'-UTR and 3'-UTR.

Exemplary SION minigene cassettes

[2431] FIG. 1E illustrates an exemplary SION minigene cassette configuration in which the 3' end of the middle second exon has the nucleotide sequence "NDGA" corresponding to positions -4 to -1 of a non-canonical 5' splice site, where "N" means A, T/U, C or G; "D" means A, T/U or G and "ND" means at least an A is present. The downstream third exon has a "TG" dinucleotide at its 5' end. In the absence of an HD/SMA compound as defined herein, with splicing, the middle second exon is skipped, or, in the absence of splicing, the intron(s) are retained. In both scenarios, the transgene's AUG start codon is not restored and translation initiation cannot occur. Moreover, nonsense codons, e.g., UAA sequences, in frame with the transgene's coding region are situated in the upstream second exon and/or intron to terminate any potential upstream translation initiation. In the presence of an HD/SMA compound as defined herein, splicing results in the inclusion of the middle second exon into the spliced mRNA. Consequently, splicing between the second and third exons brings together the "A" nucleotide at the 3' end of the middle second exon and the "UG" dinucleotide at the 5' end of the downstream third exon to reinstate the "AUG" start codon of the transgene's coding region. Translation initiation of the spliced transgene mRNA is therefore restored. In one aspect, the middle second exon can contain a stop codon, e.g., "UAA," positioned upstream and in frame with the newly formed "AUG" start codon to preclude spurious translation initiation.

[2432] FIG. 1F illustrates an exemplary SION minigene cassette configuration in which the 3' end of the middle second exon has an "CAA" dinucleotide corresponding to positions -3 to -1 of a non-canonical 5' splice site. The downstream third exon has a "TG" nucleotide at its 5' end. In the absence of an FD compound as defined herein, with splicing, the middle second exon is skipped, or, in the absence of splicing, the intron(s) are retained. In both scenarios, the transgene's AUG start codon is not restored and translation initiation cannot occur. Moreover, nonsense codons, e.g., UAA sequences, in frame with the transgene's coding region can be situated in the upstream second exon and/or intron to terminate any potential upstream translation initiation. In the presence of an FD compound as defined herein, splicing results in the inclusion of the middle second exon into the spliced mRNA. Consequently, splicing between the second and third exons brings together the "AU" dinucleotide at the 3' end of the

middle second exon and the “G” dinucleotide at the 5’ end of the downstream third exon to reinstate the “AUG” start codon of the transgene’s coding region. Translation initiation of the spliced transgene mRNA can then proceed. In one aspect, the middle second exon can contain a stop codon, e.g., “UAA,” positioned upstream and in frame with the newly formed “AUG” start codon to preclude spurious translation initiation.

[2433] FIG. 1G illustrates an exemplary SION minigene cassette configuration in which the 3’ end of the middle second exon has an “T” nucleotide sequence corresponding to positions -1 of a non-canonical 5’ splice site. The upstream exon has a “AUG” start codon at its 3’ end. In the absence of an FD compound as defined herein, splicing results in the inclusion of the middle second exon into the spliced mRNA. Consequently, splicing between the second and third exons brings together the “U” nucleotide at the 3’ end of the middle second exon and the 5’ end of the downstream third exon comprising the second codon of the transgene’s coding region. Thus, in the absence of FD compound, splicing fails to reinstate the “AUG” start codon of the transgene’s coding region and translation initiation of the spliced transgene mRNA does not occur. In one aspect, the middle second exon can contain a stop codon, e.g. “UAA,” positioned upstream and in frame with the second codon of the transgene’s coding region to preclude spurious translation initiation. In the presence of an FD compound as defined herein, with splicing, the middle second exon is skipped and the AUG at the 3’ end of the first exon is joined in frame with the second codon of the transgene’s coding region at the 5’ end of the 3rd exon to permit translation of the transgene’s spliced mRNA.

Exemplary SIOFF minigene cassettes

[2434] FIG. 1H illustrates an exemplary SIOFF minigene cassette configuration in which the 3’ end of the middle second exon has an “AT” dinucleotide corresponding to positions -2 to -1 of a non-canonical 5’ splice site. The downstream third exon has a “G” nucleotide at its 5’ end. In the absence of an FD compound as defined herein, splicing results in the inclusion of the middle second exon into the spliced mRNA. Consequently, splicing between the second and third exons brings together the “AU” dinucleotide at the 3’ end of the middle second exon and the “G” dinucleotide at the 5’ end of the downstream third exon to reinstate the “AUG” start codon of the transgene’s coding region. Translation initiation of the spliced transgene mRNA can then proceed. In one aspect, the middle second exon can contain a stop codon, e.g. “UAA,” positioned upstream and in frame with the newly formed “AUG” start codon to preclude spurious translation initiation. In the presence of an FD compound as defined herein, with

splicing, the middle second exon is skipped, or, in the absence of splicing, the intron(s) are retained. In both scenarios, the transgene's AUG start codon is not restored and translation initiation cannot occur. Nonsense codons, e.g., UAA sequences, in frame with the transgene's coding region can be situated in the upstream second exon and/or intron to terminate any potential upstream translation initiation.

[2435] FIG. 1I illustrates an exemplary SIOFF minigene cassette configuration in which the 3' end of the first exon has an "ATG" nucleotide sequence at its 3' end. The 3' end of the middle second exon has an "CAA" nucleotide sequence corresponding to positions -3 to -1 of a non-canonical 5' splice site. The 5' end of the downstream third exon starts with the second codon of the transgene's coding region. In the absence of an FD compound as defined herein, with splicing, the middle second exon is skipped. The transgene's AUG start codon is placed adjacent to the second codon of the transgene's coding region and translation initiation can proceed. In the presence of an FD compound as defined herein, splicing results in the inclusion of the middle second exon into the spliced mRNA. Consequently, splicing between the second and third exons brings together the "CAA" dinucleotide at the 3' end of the middle second exon and the second codon of the transgene's coding region. Consequently, translation initiation of the spliced transgene mRNA can not proceed. In one aspect, the middle second exon can further contain a stop codon, e.g., "UAA," positioned upstream and in frame with the newly formed "AUG" start codon to preclude spurious translation initiation.

Exemplary Regulatory elements (REs)

[2436] As disclosed herein, a minigene cassette's regulatory element (RE) refers to any RNA sequence whose functionality is contingent on minigene splicing induced by an SMSM compound.

[2437] In certain aspects, the minigene cassette's regulatory element (RE) can control the post-transcriptional expression of a transgene operably linked to the minigene cassette. In one aspect, the minigene cassette's regulatory element (RE) can be a cis-acting RNA element.

[2438] In one aspect, the minigene cassette's regulatory element can refer to an RNA sequence encoding a regulatory polypeptide sequence that can modulate the activity of the protein encoded by the transgene.

[2439] In certain aspects, the minigene cassette's regulatory element (RE) can be split between a first and a second exon which abolishes the activity of the regulatory element provided each

part of a split regulatory element (RE) is inactive by itself. However, the activity of the regulatory element can be rescued by SMSM compound induced splicing between the two exons which restores the integrity and functionality of the regulatory element.

[2440] In one aspect, the minigene cassette's exon 1 does not contain a functional regulatory element (RE), e.g., an "ATG" translation initiation codon.

[2441] In one aspect, the minigene cassette's exon 2 does not contain a functional regulatory element (RE), e.g., an "ATG" translation initiation codon.

[2442] In one aspect, the minigene cassette's exon 3 does not contain a functional regulatory element (RE), e.g., an "ATG" translation initiation codon.

[2443] In one aspect, the minigene cassette's exon 1, exon 2, and exon 3 do not contain a functional regulatory element (RE), e.g., an "ATG" translation initiation codon.

[2444] In certain aspects, the minigene cassette can be located upstream (see, for example, FIG. 1Bi) or downstream of a transgene's protein coding region (see, for example, FIG. 1Bii).

[2445] In certain aspects, a minigene cassette can have more than one regulatory element.

[2446] In one aspect, the regulatory element can be split into a first inactive portion of the regulatory element (RE(1)) and a second inactive portion of the regulatory element (RE(2)).

[2447] Thus, for example, the first inactive portion of the regulatory element (RE(1)) can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 nucleotides in length.

[2448] In another example, the second inactive portion of the regulatory element (RE(1)) can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 nucleotides in length.

[2449] In yet another example, if a regulatory element is 25 nucleotides in length, the length of the first and second inactive portions can be:

SPLIT REGULATORY ELEMENT		Regulatory element
First inactive portion (length nt.)	Second inactive portion (length nt.)	Splicing of first and second inactive portions (length nt.)
1	24	25
2	23	25
3	22	25
4	21	25
5	20	25
6	19	25
7	18	25
8	17	25
9	16	25
10	15	25
11	14	25
12	13	25
13	12	25
14	11	25
15	10	25
16	9	25
17	8	25
18	7	25
19	6	25
20	5	25
21	4	25
22	3	25
23	2	25
24	1	25

[2450] For example, a first inactive portion of the regulatory element (RE(1)) can be located at the 3' end of the minigene cassette's middle exon 2 and a second inactive portion of the regulatory element (RE(2)) can be situated at the 5' end of the minigene cassette's exon 3 (see, for example FIG, 1Bi). SMSM compound inducible splicing between exon 2 and exon 3 results in the inclusion of exon 2 into the spliced transgene mRNA thereby restoring the integrity and functionality of the regulatory element.

[2451] In another example, the first inactive portion of the regulatory element (RE(1)) can be located at the 3' end of exon 1 and the second inactive portion of the regulatory element (RE(2)) is located at the 5' end of exon 3. Accordingly, functionality of the regulatory element can only be restored through SMSM compound induced splicing between exon 1 and exon 3.

[2452] In other examples, the activity of an otherwise functional intact regulatory element can be dependent on its proximity to the operably linked transgene. According to this scenario, the

minigene cassette's regulatory element (RE) is rendered inactive because of its distal location from the transgene. For example, the regulatory element (RE) can be located at the 3' end of the minigene cassette's exon 1 and the transgene can be situated downstream of exon 3's 5' end. SMSM compound induced splicing and subsequent exon 2 skipping brings exon 1 in proximity to the transgene of exon 3 thereby restoring the functionality of the regulatory element to promote transgene expression.

[2453] The minigene cassette's regulatory element can act on many different aspects of a transgene's mRNA post-transcriptional regulation.

Transgene mRNA translation

[2454] In one aspect, the minigene cassette's regulatory element (RE) can refer to a cis-acting RNA sequence required for transgene mRNA translation initiation.

[2455] In one aspect, the minigene cassette's regulatory element (RE) can refer to a cis-acting RNA sequence required for transgene mRNA translation termination.

[2456] For example, the regulatory element can be the transgene's protein coding region AUG start codon (see, for example, FIG. 1C). In another example, the regulatory element can be the transgene's protein coding region stop codon (UAA, UGA or UAG).

[2457] In one aspect, the first nucleotide at the 5' end of exon 3 is the "G" nucleotide of the transgene's ATG start codon and the two nucleotides at the 3' end of the first or second exon is the dinucleotide "AT". In one aspect, the "G" nucleotide and the "AT" are separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256,

257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, or about 1000 nucleotides.

[2458] In one aspect, the first two nucleotides at the 5' end of exon 3 are "TG" of the transgene's ATG start codon and the nucleotide at the 3' end of the first or second exon is the dinucleotide "A". In one aspect, the "TG" nucleotide and the "A" nucleotide are separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311,

312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, or about 1000 nucleotides.

[2459] In one aspect, the first nucleotide at the 5' end of exon 3 corresponds to the first nucleotide of the transgene's second codon and the three terminal nucleotides at the 3' end of the first or second exon are "ATG." In one aspect, the "ATG" codon and the transgene's second codon are separated by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363,

364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, or about 1000 nucleotides.

[2460] In one aspect, the nucleotides at the 3' end of exon 1 or exon 2 may have an open reading frame that after splicing is in frame with the reading frame of the transgene's protein coding region.

[2461] In one aspect, the nucleotides at the 3' end of exon 1 or exon 2 may have an open reading frame that after splicing is not in frame with the reading frame of the transgene's coding region.

[2462] In one aspect, a minigene cassette disclosed herein does not contain a sequence of 25 or more nucleotides from anyone of the genes: SF3B3, BENC1, SMN2, GXYLT1, C12orf4, RARS, WNK1, WDR27, CIP2A, IFT57, or PDXDC2.

[2463] In one aspect, a minigene cassette disclosed herein can contain a sequence of 25 or more nucleotides from anyone of the genes: SF3B3, BENC1, SMN2, GXYLT1, C12orf4, RARS, WNK1, WDR27, CIP2A, IFT57, or PDXDC2.

[2464] In one aspect, a transgene operably linked to the minigene cassette does not contain a nucleotide sequence not found in a cDNA of the native gene from which the transgene is derived. For example, SMSM compound induced splicing does not generate a spliced transgene mRNA in which an exogenous sequence is inserted between the start codon and the remainder of the transgene's coding region.

[2465] In another example, the SMSM compound responsive minigene cassette and operably linked transgene do not contain an engineered protein cleavage site (e.g., a furin, PCSK1, PCSK5, PCSK6, PCSK7, cathepsin B, granzyme B, factor XA, enterokinase, genenase, sortase, preScission protease, thrombin, TEV protease or elastase 1 cleavage site).

[2466] In one aspect, the minigene cassette's regulatory element (RE) refers to a cis-acting RNA sequence required for transgene mRNA translation. Examples of cis-acting regulatory elements affecting mRNA translation are described below.

i. Splicing enhancer or silencer sequence

[2467] In one aspect, a minigene cassette's split regulatory element (RE) can comprise cis acting sequences required for splicing including exonic splicing enhancer (ESE) or exonic splicing silencers (ESS).

ii. Kozak sequence

[2468] In one aspect, a minigene cassette's split regulatory element (RE) can comprise sequences required for translation initiation, e.g., a Kozak sequence.

[2469] During translation initiation, the small (40S) ribosomal subunit binds to the mRNA at the 5'-untranslated region (5'-UTR) and scans in the 5' to 3' direction to reach the coding sequence (CDS) start codon, most usually an AUG. The scanning model predicts that translation initiates at the AUG codon closest to the 5' end of the mRNA, which is termed the 'first-AUG rule.' Kozak analyzed 699 vertebrate mRNAs, and from this study an expanded consensus for the translation initiation site (TIS) context emerged, namely (GCC)GCC**RCCAUGG** in which "R" at position -3, in italic font, is A or G (97% of mRNAs have a purine, most often an A (61%)) and the AUG initiation codon is bold and underlined). Mutational analysis indicated positions -3R (most often A) and +4G are both the most conserved nucleotides and exert the most critical influence on translational efficiency (reviewed by Hernández et al. (2019) Trends in Biochemical Sciences 44 (12): 1009–21).

[2470] In certain aspects, the regulatory element can be a Kozak sequence.

iii. Internal Ribosome Entry Site (IRES) Site

[2471] An internal ribosome entry site, abbreviated IRES, is an RNA element that allows recruitment of eukaryotic ribosomes to naturally uncapped mRNAs or to capped mRNAs under conditions in which cap-dependent translation is inhibited. Most IRESs obviate the need of the eukaryotic pre-initiation ribosomal complexes (PICs) for scanning the 5' Untranslated Region (UTR) of mRNA for the AUG start codon as they directly place the initiating codon in the ribosomal P-site. IRESs are utilized mostly by various invading viruses, although several putative cellular IRESs have been also reported and proposed to play important roles in stress responses, development, apoptosis, cell cycle control, and neuronal function.

[2472] In one aspect, the minigene cassette's regulatory element can be an internal ribosome entry site (IRES) site (see, for example, Roberts et al. (2018) *Biotechnology & Genetic Engineering Reviews* 34 (1): 60–75; Gritsenko et al. (2017) *PLoS Computational Biology* 13 (9): e1005734; Venkatesan et al. (2001) *Molecular and Cellular Biology* 21 (8): 2826–37 and Owens et al. (2001) *Proc. Natl. Acad. Sci USA* 98 (4): 1471–76, the contents of which are incorporated by reference herein in their entireties).

[2473] In one aspect, a minigene cassette's regulatory element (RE) can refer to an IRES element whose functionality is contingent on minigene splicing induced by an SMSM compound. For example, an IRES element can be rendered inactive by dividing the sequence between the 3' end of a first exon having an SMSM compound inducible 5' non-canonical splice site and the 5' end of a downstream second exon. Activity of the IRES element can then be restored by SMSM compound induced splicing between the first and second exons that reconstitutes the IRES element within the spliced mRNA.

iv. *cis-repressive RNA or crRNA*

[2474] In one aspect, the minigene's regulatory element can be a cis-repressive or crRNA regulatory element within the transgene's the 5' untranslated region (5' UTR) that encodes an RNA having a hairpin (stem/loop) structure that prevents ribosomes from gaining access to a transgene's start codon to begin translation. For example, the crRNA regulatory element can be rendered inactive by dividing the sequence between the 3' end of a first exon having an SMSM compound inducible 5' non-canonical splice site and the 5' end of a second exon upstream of a transgene's start codon. According to this SIOFF scenario, in the absence of an SMSM compound and induced splicing, the crRNA is split and thus unable to form a secondary structure to impede transgene expression. However, in the presence of an SMSM compound, splicing between the first and second exons reconstitutes the crRNA regulatory element and inhibits transgene expression.

[2475] In one aspect, the minigene cassette's regulatory element can be the cis-repressive RNA or crRNA (see, for example, the U.S. Patent No. 10,208,312, the content of which is incorporated by reference herein in its entirety).

mRNA stability and RNA 3' end formation

[2476] In one aspect, the minigene cassette's regulatory element (RE) can refer to a cis-acting RNA sequences required for posttranscriptional control of transgene mRNA stability.

i. Polyadenylation sequence

[2477] With the notable exception of replication-dependent histone transcripts, most eukaryotic mRNAs have a poly(A) tail at their 3' ends. 3' end processing is a nuclear co-transcriptional process that promotes transport of mRNAs from the nucleus to the cytoplasm and affects the stability and the translation of mRNAs. Formation of this 3' end occurs in a two-step process requiring the presence of two sequence elements in mRNA precursors (pre-mRNAs); a highly conserved hexanucleotide AAUAAA (polyadenylation signal) and a downstream G/U-rich sequence. In a first step, pre-mRNAs are cleaved between these two elements 10-35 nucleotides downstream of the AAUAAA sequence. In a second step, tightly coupled to the first step, the newly formed 3' end is extended by addition of a poly(A) sequence consisting of 200-250 adenylates which affects subsequently all aspects of mRNA metabolism, including mRNA export, stability and translation (Dominski, Z. and W. F. Marzluff (2007), *Gene* 396(2): 373-90, the content of which is incorporated by reference herein in its entirety). Polyadenylation signals known in the art include, but are not limited, polyadenylation signals from simian virus 40 (SV40) (Schek et al., *Mol. Cell Biol.* 12(12): 5386-93 (1992)), α -globin (Thein et al., *Blood* 71(2): 313-19), β -globin (Orkin et al., *EMBO J.* 4(2): 453-6 (1985)), human collagen, polyoma virus (Batt et al., *Mol. Cell Biol.* 15(9): 4783-90 (1995)) and bovine growth hormone (bGH) (Woychik et al., *Proc. Natl. Acad. Sci. USA* 81(13): 3944-8 (1984); U.S. Pat. No. 5,122,458, the content of which is incorporated by reference herein in its entirety).

[2478] Thus, in one aspect, the minigene cassette's regulatory element can be a polyadenylation sequence comprising the AATAAA poly A site and the downstream GT-rich element.

[2479] An exemplary minigene cassette, as described herein, can have the configuration depicted in FIG. 1D. According to this scenario, a minigene comprising a polyadenylation sequence is located within the transgene's 3'-UTR. The polyA sequence is rendered inactive by dividing the sequence between the 3' end of a first exon having an SMSM compound inducible 5' non-canonical splice site and the 5' end of a downstream second exon. According to this SION scenario, in the absence of an SMSM compound and induced splicing, the polyadenylation sequence is split and thus unable to cleave and/ or polyadenylate the 3' ends of nascent pre-mRNAs. The non-polyadenylated mRNAs are degraded in the cell before translation can occur. However, in the presence of an SMSM compound, splicing between the

first and second exons reconstitutes the polyadenylation sequence thereby allowing for the synthesis of stable polyA⁺ mRNAs that can be translated.

[2480] In certain aspects, a transcription unit as disclosed herein can have a minigene in the 5'-UTR having a translation initiation regulatory element, e.g., an AUG initiation codon, and a second minigene in the 3'-UTR having a polyadenylation sequence. In the presence of an SMSM compound, splicing of the first and second minigene sequences as described herein enhances transgene expression by allowing translation initiation and polyadenylation of the nascent transgene mRNA.

ii. *Histone pre-mRNA 3' end processing*

[2481] Replication-dependent histone mRNAs are not polyadenylated but end with a histone stem-loop instead of a poly(A) sequence. Exemplary histone stem-loop sequences are described in Lopez et al. (Dávila López, M., & Samuelsson, T. (2008), RNA (New York, N.Y.), 14(1), 1-10, the content of which is incorporated by reference herein in its entirety). Downstream of the stem and loop in a histone pre-mRNA is a purine-rich sequence known as the histone downstream element (HDE). Histone pre-mRNAs are processed in the nucleus by a single endonucleolytic cleavage approximately 5 nucleotides downstream of the stem-loop, which is catalyzed by a U7 snRNP through base pairing of the U7 snRNA with the HDE.

[2482] In one aspect, the minigene cassette's regulatory element can be a histone pre-mRNA processing sequence including a stem and loop and histone downstream element (HDE).

[2483] Thus, in one aspect, an SMSM compound inducible minigene comprising a 3' histone pre-mRNA processing regulatory sequence can be inserted within a transgene's 3'-UTR in which the polyadenylation sequence is deleted. As previously, the 3' histone pre-mRNA processing sequence is rendered inactive by splitting the sequence between the 3' end of a first exon having an SMSM compound inducible 5' non-canonical splice site and the 5' end of a downstream second exon. In the absence of an SMSM compound and induced splicing, the 3' histone pre-mRNA processing sequence is split and thus unable to cleave the 3' ends of nascent pre-mRNAs. The non-polyadenylated mRNAs are degraded in the cell before translation can occur. However, in the presence of an SMSM compound, splicing between the first and second exons reconstitutes the 3' histone pre-mRNA processing signal thereby generating stable mRNAs having a stem and loop structure at their 3' ends that can be translated.

[2484] Because the 3' histone pre-mRNA processing machinery is only active during the S phase of the cell cycle, transgene expression can be coordinated with cellular proliferation (see, for example, Dominski (2010) *Cell Cycle* 9 (7): 1308–12).

[2485] In one aspect, the minigene cassette's regulatory element can be a combination of one or more histone pre-mRNA stem loops and a polyadenylation sequence, as disclosed in U.S. Patent No. 10,653,799, the content of which is incorporated by reference herein in its entirety.

iii. miRNAs

[2486] MicroRNAs (or miRNAs or miRs) are small, non-coding, single stranded ribonucleic acid molecules (RNAs), which are usually 19-25 nucleotides in length. Mature microRNAs primarily bind to the 3' untranslated region (3'-UTR) of target messenger RNAs (mRNAs) through partially or fully pairing with the complementary sequences of target mRNAs, promoting the degradation of target mRNAs at a post-transcriptional level, and in some cases, inhibiting the initiation of translation. miRNA genes are generally transcribed as long primary transcripts of miRNAs (i.e. pri-miRNAs). The pri-miRNA is cleaved into a precursor of a miRNA (i.e. pre-miRNA) which is further processed to generate the mature and functional miRNA (see, for example, U.S. Patent No. 10,570,395, the content of which is incorporated by reference herein in its entirety).

[2487] In one aspect, the minigene cassette's regulatory element can be one or more miRNA binding sites. Thus, in one aspect, an SMSM compound inducible minigene comprising a plurality of miRNA binding sites within exon 2 of the minigene cassette can be inserted, for example, within a transgene's 3'-UTR. Thus, according to a SION scenario, the presence of SMSM compound induces exon 2 inclusion to generate an mRNA having the plurality of miRNA binding sites within its 3'-UTR that can repress translation of the transgene mRNA. In contrast, removal of the SMSM compound leads to exon 2 skipping and the production of mRNAs without the miRNA binding sites in their 3'-UTRs and consequently translation of the transgene mRNA is not repressed.

[2488] In one aspect, a regulatory element can be a miRNA binding site that is split between a first exon and a second exon. Thus, activity of the miRNA binding site can be rescued by SMSM compound induced splicing between the two exons which restores the integrity and functionality of the miRNA binding site.

[2489] In another aspect, the regulatory element can be, for example, a plurality of tissue-specific miRNA binding sites. Examples of tissue-specific miRNA binding sites include, but are not limited to, binding sites for CNS-specific miRNAs, e.g., miR-124a or miR-9, muscle-specific miRNAs (e.g., miR-1, miR-133 or miR-206), hematopoietic miRNAs (e.g., miR-142, miR-150 or miR-223) or liver-specific miRNAs (e.g., miR-122).

[2490] For example, a minigene cassette comprising a plurality of miR-122 binding sites within, for example, the middle exon 2 (FIG. 6Civ), is placed within a transgene's 3'-UTR where it inhibits expression of the operably linked transgene in the liver. SMSM compound induced splicing between exons 1 and 3 (exon 2 skipping) can then remove exon 2 and its associated miR-122 binding sites thereby increasing transgene expression in the liver.

Post-transcriptional control of gene expression

[2491] In other aspects, a minigene cassette's regulatory element can be any cis-acting regulatory element, including but not limited to, a self-cleaving ribozyme, e.g. hammerhead ribozymes, antisense morpholino oligonucleotide regulated ribozymes, ribozyme-based riboswitches (see, for example, Wieland et al. (2012) *Methods* 56 (3): 351–57, the content of which is incorporated by reference herein in its entirety), aptazymes (see, for example, Stifel et al. (2019) *Synthetic Biology* 4(1): sy022, the content of which is incorporated by reference herein in its entirety), long non-coding RNA, transactivation response (TAR) element, Rev response element (RRE) or any structured mRNA motif required for eukaryotic translation and mRNA stability (see, for example, Wachter (2014) *Trends in Genetics: TIG* 30 (5): 172–81, the content of which is incorporated by reference herein in its entirety).

[2492] In certain aspects, a minigene cassette's regulatory element can be, for example, a small-molecule-responsive riboswitch (see, for example, the published U.S. Patent Application 2020/0063137 and Strobel et al. (2020) *ACS Synthetic Biology* 9 (6): 1292–1305 and Zhong et al. (2020) *Nature Biotechnology* 38 (2): 169–75, the content of each of which is incorporated by reference herein in its entirety).

[2493] In one aspect, the minigene cassette's regulatory element can refer to a self-cleaving RNA motifs that, in the absence of SMSM induced splicing, can lead to potent inhibition of gene or vector expression, owing to the spontaneous cleavage of the RNA transcript. In certain aspects, removal of the self-cleaving RNA motifs can be made contingent on SMSM inducible splicing as described herein. Alternatively, oligonucleotides complementary to

regions of the self-cleaving motif or specific small molecules may inhibit the activity of the self-cleaving RNA motif (see, for example, Yen et al. (2004) *Nature* 431 (7007): 471–76 and the U.S. Patent No. 10,233,447, the content of each of which is incorporated by reference herein in its entirety).

[2494] In one aspect, the minigene cassette's regulatory element can refer to a cis-acting RNA sequence required for transgene mRNA transport and/or localization (see, for example, Fernandopulle et al. (2021) *Nature Neuroscience*, 1-11).

[2495] In one aspect, the minigene cassette's regulatory element can refer to an RNA sequence encoding a protein sorting signal that targets a protein to subcellular compartments such as the endoplasmic reticulum, Golgi or mitochondria (see, for example, Dunn et al. (2019). *Current Opinion in Genetics & Development* 58-59: 9–16).

[2496] In other aspects, the minigene cassette's regulatory element controls the expression of RNA sequences for controlling endogenous genes, *in trans*, including but not limited to, RNA interference molecules (siRNAs, aiRNAs, piwiRNAs, shRNAs etc.), aptamers, riboswitches (see, for example, Wieland et al. (2012) *Methods* 56 (3): 351–57 and Strobel et al. (2020) *ACS Synthetic Biology* 9 (6): 1292–1305, the contents of which are incorporated by reference herein in their entireties), antisense RNAs, recombinant U7 snRNA antisense molecules (see, for example, the published U.S. Patent Application 2003/0036519, the content of which is incorporated by reference herein in its entirety), recombinases (Cre or Flp), gene editing enzymes (CRISPR/cas 9, TALENs, ZFNs reviewed in Bak et al. (2018) *Trends in Genetics: TIG* 34 (8): 600–611), RNA editing (CRISPR/cas13; see, for example, U.S. Patent No. 10,392,616 and published U.S. Patent Application No. 2020/0199,556, the content of each is incorporated by reference herein in their entireties) or nucleotide editing (see, for example, the published International PCT Patent Application No. PCT/US2020/049975, the content of which is incorporated by reference herein in its entirety).

[2497] In other aspects, a regulatory element can be found by a search of specialized database, including, but not limited to, Riboswitch finder (web site: riboswitch.bioapps.biozentrum.uni-wuerzburg.de; Bengert et al. (2004) *Nucleic Acids Research* 32 (suppl_2): W154–59), Rfam (web site: rfam.xfam.org; Griffiths-Jones et al. (2005) *Nucleic Acids Research* 33 (Database issue): D121–24.), UTRsite and UTRdb (web site: utrsite.ba.itb.cnr.it; Mignone et al. (2005) *Nucleic Acids Research* 33 (Database issue): D141–46), ESEfinder v. 3.0 (web site: krainer01.cshl.edu; Cartegni et al. (2003) *Nucleic Acids Research* 31 (13): 3568–71),

RNA motif (web site: casegroup.rutgers.edu; Mackee et al. (2001) *Nucleic Acids Research* 29 (22): 4724–35), miRBase (web site: www.mirbase.org; Griffiths-Jones et al. (2006) *Nucleic Acids Research* 34 (Database issue): D140–44), PatSearch/UTRBLAST/UTRscan (web site: itbtools.ba.itb.cnr.it/patsearch; Grillo et al. (2003) *Nucleic Acids Research* 31 (13): 3608–12), TransTerm (web site: crispr.otago.ac.nz/TT; Jacobs et al. (2006) *Nucleic Acids Research* 34 (suppl_1): D37–40), TargetScan (web site: www.targetscan.org/vert_72; Grimson et al. (2007) *Molecular Cell* 27 (1): 91–105) or HOMER (web site: homer.ucsd.edu/homer/motif/rnaMotifs).

Recombinant protein domains

[2498] In certain aspects, a minigene cassette as disclosed herein can regulate the inclusion of a protein domain encoded by an operably linked transgene.

[2499] In one aspect, the minigene cassette's regulatory element can refer to an RNA sequence encoding a regulatory polypeptide sequence that can modulate the activity of the protein encoded by the transgene, for example, an mRNA sequence encoding a nuclear localization signal, a signal sequence, a cell penetrating peptide (CPP), a protease cleavage site (e.g., furin, PCSK1, PCSK5, PCSK6, PCSK7, cathepsin B, granzyme B, factor XA, enterokinase, genenase, sortase, preScission protease, thrombin, TEV protease or elastase 1), a destabilization domain (DD) (e.g. an FKBP12 protein), a nucleic acid binding domain, a protein binding domain, or any protein domain of a native protein or recombinant fusion protein having a regulatory function.

VI. DESIGN OF SMSM COMPOUND INDUCIBLE EXPRESSION VECTORS

[2500] The term “expression vector”, as used herein, refers to a nucleic acid construct comprising nucleic acid elements sufficient for the expression of a transgene product in a cell or in an *in vitro* assay. For example, a transgene expression vector, disclosed herein, comprises a promoter operatively linked to a transgene transcription unit comprising a transcription initiation site, a 5' untranslated region (UTR), a transgene nucleotide sequence and a 3' untranslated region (UTR) comprising one or more post-transcriptional regulatory elements, e.g., a polyadenylation sequence.

[2501] The term “operably linked” refers to a functional relationship between two or more polynucleotide (e.g., DNA) segments. Typically, the term refers to the functional relationship of a transcriptional regulatory sequence and a transgene to be transcribed.

For example, a promoter or enhancer sequence is operably linked to a transgene if it, e.g., stimulates or modulates the transgene transcription in an appropriate host cell or other expression system. Generally, promoter transcriptional regulatory sequences that are operably linked to a sequence are contiguous to that sequence or are separated by short spacer sequences, i.e., they are cis-acting. However, some transcriptional regulatory sequences, such as enhancers, need not be physically contiguous or located in close proximity to the coding sequences whose transcription they enhance.

[2502] A "transgene" is a polynucleotide sequence that may encode an RNA (mRNA) that is translated into protein or a polynucleotide may encode an RNA that is not translated into protein (e.g. guide RNAs, ribozymes, aptamers, antisense RNAs, piwi-interacting RNAs (piRNAs), short interfering RNAs (siRNAs), microRNAs (miRNAs), shRNAs or recombinant U RNAs). In some aspects, a transgene sequence encodes a therapeutic protein or a recombinant protein. In some aspects, a transgene nucleotide sequence is a cDNA sequence. In some aspects, the transgene nucleotide sequence may comprise one or more introns. In other aspects, the transgene can be polycistronic (e.g., two coding regions separated by internal ribosome entry site (IRES)). In some aspects, a transgene may encode more than one protein. In some aspects, a transgene may encode more than one non-coding RNA molecule.

[2503] In one aspect, a transgene comprises a "protein coding sequence" or a sequence that encodes a particular protein or polypeptide, i.e., a nucleic acid sequence that is capable of being transcribed into mRNA and translated into a polypeptide *in vitro* or *in vivo* when placed under the control of appropriate regulatory sequences. The boundaries of the coding sequence may be determined by a start codon at the 5' terminus (N-terminus) and a translation stop nonsense codon at the 3' terminus (C-terminus). A coding sequence can include, but is not limited to, cDNA from prokaryotic or eukaryotic mRNA, genomic DNA sequences from prokaryotic or eukaryotic DNA, and synthetic nucleic acids. A transcription termination sequence will usually be located 3' to the coding sequence.

[2504] In certain aspects, a minigene cassette nucleotide sequence, as disclosed herein, may be inserted into a transgene transcription unit anywhere between the transcription initiation site and the transcription termination site or 3'-end processing sites.

[2505] In certain aspects, a minigene cassette nucleotide sequence, as disclosed herein, may be inserted downstream of the transcription initiation site (see, for example, FIG. 1B).

[2506] In one aspect, a minigene cassette nucleotide sequence may be inserted into a transgene's 5' untranslated region (FIG. 1Bi).

[2507] In one aspect, a minigene cassette nucleotide sequence may be inserted into a transgene's 3' untranslated region (FIG. 1Bii).

[2508] In one aspect, a minigene cassette nucleotide sequence may be inserted into a transgene's exon.

[2509] In one aspect, a minigene cassette nucleotide sequence may be inserted into a transgene's intron.

[2510] In one aspect, a minigene cassette nucleotide sequence may be inserted into the transgene's coding region.

[2511] In one aspect, the minigene cassette's transgene may have a coding or non-coding sequence or both a non-coding untranslated sequence and a protein coding sequence.

Exemplary Promoters

[2512] The term "promoter" or "promoter sequence" as used herein is a DNA regulatory sequence capable of facilitating transcription (e.g., capable of causing detectable levels of transcription and/or increasing the detectable level of transcription over the level provided in the absence of the promoter) of an operatively linked to a downstream (3' direction) coding or non-coding sequence. In some aspects, the promoter sequence is bounded at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements needed to initiate transcription at levels detectable above background. In some aspects, a promoter sequence may comprise a transcription initiation site, as well as binding sites for transcription factors. In addition to sequences sufficient to initiate transcription, a promoter may also include sequences of other cis-acting regulatory elements that are involved in modulating transcription (e.g., enhancers, silencers and/or insulators, such as locus control regions (LCRs) or matrix attachment regions (MARs)).

[2513] Examples of promoters known in the art that may be used in some aspects, e.g., in viral vectors disclosed herein, include constitutive promoters, e.g., unregulated promoters

that allow for the continual transcription of its associated transgene in any cell type and/or under any conditions. Examples of constitutive promoters include, but are not limited to, a human β -actin promoter, a human elongation factor-1 α promoter (Kim, D.W., Uetsuki, T., Kaziro et al.(1990) *Gene* 91, 217–223), a cytomegalovirus (CMV) promoter (Thomsen et al. (1984) *Proc. Natl. Acad. Sci. U.S.A.* 81, 659–663), a modified CMV promoter that is resistant to gene silencing (see, for example, published U.S. Patent Application No. 2014/0017726 and International PCT patent application WO2012099540, the contents of which are incorporated by reference herein in their entireties), a chicken β -actin promoter combined with cytomegalovirus early enhancer (CBA) (see, for example, U.S. Patent No. 5,770,400, the content of which is incorporated by reference herein in its entirety), a truncated chimeric CMV-chicken β -actin (smCBA) promoter (see, for example, U.S. Patent No. 8,298,818, the content of which is incorporated by reference herein in its entirety), a Cbh promoter (see, for example, Gray et al. (2011) *Human Gene Therapy* 22 (9): 1143–53, the content of which is incorporated by reference herein in its entirety); a CMVd2 promoter; an shCMV promoter; a SCP3 promoter (Even et al. (2016) *PLoS ONE* 11(2): e0148918; a PGK promoter (Gilham et al. (2010) *J. Gene Med.* 12, 129–136; a UbC promoter (Gill et al., *Gene Ther.* 8, 1539–154), an SV40 minimal promoter, an RSV promoter (Yamamoto et al.(1980) *Cell* 22, 787–797), or a murine stem cell virus (MSCV) promoter (Hawley et al. (1994) *Gene Ther.* 1, 136–138).

[2514] In addition, standard techniques are known in the art for creating functional promoters by mixing and matching known regulatory elements. Fragments of promoters, e.g., those that retain at least minimum number of bases or elements to initiate transcription at levels detectable above background, may also be used. In some aspects, a CMV enhancer may be combined with a tissue-specific promoter.

[2515] In some aspects, a promoter can be a synthetic promoter (see, for example, Jüttner et al. (2019) *Nature Neuroscience* 22 (8): 1345–56; Leeuw et al. (2016) *Molecular Brain* 9 (1): 52; Sanches-Medeiros et al. (2019) *J Med Artif. Intell.* 2:25; Wu et al. (2019) *Nature Communications* 10 (1): 2880, the contents of which are incorporated by reference herein in their entireties).

[2516] In some aspects, the promoter is tissue-specific such that, in a multi-cellular organism, the promoter drives expression only in a subset of specific cells. For example, a tissue-specific promoter is constitutively active in a connective, epithelial, muscle or nervous tissue. For example, tissue-specific promoters include, but are not limited to, neuron-

specific promoters, adipocyte-specific promoters, cardiomyocyte-specific promoters, smooth muscle-specific promoters, photoreceptor-specific promoters, etc.

[2517] A neuron-specific promoter refers to a promoter that, when administered e.g., peripherally, directly into the central nervous system (CNS), or delivered to neuronal cells, including *in vitro*, *ex vivo*, or *in vivo*, preferentially drives or regulates expression of an operatively-linked transgene in neurons as compared to expression in non-neuronal cells.

[2518] Non-limiting example of tissue-specific expression elements for neurons include neuron-specific enolase (NSE) (see, e.g., EMBL HSEN02, X51956); an aromatic amino acid decarboxylase (AADC) promoter; a neurofilament promoter (see, e.g., GenBank HUMNFL, L04147); a synapsin promoter (see, e.g., GenBank HUMSYNIB, M55301); a thy-1 promoter (see, e.g., Chen et al., (1987) Cell, 51 :7-19; Llewellyn et al. (2010) Nat. Med., 16(10):1 161-1 166); a serotonin receptor promoter (see, e.g., GenBank S62283); a tyrosine hydroxylase promoter (TH) (see, e.g., Oh et al., (2009) Gene Ther., 16:437; Sasaoka et al., (1992) Mol. Brain Res., 16:274; Boundy et al., (1998) J. Neurosci. , 18:9989; and Kaneda et al., (1991) Neuron, 6:583-594); a methyl-CpG binding protein 2 (MeCP2) promoter, an optimized methyl-CpG binding protein 2 (MeCP2) promoter (the published International Patent Application No. WO2020180928, the content of which is incorporated by reference herein in its entirety), a Ca²⁺-calmodulin-dependent protein kinase II-alpha (CaMKII α) promoter (see, e.g., Mayford et al., (1996) Proc. Natl. Acad. Sci. USA, 93:13250; and Casanova et al., (2001) Genesis, 31 :37); a GnRH promoter (see, e.g., Radovick et al., (1991) Proc. Natl. Acad. Sci. USA, 88:3402-3406); an L7 promoter (see, e.g., Oberdick et al., (1990) Science, 248:223-226); a DNMT promoter (see, e.g., Badge et al., (1988) Proc. Natl. Acad. Sci. USA, 85:3648-3652); an enkephalin promoter (see, e.g., Comb et al., (1988) EMBO J., 17:3793-3805); a myelin basic protein (MBP) promoter; a CMV enhancer/platelet-derived growth factor-p promoter (see, e.g., Liu et al., (2004) Gene Ther., 11 :52-60); and the like. In some aspects, a portion of or all the minimal human synapsin 1 promoter (SYN) can be used (Kugler et al., (2003) Gene Ther., 10(4): 337-47; Thiel et al, (1991) Proc. Natl. Acad. Sci. USA, 88(8) 3431 -5; Castle et al., (2016) Methods Mol. Biol., 1382: 133-49; McLean et al., (2014) Neurosci. Lett., 576: 73-78; Kugler et al., (2003) Virology, 311 (1): 89-95). In other aspects, the neural-specific promoter can be mGluR2, NFL, NFH, n β 2, PPE, Enk and EAAT2 promoters. A non-limiting example of a tissue-specific expression elements for astrocytes include the glial fibrillary acidic protein

(GFAP) and EAAT2 promoters. A non-limiting example of a tissue-specific expression element for oligodendrocytes include the myelin basic protein (MBP) promoter. In certain aspects, a neuronal promoter can include a neuronal enhancer to direct expression to specific regions of the brain (see, for example, published U.S. Patent Application No. 2019/0247516, the content of which is incorporated by reference herein in its entirety). In one aspect, the promoter can be a fugu SST (somatostatin) promoter (Nathanson, et al. *Frontiers in Neural Circuits* 3: 19).

[2519] Examples of retinal-specific promoters include, but are not limited to, NA65p (RPE cells), Nefh (ganglion cells), hGRK1 (rod and cone photoreceptor cells), hRLBP1 (Müller glial cells and RPE cells), human RHO (rhodopsin), human rhodopsin kinase (RHOK/GRK1) (an exemplary list of retina cell-specific promoters can be found in Buck et al. (2020) *International Journal of Molecular Sciences* 21 (12), the content of which is incorporated by reference in its entirety). Non-limiting examples of liver promoters include hAAT and TBG. Non-limiting examples of skeletal muscle promoters include Desmin, MCK and C5-12. Additional exemplary tissue-specific promoters can be found in the TiProD (Tissue specific promoter database webpage tiprod.bioinf.med.uni-goettingen.de).

[2520] In other aspects, a promoter can be an inducible promoter (i.e., a promoter whose activity is controlled by an external stimulus, e.g., the presence of a particular temperature, compound, or protein). In some aspects, a promoter may be a temporally restricted promoter that drives expression depending on the temporal context in which the promoter is found. For example, a temporally restricted promoter may drive expression only during specific stages of a biological process.

[2521] Prokaryotic (Gossen et al. *TIBS* 18: 471475, 1993) and insect regulatory systems (No et al. *Proc. Natl. Aced. Sci. USA* 93: 3346-3351, 1996) have been adapted to construct gene switches that function in mammalian cells. Since inducer molecules are not expected to have targets in mammalian cells, the possibility of interference with cellular processes is reduced. Of the prokaryotic proteins, the repressors from the lac operon (Brown, M., et al. *Cell* 49: 603-612, 1987; and Hu, M. C. -T. and N. Davidson *Cell* 48: 555-566, 1987), the tet operon (e.g., U.S. Patent No. 7,541,446, the content of which is incorporated by reference herein in its entirety) and the cumate operon (e.g., U.S. Patent No. 7,745,592, the content of which is incorporated by reference herein in its entirety) have been shown to function in mammalian cells. Many have been incorporated in eukaryotic inducible expression systems using different strategies to control activation and repression of expression. Activation of expression is

mediated by a chimeric transactivator protein formed by the fusion of the bacterial repressor with an activation domain (Gossen, M. and H. Bujard, *Proc. Natl. acad. sci. USA* 89: 5547-5551, 1992, and Gossen, M., et al. *Science* 268: 1766-1769, 1995; U.S. Patent No. 7,745,592, the contents of which are incorporated by reference herein in their entireties). The transactivator can activate transcription when bound to its DNA recognition sequence placed upstream of the minimal promoter. The ability of the activator to bind DNA is dependent on the presence/absence of the inducer molecule (e.g., doxycycline or cumate depending on the inducible system being used). Repression of expression is mediated by the repressor bound to operator sites placed downstream of the minimal promoter in the absence of inducer and repression is relieved on the addition of the inducer (Brown, M., et al. *Cell* 49: 603-612, 1987).

[2522] In one aspect, the promoter may be a promoter which is less than 1 kb. The promoter may have a length of 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800 or more than 800. The promoter may have a length between 200-300, 200-400, 200-500, 200-600, 200-700, 200-800, 300-400, 300-500, 300-600, 300-700, 300-800, 400-500, 400-600, 400-700, 400-800, 500-600, 500-700, 500-800, 600-700, 600-800 or 700-800 nucleotides.

[2523] In one aspect, the promoter can be a pol III-dependent promoter, e.g., a U6 snRNA or H1-RNA promoter, for the expression of non-coding RNAs including, but not limited to, U snRNAs or miRNAs. In another aspect, the promoter can be a polymerase II U snRNA-dependent promoter, e.g., a human U1 snRNA gene and of its promoter and terminator regions (see, for example, published U.S. Patent No. 7,947,823, the content of which is incorporated by reference herein in its entirety).

Cis-acting regulatory elements

[2524] Non-limiting examples of elements to enhance the transgene target specificity and expression include endogenous miRNAs, post-transcriptional regulatory elements (PREs), polyadenylation (polyA) sequences and 5'-UTR introns.

[2525] In one aspect, an expression vector may comprise at least one element to enhance the transgene target specificity and expression (See e.g., Powell et al. *Viral Expression Cassette Elements to Enhance Transgene Target Specificity and Expression in Gene Therapy*, 2015; the

contents of which are herein incorporated by reference in its entirety). In one aspect, the 5'-UTR may include an intron. Non-limiting examples of 5'-UTR introns include, CBA-MVM 5'-UTR intron, MVM (67-97 bps), FIX truncated intron 1 (300 bps), (β -globin SD/immunoglobulin heavy chain splice acceptor (250 bps), adenovirus splice donor/immunoglobulin splice acceptor (500 bps), SV40 late splice donor/splice acceptor (19S/16S) (180 bps) and hybrid adenovirus splice donor/IgG splice acceptor (230 bps). In one aspect, the 5'-UTR introns may be 100-500 nucleotides in length. The 5'-UTR introns may have a length of 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490 or 500.

[2526] In certain aspects, an expression vector may comprise a "post-transcriptional regulatory element" ("PRE") that can form a tertiary structure enhancing expression of an mRNA transcript. Examples of post-transcriptional regulatory element that may be used with the nucleic acid molecules and vectors disclosed herein include a PRE derived from hepatitis B (HPRE), bat (BPRE), ground squirrel (GSPRE), arctic squirrel (ASPRE), duck (DPRE), chimpanzee (CPRE) and woolly monkey (WMPRE) or woodchuck (WPRE), optionally wherein said post-transcriptional regulatory element is disposed 3' to the transgene.

[2527] WPRE is a tripartite regulatory element with gamma, alpha, and beta components. The alpha component is 80bp long:

GCCACGGCGGAACATCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGC
TGTTGGGCACTGACAATTCCGTGGT (SEQ ID NO: 64)

[2528] When used alone without the gamma and beta WPRE components, the alpha component is only 9% as active as the full tripartite WPRE. The sequence for full tripartite WPRE is:

AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTT
GCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTT
CCCGTATGGCTTTCATTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCTTTATGA
GGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGAC
GCAACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTT
TCGCTTTCCCCCTCCCTATTGCCACGGCGGAACATCATCGCCGCCTGCCTTGCCCGC
TGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTTCGGGGA

AGCTGACGTCCTTTCCATGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGG
ACGTCCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGG
CCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTC
GGATCTCCCTTTGGGCCGCCTCCCCGCCTG (SEQ ID NO: 65)

[2529] This sequence has 100% homology with base pairs 1093 to 1684 of the Woodchuck hepatitis B virus (WHV8) genome. Usually, unspliced mRNAs are exported into the cytoplasm with low efficiency. PRE cis-acting RNA elements can increase the accumulation of cytoplasmic mRNA of an intronless gene by promoting mRNA exportation from the nucleus to the cytoplasm, enhancing 3' end processing and stability.

VII. DESIGN OF SMSM COMPOUND INDUCIBLE VIRAL EXPRESSION VECTORS

[2530] A recombinant adeno associated virus or rAAV is a replication-deficient parvovirus, the single stranded DNA genome of which is about 4.7 kb in length including 145 nucleotide inverted terminal repeat (ITRs). The nucleotide sequence of the AAV serotype 2 (AAV2) genome is presented in Srivastava et al., J Virol, 45: 555-564 (1983) as corrected by Ruffing et al., J Gen Virol, 75: 3385-3392 (1994). Cis-acting sequences directing viral DNA replication (rep), encapsidation/packaging and host cell chromosome integration are contained within the ITRs. Three AAV promoters (named p5, p19, and p40 for their relative map locations) drive the expression of the two AAV internal open reading frames encoding rep and cap genes. The two rep promoters (p5 and p19), coupled with the differential splicing of the single AAV intron (at nucleotides 2107 and 2227), result in the production of four rep proteins (rep 78, rep 68, rep 52, and rep 40) from the rep gene. Rep proteins possess multiple enzymatic properties that are ultimately responsible for replicating the viral genome. The cap gene is expressed from the p40 promoter and it encodes the three capsid proteins VP1, VP2, and VP3. Alternative splicing and non-consensus translational start sites are responsible for the production of the three related capsid proteins.

[2531] As the signals directing AAV replication, genome encapsidation and integration are contained within the ITRs of the AAV genome, some, or all the internal approximately 4.3 kb of the genome (encoding replication and structural capsid proteins, rep-cap) can be replaced with foreign DNA such as an expression cassette, as disclosed herein, with the rep and cap proteins provided in trans. The sequence located between ITRs of an AAV vector genome is referred to herein as the “payload”.

[2532] The actual capacity of any AAV particle may vary depending on the viral proteins employed. Typically, the vector genome (including ITRs) is not more than about 5 kb, e.g., not more than about 4.9 kb, 4.8 kb or 4.7 kb.

[2533] The ITRs are each 145 bases in length. Thus, the payload is typically not more than about 4.7 kb, 4.6 kb, 4.5 kb or 4.4 kb in length. Preferably it is not more than 4.4 kb in length. A recombinant AAV (rAAV) may therefore contain up to about 4.7 kb, 4.6 kb, 4.5 kb or 4.4 kb of unique payload sequence.

[2534] However, following infection of a target cell, protein expression and replication from the vector requires synthesis of a complementary DNA strand to form a double stranded genome. This second strand synthesis represents a rate limiting step in transgene expression. The requirement for second strand synthesis can be avoided using so-called “self-complementary AAV” (scAAV) vectors in which the payload contains two copies of the same transgene payload in opposite orientations to one another, i.e., a first payload sequence followed by the reverse complement of that sequence. These scAAV genomes can adopt either a hairpin structure, in which the complementary payload sequences hybridize intramolecularly with each other, or a double stranded complex of two genome molecules hybridized to one another. Transgene expression from such scAAVs is much more efficient than from conventional rAAVs, but the effective payload capacity of the vector genome is halved because of the need for the genome to carry two complementary copies of the payload sequence.

[2535] An scAAV vector genome may contain one or more mutations in one of the ITR sequences to inhibit resolution at one terminal repeat, and consequently increase yield in an scAAV preparation. Thus, one of the ITRs in an scAAV may be deleted for the terminal resolution site or may contain an inactivating mutation in the terminal resolution site. See, for example, Wang et al., *Gene Therapy* (2003) 10, 2105-2111 and McCarty et al., *Gene Therapy* (2003) 10, 2112-2118. It will therefore be apparent that the two ITR sequences at either end of an AAV genome need not be identical.

[2536] scAAVs are reviewed in McCarty (2008) *Molecular Therapy*, 16(10), 1648-1656.

[2537] In this specification, the term “rAAV vector” is generally used to refer to vectors having only one copy of any given payload sequence (i.e., a rAAV vector is not an scAAV vector), and the term “AAV vector” is used to encompass both rAAV and scAAV vectors.

[2538] AAV sequences in the AAV vector genomes (e.g., ITRs) may be from any AAV serotype for which a recombinant virus can be derived including, but not limited to, AAV serotypes AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-6, AAV-7, AAV-8, AAV-9, AAV-10, AAV-11 and AAV PHP.B. The nucleotide sequences of the genomes of the AAV serotypes are known in the art. For example, the complete genome of AAV-1 is provided in GenBank Accession No. NC_002077; the complete genome of AAV-2 is provided in GenBank Accession No. NC_001401 and Srivastava et al., *J. Virol.*, 45: 555-564 (1983); the complete genome of AAV-3 is provided in GenBank Accession No. NC_1829; the complete genome of AAV-4 is provided in GenBank Accession No. NC_001829; the AAV-5 genome is provided in GenBank Accession No. AF085716; the complete genome of AAV-6 is provided in GenBank Accession No. NC_001862; at least portions of AAV-7 and AAV-8 genomes are provided in GenBank Accession Nos. AX753246 and AX753249, respectively; the AAV-9 genome is provided in Gao et al., *J. Virol.*, 78: 6381-6388 (2004); the AAV-10 genome is provided in *Mol. Ther.*, 13(1): 67-76 (2006); the AAV-11 genome is provided in *Virology*, 330(2): 375-383 (2004); AAV PHP.B is described by Deverman et al., *Nature Biotech.* 34(2), 204-209 and its sequence deposited under GenBank Accession No. KU056473.1.

[2539] Virion particles comprising vector genomes are generated in packaging cells capable of replicating viral genomes, expressing viral proteins (e.g. rep and cap proteins), and assembling virion particles. Packaging cells may also require helper virus functions, e.g. from adenovirus, El-deleted adenovirus or herpesvirus. Techniques to produce AAV vector particles in packaging cells are standard in the art. Production of pseudotyped AAV is disclosed in, for example, WO 01/83692, the content of which is incorporated by reference herein in its entirety. In various aspects, AAV capsid proteins may be modified to enhance delivery of the recombinant vector. Modifications to capsid proteins are generally known in the art (see, for example, published U.S. Patent Application Nos. US 2005/0053922 and US 2009/0202490, the contents of which are incorporated by reference herein in their entireties).

[2540] One method of generating a packaging cell is to create a cell line that stably expresses all the necessary components for AAV particle production. For example, a plasmid (or multiple plasmids) comprising an AAV genome lacking AAV rep and cap genes, AAV rep and cap genes separate from the AAV genome, and a selectable marker, such as a neomycin resistance gene, are integrated into the genome of a cell. AAV genomes have been introduced into bacterial plasmids by procedures such as GC tailing (Samulski et al., 1982, *Proc. Natl. Acad. Sci. USA*,

79:2077-2081), addition of synthetic linkers containing restriction endonuclease cleavage sites (Laughlin et al., 1983, *Gene*, 23:65-73) or by direct, blunt-end ligation (Senapathy & Carter, 1984, *J. Biol. Chem.*, 259:4661-4666). The packaging cell line is then infected with a helper virus such as adenovirus. The advantages of this method are that the cells are selectable and are suitable for large-scale production of AAV. Other examples of suitable methods employ adenovirus or baculovirus rather than plasmids to introduce AAV genomes and/or rep and cap genes into packaging cells.

[2541] Alternatively, a packaging cell can be generated by simply transforming a suitable cell with one or more plasmids encoding an AAV genome, AAV proteins, and any required helper virus functions. The so-called “triple transfection” method utilizes three plasmids each carrying one of these sets of genes. See Grieger et al., *Nature Protocols* 1(3), 1412-128 (2006) and references cited therein. General principles of AAV production are reviewed in, for example, Carter, 1992, *Current Opinions in Biotechnology*, 1533-539; and Muzyczka, 1992, *Curr. Topics in Microbial, and Immunol.*, 158:97-129). Various approaches are described in Ratschin et al., *Mol. Cell. Biol.* 4:2072 (1984); Hermonat et al., *Proc. Natl. Acad. Sci. USA*, 81:6466 (1984); Tratschin et al., *Mol. Cell. Biol.* 5:3251 (1985); McLaughlin et al., *J. Virol.*, 62:1963 (1988); and Lebkowski et al., 1988 *Mol. Cell. Biol.*, 7:349 (1988). Samulski et al. (1989, *J. Virol.*, 63:3822-3828); U.S. Pat. No. 5,173,414; WO 95/13365 and corresponding U.S. Pat. No. 5,658,776; WO 95/13392; WO 96/17947; PCT/US98/18600; WO 97/09441 (PCT/US96/14423); WO 97/08298 (PCT/US96/13872); WO 97/21825 (PCT/US96/20777); WO 97/06243 (PCT/FR96/01064); WO 99/11764; Perrin et al. (1995) *Vaccine* 13:1244-1250; Paul et al. (1993) *Human Gene Therapy* 4:609-615; Clark et al. (1996) *Gene Therapy* 3:1124-1132; U.S. Pat. Nos. 5,786,211; 5,871,982; and 6,258,595, the contents of each of which are incorporated by reference herein in their entireties.

[2542] Techniques for scAAV production are described, for example, in Grieger et al., *Molecular Therapy* 24(2), 287-297, 2016, the content of which is incorporated by reference herein in its entirety.

[2543] In one aspect packaging cells may be stably transformed cell lines such as HeLa cells, 293 cells and PerC.6 cells (a cognate 293 line). In another aspect, packaging cells are cells that are not transformed cells such as low passage 293 cells (human fetal kidney cells transformed with El of adenovirus), MRC-5 cells (human fetal fibroblasts), WI-38 cells (human fetal fibroblasts), Vero cells (monkey kidney cells) and FRhL-2 cells (rhesus fetal lung cells).

[2544] The term "recombinant virus" as used herein is intended to refer to a non-wild-type and/or an artificially produced recombinant virus (e.g., a parvovirus, adenovirus, lentivirus or adeno-associated virus etc.) that comprises a transgene or other heterologous nucleic acid. The recombinant virus may comprise a recombinant viral genome (e.g. comprising a minigene cassette as described herein and a transgene) packaged within a viral (e.g.: AAV) capsid.

[2545] In one aspect, a rAAV vector, including an rAAV vector genome as described herein, comprises at least one synthetic AAV ITR, wherein one or more CpG islands (a cytosine base followed immediately by a guanine base (a CpG) in which the cytosines in such arrangement tend to be methylated) that typically occur at, or near the transcription start site in an ITR are deleted and/or substituted. In one aspect, deletion, or reduction in the number of CpG islands can reduce the immunogenicity of the rAAV vector. This results from a reduction or complete inhibition in TLR-9 binding to the rAAV vector DNA sequence, which occurs at CpG islands. It is also well known that methylation of CpG motifs results in transcriptional silencing. Removal of CpG motifs in the ITR is expected to result in decreased TLR-9 recognition and/or decreased methylation and therefore decreased transgene silencing. In some aspects, it is the minimal functional ITR in which one or more CpG islands are deleted and/or substituted. In one aspect, AAV ITR2 is known to contain 16 CpG islands of which one or more, or all 16 can be deleted.

[2546] In some aspects, at least 1 CpG motif is deleted and/or substituted, e.g., at least 4 or more or 8 or more CpG motifs, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 CpG motifs. The phrase "deleted and/or substituted" as used herein means that one or both nucleotides in the CpG motif is deleted, substituted with a different nucleotide, or any combination of deletions and substitutions.

[2547] In certain aspects, the transgene nucleic acid sequence can also be codon optimized to enhance expression *in vivo* and/or to reduce the number of CpG islands and avoid an innate immune response to the vector.

VIII. PHARMACEUTICAL COMPOSITIONS AND MODES OF ADMINISTRATION

SMSM Compound Administration in vitro

[2548] In certain aspects described herein, cell(s) or a tissue sample, comprising an SMSM compound responsive expression vector, may be contacted with an SMSM compound, or a DMSO negative control for a period of 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 12 hours, 18 hours, 24 hours, 48 hours, 72 hours or longer. In other aspects described herein, cell(s) or tissue sample can be contacted or cultured with an SMSM compound or a negative control for a period of 15 minutes to 1 hour, 1 to 2 hours, 2 to 4 hours, 6 to 12 hours, 12 to 18 hours, 12 to 24 hours, 28 to 24 hours, 24 to 48 hours, 48 to 72 hours.

[2549] In certain aspects described herein, the cell(s) or a tissue sample, comprising an SMSM compound responsive expression vector, can be contacted, or cultured with an SMSM compound at a concentration of 0.0001 μ M, 0.0003 μ M, 0.001 μ M, 0.003 μ M, 0.01 μ M, 0.5 μ M, 1 μ M, 2 μ M, 5 μ M, 10 μ M, 15 μ M, 20 μ M, 25 μ M, 50 μ M, 75 μ M, 100 μ M, or 150 μ M.

[2550] In other aspects described herein, the cell(s) or a tissue sample, comprising an SMSM compound responsive expression vector, can be contacted, or cultured with a certain concentration of an SMSM compound, wherein the certain concentration is about 0.0001 μ M, 0.0003 μ M, 0.0005 μ M, 0.001 μ M, 0.003 μ M, 0.005 μ M, 0.01 μ M, 0.3 μ M, 0.5 μ M, 0.1 μ M, 0.3 μ M, 0.5 μ M or 1 μ M.

[2551] In other aspects described herein, the cell(s) or a tissue sample, comprising an SMSM compound responsive expression vector, can be contacted, or cultured with a certain concentration of an SMSM compound, wherein the certain concentration is about 175 μ M, 200 μ M, 250 μ M, 275 μ M, 300 μ M, 350 μ M, 400 μ M, 450 μ M, 500 μ M, 550 μ M, 600 μ M, 650 μ M, 700 μ M, 750 μ M, 800 μ M, 850 μ M, 900 μ M, 950 μ M or 1 mM. In some aspects described herein, the cell(s) or a tissue sample, comprising an SMSM compound responsive expression vector, can be contacted or cultured with a certain concentration of an SMSM compound, wherein the certain concentration is about 5 nM, 10 nM, 20 nM, 24nM, 30 nM, 40 nM, 50 nM, 60 nM, 70 nM, 80 nM, 90 nM, 100 nM, 150 nM, 200 nM, 250 nM, 300 nM, 350 nM, 400 nM, 450 nM, 500 nM, 550 nM, 600 nM, 650 nM, 700 nM, 750 nM, 800 nM, 850 nM, 900 nM, or 950 nM. In certain aspects described herein, the cell(s) or a tissue sample, comprising an SMSM compound responsive expression vector, can be contacted or cultured with a certain

concentration of an SMSM compound, wherein the certain concentration is between 0.0001 μM to 0.001 μM , 0.0001 μM to 0.01 μM , 0.0003 μM to 0.001 μM , 0.0003 μM to 0.01 μM , 0.001 μM to 0.01 μM , 0.003 μM to 0.01 μM , 0.01 μM to 0.1 μM , 0.1 μM to 1 μM , 1 μM to 50 μM , 50 μM to 100 μM , 100 μM to 500 μM , 500 μM to 1 nM, 1 nM to 10 nM, 10 nM to 50 nM, 50 nM to 100 nM, 100 nM to 500 nM, 500 nM to 1000 nM.

[2552] In another aspect, provided herein is a method for determining whether an SMSM compound modulates the amount of a minigene-containing RNA transcript (e.g., an mRNA transcript), comprising: (a) administering an SMSM compound to a subject (in certain aspects, a non-human animal); and (b) determining the amount of the minigene-containing RNA transcript in a sample obtained from the subject, wherein modulation in the amount of the RNA transcript measured in the sample from the subject administered the SMSM compound, or form thereof, relative to the amount of the RNA transcript in a sample from the subject prior to administration of the SMSM compound, or form thereof, or a sample from a different subject from the same species not administered the SMSM compound, or form thereof, indicates that the SMSM compound modulates the amount of the RNA transcript.

[2553] In another aspect, provided herein is a method for determining whether an SMSM compound modulates the splicing of an minigene-containing RNA transcript (e.g., an mRNA transcript) in a subject, comprising: (a) administering an SMSM compound to a subject expressing a minigene-containing RNA transcript (in certain aspects, a non-human animal); and (b) determining the amount of two or more minigene-containing RNA transcript splice variants in a sample obtained from the subject, wherein modulation in the amount of the two or more minigene-containing RNA transcript splice variants measured in the sample from the subject administered the SMSM compound, or form thereof, relative to the amount of the two or more RNA transcript minigene-containing splice variants in a sample from the subject prior to administration of the SMSM compound, or form thereof, indicates that the SMSM compound, or form thereof, modulates the splicing of the minigene-containing RNA transcript.

[2554] In another aspects, provided herein is a method for determining whether an SMSM compound modulates the splicing of an minigene-containing RNA transcript (e.g., an mRNA transcript), comprising: (a) administering an SMSM compound to a first subject expressing a minigene-containing RNA transcript (in certain aspects, a non-human animal); (b) administering a negative control (e.g., a pharmaceutical carrier) to a second subject expressing the minigene-containing RNA transcript (in certain aspects, a non-human animal) of the same

species as the first subject; (c) determining the amount of two or more minigene-containing RNA transcript splice variants in a first tissue sample from the first subject and the amount of two or more minigene-containing RNA transcript splice variants in the second tissue sample from the second subject; and (d) comparing the amount of the two or more RNA transcript splice variants in the first tissue sample to the amount of the two or more RNA transcript splice variants in the second tissue sample, wherein modulation in the amount of the two or more RNA transcript splice variants in the first tissue sample relative to the amount of the two or more RNA transcript splice variants in the second tissue sample indicates the SMSM compound, or form thereof, modulates the splicing of the minigene-containing RNA transcript.

[2555] Techniques known to one skilled in the art may be used to determine the amount of a minigene-containing RNA transcript(s). In some aspects, the amount of one, two, three or more RNA transcripts can be measured using deep sequencing, such as ILLUMINA® RNASeq, ILLUMINA® next generation sequencing (NGS), ION TORRENT™ RNA next generation sequencing, 454™ pyrosequencing, or Sequencing by Oligo Ligation Detection (SOLID™), Single Molecule, Real-Time (SMRT) sequencing, and Nanopore sequencing. In certain aspects, the amount of one, two, three or more minigene-containing RNA transcripts can be determined by RT-PCR. In other aspects, the amount of one, two, three or more minigene-containing RNA transcripts can be measured by RT-qPCR or digital color-coded barcode technology. Techniques for conducting these assays are known to one skilled in the art.

[2556] In some aspects, analysis can be performed on data derived from the assay to measure the magnitude of splicing to determine the number of exons spliced into a minigene-containing mRNA transcript that is produced in the presence of an SMSM compound relative to the amount in the absence of SMSM compound or presence of a negative control. In a preferred aspect, the method utilized is calculation of change in Percent Spliced In (Δ PSI) as described herein under section IV.

[2557] In some aspects, a statistical analysis or other probability analysis is performed on data from the assay utilized to measure a minigene-containing RNA transcript. In certain aspects, for example, a Fisher's Exact Test statistical analysis is performed by comparing the total number of reads for the inclusion and exclusion of a pseudoexon (or region) based on data from one or more assays used to measure whether the amount of a minigene-containing RNA transcript is modulated in the presence of an SMSM compound relative to the amount in the absence of an SMSM compound or presence of a negative control. In specific aspects, the

statistical analysis results in a confidence value for those modulated minigene-containing RNA transcripts of 10%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.01%, 0.001% or 0.0001%. In some specific aspects, the confidence value is a p value for those modulated minigene-containing RNA transcripts of 10%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.01%, 0.001% or 0.0001%. In certain specific aspects, an exact test, student t-test or p value for those modulated minigene-containing RNA transcripts is 10%, 5%, 4%, 3%, 2%, 1%, 0.5% or 0.1% and 10%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.01%, 0.001% or 0.0001%, respectively.

[2558] In certain aspects, a further analysis is performed to determine how an SMSM compound can change the amount of a minigene-containing RNA transcript(s). In specific aspects, a further analysis is performed to determine if modulation in the amount of a minigene-containing RNA transcript(s) in the presence of an SMSM compound relative the amount of the RNA transcript(s) in the absence of the SMSM compound, or a form thereof, or the presence of a negative control, is due to changes in transcription, splicing, and/or stability of the RNA transcript(s). Techniques known to one skilled in the art may be used to determine whether an SMSM compound changes, e.g., the transcription, splicing and/or stability of an RNA transcript(s).

[2559] In certain aspects, the stability of one or more minigene-containing RNA transcripts is determined by serial analysis of gene expression (SAGE), differential display analysis (DD), RNA arbitrary primer (RAP)-PCR, restriction endonuclease-lytic analysis of differentially expressed sequences (READS), amplified restriction fragment-length polymorphism (ALFP), total gene expression analysis (TOGA), RT-PCR, RT-RPA (recombinase polymerase amplification), RT-qPCR, RNA-Seq, digital color-coded barcode technology, high-density cDNA filter hybridization analysis (HDFCA), suppression subtractive hybridization (SSH), differential screening (DS), cDNA arrays, oligonucleotide chips, or tissue microarrays. In other aspects, the stability of one or more minigene-containing RNA transcripts can also be determined by Northern blot, RNase protection, or slot blot.

[2560] In some aspects, the transcription in a cell(s) or tissue sample is inhibited before (e.g., 5 minutes, 10 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, or 72 hours before) or after (e.g., 5 minutes, 10 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, or 72 hours) the cell or the tissue sample is contacted or cultured with an inhibitor of transcription, such as α -amanitin, DRB, flavopiridol, triptolide, or actinomycin-D. In other

aspects, the transcription in a cell(s) or tissue sample is inhibited with an inhibitor of transcription, such as α -amanitin, DRB, flavopiridol, triptolide, or actinomycin-D, while the cell(s) or tissue sample is contacted or cultured with an SMSM compound.

[2561] In certain aspects, the level of transcription of one or more minigene-containing RNA transcripts is determined by nuclear run-on assay or an *in vitro* transcription initiation and elongation assay. In some aspects, the detection of transcription is based on measuring radioactivity or fluorescence. In some aspects, a PCR-based amplification step is used.

[2562] In certain aspects, an SMSM compound can enhance SION transgene expression *in vitro* by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, about 100%, about 105%, about 110%, about 115%, about 120%, about 125%, about 130%, about 135%, about 140%, about 145% or about 150% or more of transgene expression from a CMV SION transgene expression vector.

[2563] In certain aspects, an SMSM compound can enhance SION transgene expression *in vitro* by about 2 fold, about 3 fold, about 4 fold, about 5 fold, about 6 fold, about 7 fold, about 8 fold, about 9 fold, about 10 fold, about 11 fold, about 12 fold, about 13 fold, about 14 fold, about 15 fold, about 16 fold, about 17 fold, about 18 fold, about 19 fold, about 20 fold, about 21 fold, about 22 fold, about 23 fold, about 24 fold, about 25 fold, about 26 fold, about 27 fold, about 28 fold, about 29 fold, about 30 fold, about 31 fold, about 32 fold, about 33 fold, about 34 fold, about 35 fold, about 36 fold, about 37 fold, about 38 fold, about 39 fold, about 40 fold, about 41 fold, about 42 fold, about 43 fold, about 44 fold, about 45 fold, about 46 fold, about 47 fold, about 48 fold, about 49 fold, about 50 fold, about 51 fold, about 52 fold, about 53 fold,

about 54 fold, about 55 fold, about 56 fold, about 57 fold, about 58 fold, about 59 fold, about 60 fold, about 61 fold, about 62 fold, about 63 fold, about 64 fold, about 65 fold, about 66 fold, about 67 fold, about 68 fold, about 69 fold, about 70 fold, about 71 fold, about 72 fold, about 73 fold, about 74 fold, about 75 fold, about 76 fold, about 77 fold, about 78 fold, about 79 fold, about 80 fold, about 81 fold, about 82 fold, about 83 fold, about 84 fold, about 85 fold, about 86 fold, about 87 fold, about 88 fold, about 89 fold, about 90 fold, about 91 fold, about 92 fold, about 93 fold, about 94 fold, about 95 fold, about 96 fold, about 97 fold, about 98 fold, about 99 fold, about 100 over SION transgene expression observed in the presence of DMSO.

[2564] In certain aspects, an SMSM compound can decrease SIOFF transgene expression *in vitro* to about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% of the transgene expression of a CMV transgene expression vector.

Minigene-containing expression vector administration in vivo

[2565] In one aspect, the SMSM compound inducible expression vectors described herein may be delivered to a target site by a viral or a non-viral vector.

[2566] As it is well known in the art, a vector is a tool that allows or facilitates the transfer of an entity from one environment to another. By way of example, some vectors used in recombinant DNA techniques allow entities, such as a segment of DNA (such as a heterologous DNA segment, such as a heterologous cDNA segment), to be transferred into a target cell. Optionally, once within the target cell, the vector may then serve to maintain the heterologous

DNA within the cell. Examples of vectors used in recombinant DNA techniques include plasmids, chromosomes, artificial chromosomes, or viruses.

[2567] Non-viral delivery systems include but are not limited to DNA transfection methods. Here, transfection includes a process using a non-viral vector to deliver a gene to a target mammalian cell. Typical transfection methods include electroporation, DNA biolistics, lipid-mediated transfection, compacted DNA-mediated transfection, liposomes, immunoliposomes, lipofectin, cationic agent-mediated, cationic facial amphiphiles (CFAs) (Nature Biotechnology 1996 14; 556), and combinations thereof.

[2568] Viral delivery systems include but are not limited to adenovirus vector, an adeno-associated viral (AAV) vector, a herpes viral vector, retroviral vector, lentiviral vector, baculoviral vector. Other examples of vectors include ex vivo delivery systems, which include but are not limited to DNA transfection methods such as electroporation, DNA biolistics, lipid-mediated transfection, compacted DNA-mediated transfection.

[2569] For gene therapy applications, the expression vectors disclosed herein can be incorporated into a non-replicating viral vector, for example, an adeno-associated virus (AAV).

[2570] In certain aspects, the rAAV vectors and/or rAAV genome as disclosed herein can be formulated in a solvent, emulsion, or other diluent in an amount sufficient to obtain a desired titer of an rAAV vector disclosed herein. In other aspects, the rAAV vectors and/or rAAV genome as disclosed herein may be formulated in a solvent, emulsion or a diluent in an amount of, e.g., less than about 90% (v/v), less than about 80% (v/v), less than about 70% (v/v), less than about 65% (v/v), less than about 60% (v/v), less than about 55% (v/v), less than about 50% (v/v), less than about 45% (v/v), less than about 40% (v/v), less than about 35% (v/v), less than about 30% (v/v), less than about 25% (v/v), less than about 20% (v/v), less than about 15% (v/v), less than about 10% (v/v), less than about 5% (v/v), or less than about 1% (v/v). In other aspects, the rAAV vectors and/or rAAV genome as disclosed herein can disclosed herein may comprise a solvent, emulsion or other diluent in an amount in a range of, e.g., about 1% (v/v) to 90% (v/v), about 1% (v/v) to 70% (v/v), about 1% (v/v) to 60% (v/v), about 1% (v/v) to 50% (v/v), about 1% (v/v) to 40% (v/v), about 1% (v/v) to 30% (v/v), about 1% (v/v) to 20% (v/v), about 1% (v/v) to 10% (v/v), about 2% (v/v) to 50% (v/v), about 2% (v/v) to 40% (v/v), about 2% (v/v) to 30% (v/v), about 2% (v/v) to 20% (v/v), about 2% (v/v) to 10% (v/v), about 4% (v/v) to 50% (v/v), about 4% (v/v) to 40% (v/v), about 4% (v/v) to 30% (v/v), about 4% (v/v) to 20% (v/v), about 4% (v/v) to 10% (v/v), about 6% (v/v) to 50% (v/v), about 6% (v/v)

to 40% (v/v), about 6% (v/v) to 30% (v/v), about 6% (v/v) to 20% (v/v), about 6% (v/v) to 10% (v/v), about 8% (v/v) to 50% (v/v), about 8% (v/v) to 40% (v/v), about 8% (v/v) to 30% (v/v), about 8% (v/v) to 20% (v/v), about 8% (v/v) to 15% (v/v), or about 8% (v/v) to 12% (v/v).

[2571] A viral composition may optionally comprise a pharmaceutically acceptable carrier, diluent, excipient, or adjuvant. The choice of pharmaceutical carrier, excipient or diluent can be selected regarding the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as - or in addition to - the carrier, excipient, or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilizing agent(s), and other carrier agents that may aid or increase the viral entry into the target site (such as for example a lipid delivery system).

[2572] In certain aspects, the pharmaceutically acceptable excipient is 1×PBS, (e.g., 0.154M NaCl, 0.056M Na₂HPO₄, and 0.0106 M KH₂PO₄) or DPBS (e.g., 0.337M NaCl, 0.27 M KCl, 0.015M Na₂HPO₄, and 0.0015M KH₂PO₄).

[2573] In certain aspects, the viral vector is present at a concentration of 2.5×10^1 vg/ml, 7.5×10^{11} vg/ml, or 2.5×10^{12} vg/ml.

[2574] In certain aspects, the pH of the composition is 6.5 to 7.5; 7.0 to 7.5; 6.8 to 7.2. In some aspects, the pH of the composition is 7.0 or 7.4.

[2575] The composition may further comprise empty capsids at a percentage of about 95% cp/cp, 90% cp/cp, 85% cp/cp, 80% cp/cp, 75% cp/cp, 70% cp/cp, 65% cp/cp, 60% cp/cp, 55% cp/cp, 50% cp/cp, 45% cp/cp, 40% cp/cp, 35% cp/cp, 30% cp/cp, 25% cp/cp, 20% cp/cp, 15% cp/cp, 10% cp/cp, 5% cp/cp or less.

[2576] For example, a conventional syringe and needle can be used to inject a rAAV virion suspension into a subject. Parenteral administration of rAAV vectors, by injection can be performed, for example, by bolus injection or continuous infusion, intracavernosally, intravenously, intramuscularly or subcutaneously. Formulations for injection may be presented in unit dosage form, for example, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain agents for a pharmaceutical formulation, such as suspending, stabilizing and/or dispersing agents or enough salts or monosaccharides to make the solution isotonic with blood. Alternatively, the rAAV vectors and/or rAAV genome as

disclosed herein can be in powder form (e.g., lyophilized) for constitution with a suitable vehicle, for example, sterile pyrogen-free water, before use.

[2577] For example, administration to skeletal muscle includes, but is not limited to, administration to skeletal muscle in the limbs (e.g., upper arm, lower arm, upper leg, and/or lower leg), back, neck, head (e.g., tongue), thorax, abdomen, pelvis/perineum, and/or digits. Administration to cardiac muscle includes administration to the left atrium, right atrium, left ventricle, right ventricle and/or septum. The virus vector and/or capsid can be delivered to cardiac muscle by intravenous administration, intra-arterial administration such as intra-aortic administration, direct cardiac injection (e.g., into left atrium, right atrium, left ventricle, right ventricle), and/or coronary artery perfusion. Administration to a diaphragm muscle can be by any suitable method including intravenous administration, intra-arterial administration, and/or intra-peritoneal administration.

[2578] Alternatively, one may administer the virus vector and/or virus capsids disclosed herein in a local rather than systemic manner, for example, in a bolus or sustained-release formulation. Further, the virus vector and/or virus capsid can be delivered adhered to a surgically implantable matrix (see, for example, published U.S. Patent Application No. 2004/0013645, the content of which is incorporated by reference herein in its entirety). The virus vectors and/or virus capsids disclosed herein can be administered to the lungs of a subject by any suitable means, optionally by administering an aerosol suspension of respirable particles comprised of the virus vectors and/or virus capsids, which the subject inhales. The respirable particles can be liquid or solid. Aerosols of liquid particles comprising the virus vectors and/or virus capsids may be produced by any suitable means, such as with a pressure-driven aerosol nebulizer or an ultrasonic nebulizer, as is known to those of skill in the art. See, e.g., U.S. Patent No. 4,501,729, the content of which is incorporated by reference herein in its entirety). Aerosols of solid particles comprising the virus vectors and/or capsids may likewise be produced with any solid particulate medicament aerosol generator, by techniques known in the pharmaceutical art.

[2579] In one aspect, a pharmaceutical formulation comprising a viral vector as disclosed herein, having an SMSM compound inducible viral expression vector and a pharmaceutically-acceptable excipient to at least one target site in the CNS of the subject in a dose of at least about 1×10^9 vg, 1×10^{10} vg, 1×10^{11} vg, or 1×10^{12} vg, or more. In some aspects, the dose is at least about 1×10^{13} vg, 5×10^{13} vg, 1.5×10^{14} vg, or 5×10^{14} vg.

[2580] In certain aspects, the target site is the cerebrospinal fluid (CSF) space (e.g., lumbar puncture); sub-arachnoid space, (e.g., cisterna magna); brain, (e.g., cerebroventricular space, cerebellum, cerebrum, hippocampus, interior cortex, dorsal root ganglion, or caudate nucleus); or the spine (e.g., the lumbar spine, thoracic spine, cervical spine). In some aspects, the active ingredient is delivered in two injections: one in the right cerebellum and one in the left cerebellum. In some aspects, these are two equal injections. In some aspects, the active ingredient is administered by injecting the cerebellum and providing it systemically.

[2581] In certain aspects, the pharmaceutical formulation may be administered intraparenchymally, intrathecally, intracerebroventricularly, intracisternally, systemically or a combination of these. In some aspects, the pharmaceutical formulation is administered by intrathecally in equal portions to the cisterna magna and the lumbar spine.

[2582] In some aspects, the dose is an amount of at least 3.7×10^{10} vg/g, 1.11×10^{11} vg/g, or 3.7×10^{11} vg/g on a brain weight basis. In some aspects, the pharmaceutical formulation comprises a vector concentration of at least 2×10^{12} vg/ml, 7×10^{12} vg/ml, or 2×10^{13} vg/ml.

[2583] In some aspects, the dose is an amount of about 1×10^{11} vg/g, 2×10^{11} vg/g, 3×10^{11} vg/g, 4×10^{11} vg/g, 5×10^{11} vg/g, 6×10^{11} vg/g, 7×10^{11} vg/g, 8×10^{11} vg/g, 9×10^{11} vg/g, 1×10^{12} vg/g, 2×10^{12} vg/g, 3×10^{12} vg/g, 4×10^{12} vg/g, 5×10^{12} vg/g, 6×10^{12} vg/g, 7×10^{12} vg/g, 8×10^{12} vg/g, 9×10^{12} vg/g, 1×10^{13} vg/g, 2×10^{13} vg/g, 3×10^{13} vg/g, 4×10^{13} vg/g, 5×10^{13} vg/g, 6×10^{13} vg/g, 7×10^{13} vg/g, 8×10^{13} vg/g, 9×10^{13} vg/g, 1×10^{14} vg/g.

[2584] In some aspects of the method, the pharmaceutical formulation can be administered as a single bolus injection of about 0.1 ml, 0.2 ml, 0.3 ml, 0.4 ml, 0.5 ml, 0.6 ml, 0.7 ml, 0.8 ml, 0.9 ml, 1 ml, 2 ml, 3 ml, 4 ml, or 5 ml. In other aspects, the pharmaceutical formulation is delivered as an infusion at a rate of 0.001 ml/min to 1 ml/min, (e.g., 0.01 ml/min).

[2585] In certain aspects, more than one administration (e.g., two, three, four, five, six, seven, eight, nine, 10, etc., or more administrations) may be employed to achieve the desired level of gene expression over a period of various intervals, e.g., hourly, daily, weekly, monthly, yearly, etc. Dosing can be single dosage or cumulative (serial dosing), and can be readily determined by one skilled in the art. For instance, treatment of a disease or disorder may comprise a one-time administration of an effective dose of a pharmaceutical composition virus vector disclosed herein. Alternatively, treatment of a disease or disorder may comprise multiple administrations

of an effective dose of a virus vector carried out over a range of time periods, such as, e.g., once daily, twice daily, trice daily, once every few days, or once weekly. In certain aspects, rAAV particles may be administered to multiple locations, for example, 1, 2, 3, 4, or 5 location simultaneously or staggered over time.

[2586] The timing of administration can vary from individual to individual, depending upon such factors as the severity of an individual's symptoms. For example, an effective dose of a virus vector disclosed herein can be administered to an individual once every six months for an indefinite period, or until the individual no longer requires therapy. A person of ordinary skill in the art will recognize that the condition of the individual can be monitored throughout the course of treatment and that the effective amount of a virus vector disclosed herein that is administered can be adjusted accordingly.

SMSM Compound administration in vivo

[2587] In certain aspects, an SMSM compound can be administered to a subject about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days after injection of the SMSM compound inducible AAV viral vector.

[2588] When administered to a patient, an SMSM compound is preferably administered as a component of a composition that optionally comprises a pharmaceutically acceptable carrier, excipient or diluent. The composition can be administered orally, or by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal, and intestinal mucosa) and may be administered together with another biologically active agent. Administration can be systemic or local. Various delivery systems are known, e.g., encapsulation in liposomes, microparticles, microcapsules, capsules, and can be used to administer the compound.

[2589] In a specific aspect and in this context, the term “pharmaceutically acceptable carrier, excipient or diluent” means a carrier, excipient or diluent approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term “carrier” refers to a diluent, adjuvant (e.g., Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which a therapeutic agent is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the

like. Water is a specific carrier for intravenously administered pharmaceutical compositions. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions.

[2590] Typical compositions and dosage forms comprise one or more excipients. Suitable excipients are well-known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient and the specific active ingredients in the dosage form. Further provided herein are anhydrous pharmaceutical compositions and dosage forms comprising an SMSM compound as described herein. The compositions and single unit dosage forms can take the form of solutions or syrups (optionally with a flavoring agent), suspensions (optionally with a flavoring agent), emulsions, tablets (*e.g.*, chewable tablets), pills, capsules, granules, powder (optionally for reconstitution), taste-masked or sustained-release formulations and the like.

[2591] Pharmaceutical compositions provided herein that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets, caplets, capsules, granules, powder, and liquids. Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art.

[2592] Examples of excipients that can be used in oral dosage forms provided herein include, but are not limited to, binders, fillers, disintegrants, and lubricants.

[2593] Methods of administration include, but are not limited to, parenteral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intranasal, intraocular, intratumoral, intracerebral, intravaginal, transdermal, ocularly, rectally, by inhalation, or topically, particularly to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the practitioner. In most instances, administration will result in the release of a compound into the bloodstream, tissue, or cell(s). In a specific aspect, a compound is administered orally.

[2594] The amount of SMSM compound that will be effective at regulating transgene expression depends, *e.g.*, on the route of administration, the disease being treated, the general health of the subject, ethnicity, age, weight, and gender of the subject, diet, time, and the severity of disease progress, and should be decided according to the judgment of the practitioner and each patient's or subject's circumstances.

[2595] In specific aspects, an "effective amount" in the context of the administration of an SMSM compound, or composition or medicament thereof refers to an amount of SMSM compound administered to a patient that is sufficient to induce SION transgene expression and have a therapeutic effect and/or beneficial effect in the patient being treated. In certain specific aspects, an "effective amount" in the context of the administration of SMSM compound and SMSM compound inducible transgene expression, or composition or medicament thereof to a patient results in one, two or more of the following effects: (i) reduces or ameliorates the severity of a disease; (ii) delays onset of a disease; (iii) inhibits the progression of a disease; (iv) reduces hospitalization of a subject; (v) reduces hospitalization length for a subject; (vi) increases the survival of a subject; (vii) improves the quality of life of a subject; (viii) reduces the number of symptoms associated with a disease; (ix) reduces or ameliorates the severity of a symptom(s) associated with a disease; (x) reduces the duration of a symptom associated with a disease associated; (xi) prevents the recurrence of a symptom associated with a disease; (xii) inhibits the development or onset of a symptom of a disease; and/or (xiii) inhibits of the progression of a symptom associated with a disease. In certain aspects, an effective amount of an SMSM compound is an optimal amount effective at inducing SION transgene expression in the patient being treated.

[2596] Non-limiting examples of effective amounts of an SMSM compound are described herein. For example, the effective amount may be the amount required to sustain transgene expression from an SMSM compound inducible viral vector that can prevent and/or treat a disease in a human subject.

[2597] In general, the effective amount will be in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day for a patient having a weight in a range of between about 1 kg to about 200 kg. The typical adult subject is expected to have a median weight in a range of between about 70 and about 100 kg.

[2598] Within the scope of the present description, the "effective amount" of an SMSM compound for use in the manufacture of a medicament, the preparation of a pharmaceutical kit

or in a method for preventing and/or treating a disease in a human subject in need thereof, is intended to include an amount in a range of from about 0.001 mg to about 35,000 mg.

[2599] In one aspect, the dose of an SMSM compound administered to achieve an effective target plasma concentration may be administered based upon subject or patient specific factors, wherein the doses administered on a weight basis may be in the range of from about 0.001 mg/kg/day to about 3500 mg/kg/day, or about 0.001 mg/kg/day to about 3000 mg/kg/day, or about 0.001 mg/kg/day to about 2500 mg/kg/day, or about 0.001 mg/kg/day to about 2000 mg/kg/day, or about 0.001 mg/kg/day to about 1500 mg/kg/day, or about 0.001 mg/kg/day to about 1000 mg/kg/day, or about 0.001 mg/kg/day to about 500 mg/kg/day, or about 0.001 mg/kg/day to about 250 mg/kg/day, or about 0.001 mg/kg/day to about 200 mg/kg/day, or about 0.001 mg/kg/day to about 150 mg/kg/day, or about 0.001 mg/kg/day to about 100 mg/kg/day, or about 0.001 mg/kg/day to about 75 mg/kg/day, or about 0.001 mg/kg/day to about 50 mg/kg/day, or about 0.001 mg/kg/day to about 25 mg/kg/day, or about 0.001 mg/kg/day to about 10 mg/kg/day, or about 0.001 mg/kg/day to about 5 mg/kg/day, or about 0.001 mg/kg/day to about 1 mg/kg/day, or about 0.001 mg/kg/day to about 0.5 mg/kg/day, or about 0.001 mg/kg/day to about 0.1 mg/kg/day, or from about 0.01 mg/kg/day to about 3500 mg/kg/day, or about 0.01 mg/kg/day to about 3000 mg/kg/day, or about 0.01 mg/kg/day to about 2500 mg/kg/day, or about 0.01 mg/kg/day to about 2000 mg/kg/day, or about 0.01 mg/kg/day to about 1500 mg/kg/day, or about 0.01 mg/kg/day to about 1000 mg/kg/day, or about 0.01 mg/kg/day to about 500 mg/kg/day, or about 0.01 mg/kg/day to about 250 mg/kg/day, or about 0.01 mg/kg/day to about 200 mg/kg/day, or about 0.01 mg/kg/day to about 150 mg/kg/day, or about 0.01 mg/kg/day to about 100 mg/kg/day, or about 0.01 mg/kg/day to about 75 mg/kg/day, or about 0.01 mg/kg/day to about 50 mg/kg/day, or about 0.01 mg/kg/day to about 25 mg/kg/day, or about 0.01 mg/kg/day to about 10 mg/kg/day, or about 0.01 mg/kg/day to about 5 mg/kg/day, or about 0.01 mg/kg/day to about 1 mg/kg/day, or about 0.01 mg/kg/day to about 0.5 mg/kg/day, or about 0.01 mg/kg/day to about 0.1 mg/kg/day, or from about 0.1 mg/kg/day to about 3500 mg/kg/day, or about 0.1 mg/kg/day to about 3000 mg/kg/day, or about 0.1 mg/kg/day to about 2500 mg/kg/day, or about 0.1 mg/kg/day to about 2000 mg/kg/day, or about 0.1 mg/kg/day to about 1500 mg/kg/day, or about 0.1 mg/kg/day to about 1000 mg/kg/day, or about 0.1 mg/kg/day to about 500 mg/kg/day, or about 0.1 mg/kg/day to about 250 mg/kg/day, or about 0.1 mg/kg/day to about 200 mg/kg/day, or about 0.1 mg/kg/day to about 150 mg/kg/day, or about 0.1 mg/kg/day to about 100 mg/kg/day, or about 0.1 mg/kg/day to about 75 mg/kg/day, or about 0.1 mg/kg/day to about 50 mg/kg/day, or about 0.1 mg/kg/day to about

25 mg/kg/day, or about 0.1 mg/kg/day to about 10 mg/kg/day, or about 0.1 mg/kg/day to about 5 mg/kg/day, or about 0.1 mg/kg/day to about 1 mg/kg/day, or about 0.1 mg/kg/day to about 0.5 mg/kg/day.

[2600] Effective amounts for a given subject may be determined by routine experimentation that is within the skill and judgment of a clinician or a practitioner skilled in the art in light of factors related to the subject. Dosage and administration may be adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect without toxicity from transgene overexpression. Factors which may be considered include genetic screening, severity of the disease state, status of disease progression, general health of the subject, ethnicity, age, weight, gender, diet, time of day and frequency of administration, drug combination(s), reaction sensitivities, experience with other therapies, and tolerance/response to therapy.

[2601] The dose of an SMSM compound administered to achieve an effective target plasma concentration may be orally administered once (once in approximately a 24 hour period; i.e., “q.d.”), twice (once in approximately a 12 hour period; i.e., “b.i.d.” or “q.12h”), thrice (once in approximately an 8 hour period; i.e., “t.i.d.” or “q.8h”), or four times (once in approximately a 6 hour period; i.e., “q.d.s.”, “q.i.d.” or “q.6h”) daily.

[2602] In certain aspects, the dose administered to achieve an effective target plasma concentration may also be administered in a single, divided, or continuous dose for a patient or subject having a weight in a range of between about 40 to about 200 kg (which dose may be adjusted for patients or subjects above or below this range, particularly children under 40 kg).

[2603] The typical adult subject is expected to have a median weight in a range of about 70 kg. Long-acting pharmaceutical compositions may be administered every 2, 3 or 4 days, once every week, or once every two weeks depending on half-life and clearance rate of the formulation.

[2604] In certain aspects, an SMSM compound can enhance SION transgene expression *in vivo* by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%,

about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, about 100%, about 105%, about 110%, about 115%, about 120%, about 125%, about 130%, about 135%, about 140%, about 145% or about 150% or more as compared to transgene expression of a CMV SION transgene expression vector.

[2605] In certain aspects, an SMSM compound can enhance SION transgene expression *in vivo* by about 2 fold, about 3 fold, about 4 fold, about 5 fold, about 6 fold, about 7 fold, about 8 fold, about 9 fold, about 10 fold, about 11 fold, about 12 fold, about 13 fold, about 14 fold, about 15 fold, about 16 fold, about 17 fold, about 18 fold, about 19 fold, about 20 fold, about 21 fold, about 22 fold, about 23 fold, about 24 fold, about 25 fold, about 26 fold, about 27 fold, about 28 fold, about 29 fold, about 30 fold, about 31 fold, about 32 fold, about 33 fold, about 34 fold, about 35 fold, about 36 fold, about 37 fold, about 38 fold, about 39 fold, about 40 fold, about 41 fold, about 42 fold, about 43 fold, about 44 fold, about 45 fold, about 46 fold, about 47 fold, about 48 fold, about 49 fold, about 50 fold, about 51 fold, about 52 fold, about 53 fold, about 54 fold, about 55 fold, about 56 fold, about 57 fold, about 58 fold, about 59 fold, about 60 fold, about 61 fold, about 62 fold, about 63 fold, about 64 fold, about 65 fold, about 66 fold, about 67 fold, about 68 fold, about 69 fold, about 70 fold, about 71 fold, about 72 fold, about 73 fold, about 74 fold, about 75 fold, about 76 fold, about 77 fold, about 78 fold, about 79 fold, about 80 fold, about 81 fold, about 82 fold, about 83 fold, about 84 fold, about 85 fold, about 86 fold, about 87 fold, about 88 fold, about 89 fold, about 90 fold, about 91 fold, about 92 fold, about 93 fold, about 94 fold, about 95 fold, about 96 fold, about 97 fold, about 98 fold, about 99 fold, about 100 over SION transgene expression observed in the presence of DMSO.

[2606] In certain aspects, an SMSM compound can decrease SIOFF transgene expression *in vivo* to about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%,

about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% of the transgene expression of a CMV transgene expression vector.

[2607] References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, have been made in this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes. Any material, or portion thereof, that is said to be incorporated by reference herein, but which conflicts with existing definitions, statements, or other disclosure material explicitly set forth herein is only incorporated to the extent that no conflict arises between that incorporated material and the present disclosure material. In the event of a conflict, the conflict is to be resolved in favor of the present disclosure as the preferred disclosure.

IX. KITS

[2608] The term “kit” as used herein refers to a packaged product or article of manufacture comprising components. The kit preferably comprises a box or container that holds the components of the kit. The box or container is affixed with a label or a Food and Drug Administration approved protocol. The box or container holds components of the disclosure which are preferably contained within plastic, polyethylene, polypropylene, ethylene, or propylene vessels. The vessels can be capped tubes or bottles. The kit can also include instructions for use of the reagents.

[2609] In another aspect, provided herein are kits comprising, in a container, an SMSM compound as described herein, and instructions for use. In some aspects, the kits further comprise a negative control, such as phosphate buffered saline or an SMSM compound that does not recognize the minigene cassette, in a separate container.

[2610] In one aspect, the kits further comprise primers and/or antibodies, in one or more separate containers, for assessing the production of an mRNA transcript from a modulated transgene and/or protein production therefrom.

[2611] In one aspect, the kits comprise one or more of the SMSM compounds depicted in FIG. 3Ai-ii.

EXAMPLES

[2612] Examples have been set forth below for the purpose of illustration and to describe certain specific aspects of the disclosure. However, the scope of the claims is not to be in any way limited by the examples set forth herein. Various changes and modifications to the disclosed aspects will be apparent to those skilled in the art and such changes and modifications may be made without departing from the spirit of the disclosure and the scope of the appended claims.

[2613] The practice of the present disclosure employs, unless otherwise indicated, conventional techniques of immunology, biochemistry, chemistry, molecular biology, microbiology, cell biology, genomics, and recombinant DNA, which are within the skill of the art. See, e.g., Bailey, J. E. and Ollis, D. F., *Biochemical Engineering Fundamentals*, McGraw-Hill Book Company, NY, 1986; *Current Protocols in Immunology*, John Wiley & Sons, Inc., NY, N.Y. (1991-2015), including all supplements; Green and Sambrook, (*Molecular Cloning: A Laboratory Manual*. 4th, ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 2014); *Current Protocols In Molecular Biology* (F. M. Ausubel, et al. eds., (2017)) including all supplements; *Short Protocols in Molecular Biology*, (Ausubel et al., 1999)) including all supplements; the series *Methods In Enzymology* (Academic Press, Inc.): *PCR 2: A Practical Approach* (M. J. MacPherson, B. D. Hames and G. R. Taylor eds. (1995)), *Antibodies, A Laboratory Manual*, Second Edition (Harlow and Lane, eds. (2014) and *Culture Of Animal Cells: A Manual Of Basic Technique*, 7th Edition (R. I. Freshney, ed. (2016)), all the contents of which are incorporated by reference herein in their entireties.

**EXAMPLE I: IDENTIFICATION OF 5' SPLICE SITE SEQUENCES
REQUIRED FOR THE INDUCTION OF SPLICING IN THE
PRESENCE OF SMALL MOLECULE SPLICING MODIFIER
(SMSM) COMPOUNDS**

RNA-Seq library preparation

[2614] RNA sequencing (RNA-seq) experiments were performed using cells, e.g., HEK293 cells, treated with a FD, HD or SMA-series compound together with control cells treated solely with DMSO. Cells were seeded in 6-well plates at 6×10^5 cells/well in 2 mL 10% FBS, DMEM and incubated for 4 hours at 37°C. Cells were then treated with an FD, HD or SMA-series compound (in 0.1% DMSO), or vehicle control (DMSO) for an additional 24 hours at 37 °C in 5% CO₂, 100% relative humidity).

[2615] Total RNA was then extracted using the RNeasy[®] plus mini kit. RNA concentration and quality were assessed using a NanoDrop spectrophotometer (ThermoFisher Scientific). For library preparation and sequencing, mRNA was enriched from about 3 µg of total RNA using oligo(dT) beads. The mRNA was fragmented randomly using fragmentation buffer followed by cDNA synthesis using mRNA template and random hexamer primers. Second-strand synthesis buffer (Illumina), deoxynucleotides, ribonuclease H and DNA polymerase I were added to initiate second-strand synthesis. After a series of terminal repair, A-ligation and sequencing adaptor ligations, the double-stranded cDNA library was completed through size selection and PCR enrichment. RNA libraries were sequenced in a HiSeq[®] sequencer (Illumina).

RNA-Seq analysis of pre-mRNA splicing

[2616] RNA sequencing reads were mapped to the human genome (hg19) using STAR program (version 2.5; Dobin, Alexander, Carrie A. Davis, Felix Schlesinger, Jorg Drenkow, Chris Zaleski, Sonali Jha, Philippe Batut, Mark Chaisson, and Thomas R. Gingeras. 2013. "STAR: Ultrafast Universal RNA-Seq Aligner." *Bioinformatics* 29 (1): 15–21), only uniquely mapped reads (with MAPQ>10) with <5nt/100nt mismatches and properly paired reads were used for further study.

[2617] For splicing analysis, all junction reads (read with a gap in alignment indicating splicing) were analyzed including those reads mapping to unannotated (novel) splice sites. Reads were counted for different exons. For each splicing event, a Percent-Spliced-In (PSI) value was calculated using the percent of average read number supporting the inclusion of the

exon among all reads supporting either the inclusion or the exclusion of an exon. A minimal of 20 for the denominator of PSI calculation was required. Otherwise, a “NA” value would be generated. PSI values for biological replicates were averaged and the PSI difference between two treatment groups was calculated. For statistical test, a 2x2 read counts table was made for each event with rows for reads supporting inclusion or exclusion and columns for the two comparing sample groups (biological replicates were combined). Fisher’s Exact Test was used for statistical test. PSI change of >10% (or < -10%) and P-value <0.001 was used to select splicing events being regulated by the treatment.

k-mer analysis

[2618] For comparing sequence difference of a particular region for two groups of exons (e.g. INCLUSION vs. NO CHANGE), we compared the k-mer (k=4 to 6) frequencies of the two groups by Fisher’s Exact Test (one k-mer vs. all other k-mers, group 1 vs. group 2). The resulting P-value was converted to a significance score ($SS = -S \times \log_{10} P\text{-value}$), in which S is the sign indicating enrichment (1) or depletion (-1) of the k-mer in group 1.

Analysis of SMSM compound responsive 5’ splice site (ss) sequences.

[2619] Splicing of exons responding to an SMSM compound (inclusion or skipping) was identified by RNAseq analysis. The -4 to -1 positions of the 5’ splice site of targeted exons were compared to the exons showing no significant changes by Fisher’s exact test (see method “k-mer analysis”). The resulting P-value was converted to a significance score, indicating enrichment of the 4-mer amongst the targeted exons. As shown in FIG. 1Ai-iv, positions -4 to +6 of an exemplary 5’ splice site are depicted (uppercase: exon; lowercase: intron) including the “gt” dinucleotide at the intron boundary.

[2620] FIG. 1i shows the enrichment of 5’ splice site sequences at positions -4 to -1 in FD compound responsive exons, the splicing of which results in exon inclusion. The FD compound responsive 5’ss sequence found in exon 20 of mutant IKBKAP gene is shown in the third row.

[2621] FIG. 1ii shows the enrichment of 5’ splice site sequences at positions -4 to -1 in FD compound responsive exons, the splicing of which results in exon skipping.

[2622] FIG. 1iii shows the enrichment of 5’ splice site sequences at positions -4 to -1 in HD compound responsive exons, the splicing of which results in exon inclusion. The HD compound responsive 5’ss sequence found in psiExon 49a of the HTT gene is shown in the third row.

[2623] FIG. 1iv shows the enrichment of 5' splice site sequences at positions -4 to -1 in SMA compound responsive exons, the splicing of which results in exon inclusion. The SMA compound responsive 5'ss sequence found in exon 7 of the SMN2 gene is shown in the third row.

EXAMPLE II: GENERATION OF INDUCIBLE SPLICING MINIGENES

[2624] A splicing-induced-on-system (SION) and splicing-induced-off-system (SIOFF) were developed to study gene expression controlled by a small molecule which modulates a splice cassette. For this purpose, minigene splicing cassette were cloned into pAAV-GFP expression vector backbone (see, for example, FIG. 2A) and transfected into HEK 293 cells in the presence or absence of an SMSM compound to evaluate how an SMSM compound impacts transgene expression.

[2625] Depending on the design and the regulatory element to be controlled by SMSM-induced splicing, the minigene splicing cassette can be inserted anywhere with the transgene transcription unit, including the 5' or 3' untranslated region of the transgene (see, e.g., FIG. 1Bi-iii).

[2626] In a SION system, the splice cassette is in an OFF state without compound (see, for example, FIGs. 1E-1G). SMSM compound-induced splicing results in the inclusion (FIGs. 1E-1F) or skipping (FIG. 1G) of an exon resulting in the reconstitution of a regulatory element (for example, the transgene's AUG start codon (FIG. 1C) or polyadenylation sequence (FIG. 1D) to turn on transgene expression.

[2627] In a SIOFF system, the splice cassette is in the ON state without compound. According to this scenario, exon inclusion (FIG. 1I) or skipping (FIG. 1H) resulting from SMSM compound-induced splicing disrupts the open reading frame of the transgene's coding region (e.g., stop codon) to turn off translation of the spliced transgene pre-mRNA (see, for example, FIGs. 1H-1I).

EXAMPLE III: MINIGENE GFP EXPRESSION VECTORS

[2628] HD/SMA or FD compound responsive splicing was identified by RNA seq analysis. SION/SIOFF constructs were then generated from the genomic sequences of the regulated exons and their flanking intron and upstream exon sequences of those genes found to be regulated by SMSM compounds. Intron sequences were truncated in the middle if they were

too big for the minigene cassette. Mutations in the intron or upstream exon introduced stop codons to block unwanted translation initiation upstream of the coding region of the EGFP open reading frame (ORF).

[2629] Eight SION (SION 1-8) and two SIOFF (SIOFF 1-2) constructs were cloned into the pAAV-GFP backbone plasmid (see FIG. 2A-2Bi-vi). The constructs were then screened for GFP fluorescence in the absence of an SMSM compound to determine base line expression.

Minigene Baseline Expression

GFP fluorescence

[2630] HEK293-AAV cells (Cell Biolabs Inc.) plated in 6-well dishes were transfected using Lipofectamine LTX with Plus Reagent (Thermo Fisher) with a total of 2µg plasmid DNA per one well of the 6-well dish according to the manufacturer's instructions. The ratio of µg plasmid DNA to µL PLUS reagent to µL LTX reagent used was 1:1:2. 18-24 hours post transfection, the media was aspirated and replaced with fresh media to remove transfection reagents. ~48 hours after the initiation of compound treatment, the 6-well dishes are imaged using a Cytation 5 Cell Imaging Reader using a positive control (pAAV-GFP) as calibrator for focus and exposure. Images were taken of the center of each well.

[2631] In the absence of SMSM compound, the lowest amount of GFP fluorescence was observed with SION 2, SION 3, SION-5, SION 6, whereas SIOFF-1 gave the greatest amount of GFP fluorescence (FIG. 3Bi-iv).

Western blot analysis

[2632] For Western blot analysis, the transfected cells were lysed in 75 µl Laemmli buffer (Bio-Rad Laboratories, Inc.). Samples were then mixed with loading buffer, boiled for 10 min and 45µl was loaded per well and electrophoresed in a 3-8% Tris-Acetate gel @ 130V for 5-6 hrs. (12+2 wells; Invitrogen™ NuPAGE™ 3 to 8%, Tris-Acetate, 1.0 mm, Midi Protein Gel, 12+2-well). The protein MW ladder used was Invitrogen Himark HMW ladder (10 uL per well). Following electrophoresis, protein was electro-transferred to a 0.45 µM Nitrocellulose membrane (Bio-Rad) at 150 mA for 90 min and then incubated with Li-Cor Blocking buffer overnight at 4°C with agitation. The blot was then incubated first with a Cell Signaling anti-GFP (D5.1) XP® (Cat#2956S; 1:1,000) rabbit mAb and a Sigma Aldrich Anti-β-Actin mouse monoclonal antibody (Cat#A1978; 1:5,000) at room temperature for 1-2 hours, then washed and incubated with secondary antibodies Alexa Fluor® 680 goat anti-mouse IgG (Thermo

Fisher Scientific) and IRDye® 800CW donkey anti-Rabbit IgG (LI-COR; dilution 1:10,000) + 0.1% Tween at RT for 1 hr. Blots were washed 4-5 min in PBS-T, washed again in PBS-T for 10 minutes and rinsed in PBS prior to scanning in an Odyssey Imager according to the manufacturer's instructions (channels 700 (red) and 800 (green)).

[2633] The Western blot confirmed the results of the GFP fluorescence. Accordingly, SION 2, SION 3, SION-5, SION 6, and SIOFF-1 were selected for further analysis.

Minigene splicing in the presence of an SMA, HD or FD compound

[2634] The chemical structure of SMSM compounds, SMA1-2, HD1-3 and FD1-3 shown in FIG. 3Ai-ii. The activity of SMSM compounds was determined in HEK293 cells transfected with the minigene-GFP vectors. Transgene (GFP) expression was compared to the expression of pAAV-GFP+DMSO (positive control) and Mock+DMSO (negative control).

[2635] On day 1, 500,000 HEK293 cells/well were plated in 6-well plates (2 ml/well, 2.5×10^5 cells/ml). Cells were then transfected with 2 µg plasmid (one of SION 1-8 and SIOFF 1-2) for ~24h. 6 µl Fugene6 was added to 500 µl Opti-MEM medium incubated for ~5 min at room temperature. 2 µg plasmid was then added and incubated ~15 min at room temperature, before being added to the plated cells and further incubated for ~24h under standard cell culture conditions (37 °C, 5% CO₂, 100% relative humidity). On day 2, 1 µM of SMA1, SMA2, HD1, HD2, HD3, FD1, FD2, FD3, or DMSO (final DMSO = 0.1%) was added to the cells. After culturing for another ~24h, GFP transgene expression was evaluated by (1) GFP fluorescence (2) Western blot analysis (FIG. 4A-4G) and (3) RT-PCR (FIG. 5A-5D).

GFP fluorescence

[2636] Green fluorescence of transfected cells was evaluated by visual inspection using a Cytation 5 Cell Imaging Reader (FIG. 3Bi-iv). A positive control (pAAV-GFP) was used as calibrator for focus and exposure. Images were taken of the center of each well.

Western blot analysis

[2637] Western blots of whole cell extract of HEK293 cells transfected with SION and SIOFF constructs in the presence of 1 µM SMA 1, SMA2, HD1, HD2, HD3, FD1, FD2 compounds or DMSO were probed with anti-GFP and β-actin antibodies as described above (FIGs. 4A and 4D). The fold GFP expression over the GFP expression in DMSO mock transfected cells is

depicted in FIGs. 4B and 4E. The fold GFP expression over the GFP expression in pAAV-GFP + DMSO mock transfected cells is depicted in FIGs. 4C, 4F and 4G.

[2638] A Western blot of SION2 and SION3 GFP expression (FIG. 4A) in the presence or absence of SMA1, SMA2, HD1, HD2 and HD3 compounds was quantified and compared to the expression of pAAV-GFP (FIG. 4C; positive control) and DMSO (FIG. 4B). The fold GFP expression over DMSO is shown in the Table below:

	SION2	SION3	SION5	SION6	SIOFF1
1mM SMA1	3.45	2.45	-	-	
1mM SMA2	7.01	7.2	-	-	
1mM HD1	6.62	13.25	-	-	
1mM HD2	9.42	12.25	-	-	
1mM HD3	8.71	14.49	-	-	
1mM FD1	-	-	5.69	6.66	1.6
1mM FD2	-	-	4.46	7.36	.99
DMSO	1	1	1	1	1

RT-PCR Analysis

[2639] FIG 5A shows a schematic overview of different splicing scenarios and their resulting RT-PCR products. The top panel shows exon skipping, the middle panel shows exon inclusion, and the bottom panel shows intron retention. In each panel, the construct is shown on the top, with exons indicated by boxes and introns indicated by lines. Arrows below the construct indicate forward and reverse RT-PCR primer binding, and the RT-PCR product is shown at the bottom.

[2640] The Table in FIG. 5B shows an overview of different SION and SIOFF constructs and their properties and expected RT-PCR product lengths. The numbers for the different RT-PCR products relate to the scenarios in FIG. 5A and are in nucleotides.

[2641] Changes in minigene splicing in response to SMSM compounds were analyzed by RT-PCR analysis. 5×10^5 HEK293 cells were transiently transfected with 2 μ g of different SION/SIOFF plasmids in 6-well plates, using 6 μ l Fugene6® (Promega) according to the protocol provided by the manufacturer. After overnight incubation, 1 μ M of the different compounds (as indicated SMA2, HD1, FD1, FD2, or DMSO) dissolved in DMSO (as indicated in the figure, final DMSO concentration in cell culture 0.5%) were added and incubated for additional ~24h. Total RNA was isolated using the RNeasy plus mini kit (Qiagen). RNA concentration and quality were assessed using a NanoDrop spectrophotometer (ThermoFisher).

[2642] cDNA was synthesized using the iScript™ cDNA synthesis kit (Biorad) according to the manufacturer's instructions. Primers annealing to shared sequences flanking each minigene cassette constructs were synthesized:

SION-F-KE: 5'-GGCAAAGAATTGGGATTCGAACAT-3' (SEQ ID NO: 58)
 SION-R-KE: 5'-CACCCCGGTGAACAGCTC-3' (SEQ ID NO: 59).

[2643] Endpoint PCRs were set up using Platinum™ PCR SuperMix High Fidelity (Invitrogen), and the resulting PCR products were separated on 2% eGels (Invitrogen; see FIG. 5Ci-ii).

[2644] To determine changes in the splicing of known endogenous SMSM compound responsive genes, the AgPath-IDTM One-Step RT-PCR reagents from Applied Biosystems were used according to the protocol provided by the manufacturer together with gene-specific primers listed in the Table below. The primers were directed against the flanking exons. The resulting RT-PCR products were separated on 2% eGels (Invitrogen; see FIG. 5Ci-ii)

TARGET GENE	SEQ ID NO	F SEQ 5'-3'	SEQ ID NO	R SEQ 5'-3'
POMT2	85	ACCCTTCCTTCCCAGTGGAG	86	CTGATAGTGCTTCCGGGTCA
c12orf4	87	GCCCAGGACTTCGGAACATA	88	TGACTGGCATTCTCTTGAACA
HTT 49a	89	TTCGTGGTGGCAACCCTTGA	90	GGCGTGGGTACAAACTCTG
ZNF37BP	91	TGTTGAGCTGCTGGCATATT	92	GTGTTGGCAGAGCAGAGAAAAC
HSD17B4	93	GCAGAAAGAGGAGCGTTAGT	94	AGTTGGCCACTGCTTTTCCA
ZNF207	95	AGGTGTTCTCCTCTGATGC	96	CATCATTCCACCCATTGGCA
RPP14	97	TTGCGGCGAATAGGAGTCTG	98	CTGTGCAGCATTCACTCCAAC
FANCI	99	TACTTGTTCTGAGTCAGGCCG	100	AATTCCTCCGGAGCTCTGAC

[2645] FIGs. 5Di-ii shows a dose response RT-PCR analysis for selected cassettes. Experimental conditions were the same as described in FIG. 5C, with the top row showing cassette splicing and the bottom row showing endogenous splicing. Compound concentrations used were DMSO, 10 nM, 100 nM, 1 μ M. Compounds used were HD1 for cassettes responding to HD/SMA compounds, and FD1 for cassettes responding to FD compounds. Primers were the same as used in FIG. 5C.

EXAMPLE IV: MINIGENE CASSETTE DELETION MUTANTS

[2646] Based on the initial data of Examples II and III, the SION3 minigene cassette showed low background GFP expression (expression without SMSM compound treatment) and up to a 14 fold increase in expression after SMSM compound treatment. The SION3 minigene cassette has a length of 622 nt, which is longer than the other SION minigenes (FIGs. 2Bi-v). Moreover, the RT-PCR analysis revealed a complex splicing pattern after compound treatment that may be indicative of partial intron retention or alternative 3' splice site usage. Consequently, 10 truncated SION3 mutants were engineered to optimize the size of the minigene to be more compatible with the size constraints imposed by AAV vector packaging, minimize background expression, maximize induced expression, and simplify the splicing pattern. FIG. 6A shows a schematic representation of 10 SION3-truncation mutant constructs and their GFP expression Western Blot data expressed as fold over GFP expression in the presence of DMSO. A: 5' splice site -4 position C>A mutation; t: 5' splice site +6 position g>t mutation; *: mutated to create a uORF. The sizes of different regions are indicated. The nucleotides sequences of each SION 3 deletion mutants can be found in FIGs. 6Bi-vi.

EXAMPLE V: INDUCED SPLICING OF MINIGENE CASSETTE DELETION MUTANTS

[2647] FIGs. 6Ci-iv shows an RT-PCR analysis of different minigene cassettes. 5×10^5 HEK293 cells were transiently transfected with 2 μ g of different SION/SIOFF plasmids in 6-well plates, using 6 μ l Fugene6® (Promega) according to the protocol provided by the manufacturer. After overnight incubation, varying concentration of compound HD1 dissolved in DMSO (DMSO, 10 nM, 1 μ M, final DMSO concentration in cell culture 0.5%) were added and incubated for additional ~24h. Total RNA was isolated using the RNeasy plus mini kit (Qiagen). RNA concentration and quality were assessed using a NanoDrop spectrophotometer (ThermoFisher).

[2648] Changes in minigene splicing in response to SMSM compounds were analyzed by RT-PCR. cDNA was synthesized using the iScript™ cDNA synthesis kit (Biorad) according to the manufacturer's instructions. Endpoint PCRs were set up using Platinum™ PCR SuperMix High Fidelity (Invitrogen) using the following primers that anneal to shared sequences flanking each minigene cassette construct:

SION-F-KE: 5'-GGCAAAGAATTGGGATTCGAACAT-3' (SEQ ID NO: 58)

SION-R-KE: 5'-CACCCCGGTGAACAGCTC-3' (SEQ ID NO: 59).

[2649] The resulting PCR products were separated on 2% eGels (Invitrogen; FIG. 6Ci-ii). The Table in FIG. 6Ciii shows the expected RT-PCR product lengths for each SION construct depending on the type of splicing event. FIG. 6Civ shows the possible splicing events (exon 2 inclusion, exon skipping and intron retention. Exons are indicated by boxes and introns indicated by lines. Arrows below the construct indicate forward and reverse RT-PCR primer binding sites.

[2650] FIGs. 6Di-ii show endogenous splicing changes under the same conditions as FIG. 6C. To determine endogenous splicing changes, the AgPath-ID™ One-Step RT-PCR reagents from Applied Biosystems were used according to the protocol provided by the manufacturer. The resulting RT-PCR products were separated on 2% eGels (Invitrogen). Primers listed in the Table below anneal to flanking exons.

TARGET	SEQ ID NO:	F SEQ 5'-3'	SEQ ID NO:	R SEQ 5'-3'
POMT2	85	ACCCTTCCTTCCCAGTGGAG	86	CTGATAGTGCTTCCGGGTCA
HTT 49a	89	TTCGTGGTGGCAACCCTTGA	90	GGCGTGGGTCAAACTCTG
c12orf4	87	GCCCAGGACTTCGGAACATA	88	TGACTGGCATTCTCTTGAACA
CENPI	101	TCATCCTTCTTTCTTGAGTTACGCT	102	CATTTACTGTCCTTTCTTCTGGGCT

[2651] FIG. 7A shows an exemplary HD/SMA compound inducible expression vector comprising an enhancer/promoter, 5'UTR β -globin intron, SION3 minigene cassette, GFP transgene and 3'UTR with polyA sequence. Arrows indicate locations where the following 3 pairs of endpoint PCR primers anneal within the expression vector relative to the cassette.

TARGET	SEQ ID NO:	F SEQ 5'-3'	SEQ ID NO:	R SEQ 5'-3'
CASSETTE	58	GGCAAAGAATTGGGATTCTGAACAT (SION-F-KE)	59	CACCCCGGTGAACAGCTC (SION-R-KE)
Outside 1	103	CTCCATAGAAGACACCGGGAC (β -globin-F1-SION-KE)	59	CACCCCGGTGAACAGCTC (SION-R-KE)
Outside 2	103	CTCCATAGAAGACACCGGGAC (β -globin-F1-SION-KE)	104	CCGGACACGCTGAACTTGTG (SION-Rev)

[2652] 5×10^5 HEK293 cells were transiently transfected with 2 μ g of different SION plasmids in 6-well plates, using 6 μ l Eugene6® (Promega) according to the protocol provided by the manufacturer. After overnight incubation, varying concentration of compound HD1 dissolved in DMSO (DMSO, 10 nM, 1 μ M, final DMSO concentration in cell culture 0.5%) was added

and the cells were cultured for additional ~24h. Total RNA was then isolated using the RNeasy plus mini kit (Qiagen). RNA concentration and quality were assessed using a NanoDrop spectrophotometer (ThermoFisher). To determine splicing changes in the constructs, cDNA was synthesized using the iScript™ cDNA synthesis kit (Biorad) according to the manual. PCR assays were set up using Platinum™ PCR SuperMix High Fidelity (Invitrogen) with the 3 endpoint primer pairs, and the resulting PCR products were separated on 2% eGels (Invitrogen). FIG. 7B shows the results of the RT-PCR analysis. Predicted lengths of RT-PCR products according to the SION construct (SION1, SION2, SION3T1, T2, T3, T8 and T10), the primer pair used (cassette, outside 1, outside 2) and the splicing event (exon skipping, exon inclusion or intron retention) are depicted in the table below.

EP PCR product lengths

cassette	cassette			outside 1			outside 2		
	skip	incl	intr ret	skip	incl	intr ret	skip	incl	intr ret
control	74	74	74	213	213	213	272	272	272
SION1	80	119	419	219	258	558	278	317	617
SION3	80	195	690	219	334	829	278	393	888
SION3T1	86	201	552	225	340	691	284	399	750
SION2T2	86	201	567	225	340	706	284	399	765
SION3T3	86	138	504	225	277	643	284	336	702
SION3T8	86	138	363	225	277	502	284	336	561
SION3T10	86	201	431	225	340	570	284	399	629

EXAMPLE VI: ANALYSIS OF SPLICING OF MINIGENE CASSETTES WITH DELETION MUTATIONS

[2653] The RT-PCR analyses of FIG. 6C and FIG. 7B suggest SMSM compound induced splicing events were occurring at different locations within the minigene presumably at cryptic 5' and/or 3' splice sites. To pinpoint the location of these splicing events, spliced RNA transcripts were examined by Ampliseq analysis.

Ampliseq analysis

[2654] HEK293-AAV cells (Cell Biolabs Inc.) in 6-well dishes were transfected with 2μg of plasmid DNA per well using Lipofectamine LTX with Plus Reagent (Thermo Fisher) as per the manufacturer's instructions. The ratio of μg plasmid DNA to μL PLUS reagent to μL LTX

reagent used was 1:1:2. 18-24 hours post transfection, media was aspirated and replaced with fresh media to remove transfection reagents. HEK293-AAV cells were then treated with 1 μ M HD1, 10nM HD1 compound or DMSO. After ~24 hours of HD1 compound treatment, the HEK293-AAV cells in each well were harvested and total RNA was extracted using the Qiagen RNeasy kit per manufacturer's instructions. 800ng- 1 μ g total RNA was reverse-transcribed in the presence of random hexamers using SuperScript III First-Strand Synthesis System (Invitrogen/Thermo Fisher).

[2655] cDNA was then subjected to library preparation via amplicon PCR. An exemplary flowchart of the Ampliseq protocol is depicted in FIG. 8A. Briefly, HEK293 cells were transfected with a minigene and grown for 16h and treated with an SMSM compound or DMSO control for 1 day. Total RNA was extracted. Reverse transcription (RT) was performed using random hexamer. cDNA of the minigene were amplified using two rounds of PCRs. The final product was sequenced using an Illumina iSeq 100 sequencer. Multiple samples (treatment) can be sequenced together by using primers with different i5 or i7 indexes.

[2656] In the first round of PCR, amplicon products were generated having universal tails/tags/overhangs on both ends using the following custom Ampliseq Forward/Reverse Primers:

Forward (P5Tag): 5'-TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGNNNNN
GCATTGGAACGCGGATT-3' (SEQ ID NO: 105)

Reverse (P7Tag): 5'-GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGNNNNN
TTTACGTCGCCGTCCAG-3' (SEQ ID NO: 106)

(bold underlined sequence anneal to locus specific sequences).

[2657] Amplicon PCR was generated using KAPA HiFi HotStart ReadyMix with Biorad T100 thermocycler conditions set at: 95°C for 3 mins; 16-18 PCR cycles, each cycle having the following parameters: 95°C for 30 sec, 62.5°C for 30 sec, 72°C for 1 min; 72°C for 5 mins. The PCR reaction was terminated by a hold at 4°C. A fraction of the 1^o PCR library was visualized on an electrophoresis gel for quality control and the remainder was purified using the Qiagen PCR Purification kit and eluted in water. The library was then subjected (0.8x) Ampure bead cleanup and eluted in 10mM Tris-Cl pH=8.5.

[2658] The purified 1st PCR library was then barcoded via indexing PCR (2nd PCR) using Nextera XT Index Primers (N7xx)/(S5xx) (Illumina, cat# FC-131-1001):

Index 1 Read:

5'-CAAGCAGAAGACGGCATACGAGAT[i7]GTCTCGTGGGCTCGG (SEQ ID NO: 107)

Index 2 Read:

5'-AATGATACGGCGACCACCGAGATCTACAC[i5]TCGTCCGGCAGCGTC (SEQ ID NO:108)

[2659] Examples of Index 1 (i7) and Index 2 (i5) adapter sequences are shown below:

Nextera XT Index Kit v2 - Index 1 (i7) Adapters

i7 Bases in Adapter	i7 Index Name
TCGCCTTA	N701
CTAGTACG	N702
TTCTGCCT	N703
GCTCAGGA	N704
AGGAGTCC	N705
CATGCCTA	N706
GTAGAGAG	N707
CAGCCTCG	N710
TGCCTCFF	N711
TCCTCTAC	N712
TCATGAGC	N714
CCTGAGAT	N715
TAGCGAGT	N716
GTAGCTCC	N718
TACTACGC	N719
AGGCTCCG	N720
GCAGCGTA	N721
CTGCGCAT	N722
GAGCGCTA	N723
CGCTCAGT	N724
GTCTTAGG	N726
ACTGATCG	N727
TAGCTGCA	N728
GACGTCGA	N729

Nextera XT Index Kit v2 - Index 2 (i5) Adapters

i5 Bases in Adapter	i5 Index Name
CTCTCTAT	S502
TATCCTCT	S503
GTAAGGAG	S505
ACTGCATA	S506
AAGGARTA	S507
CTAAGCCT	S508
CGTCTAAT	S510
TCTCTCDB	S511
TCGACTAG	S513
TTCTAGCT	S515
CCTAGAGT	S516
GCCTAAGA	S517
CTATTAAG	S518
AAGGCTAT	S520
GAGCCTTA	S521
TTATGCGA	S522

[2660] Indexed amplicons were generated using KAPA HiFi HotStart ReadyMix with the following Biorad T100 thermocycler conditions: 95°C for 3 mins; 6-8 cycles of: 95°C for 30 sec, 56°C for 30 sec, 72°C for 1 min; 72°C for 5 mins followed by a hold at 4°C. A fraction of the 2nd PCR library was visualized on an electrophoresis gel for quality control and the remainder was purified using a Qiagen PCR Purification kit and (0.9x) Ampure bead cleanup and eluted in 10mM Tris-Cl pH=8.5. Final quantification of barcoded libraries was performed using Qubit Fluorometer and then subsequently diluted and pooled together. Final loading concentration was 30-50pM with 5% PhiX spike-in onto Illumina iSeq100 sequencer.

Ampliseq Data analysis and visualization

[2661] The fastq format of Ampliseq reads were mapped to the minigene sequences using STAR (Dobin et al. (2013) *Bioinformatics* 29 (1): 15–21). The read mapping was visualized using an Integrative Genomics Viewer (IGV) (Robinson et al. (2011) *Nature Biotechnology* 29 (1): 24–26). Desired splicing is defined as the wanted (desired) splicing change (inclusion or skipping) in the SMSM compound-treated condition to induce (for SION) or turn-off (for SIOFF) transgene expression. In Ampliseq data, the desired splicing was defined as the reads supporting the splicing of desired junctions (DS). All other junction reads with the usage of the common splice sites as the desired splicing reads were defined as undesired junction reads (uDJ). The Percent of Desired Splicing (pDS, %) was calculated using $DS / (DS + uDJ) (\%)$, in which DS and uDJ are reads counts.

[2662] FIG. 8B shows Ampliseq results for SION3 minigene cassette in the form of a Sashimi plot. Undesired splice sites (ss) were identified. “a” and “d” represent acceptor and donor sites respectively.

[2663] FIG. 8C shows the location of splice sites within the SION3 minigene cassette that were identified by Ampliseq. Individual reads suggestive of undesired splice sites were mapped to the minigene and visualized using an Integrative Genomics Viewer (IGV). “a” and “d” represent undesired acceptor and donor site respectively.

[2664] FIG. 8D depicts a diagram of the SION3 minigene cassette and the location of undesired acceptor sites (a) or donor sites (d) that were deleted in SION3T1 and SION3T3. “a1_247” and “a2_146” are undesired acceptor sites in SION3 that when present would include a 247nt and a 146nt psiExon, respectively (when the downstream desired donor site of HTT-psiExon49a is also used). “a1_247” and “d1” were deleted in SION3T1. “d1”, “a2_146” and the acceptor site

creating the 115nt psiExon (3'ss_115) were deleted in SION3T3. SION3T3 uses "a1_247" instead as the acceptor site of the psiExon.

[2665] FIG. 8E shows a Sashimi plot of Ampliseq results for SION2 showing undesired splice sites (ss). "a" and "d" represent acceptor and donor sites respectively.

[2666] FIG. 8F shows an Integrative Genomics Viewer diagram of Ampliseq results for the SION2 minigene. Individual reads suggestive of undesired splice sites were mapped to the minigene and visualized using an Integrative Genomics Viewer (IGV). "a" and "d" represent undesired acceptor and donor sites, respectively.

[2667] FIG. 8G shows an exemplary diagram of the Ampliseq Percent of Desired Splicing (pDS) calculation method.

[2668] FIGs. 8H -8K show the percent of desired splicing and fold increase in GFP expression over GFP expression in the presence of DMSO in HEK293 cells respectively for endogenous HTT exons 49-50, pAAV-GFP-SION1, pAAV-GFP-SION2, pAAV-GFP-SION3, pAAV-GFP-SION3T1, pAAV-GFP-SION3T3 in the presence of 1mM HD1, 10nM HD1 or DMSO and pAAV-GFP-SION5, pAAV-GFP-SION6 in the presence of 100nM and 1nM FD1 or DMSO. pAAV-GFP-SION3 showed the lowest %pDS in the absence of HD1 and the greatest fold increase in GFP expression over that observed with DMSO.

EXAMPLE VII: CONSTRUCTION OF MINIGENE CASSETTES WITH TARGETED MUTATIONS

[2669] The Ampliseq data of Example VI identified undesired splice sites within the SION2 and SION3 minigenes. 9 mutant SION minigenes based on parent SION minigenes SION3T1, SION3T3, SION1, SION2 and SION6 were engineered with targeted mutations predicted to inactivate the undesired splicing identified by the Ampliseq analysis. Additional mutations were made to remove CpG island, ATG start codon, TATA-box and predicted 5' or 3' splice sites on both strands of the minigene cassette sequence without altering sequences proximal to the desired 5' and 3' splice site.

[2670] In ON6m3, the 5' splice site sequence ACAAgtaagc (SEQ ID NO:109) of the middle exon 2 of ON6m2 was replaced by CAGAgtaagg (SEQ ID NO:12) from SION3 HTT-psiExon49a) to change an FD-compound responsive 5' splice site to a SMA/HD-compound responsive 5' splice site.

[2671] The sequences and characteristics of 9 SION minigenes with targeted mutations are shown in FIG. 9A-9D. A sequence alignment was performed using “Clustal Omega” (web page: www.ebi.ac.uk/Tools/msa/clustalo/). Nucleotide changes relative to SION3, SION3T1, SION3T3, SION1, SION2 and SION6 are shown below.

SEQ ID NO:	MINIGENE CASSETTE ALIGNMENT
109 98 110	AACCTTGAGgtaagagggcagcttggagctcagtgttgctgtgggagggggcagggg 60 ON3m2 AACCTTGAGgtaagagggcagctgggagctcagtgttgctgtgggagggggcagggg 60 SION3 AACCTTGAGgtaagagggcagctgggagctcagtgttgctgtgggagggggcagggg 60 ON3m1 *****
	tgtgttgcaggttgaataactttgggtgtttcaacttgggtgactctcacaacccct 120 tgtgtatgcaggatgaataactttatatgcgtcatcttattgactctcacaacccct 120 tgtgtatgcaggatgaataactttatatgcgtcatcttattgactctcacaacccct 120 *****
	aagagataggctctgttactcccaattgactgaagaggaaacaaaggcttagagaatttc 180 gtgagataggctctgttactcccaattgactgaagaggaaacaaaggcttagagaatttc 180 gtgagataggctctgttactcccaattgactgaagaggaaacaaaggcttagagaatttc 180 * *****
	agtgacttgcccaggctcctctgagctaggaagtagccaatctggcaagggaacccaaggc 240 agtgacttgcccaggctcctctgagctaggaagtagccaatctggcaatttgaacccaaggc 240 agtgacttgcccaggctcctctgagctaggaagtagccaatctggcaatttgaacccaaggc 240 *****
	ctgctatcccttgaacccacgctctcaaattcaacctatgacagAGGCAAGCCCTGGTGT 300 ctgctatcccttgaacccacgctctcaaattcaacctatgacagAGGCAAGCCCTGGTGT 300 ctgctatcccttgaacccacgctctcaaattcaacctatgacagAGGCAAGCCCTGGTGT 300 *****
	TGTGGGAGCCCCAAGGAAGAGCCTCTGGCTTGGTGCCCAATTAGCCAGGAGAGATTTT 360 TGTGGGAGCCCCAAGGAAGAGCCTCTGGCTTGGTGCCCAAGTAGCCAGGAGAGATTTCT 360 TGTGGGAGCCCCAAGGAAGAGCCTCTGGCTTGGTGCCCAAGTAGCCAGGAGAGATTTCT 360 *****
	ACAGGAGCCCACAGTCTGAAGGAGAGAGAGGCAGCAGAgtaagggggccttgtggcaga 420 ACAGGAGCCCACAGCGCTGAAGGAGAGAGAGGCAGCAGAgtaagggggccttgtggcaga 420 ACAGGAGCCCACAGCGCTGAAGGAGAGAGAGGCAGCAGAgtaagggggccttgtggcaga 420 *****
	gaggggacttggcatttggggaataagtggtcaggattgatgtattggagccaagtca 480 gaggggacttggcatttggggaataagtggtcaggactgaatgtaatggagccaagtca 480 gaggggacttggcatttggggaataagtggtcaggactgaatgtaatggagccaagtca 480 *****
	gagttgttttttgggataagcaagggccttctggatttctgcccctcaatgctttggatt 540 gagctgtccttctggaagggaagggcacctggacgcgtgcccctcagtgtctttggacg 540 gagctgtccttctggaagggaagggcacctggacgcgtgcccctcagtgtctttggacg 540 *****
	gttcacaactgtgattcacattgcttcccctaacgaactgtacacgagtgggcattctgt 600 gttcacaactgtgattcacacggcttcccctaacgaagggtacacgagtgggcattctgt 600 gttcacaactgtgattcacacggcttcccctaacgaactgtacacgagtgggcattctgt 600 *****
	gactcgggtacttcccttttagTG 622 gactcgggtacttcccttttagTG 622 gactcgggtacttcccttttagTG 622 *****

SEQ ID NO:	MINIGENE CASSETTE ALIGNMENT
101 49	AACCTTGAGgtaagagggcagctcgggagctcagtgttgctgtgggagggggcagggg 60 SION3T1 AACCTTGAGgtaagagggcagcttgggagctcagtgttgctgtgggagggggcagggg 60 Tim2 *****
	ctaggaagtagccattctggcatttgaacccaaggcctgctatcccttgaacccaagctc 120 ctaggaagtagccattctggcagggaacccaaggcctgctatcccttgaacccaagctc 120 *****

SEQ ID NO:	MINIGENE CASSETTE ALIGNMENT	
	tcaaattcaacctatgacagAGGCAAGCCCTGGTCTGTGGGAGCCCCAAGGAAGAGCCT 180 tcaaattcaacctatgacagAGGCAAGCCCTGGTCTGTGGGAGCCCCAAGGAAGAGCCT *****	
	CTGGCTGGTGGCCAATAGCCCAGGAGAGATTCTACAGGAGCCACAGCTGAAGGA 240 CTGGCTGGTGGCCAATAGCCCAGGAGAGATTCTACAGGAGCCACAGTTCTGAAGGA 240 *****	
	GAGAGAGGCAGCAGAgtaagggggccttctgtggcagagaggggaactggcacttttggggaat 300 SION3T1 GAGAGAGGCAGCAGAgtaagggggccttctgtggcagagaggggaactggcacttttggggaat 300 T1m2 *****	
	aggtgggtcaggactgaatgtaatggagccatgtcagagctgtccttctggaagggaag 360 aagtggtcaggactgaatgtaatggagccatgtcagagctgtccttctggaagggaag 360 *****	
	ggcacttggaacgctgccccctcagtgcttggacgggtccacaactgtgattcacacgg 420 ggcacttggaatcttctgccccctcagtgcttggacgggtccacaactgtgattcacatgg 420 ***	
	cttcccctaacgaagggtacacagtggtggcattctgtgactcgggtacttcccttttagTG 478 cttcccctaacgaagggtacacagtggtggcattctgtgactcgggtacttcccttttagTG 478 *****	

SEQ ID NO:	MINIGENE CASSETTE ALIGNMENT	
101 50	AACCTTGAAGtaagaggcagctcgaggactcagtggtgtgtgtgggaggggggcatggggg 60 SION3T3 AACCTTGAAGtaagaggcagctcgaggactcagtggtgtgtgtgggaggggggcatggggg 60 T3m2 *****	
	tgctgtatgcaggatgaaatactttatatgcgtcatcttatttgactctcacaacccct 120 tgctgtatgcaggatgaaatactttatatgcgtcatcttatttgactctcacaacccct 120 **	
	gtgagataggctctgttactcccatttgacaggtgAGGAGAGATTCTACAGGAGCCAC 180 gtgagataggctctgttactcccatttgacaggtgAGGAGAGATTCTACAGGAGCCAC 180 *****	
	ACCGCTGAAGGAGAGAGAGGCAGCAGAgtaagggggccttctgtggcagagaggggaactggc 240 ACCTTGAAGGAGAGAGAGGCAGCAGAgtaagggggccttctgtggcagagaggggaactggc 240 **	
	actttggggaataagtggttcaggactgaatgtaatggagccatgtcagagctgtccttc 300 actttggggaataagtggttcaggactgaatgtaatggagccatgtcagagctgtccttc 300 *****	
	tggaaagggaaggacactggaacgctgccccctcagtgcttggacgggtccacaactg 360 tggaaagggaaggacactggaacgctgccccctcagtgcttggacgggtccacaactg 360 ****	
	tgattcacacgggttcccctaacgaagggtacacagtggtggcattctgtgactcgggtactt 420 tgattcacacgggttcccctaacgaagggtacacagtggtggcattctgtgactcgggtactt 420 *****	
	cccttttagTG 430 cccttttagTG 430 *****	

SEQ ID NO:	MINIGENE CASSETTE ALIGNMENT	
1 51	TAAACAAAGGtaagtcaatttgcagtttggataaataaatggtaacgggcaccaaggggga 60 SION1 TAAACAAAGGtaagtcaatttgcagtttggataaagggaattgaaattggcaccaaggggga 60 ON1m *****	
	aaattttataatgaacattttattttgttccagataaaaagtggagattgttatataaaa 120 aaacttttaggtgaacccttaagttgggttccagataaaaagagagattgttatataaaa 120 ***	
	ctaaataaaagctaaattaaacccctctcatctccacagATGTCCACTTAAAAAAATCT 180 ctaaataaaagctaaattaaacccctctcatctccacagATGTCCACCAAAAAAATCT 180 *****	
	GCCCATGGGAGCAGAAAGAgttaagtggcagtgaggaggttacctagctcaggccaatggcag 240 GGTTTGGGAGCAGAAAGAgttaagtggcagtgaggaggtttctagctcaggccaatggcag 240 **	
	attacaagttcttatcctgacagttgactctgaacatccttggtaaaagaagaatgtgtg 300 attacaagttcttatcctgacagttgactctgaacatccttggtaaaagaagaatgtgtg 300 *****	

	cacatcatctttctataggataatgacacttctcttttctaacttctagTG 351
	cacatcatctttctataggataatgacacttctcttttctaacttctagTG 351

SEQ ID NO:	MINIGENE CASSETTE ALIGNMENT	
52	TGAAGACGAGgtgagcccagaacttagggagggtgcccctttcaaaactgacaacttttaca	60 ON2m2
2	TGAAGACGAGgtgagcccagaaccgagtgaggatgcccctttcagactgacaaccgttaca	60 SION2
51	TGAAGACGAGgtgagcccagaaccgaggaggatgcccctttcagactgacaaccgttaca	60 ON2m1

	ccccatacaactacaaaactcctttgagtttttggtaggttttcagggttatatcttttta	120
	ccccacgacatgtacaaaagtccctttgagtttttttatatttcagggtgatatcttttta	120
	ccccacgacatctacaaaactcctttgagtttttttatatttcaggcgatatcttttta	120

	aataaccgtatgaataattttttgttctttattttttccagTGAGCACCAAAAGAAAAAA	180
	aataaccgtatgaataattttttgttctttattttttccagTGAGCACCAATAAAATAAAAA	180
	aataaccgtatgaataattttttgttctttattttttccagTGAGCACCAATAAAATAAAAA	180

	TTCCAACAATCCAACAAAATGCTTGGGTTCTTGCCAATTTCAACAATTGTTTAATAC	240
	CGCCATACAATCCAACAATTATTATTAGTTCTTGCCATTTCGCAACATCCTGCCTAATAC	240
	CGCCATACAATCCAACAATTATTATTAGTTCTTGCCATTTCGCAACATCCTGCCTAATAC	240
	* ****	
	AAAAAATACAAGACAGTATTTCCTTCCACTTCAAGAAGACTGTTTTCTAGCCAAGA	300
	ATGGAATACAAGACAGTATTTCCTTCCACTTCAAGAAGACTGTTTTCTAGCCAAGA	300
	ATGGAATACAAGACAGTATTTCCTTCCACTTCAAGAAGACTGTTTTCTAGCCAAGA	300
	* ****	
	aatagagtttgataagtgccaagattcaagggaagtctaggctaagacaaaatctcttga	360
	aatagagcgtgataagtgccaagattcaaaataagtctaggctaagacaaaatctcttga	360
	aatagagcgtgataagtgccaagattcaaaataagtctaggctaagacaaaatctcttga	360

	ttgggtggattgttttcttaaaattggggacaacaataatgaaacataatttctttatggac	420
	atgggtggaatgttttcttagaaatgggacagcaataatgaaacataatttctttatggac	420
	atgggtggaatgttttcttagaaatgggacagcaataatgaaacataatttctttatggac	420

	ttataacctactgcttttttggtagTG 447	
	ttataacctactgcttttttggtagTG 447	
	ttataacctactgcttttttggtagTG 447	

SEQ ID NO:	INIGENE CASSETTE ALIGNMENT	
6	TGAATTACAGgtaagctgggtttttcagacaagatagatagtttgattgtcatcagccaa	60 SION6
54	TGAATTACAGgtaagctgggtttttcagacaagatagatagtttgattgtcatcagccaa	60 ON6m2
55	TGAATTACAGgtaagctgggtttttcagacaagatagatagtttgattgtcatcagccaa	60 ON6m3

	ttcaaaggagtggtgatacaggcgtgacccataaggctcaaagcgaaacttttcttgaaa	120
	ttcaaaggagtggtgatacaggcgtgacccaaaggctcaaagttaaattttttttgaaa	120
	ttcaaaggagtggtgatacaggcgtgacccaaaggctcaaagttaaattttttttgaaa	120

	gtcaagataaatatagagaacaacaagattctgctaaaaagtgtgctgatttttagagagtt	180
	atcaagataaggatagagaacaacaagattctgctaaaaagtgttgatttgggagagtt	180
	atcaagataaggatagagaacaacaagattctgctaaaaagtgttgatttgggagagtt	180

	gtggtaatctctgtgaagagtttaggtaaaatgggtgatcctggctattttaaagtgtttc	240
	gtggtaatctctgtgaagagtttaggtaaaatgggtgatcctggctattttaaagtgtttc	240
	gtggtaatctctgtgaagagtttaggtaaaatgggtgatcctggctattttaaagtgtttc	240

	tacttaattaaaaatgttactgctttaattttatttaagATGCCAAGGGGAAACTTAGAAG	300
	tacttaattaaaaatgttactgctttaattttatttaagATGCCAAGGGGAAACTTAGAAG	300
	tacttaattaaaaatgttactgctttaattttatttaagATGCCAAGGGGAAACTTAGAAG	300

	TTGTTTCATCATCGAGCCCTGGTTTTAGCTCAGATTTGAAGTGGTTGGACA	360
	TTGTTCAACAATTAGCCCTGGTTTTAGCTCAGATTTGAAGTGGTTGGACA	360
	TTGTTCAACAATTAGCCCTGGTTTTAGCTCAGATTTGAAGTGGTTGGACA	360

	cattgtactgtttg cg actagttagcttgtgattt at gtgtgaagacaataagtat tt ta 420 cattgtactgtttg tt actagttagcttgtgattt gg gtgtgaagacaataagtat tt gg 420 cattgtactgtttg tt actagttagcttgtgattt gg gtgtgaagacaataagtat tt gg 420 *****
	ttacaattt cg agaa ctt aaa att atgaaaagccctcatt ac ctatatcat ca atcagat ttacaattt tt agaac cca aga att tgaaaagccctcaata ct tatatcaacaat ca aat 480 ttacaattt tt agaac cca aga att tgaaaagccctcaata ct tatatcaacaat ca aat 480 *****
	tcttagagg ct ctcttttttttttt tt ta act tttt tt actttat ct gattata act gg tt tg 540 tcttaaaa act ctcttttttttttt tt gaa act tggt tt ttttat tt gattata att ga att g 540 tcttaaaa act ctcttttttttttt tt gaa act tggt tt ttttat tt gattata att ga att g 540 *****
	tatcabaatgaaa at atgctgggccc at ggagctcagttttt gt gaatat ct tttctatt 600 tatcaaattgaa acc aagctgggccc a aggagctcagttttt gt gaatat ct tttctatt 600 tatcaaattgaa acc aagctgggccc a aggagctcagttttt gt gaatat ct tttctatt 600 *****
	ctttctctgtcttctc ac agTG 622 ctttctctgtcttctc ac agTG 622 ctttctctgtcttctc ac agTG 622 *****

EXAMPLE VIII: ANALYSIS OF SMSM COMPOUND INDUCED SPLICING OF MINIGENE CASSETTES WITH TARGETED MUTATIONS

Ampliseq analysis

[2672] Nine SION minigene cassettes with targeted mutations, SION3m1, SION3m2, SION3T1m2, SION3T3m2, SION1m2, SION2m1, SION2m2, SION6m2 and SION6m3, were transfected into HEK293 cells and cultured for 16 hours before being treated with 10nM or 1μM HD1 or DMSO for 24 hours as described above. Total RNA was extracted, and cDNA was generated by reverse transcription in presence of random hexamers. The cDNA was then amplified by Ampliseq PCR and sequenced in an Illumina iSeq 100 sequencer. Ampliseq reads were mapped to the minigene sequences using STAR and visualized with an Integrative Genomics Viewer (IGV).

[2673] FIG. 10A depicts a Sashimi plot of Ampliseq results for ON2m1 showing the mutations in ON2m1 “removed” all undesired splice sites previously observed with SION2.

[2674] Similarly, FIG. 10B shows all undesired splice sites in SION3 were “removed” by mutations in ON3m1. However, a new acceptor site was accidentally created by one of mutations (FIG. 10 C).

[2675] FIG. 10D-10E shows a dose-dependent increase of desired splicing for SION mutant constructs ON2m1, ON3m1, T1m2 and T3m2 without substantially reducing the fold increase in HD1 compound induced GFP expression over GFP expression in the presence of DMSO.

RT-PCR Analysis

[2676] FIG. 11A shows an RT-PCR analysis of different minigene cassettes. 5×10^5 HEK293 cells were transiently transfected with 2 μ g of the different SION/SIOFF plasmids in 6-well plates, using 6 μ l Eugene6® (Promega) according to the protocol provided by the manufacturer. After overnight incubation, varying concentration of the HD1 compound dissolved in DMSO (DMSO, 10 nM, 1 μ M, final DMSO concentration in cell culture 0.5%) were added and incubated for additional ~24h. The grey * indicates FD2 compound was used instead of HD1 (DMSO, 1 nM, 100 nM). Total RNA was isolated with the RNeasy plus mini kit (Qiagen). RNA concentration and quality were assessed with a NanoDrop spectrophotometer (ThermoFisher).

[2677] To analyze changes in splicing changes, cDNA was synthesized using the iScript™ cDNA synthesis kit (Biorad) according to the manufacturer's instructions. Endpoint PCRs were set up using Platinum™ PCR SuperMix High Fidelity (Invitrogen), and the resulting PCR products were separated on 2% eGels (Invitrogen). Primers were directed against common sequences in the minigene cassette constructs, as indicated in FIG. 11B.

[2678] The table in FIG. 11C shows an overview of the different SION constructs and their expected RT-PCR product lengths, using different primer combinations. The numbers for the different RT-PCR products are in nucleotides.

[2679] FIGs. 11Di-iii show endogenous splicing changes under the same conditions as FIG. 11A. To determine endogenous splicing changes, the AgPath-ID™ One-Step RT-PCR reagents from Applied Biosystems were used according to the protocol provided by the manufacturer. The resulting RT-PCR products were separated on 2% eGels (Invitrogen). Primers were directed against the flanking exons.

TARGET		F SEQ 5'-3'		R SEQ 5'-3'
POMT2	85	ACCCTTCCTTCCCAGTGGAG	86	CTGATAGTGCTTCCGGGTCA
c12orf4	87	GCCCAGGACTTCGGAACTA	88	TGACTGGCATCTCTTGAACA
HTT49a	89	TTCGTGGTGGCAACCCTTGA	90	GGCGTGGGTCACAACTCTG
LOC1507 76	111	TGGCTTCATCACTATTCGTTGG	112	GCTCCTCAGTAGGCGTGAAC

[2680] FIG. 11E shows an RT-PCR analysis of different minigene cassettes, using the same total RNA as in FIG. 11A. In addition to primers directed against common sequences upstream

and downstream of the minigene cassette constructs, a forward primer binding to the psiExon was used.

SET A:

SION-F-KE: 5'-GGCAAAGAATTGGGATTCGAACAT-3' (SEQ ID NO: 58)

SION-R-KE: 5'-CACCCCGGTGAACAGCTC-3' (SEQ ID NO: 59)

SET B:

SION-F-mut: 5'-GGCAAAGAATTGGGATTTTAACAA-3' (SEQ ID NO: 113)

SION-R-KE: 5'-CACCCCGGTGAACAGCTC-3' (SEQ ID NO: 59)

SET C:

SION-F-uni: 5'-TTTGGCAAAGAATTGGGATT-3' (SEQ ID NO: 114)

SION-R-KE: 5'-CACCCCGGTGAACAGCTC-3' (SEQ ID NO: 59)

psiEXON:

F SION3, GFP: SION3-psi-F: 5'-TGGGAGCCCCAAGGAAGA-3' (SEQ ID NO: 81)

F SION3T3: SION3T3-psi-F: 5'-CTACAGGAGCCCACAGCG-3' (SEQ ID NO: 82)

F T3_m2: T3m2-psi-F: 5'-CAGGAGCCCACAGTTCTGAAG-3' (SEQ ID NO: 83)

F On2_m1: ON2m1-psi-F: 5'-CTTGCCATTCGCAACATCCTG-3' (SEQ ID NO: 84)

R for all: SION-R-KE 5'-CACCCCGGTGAACAGCTC-3' (SEQ ID NO: 59)

[2681] The diagram below the gel images shows position of the different primers, indicated by arrows. Exons are shown as boxes and introns are shown as lines.

[2682] The table in FIG. 11F shows an overview of the different SION constructs and their expected RT-PCR product lengths for different primer combinations. The numbers for the different RT-PCR products are in nucleotides.

EXAMPLE IX: COMPARISON BETWEEN MINIGENE CASSETTES

[2683] LMI0705 (branaplam) and RG7800/RG76196 are RNA splicing modulators that modulate alternative splicing of the SMN2 gene and enhance retention of exon 7 in the mature SMN2 mRNA. Previous research discovered LMI0705 induces exon 2a SF3B3 exon 2a inclusion by more than 100 fold (published in bioRxiv by Monteys et al. (2020)).

[2684] The SION2m1 GFP expression was therefore compared one on one with that of SF3B3_e2a_Xon (SION9) and an abridged version, SF3B3_e2a (SION10) GFP expression vectors in HEK293 cells in the presence of the HD1 SMSM compound.

[2685] As shown in FIG. 12A, the Human Splicing Finder website was used to screen the SF3B3intron sequence for putative silencer and enhancer sequences that could modulate inclusion of the SF3B3 LMI070-spliced pseudoexon (see Monteys et al. (2020), Extended Data Fig 3d). Three intronic regions rich in silencing sequences that could repress splicing in the absence of the drug were identified downstream of the pseudoexon and deleted from the minigene cassette.

[2686] FIGs. 12Bi-iii compare the sequences surrounding the SF3B3_e2a with those sequences present in the SF3B3_e2a_Xon (SION9) and SF3B3_e2a (SION10) GFP expression vectors. The nucleotide sequences of SION2m1, SION9 and SION 10 are depicted in FIG. 12Ci-ii.

[2687] On day 1, 500,000 HEK293 cells/well were plated in 6-well plates (2 ml/well, 2.5×10^5 cells/ml). Cells were then transfected with 2 μ g plasmid (one of SION2m1, SION9, SION10 or AAV-GFP (positive control) or DMSO (negative control)) for ~24h. 6 μ l Fugene6 was added to 500 μ l Opti-MEM medium incubated for ~5 min at room temperature. 2 μ g plasmid was then added and incubated ~15 min at room temperature, before being added to the plated cells and further incubated for ~24h under standard cell culture conditions (37 °C, 5% CO₂, 100% relative humidity). On day 2, 1 μ M, 10nM HD1 or DMSO (final DMSO = 0.1%) was added to the cells. After culturing for another ~24h, GFP transgene expression was evaluated by Western blot analysis (FIG. 12D).

[2688] For Western blot analysis, the transfected cells were lysed in 75 μ l Laemmli buffer (Bio-Rad Laboratories, Inc.). Samples were then mixed with loading buffer, boiled for 10 min and 45 μ l was loaded per well and electrophoresed in a 3-8% Tris-Acetate gel @ 130V for 5-6 hrs. (12+2 wells; Invitrogen™ NuPAGE™ 3 to 8%, Tris-Acetate, 1.0 mm, Midi Protein Gel, 12+2-well). The protein MW ladder used was Invitrogen™ Himark HMW ladder (10 uL per well). Following electrophoresis, protein was electro-transferred to a 0.45 μ M nitrocellulose membrane (Bio-Rad™) at 150 mA for 90 min and then incubated with Li-Cor™ Blocking buffer overnight at 4°C with agitation. The blot was then incubated first with a Cell Signaling™ anti-GFP (D5.1) XP® (Cat#2956S; 1:1,000) rabbit mAb and a Sigma Aldrich™ anti- β -Actin mouse monoclonal antibody (Cat#A1978; 1:5,000) at room temperature for 1-2 hours, then

washed and incubated with secondary antibodies Alexa Fluor® 680 goat anti-mouse IgG (Thermo Fisher Scientific) and IRDye® 800CW donkey anti-Rabbit IgG (LI-COR™; dilution 1:10,000) + 0.1% Tween at RT for 1 hr. Blots were washed 4-5 min in PBS-T, washed again in PBS-T for 10 minutes and rinsed in PBS prior to scanning in an Odyssey Imager™ according to the manufacturer's instructions (channels 700 (red) and 800 (green)).

[2689] GFP expression as a % AAV-GFP expression and fold over GFP expression in the presence of DMSO are shown in FIG. 12Ei-ii.

[2690] In the presence of the HD1 compound, SION2m1 GFP expression was increased approximately 24 fold whereas SION9 and SION10 GFP expression was only induced 3-4 fold.

[2691] FIG. 13A shows an exemplary Western blot of GFP expression from 4 SION constructs (SION3, SION3T3, SION3T3m2 and SION2m1) following transfection into HEK293 cells in the presence of increasing amounts of HD1, (1.6nM, 8nM, 40nM, 200nM, 1µM and 5µM). The fold GFP expression relative to the expression from pAAV-GFP (positive control) or the 4 SION constructs in the presence of DMSO (negative control) is depicted in graphs of FIG. 13B-13E. SION2m1 has the lowest background expression in the presence of DMSO and SION3T3 has greatest induction of GFP expression equal to about 60% of GFP expression of the pAAV-GFP.

[2692] Accordingly, based on the results *in vitro*, the SION2m1- and SION3T3-controlled GFP constructs were chosen for the *in vivo* study. pAAV-GFP was used as a non-inducible positive control. Recombinant AAV9 vectors were made for the three constructs (see below).

EXAMPLE X: pAAV9-SION2m1, pAAV9-SION3T3m2 AND pAAV9-GFP PRODUCTION

[2693] AAV9-SION2m1 GFP, AAV9-SION3 GFP and AAV9-GFP viral vectors were produced in-house using proprietary helper plasmid, rep3cap9 plasmid and plasmids containing the gene of interest using standard procedures. Adherent human embryonic kidney (HEK) 293 cells cultured in Corning® CellSTACK® Culture Chambers were transfected with the plasmid constructs using Lipofectamine LTX with PLUS reagent and harvested 72 hours after transfection by cell lysis with 0.5% Triton X. The crude lysate was treated with an enzymatic cocktail containing Benzonase, RNAase A, Protease Inhibitor Cocktail and 0.001% Pluronic F68 for 3 hours at 37°C. The crude lysate was clarified by centrifugation at 2000xg at 4°C for 10 minutes. The supernatant was vacuum-filtered using 0.22µm Express Plus Stericup® Filter

Units. Viral vector was precipitated by addition of 5X Precipitation Reagent Stock Solution (PEG8000/ NaCl) to the clarified lysate (to the final 8% PEG8000) and incubating the mixture on ice at 4°C overnight.

[2694] Upon the completion of the precipitation step, the mixture was centrifuged at 3000xg at 4°C for 30 minutes. The supernatant was carefully decanted, and the viral pellet resuspended in suspension buffer (PBS (pH=7.4) with 200mM NaCl and 0.001% Pluronic F68). The suspension was centrifuged at 10,000xg at 4°C for 10 minutes, then the resulting supernatant was loaded on an iodixanol gradient. The vector was purified by centrifugation at 65,000 rpm for 2 hours 45 minutes at 18°C, and the AAV-containing iodixanol fraction was collected. The purity of the viral vectors was assessed by SDS–polyacrylamide gel electrophoresis (PAGE) gel and silver staining and analyzed by SEC-MALS to determine concentration of full vector and full/total vector ratio.

EXAMPLE XI: INDUCED SPLICING OF AAV9-SION2m1 AFTER ICV ADMINISTRATION

Animal dosing and tissue collection

[2695] Inducible splicing of the AAV9-SION2m1 construct was assessed *in vivo*. An exemplary experimental plan is shown in FIG. 14B. On post-natal day 0 (PND 0), C57BL/6 mouse pups were administered vehicle, AAV9-GFP or AAV9-SION2m1 by intracerebroventricular (ICV) injection into the cerebrospinal fluid in the left and right cerebral ventricles. Vectors were provided at a concentration of 3.59 E12vg/mL suspended in sterile PBS/0.001% Pluronic F-68 solution. The experiment had three controls: injection solution without virus, injection of the AAV9-GFP positive control and injection of SION2m1 without compound treatment as negative control (see FIG. 14C).

[2696] Briefly, mouse pups were put onto the aluminum foil on wet ice to induce hypothermia anesthesia. The anesthesia was confirmed by very gently touching a paw and monitored for lack of movement or respiration. The injection sites were identified as halfway between lambda and bregma and approximately 1 mm lateral from the sagittal suture. 2 µl of virus or vehicle was loaded in Hamilton syringe and injected slowly into the cerebral ventricles (at a depth of approximately 2 mm from the top of head). After injection, mouse pups were placed on a warming pad until their body temperature and skin color return to normal and the pups began to move. The recovered pups were returned to the same dam.

[2697] Animals were weighed and monitored weekly (see FIG. 14D). Daily oral dosing of HD1 at 20 mg/kg or HD3 at 10 mg/kg was initiated when animals were 5 weeks old. On day 3, 7, or 14 post dosing, animals were euthanized, and brains were extracted 4 hours after the final dose of oral dosing. Tissues were then snap frozen on dry ice prior to testing.

Mouse Tissue Pulverization:

[2698] All steps were performed on dry ice. 2 mL Eppendorf tubes and tissueTUBE TT01 bags (Covaris, Part Number: 520001) were labelled appropriately. A Dewar vacuum flask was filled with liquid nitrogen. Eppendorf tubes, weigh boats, and disposable scoopers were placed on dry ice. The mouse tissues were placed into the labelled tissueTUBE TT01 bags and the appropriate glass tube cap was screwed into place on top of the tissueTUBE TT01 bags. The tissueTUBE TT01 bags containing the mouse tissue were carefully submerged into the liquid nitrogen for 30 seconds. Then the glass tube cap was loosened by half a turn to prevent pressure build-up during pulverization. The tissueTUBE TT01 bags were placed into the Covaris crypPREP CP02 and the mouse tissue pulverized. The pulverization was repeated to ensure a fine powder of mouse tissue was created and the tissueTUBE TT01 bags were re-submerged in the liquid nitrogen before the second pulverization. The pulverized tissue was then transferred from the tissueTUBE TT01 bags onto a weigh boat. Disposable scoopers were used to assist with the transfer of the powder to labelled 2mL Eppendorf tubes for storage at -80°C.

Protein Extraction

[2699] A mass of 100mg of tissue powder was weighed using an analytical scale and placed into a clean, labelled 2mL Eppendorf tube. A 5mm stainless steel bead (Qiagen) and 1mL of Tissue Lysis Buffer (1X Extraction Buffer PTR (Abcam; cat #: ab193970)), 1X Cell Extraction Enhancer solution (Abcam, (50X; cat. #: ab193971) , 1X Halt Protease Inhibitor (Thermo Fisher; (100X; Catalog #: 78430), 10mM NaF (Boston BioProducts), 2mM Phenylmethylsulphonyl fluoride (PMSF; Sigma 100mg/mL final concentration) was added to the 2mL Eppendorf tube. The tissue powder was homogenized using a Qiagen TissueLyser II for 2 minutes at 30 cycles/second and was repeated until no solid tissue was visible. The 2mL Eppendorf tube was then centrifuged at max speed for 20 minutes at 4°C to clear the lysate. The supernatant was transferred to a new, clean, labelled 2mL Eppendorf tube. A Pierce™ BCA Protein Assay (Thermo Fisher; cat # 23225) was performed at 562nm absorbance. Lysates were normalized to 1mg/mL using Tissue Lysis Buffer.

GFP ELISA and data analysis

[2700] Mouse tissue protein lysates were assayed for GFP expression using a GFP SimpleStep ELISA kit (Abcam; cat #: ab171581). Briefly, all reagents were equilibrated to room temperature (18-25°C) prior to use. 1X Cell Extraction Buffer PTR was prepared by diluting the 5X Cell Extraction Buffer PTR and 50X Cell Extraction Enhancer Solution to 1X with deionized water. 1X Wash Buffer PT was prepared by diluting the 10X stock with deionized water. 1X Antibody Diluent EB was prepared by diluting the 4X stock with 1X Wash Buffer PT. The Antibody cocktail was prepared by diluting the capture and detector antibodies in 1X Antibody Diluent EB. For standard preparation, a fresh set of standards was prepared for every ELISA. The GFP protein standard was reconstituted by adding 250µL of water by pipette thus giving a 40,000 pg/ml Stock Standard Solution. Eight tubes were labeled “1” through “8”. A volume of 388uL of 1X Cell Extraction Buffer PTR was added to Tube “1” and 150uL of 1X Cell Extraction Buffer PTR into Tubes “2” through “8”. The Stock Standard Solution was used to prepare the 2-fold dilution series starting at 1,200 pg/mL and where Tube “8” contains no protein and is designated as the blank control. For the testing samples, all materials and prepared reagents were equilibrated to room temperature prior to use. A volume of 50 µL of all diluted samples and standards were added to the appropriate wells of an ELISA plate. Then a volume of 50 µL of the Antibody Cocktail was added to each well. The plate was sealed and incubated for 1 hour at room temperature on a plate shaker set to 400 rpm. Each well was subsequently washed 3 times with 200 µL 1X Wash Buffer PT by decanting from wells then dispensing 200 µL 1X Wash Buffer PT into each well. After the last wash, the plate was inverted and blotted against clean paper towels to remove excess liquid. A volume of 100 µL of TMB Development Solution was added to each well and incubated for 5 to 7 minutes in the dark on a plate shaker set to 400 rpm. Finally, a volume of 100 µL of Stop Solution was added to each well. The plate was shaken on a plate shaker for 1 minute to mix. The OD was taken using a Biotek Cytation 5 Cell Imaging Multi-Mode Reader at 450 nm as an endpoint reading.

[2701] ELISA data were analyzed and plotted using GraphPad Prism 8 software. The GFP protein concentration was quantified as pg per µg total protein.

RT-PCR analysis

[2702] 15-20 mg of pulverized mouse brain were weighed out into RLT lysis buffer containing 10 µl/ml beta-mercaptoethanol and 5 µl/ml anti-foam reagent DX (Qiagen). The tissue was disrupted and simultaneously homogenized using bead-milling according to the manufacturer's

protocol (Qiagen TissueLyser). RNA and DNA was extracted using the Qiagen AllPrep DNA/RNA/Protein Mini kit according to the protocol provided by the manufacturer. RNA concentration and quality were assessed using a NanoDrop spectrophotometer (ThermoFisher).

[2703] To determine splicing changes in the constructs, cDNA was synthesized using the iScript™ cDNA synthesis kit (Biorad) according to the manual. Endpoint PCRs were set up using Platinum™ PCR SuperMix High Fidelity (Invitrogen) according to the manual, and the resulting PCR products were separated on 2% eGels (Invitrogen). Primers were directed against common sequences in the minigene constructs:

SION-F-KE: 5'-GGCAAAGAATTGGGATTCGAACAT-3' (SEQ ID NO: 58)

SION-R-KE: 5'-CACCCCGGTGAACAGCTC-3' (SEQ ID NO: 59).

Tissue collection and GFP imaging

[2704] Animals were euthanized with CO₂ and then perfused with ice cold PBS and brains were extracted/dissected out. The brains were preserved fixed in 4% PFA after extraction/dissection for 48 hours. Sagittal sections (20µm thickness) of the brain samples were performed in Leica Cryostat and mounted on Superfrost Plus (Fisher Scientific) microscope slides. On the day of the assay, the brain sections were washed in 1 X PBS for 3 times for 10 minutes and permeabilized in 1 X PBS with 0.5% Triton X-100 for 30 minutes at room temperature followed by 3 times PBS wash. Thereafter, the brain sections were blocked with 10% goat serum diluted in PBS. After blocking, the brain sections were incubated with fluorophore-conjugated primary antibody (Alexa Fluor 647-conjugated anti-GFP polyclonal antibody; 1: 500 dilutions in PBS with 0.01% goat serum) overnight. After primary antibody incubation, the brain sections were washed 3 times in PBS and covered with coverslips with mounting media with DAPI (Vectashield antifade mounting media with DAPI; Vector Laboratories). The brain sections were imaged under Leica Thunder microscope (Leica Microsystems) using the appropriate wavelength filter. Several images were 'stitched' together as necessary using LAS X software (Leica Microsystems).

Results

[2705] HD1 and HD3 induced splicing of the ON2m1 cassette was measured by GFP ELISA (FIG. 14Fi-ii) and RT-PCR (FIG. 14E and 14Fii). The results show that the HD1 and HD3 compounds enhanced splicing over ON2m1 vehicle by approximately 2-3 fold.

[2706] FIG. 14Gi shows GFP imaging of a brain section of a mouse that was injected ICV with AAV9- SION2m1 and administered 10mg/kg HD3 over a 14 day period. GFP fluorescence was observed primarily in the olfactory bulb. FIG. 14Gii and FIGs. 14Ii-iii shows a quantification of GFP olfactory bulb fluorescence in mice treated with AAV-ON2m1 with vehicle as compared to AAV-ON2m1 treated with HD3 over 14 days.

EXAMPLE XII: INDUCED SPLICING OF AAV-SION3T3 AFTER ICV ADMINISTRATION

Animal dosing and tissue collection

[2707] Inducible splicing of the AAV-SION3T3 construct was assessed *in vivo*. An exemplary experimental plan is shown in FIG. 15A. On post-natal day 0 (PND 0), C57BL/6 mouse pups were administered vehicle, AAV9-GFP or AAV9-SION3T3 by intracerebroventricular (ICV) injection into the cerebrospinal fluid in the left and right cerebral ventricles. Vectors were provided at a concentration of 3.59 E12vg/mL suspended in sterile PBS/0.001% Pluronic F-68 solution. The experiment had three controls: injection solution without virus, injection of the AAV9-GFP positive control and injection of SION2m1 without compound treatment as negative control (see FIG. 15B).

[2708] Briefly, mouse pups were put onto the aluminum foil on wet ice to induce hypothermia anesthesia. The anesthesia was confirmed by very gently touching a paw and monitored for lack of movement or respiration. The injection sites were identified as halfway between lambda and bregma and approximately 1 mm lateral from the sagittal suture. 2 µl of virus or vehicle was loaded in Hamilton syringe and injected slowly into the cerebral ventricles (at a depth of approximately 2 mm from the top of head). After injection, mouse pups were placed on a warming pad until their body temperature and skin color return to normal and the pups began to move. The recovered pups were returned to the same dam.

[2709] Animals were weighed and monitored weekly. Daily oral dosing of HD3 at 20 mg/kg or 10 mg/kg was initiated when animals were 5 weeks old. On Day 7 or 14 post dosing, animals were euthanized, and brains were extracted 4 hours after the final dose of oral dosing. Tissues were snap frozen by dry ice.

[2710] Mouse tissue pulverization, protein extraction, GFP ELISA and data analysis, RT-PCR analysis and Tissue collection and GFP imaging were performed as described in Example XI.

Results

[2711] FIG. 15C shows the quantification of brain GFP of mice (Grps 1-8) injected with AAV9-ON3T3 and administered 0, 10 or 20 mpk HD3 as compared to brain GFP of mice injected with AAV9-ON3T3 without administration of the HD3 compound (Grp3). The graph shows administration of the HD3 compound induced a 74-1758 fold increase in brain GFP relative to control mice that did not receive the HD3 compound. As shown in FIG. 15D, GFP fluorescence in brain sections of mice injected ICV with AAV9-ON3T3 increased significantly only when the mice were administered the HD3 compound as compared to AAV9-ON3T3 + vehicle.

EXAMPLE XIII: INDUCED SPLICING OF AAV-SION3T3 AFTER SUBRETINAL ADMINISTRATION

Subretinal injections for AAV9-SION3T3 and oral dosing

[2712] C57BL/6J mice were purchased from Jackson Laboratory (Bar Harbor, ME). All animal study protocols conformed to IACUC guidelines. Six-eight-week-old C57BL/6J mice were injected subretinally with 3E9 vg of AAV9-CMV-SION3T3 or AAV9-CMV-GFP or vehicle (PBS/0.001% Pluronic F-68 solution) and two weeks later oral dosing started for AAV9-CMV-SION3T3 injected mice with either HD3 (20 mg/kg) or vehicle (0.5% HPMC with 0.1% Tween 80; see FIG. 16A). The oral dosing continued for another two weeks post-injection. At 4 weeks post subretinal injections, the mice were euthanized with CO₂ inhalation and the retina were isolated and flash frozen for RNA and protein isolation. For immunohistochemistry and flat mount imaging, the eyes were enucleated and fixed in 4% Paraformaldehyde for further processing. The experimental protocol listing the different parameters (including AAV dose, oral dosing, number of mice/group, and assays performed) is depicted in FIG. 16B.

Fundus Imaging

[2713] Mice were anesthetized with a ketamine and xylazine cocktail and the pupils were dilated with a drop of 1% tropicamide and 2.5% phenylephrine. The cornea were kept moistened with a topical application of eye lubricant (GenTeal, Alcon, Fort Worth, TX). After two weeks of oral dosing with HD3 compound, fundus imaging was performed in treated and control groups and images captured using a Micron IV Retinal Imaging Microscope and StreamPix software (Phoenix Research Labs, Pleasanton, CA).

Retinal flat mount preparation and quantification of GFP Intensity

[2714] Enucleated eye globes were fixed in 4% paraformaldehyde for 2 hours. The fixed eyes were washed with PBS 3X for 5 minutes each. The retina were isolated in PBS and four cuts were made perpendicular to each other in order to make the whole mount flat.

[2715] Confocal micrographs of fluorescent specimens from retinal flat mount preparations were captured using a Zeiss LSM 700 laser scanning confocal microscope (Carl Zeiss) equipped with argon and helium-neon lasers. The GFP intensity in captured images was quantified using ImageJ software (NIH; Bethesda, MD).

Immunohistochemistry and GFP Imaging

[2716] Cryostat retinal sections (10-12 μm) were rehydrated in PBS for 5-10 min, permeabilized and blocked with 6% normal goat serum plus 2% BSA in PBS for 1 hr and incubated overnight in a moist chamber with the primary antibody against rabbit anti-mouse cone arrestin (Sigma, St. Louis, MO, Cat: AB15282; 1:500, diluted in PBS containing 2% normal goat serum). Subsequently, sections were washed and incubated with anti-rabbit alexa fluor 594 secondary antibody (Invitrogen, Waltham, MA) to localize cone arrestin. Slides were mounted in anti-fade medium containing DAPI (Vectashield-DAPI; Vector Laboratories, Burlingame, CA) to counterstain the nuclei, and images were captured using a Zeiss LSM 700 laser scanning confocal microscope (Carl Zeiss). Similarly, GFP imaging was done in cryosections without staining for cone arrestin.

[2717] GFP ELISA and data analysis was performed as described in Example XI.

Results

[2718] Fundus imaging (FIG. 16C), a retinal flat mount preparation (FIG. 16D) and a cross section of eyes (FIG. 16E) were taken from mice (Groups 1-4; see FIG. 16B) injected subretinally with AAV9-SION3T3 in the presence or absence of compound HD3. The results show that administration of HD3 leads to a significant increase in GFP fluorescence. This result confirms that HD3 induced splicing of SION3T3 pre-mRNA restores GFP's initiation codon and subsequent GFP translation.

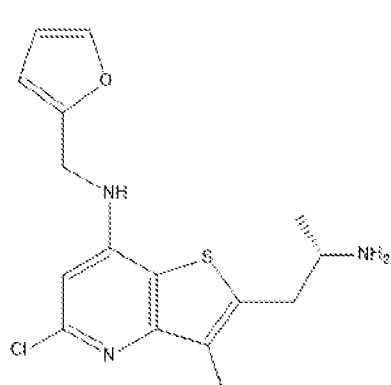
[2719] HD3 induced GFP fluorescence was also observed in the retina's outer nuclear layer (ONL, FIG. 16Fi-ii). HD3 induced GFP protein expression as measured by ELISA was 70 fold higher than the expression of AAV-SION3T3 in the absence of HD3.

[2720] FIG. 16G shows that the GFP fluorescence is primarily restricted to cones in the outer nuclear layer of the retina identified by the presence of cone-specific expression of arrestin.

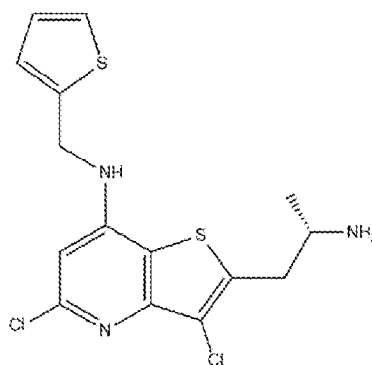
CLAIMS

1. A recombinant RNA sequence for controlling the activity of a regulatory element comprising in 5' to 3' order:
 - a first exon;
 - a second exon comprising a 3' terminal inactive first portion of a regulatory element; and
 - a third exon comprising a 5' terminal inactive second portion of a regulatory element,wherein inducible splicing between the second exon and the third exon restores the activity of the RNA regulatory element.
2. The RNA sequence of claim 1, wherein splicing between the second exon and the third exon is inducible in the presence of a small molecule splicing modifier (SMSM) compound.
3. The RNA sequence of claim 1, wherein, in the absence of the SMSM compound, the RNA regulatory element is not present within the recombinant RNA sequence.
4. The RNA sequence of claim 1, wherein, in the absence of the SMSM compound, the regulatory element is not present in the first, second or third exons.
5. The RNA sequence of claim 1, wherein the first and second exons are non-coding RNA sequences.
6. The RNA sequence of claim 1, wherein the third exon comprises a transgene's protein coding region.
7. The RNA sequence of claim 6, wherein the regulatory element comprises a cis-acting RNA regulatory element.
8. The RNA sequence of claim 6, wherein the regulatory element comprises the protein coding region's AUG start codon.
9. The RNA sequence of claim 8, wherein the protein coding region's AUG start codon is not present in the first, second or third exons.

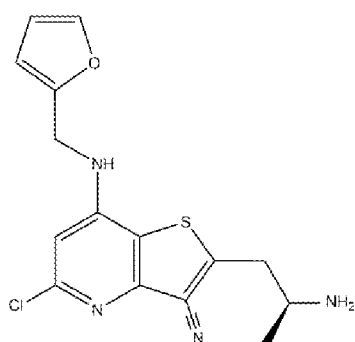
10. The RNA sequence of claim 8, wherein the nucleotide at the 3' end of the first exon is not adenosine.
11. The RNA sequence of claim 8, wherein the nucleotide at the 5' end of the third exon is not adenosine.
12. The RNA sequence of claim 8, wherein the inactive first portion of the RNA regulatory element at the 3' end of the second exon is the adenosine nucleotide of the protein coding region's AUG start codon.
13. The RNA sequence of claim 12, wherein the inactive second portion of the RNA regulatory element at the 5' end of the third exon is the UG dinucleotide of the protein coding region's AUG start codon.
14. The RNA sequence of claim 1, wherein the second exon comprises a 3' splice site and a non-canonical 5' splice site.
- 14x1. The RNA sequence of claim 1, wherein the non-canonical 5' splice site comprises the inactive first portion of the RNA regulatory element.
15. The RNA sequence of claim 14, wherein the non-canonical 5' splice site comprises an RNA sequence of 5'-CAAg-3' or 5'-Ugu-3'.
16. The RNA sequence of claim 15, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an FD compound.
17. The RNA sequence of claim 15, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:



(I),

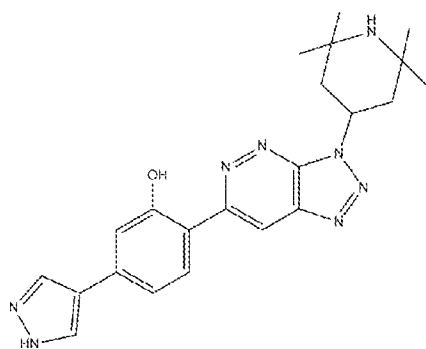


(II), or

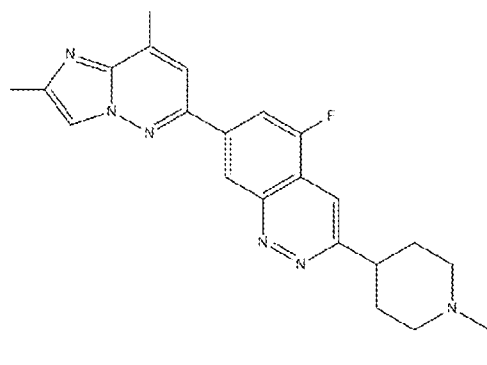


(III).

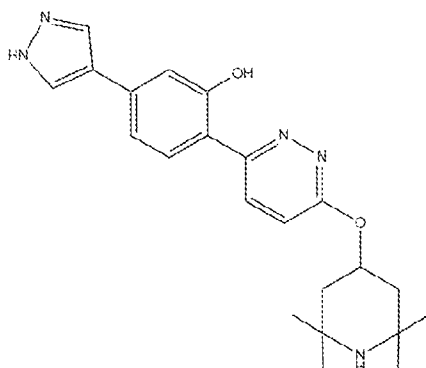
18. The RNA sequence of claim 14, wherein the non-canonical 5' splice site comprises an RNA sequence of 5'-NDGAg-3', wherein D is A, U or G and N is A, U, C or G.
19. The RNA sequence of claim 18, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an HD compound.
20. The RNA sequence of claim 18, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:



(IV),

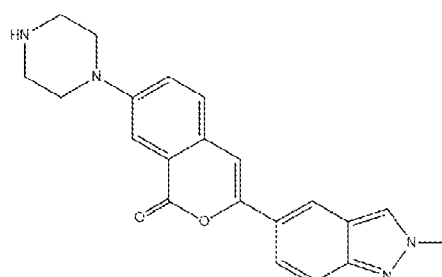


(V), or

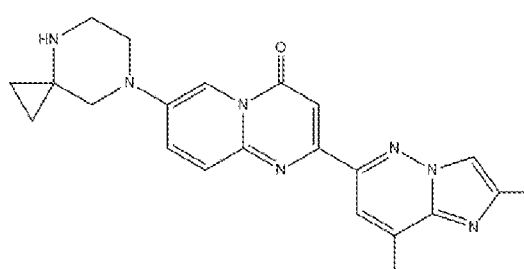


(VI).

21. The RNA sequence of claim 14, wherein the non-canonical 5' splice site comprises an RNA sequence of 5'-ANGAg-3', wherein N is A, U, C or G.
22. The RNA sequence of claim 21, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an SMA compound.
23. The RNA sequence of claim 21, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:



(VII), or



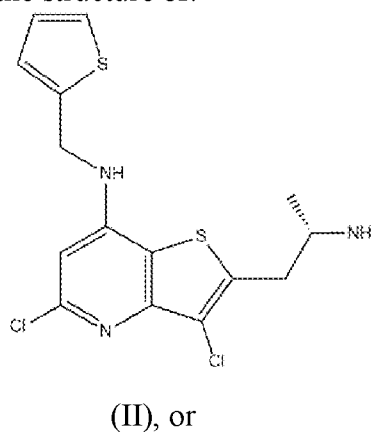
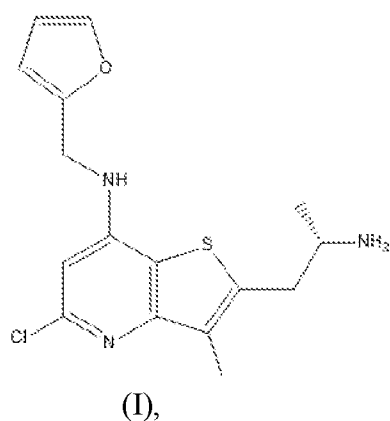
(VIII).

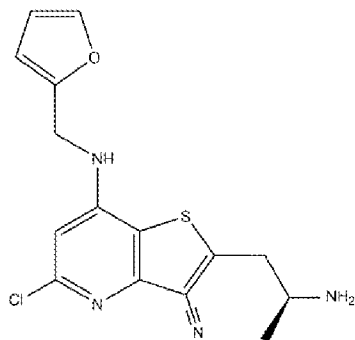
24. An RNA sequence for regulating transgene expression comprising in 5' to 3' order:

a first exon having a transgene's AUG start codon at its 3' end;
 a non-coding second exon; and
 a third exon comprising a second codon of the transgene's protein coding region at its 5' end,

wherein inducible splicing between the second and third exon prevents translation of the transgene's protein coding region.

25. The RNA sequence of claim 24, wherein the second and third exons do not comprise the AUG start codon of the protein coding region.
26. The RNA sequence of claim 24, wherein the second exon comprises a stop codon that, after splicing between the second and third exons, is in frame with the protein coding region's reading frame.
27. The RNA sequence of claim 24, wherein the second exon comprises a 3' splice site and a non-canonical 5' splice site.
28. The RNA sequence of claim 27, wherein the non-canonical 5' splice site comprises an RNA sequence of 5'-CAAg-3'.
- 28x1. The RNA sequence of claim 28, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an FD compound.
29. The RNA sequence of claim 28, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:



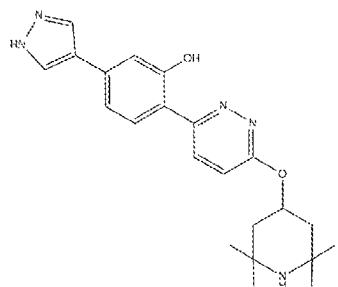


(III).

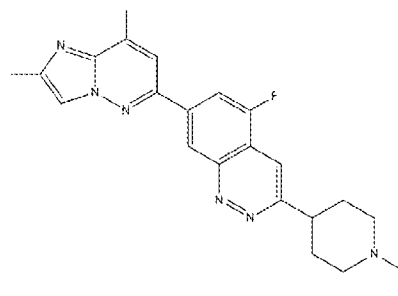
30. The RNA sequence of claim 28, wherein, in the absence of the SMSM compound, splicing between the first exon and the third exon places the transgene's protein coding region AUG start codon adjacent to the second codon of the transgene's protein coding region.
31. An expression vector comprising a promoter operably linked to a nucleotide sequence encoding the RNA sequence of claim 1.
32. The expression vector of claim 31, wherein the nucleotide sequence encoding the RNA sequence of claim 1 is operably linked to a transgene.
33. A recombinant adeno-associated virus (rAAV) comprising the expression vector of claim 32.
34. A pharmaceutical composition comprising the recombinant adeno-associated virus (rAAV) of claim 32.
35. The pharmaceutical composition of claim 34, wherein the composition is formulated to be administered intrathecally, intraocularly, intravitreally, retinally, intravenously, intramuscularly, intraventricularly, intracerebrally, intracerebellarly, or subcutaneously to a subject in need thereof.
36. A method for regulating transgene expression *in vivo*, comprising
 - delivering the recombinant adeno-associated virus (rAAV) of claim 33 into a subject in need thereof, and
 - administering an effective amount of a small molecule splicing modifier (SMSM) composition,

wherein the amount of the SMSM composition is effective at modulating the level of transgene expression in the subject.

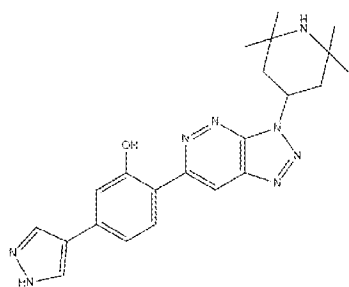
- 36x1. The method of claim 36, wherein the small molecule splicing modifier (SMSM) composition comprises an effective amount of an HD compound.
37. The method of claim 36, wherein the small molecule splicing modifier (SMSM) composition comprises an effective amount of a compound having the structure of:



(IV),



(V), or



(VI).

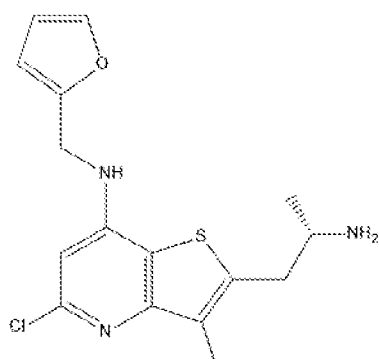
AMENDED CLAIMS

received by the International Bureau on 16 August 2022 (16.08.2022)

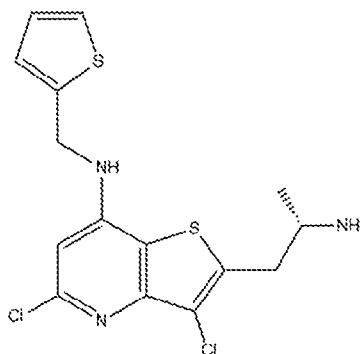
1. (Original) A recombinant RNA sequence for controlling the activity of a regulatory element comprising in 5' to 3' order:
 - a first exon;
 - a second exon comprising a 3' terminal inactive first portion of a regulatory element; and
 - a third exon comprising a 5' terminal inactive second portion of a regulatory element,wherein inducible splicing between the second exon and the third exon restores the activity of the RNA regulatory element.
2. (Original) The RNA sequence of claim 1, wherein splicing between the second exon and the third exon is inducible in the presence of a small molecule splicing modifier (SMSM) compound.
3. (Original) The RNA sequence of claim 1, wherein, in the absence of the SMSM compound, the RNA regulatory element is not present within the recombinant RNA sequence.
4. (Original) The RNA sequence of claim 1, wherein, in the absence of the SMSM compound, the regulatory element is not present in the first, second or third exons.
5. (Original) The RNA sequence of claim 1, wherein the first and second exons are non-coding RNA sequences.
6. (Original) The RNA sequence of claim 1, wherein the third exon comprises a transgene's protein coding region.
7. (Original) The RNA sequence of claim 6, wherein the regulatory element comprises a cis-acting RNA regulatory element.

8. (Original) The RNA sequence of claim 6, wherein the regulatory element comprises the protein coding region's AUG start codon.
9. (Original) The RNA sequence of claim 8, wherein the protein coding region's AUG start codon is not present in the first, second or third exons.
10. (Original) The RNA sequence of claim 8, wherein the nucleotide at the 3' end of the first exon is not adenosine.
11. (Original) The RNA sequence of claim 8, wherein the nucleotide at the 5' end of the third exon is not adenosine.
12. (Original) The RNA sequence of claim 8, wherein the inactive first portion of the RNA regulatory element at the 3' end of the second exon is the adenosine nucleotide of the protein coding region's AUG start codon.
13. (Original) The RNA sequence of claim 12, wherein the inactive second portion of the RNA regulatory element at the 5' end of the third exon is the UG dinucleotide of the protein coding region's AUG start codon.
14. (Original) The RNA sequence of claim 1, wherein the second exon comprises a 3' splice site and a non-canonical 5' splice site.
- ~~14~~15. (Original) The RNA sequence of claim 1, wherein the non-canonical 5' splice site comprises the inactive first portion of the RNA regulatory element.
- ~~15~~16. (Original) The RNA sequence of claim 14, wherein the non-canonical 5' splice site comprises an RNA sequence of 5'-CAAgu-3' or 5'-Ugu-3'.
- ~~16~~17. (Currently amended) The RNA sequence of claim ~~15~~16, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an FD compound.

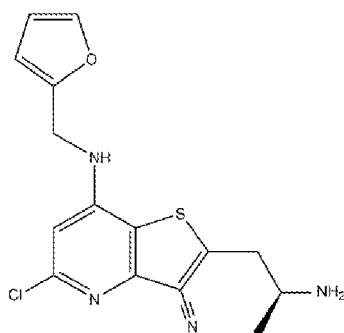
4718. (Currently amended) The RNA sequence of claim 4516, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:



(I),



(II), or

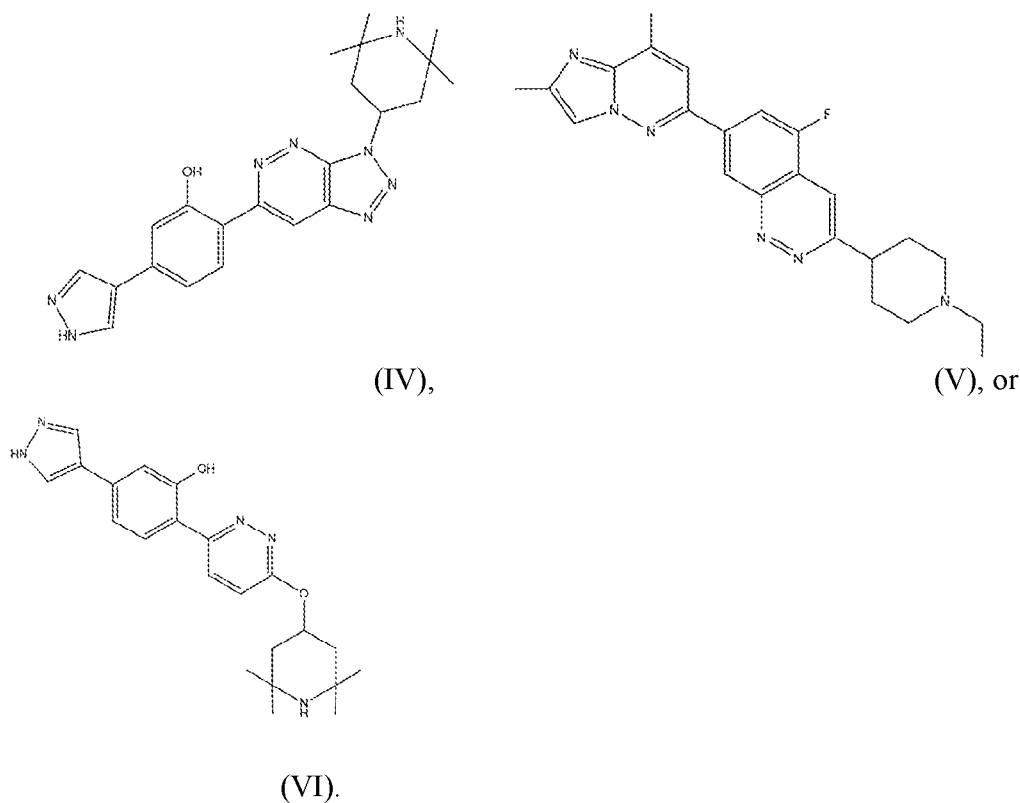


(III).

4819. (Original) The RNA sequence of claim 14, wherein the non-canonical 5' splice site comprises an RNA sequence of 5'-NDGAgU-3', wherein D is A, U or G and N is A, U, C or G.

4920. (Currently amended) The RNA sequence of claim 4819, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an HD compound.

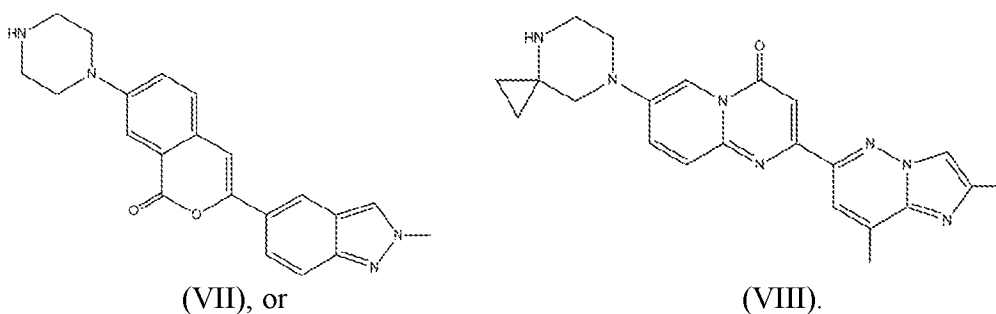
2021. (Currently amended) The RNA sequence of claim 1819, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:



2122. (Original) The RNA sequence of claim 14, wherein the non-canonical 5' splice site comprises an RNA sequence of 5'-ANGAg-3', wherein N is A, U, C or G.

2223. (Currently amended) The RNA sequence of claim 2122, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an SMA compound.

~~2324~~. (Currently amended) The RNA sequence of claim ~~2122~~, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:



~~2425~~. (Original) An RNA sequence for regulating transgene expression comprising in 5' to 3' order:

- a first exon having a transgene's AUG start codon at its 3' end;
- a non-coding second exon; and
- a third exon comprising a second codon of the transgene's protein coding region at its 5' end,

wherein inducible splicing between the second and third exon prevents translation of the transgene's protein coding region.

~~2526~~. (Currently amended) The RNA sequence of claim ~~2425~~, wherein the second and third exons do not comprise the AUG start codon of the protein coding region.

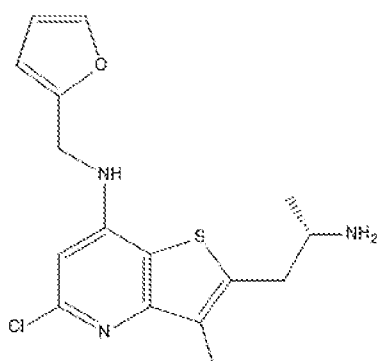
~~2627~~. (Currently amended) The RNA sequence of claim ~~2425~~, wherein the second exon comprises a stop codon that, after splicing between the second and third exons, is in frame with the protein coding region's reading frame.

~~2728~~. (Currently amended) The RNA sequence of claim ~~2425~~, wherein the second exon comprises a 3' splice site and a non-canonical 5' splice site.

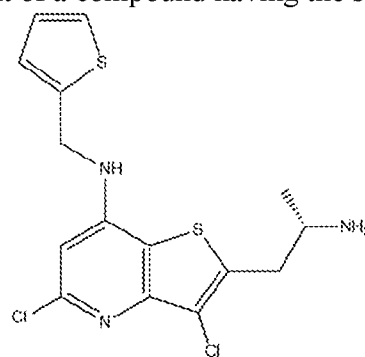
~~2829~~. (Currently amended) The RNA sequence of claim ~~2728~~, wherein the non-canonical 5' splice site comprises an RNA sequence of 5'-CAAg-3'.

2831. (Currently amended) The RNA sequence of claim 2829, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of an FD compound.

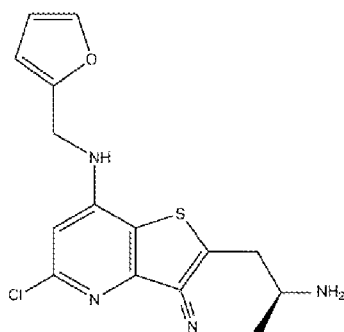
2931. (Currently amended) The RNA sequence of claim 2829, wherein splicing at the non-canonical 5' splice site can be induced with a small molecule splicing modifier (SMSM) composition comprising an effective amount of a compound having the structure of:



(I),



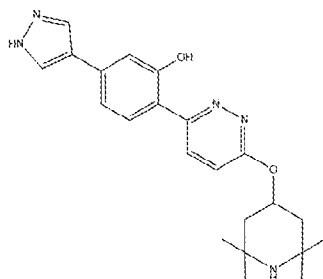
(II), or



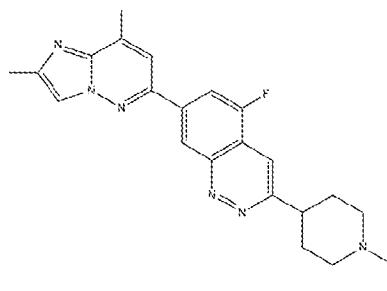
(III).

3032. (Currently amended) The RNA sequence of claim 2829, wherein, in the absence of the SMSM compound, splicing between the first exon and the third exon places the transgene's protein coding region AUG start codon adjacent to the second codon of the transgene's protein coding region.

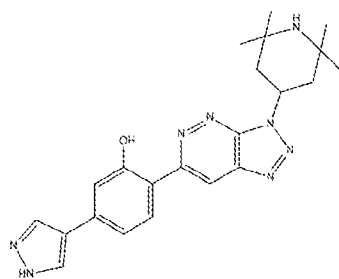
- ~~3133~~. (Original) An expression vector comprising a promoter operably linked to a nucleotide sequence encoding the RNA sequence of claim 1.
- ~~3234~~. (Currently amended) The expression vector of claim ~~3133~~, wherein the nucleotide sequence encoding the RNA sequence of claim 1 is operably linked to a transgene.
- ~~3335~~. (Currently amended) A recombinant adeno-associated virus (rAAV) comprising the expression vector of claim ~~3234~~.
- ~~3436~~. (Original) A pharmaceutical composition comprising the recombinant adeno-associated virus (rAAV) of claim 32.
- ~~3537~~. (Currently amended) The pharmaceutical composition of claim ~~3436~~, wherein the composition is formulated to be administered intrathecally, intraocularly, intravitreally, retinally, intravenously, intramuscularly, intraventricularly, intracerebrally, intracerebellarly, or subcutaneously to a subject in need thereof.
- ~~3638~~. (Currently amended) A method for regulating transgene expression *in vivo*, comprising delivering the recombinant adeno-associated virus (rAAV) of claim ~~3335~~ into a subject in need thereof, and administering an effective amount of a small molecule splicing modifier (SMSM) composition, wherein the amount of the SMSM composition is effective at modulating the level of transgene expression in the subject.
- ~~3638~~~~432~~. (Currently amended) The method of claim ~~3638~~, wherein the small molecule splicing modifier (SMSM) composition comprises an effective amount of an HD compound.
- ~~3740~~. (Currently amended) The method of claim ~~3638~~, wherein the small molecule splicing modifier (SMSM) composition comprises an effective amount of a compound having the structure of:



(IV),

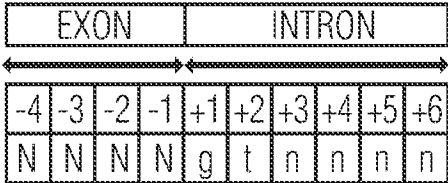


(V), or



(VI).

SEQ ID NO:	FD COMPOUNDS										
	INCLUSION										
	-4	-3	-2	-1	+1	+2	+3	+4	+5	+6	
15	T	A	A	G	g	t	n	n	n	n	8.2
16	A	C	A	A	g	t	n	n	n	n	7.1
17	C	C	A	A	g	t	n	n	n	n	5.8
18	G	A	A	G	g	t	n	n	n	n	4
19	A	A	A	G	g	t	n	n	n	n	3.4
20	T	C	A	A	g	t	n	n	n	n	3.2
21	C	A	A	G	g	t	n	n	n	n	2
22	T	A	C	A	g	t	n	n	n	n	1.9



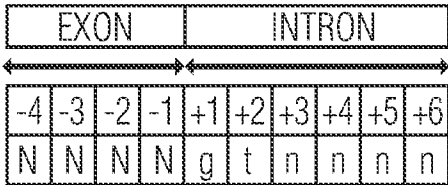
SEQ ID NO: 14

IKBKAP EXON 20 MUTANT									
C	A	A	g	t	a	a	g	c	

SEQ ID NO: 11

FIG. 1Ai

SEQ ID NO:	FD COMPOUNDS										
	SKIPPING										
	-4	-3	-2	-1	+1	+2	+3	+4	+5	+6	
23	A	A	C	T	g	t	n	n	n	n	13
24	A	T	C	T	g	t	n	n	n	n	10
25	A	A	T	T	g	t	n	n	n	n	9.1
26	T	T	C	T	g	t	n	n	n	n	8.5
27	A	C	C	T	g	t	n	n	n	n	7.3
28	C	C	C	T	g	t	n	n	n	n	5.9
29	C	A	C	A	g	t	n	n	n	n	5.5
30	C	A	C	T	g	t	n	n	n	n	5



SEQ ID NO: 14

FIG. 1Aii

SEQ ID NO:	HD COMPOUNDS										
	INCLUSION										
	-4	-3	-2	-1	+1	+2	+3	+4	+5	+6	
31	C	A	G	A	g	t	n	n	n	n	42.3
32	T	A	G	A	g	t	n	n	n	n	35.8
33	A	A	G	A	g	t	n	n	n	n	34.3
34	G	A	G	A	g	t	n	n	n	n	26.8
35	A	T	G	A	g	t	n	n	n	n	8.1
36	A	A	C	T	g	t	n	n	n	n	2
37	A	G	T	G	g	t	n	n	n	n	1.8

EXON					INTRON						
-4	-3	-2	-1	+1	+2	+3	+4	+5	+6		
N	N	N	N	g	t	n	n	n	n		

SEQ ID NO: 14

HTT EXON 49A									
C	A	G	A	g	t	a	a	g	g

SEQ ID NO: 12

FIG. 1Aiii

SEQ ID NO:	SMA COMPOUNDS											
	INCLUSION											
	-4	-3	-2	-1	+1	+2	+3	+4	+5	+6		
38	A	A	G	A	g	t	n	n	n	n		42.5
39	A	T	G	A	g	t	n	n	n	n		42
40	A	G	G	A	g	t	n	n	n	n		33.9
41	C	A	G	A	g	t	n	n	n	n		21.9
42	T	A	G	A	g	t	n	n	n	n		15.9
43	G	A	G	A	g	t	n	n	n	n		11.2
44	A	C	G	A	g	t	n	n	n	n		4.5

EXON					INTRON						
-4	-3	-2	-1	+1	+2	+3	+4	+5	+6		
N	N	N	N	g	t	n	n	n	n		

SEQ ID NO: 14

SMN EXON 7											
A	G	G	A	g	t	a	a	g	t		

SEQ ID NO: 13

FIG. 1Aiv

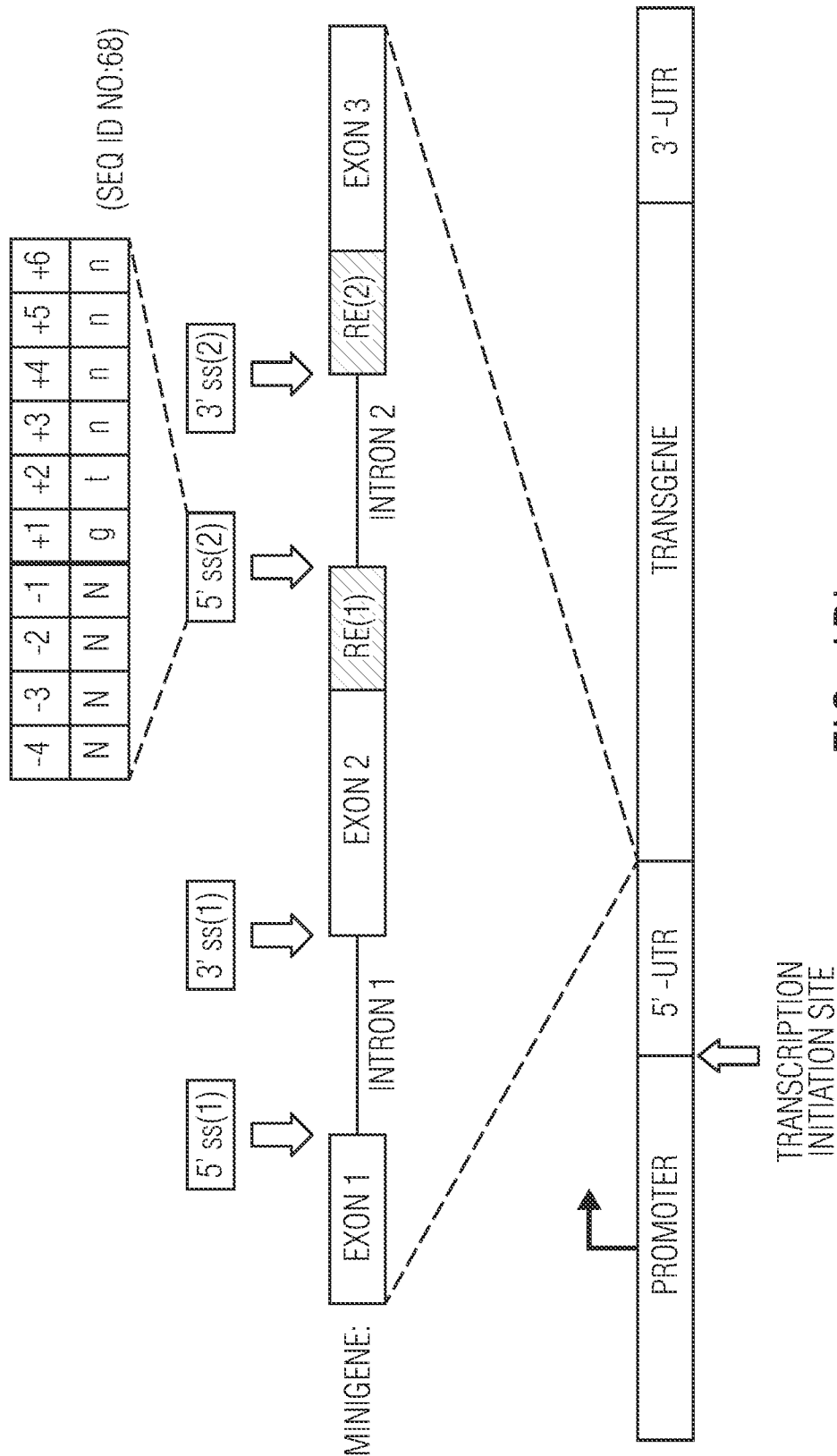


FIG. 1Bi

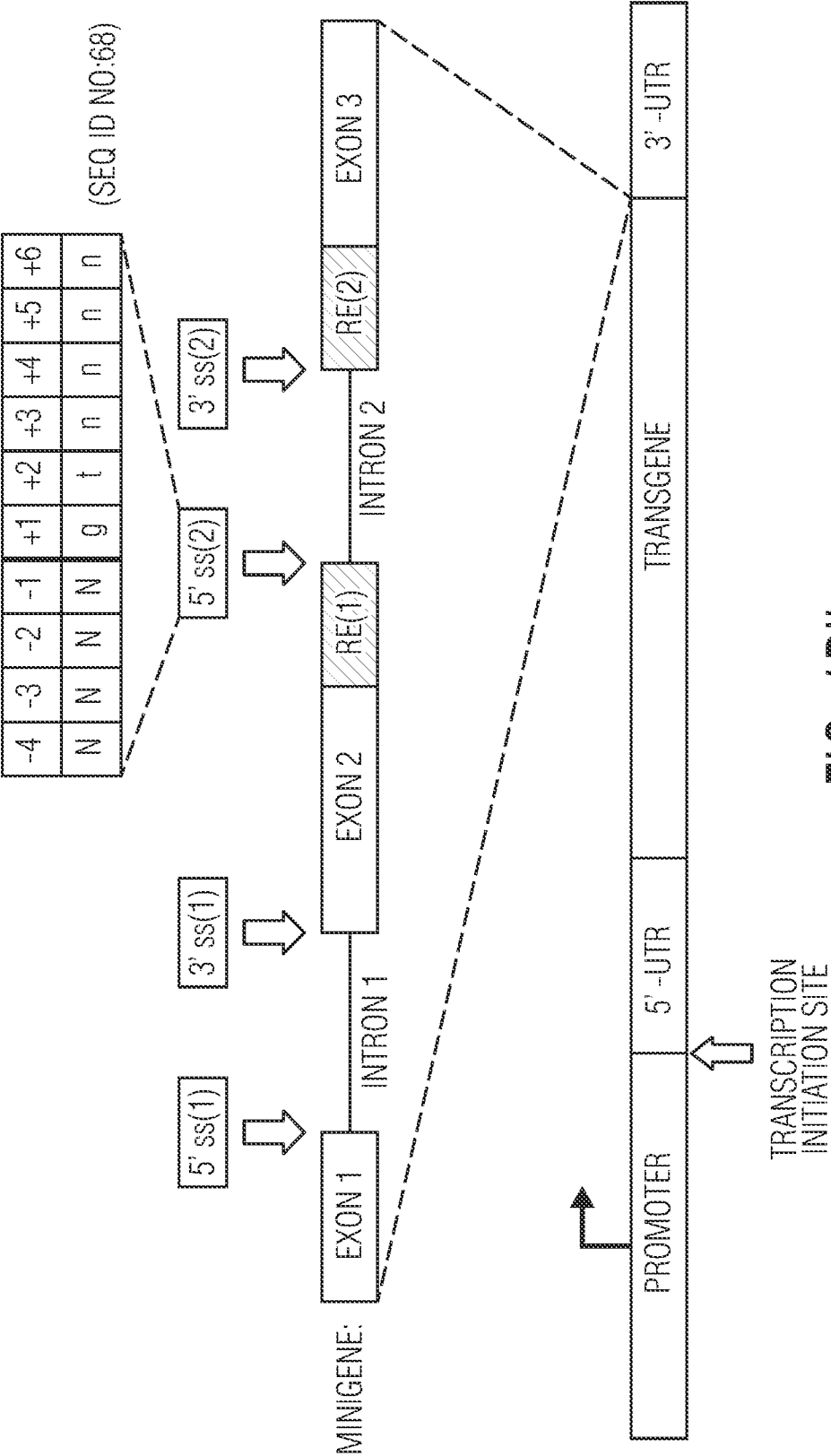


FIG. 1Bii

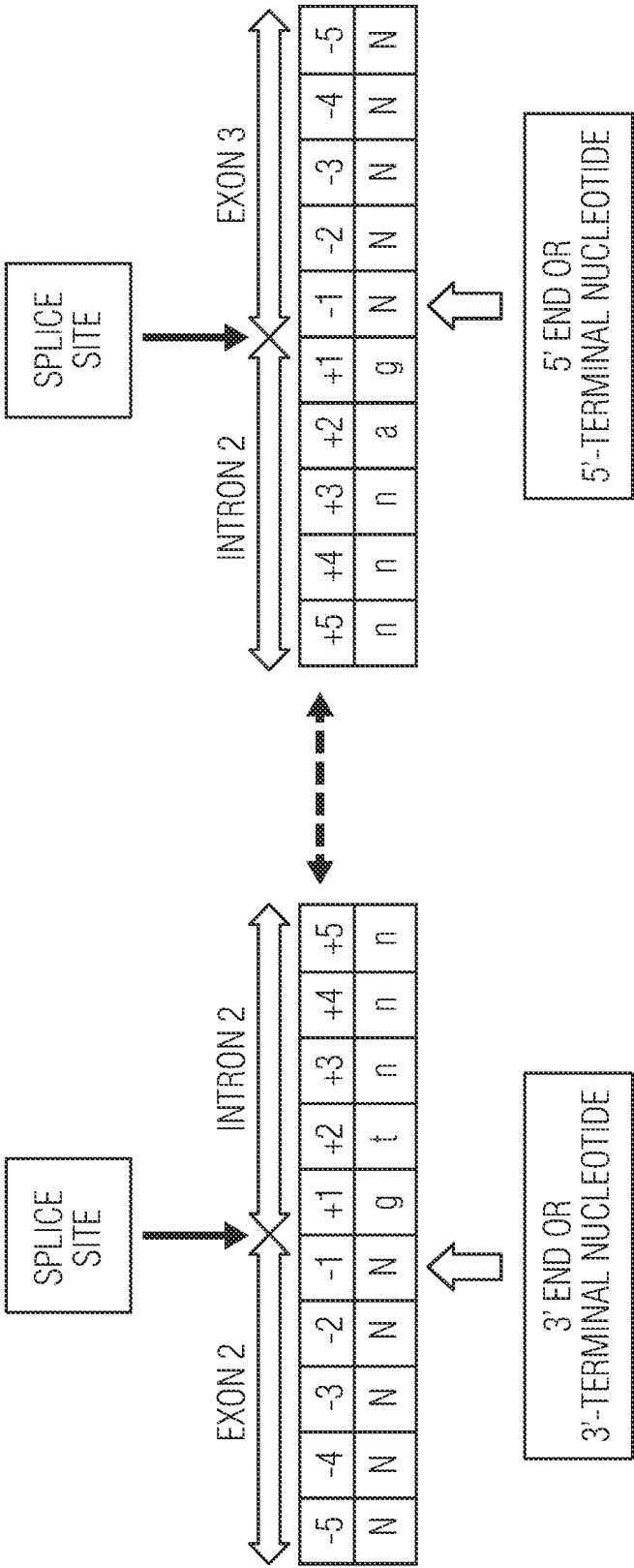


FIG. 1Biii

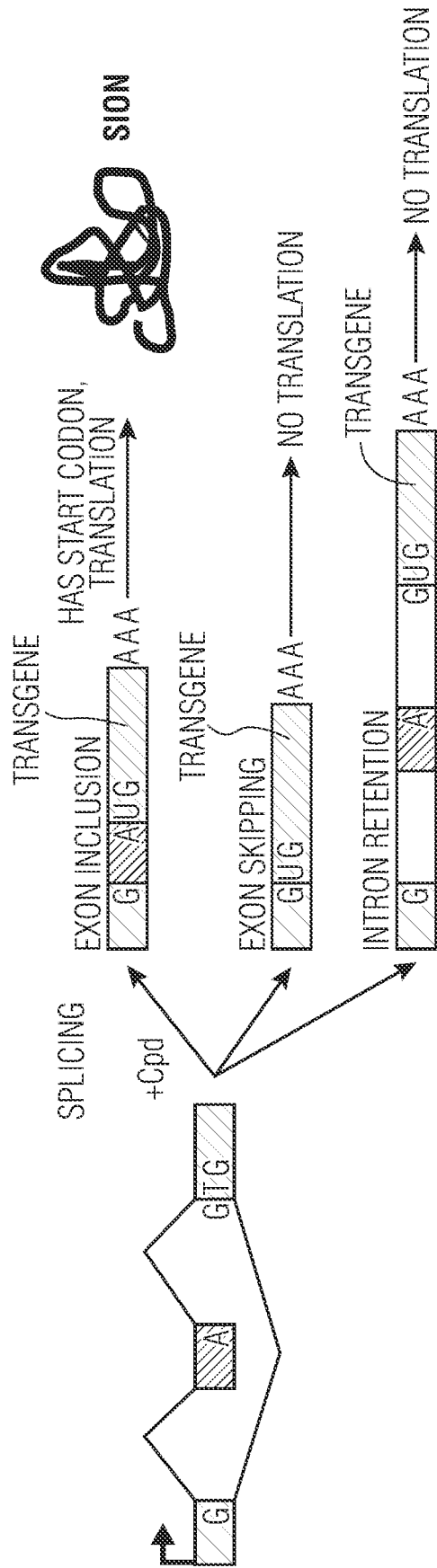


FIG. 10i

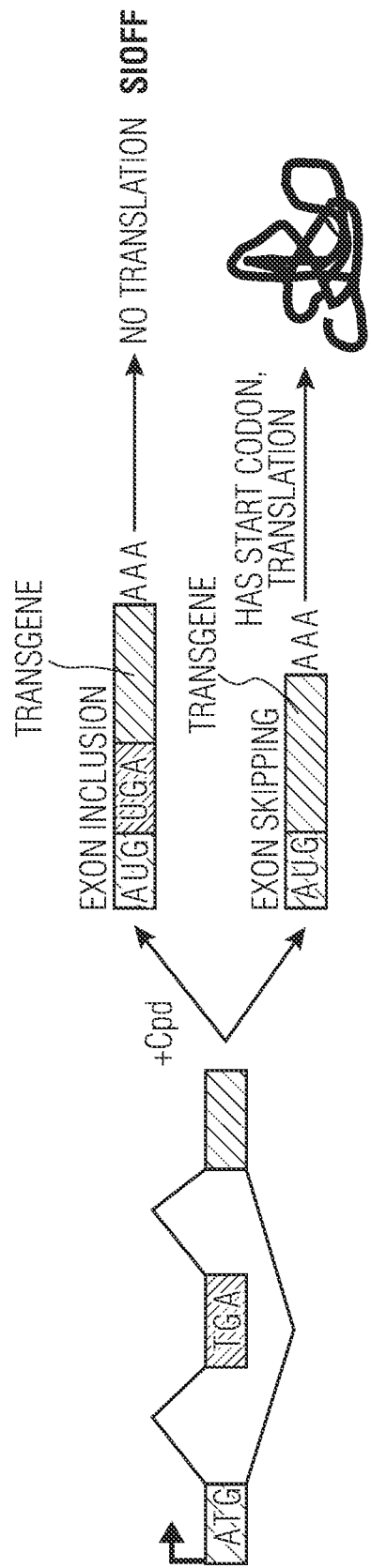


FIG. 10ii

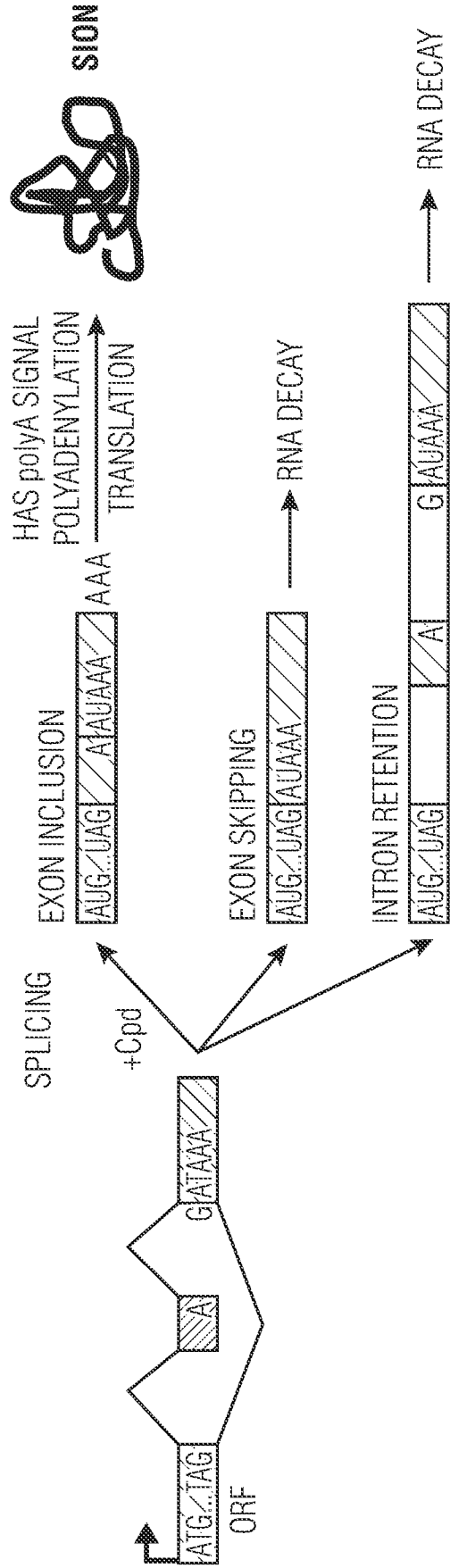
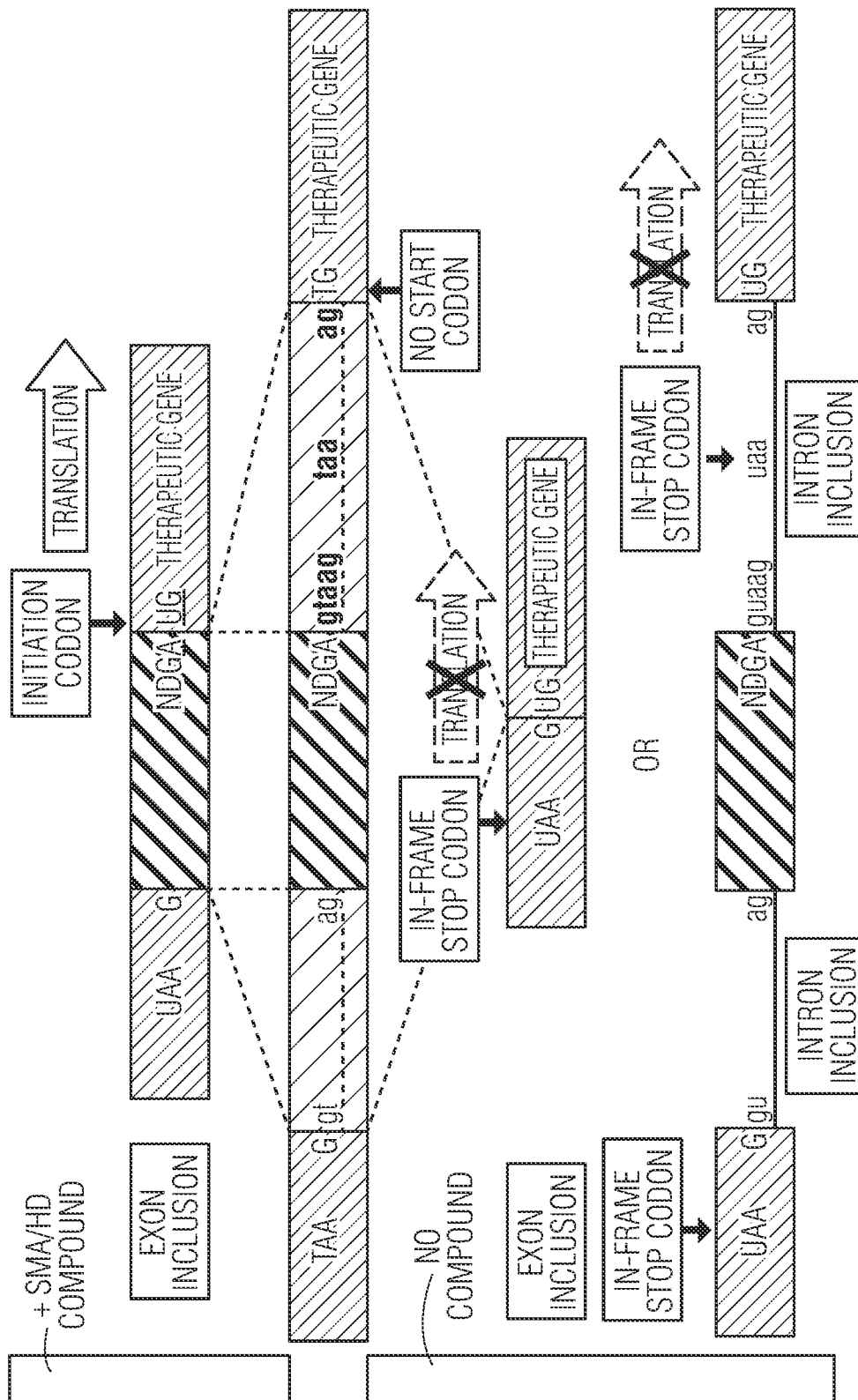


FIG. 1D



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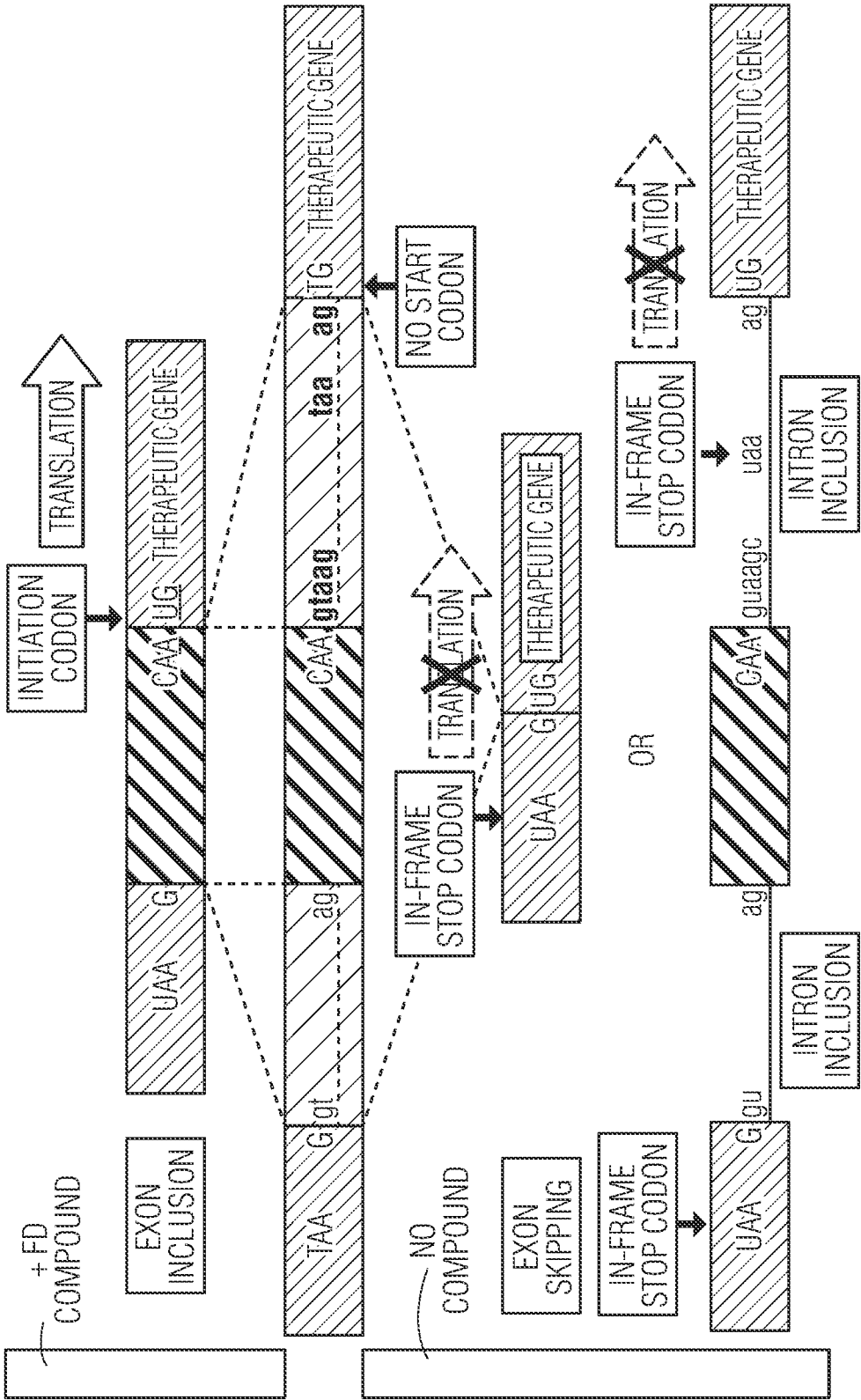


FIG. 1F

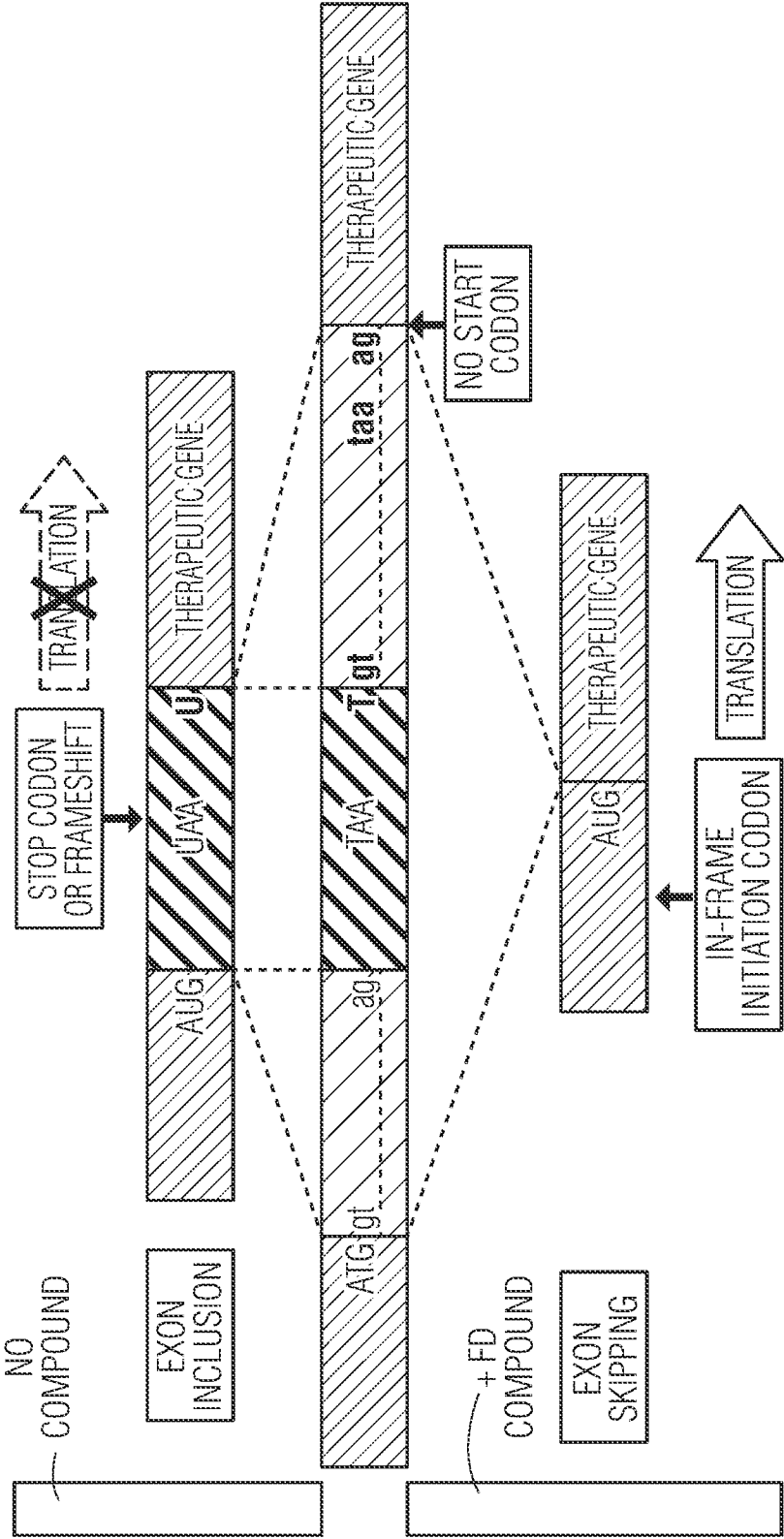


FIG. 1G

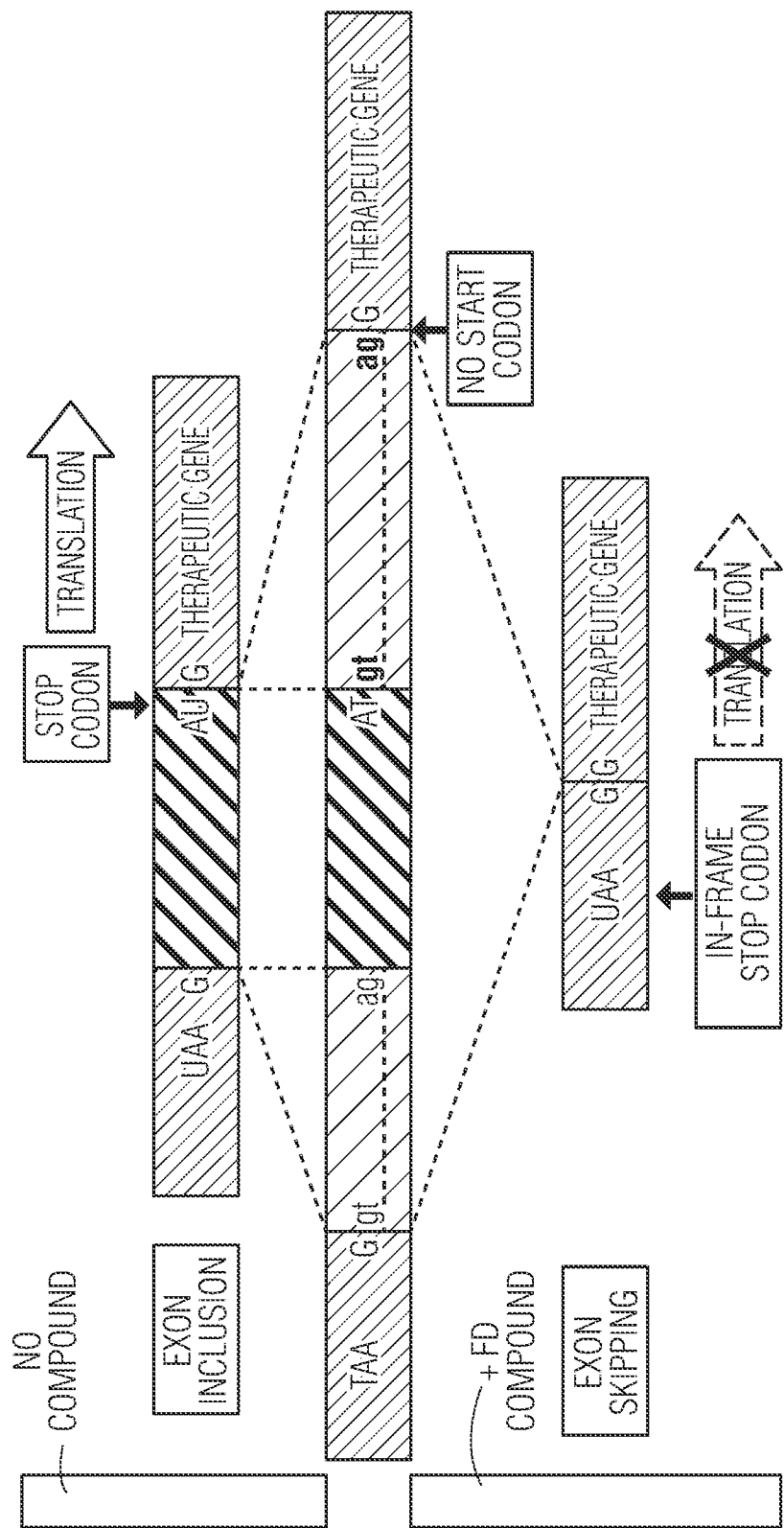


FIG. 1H

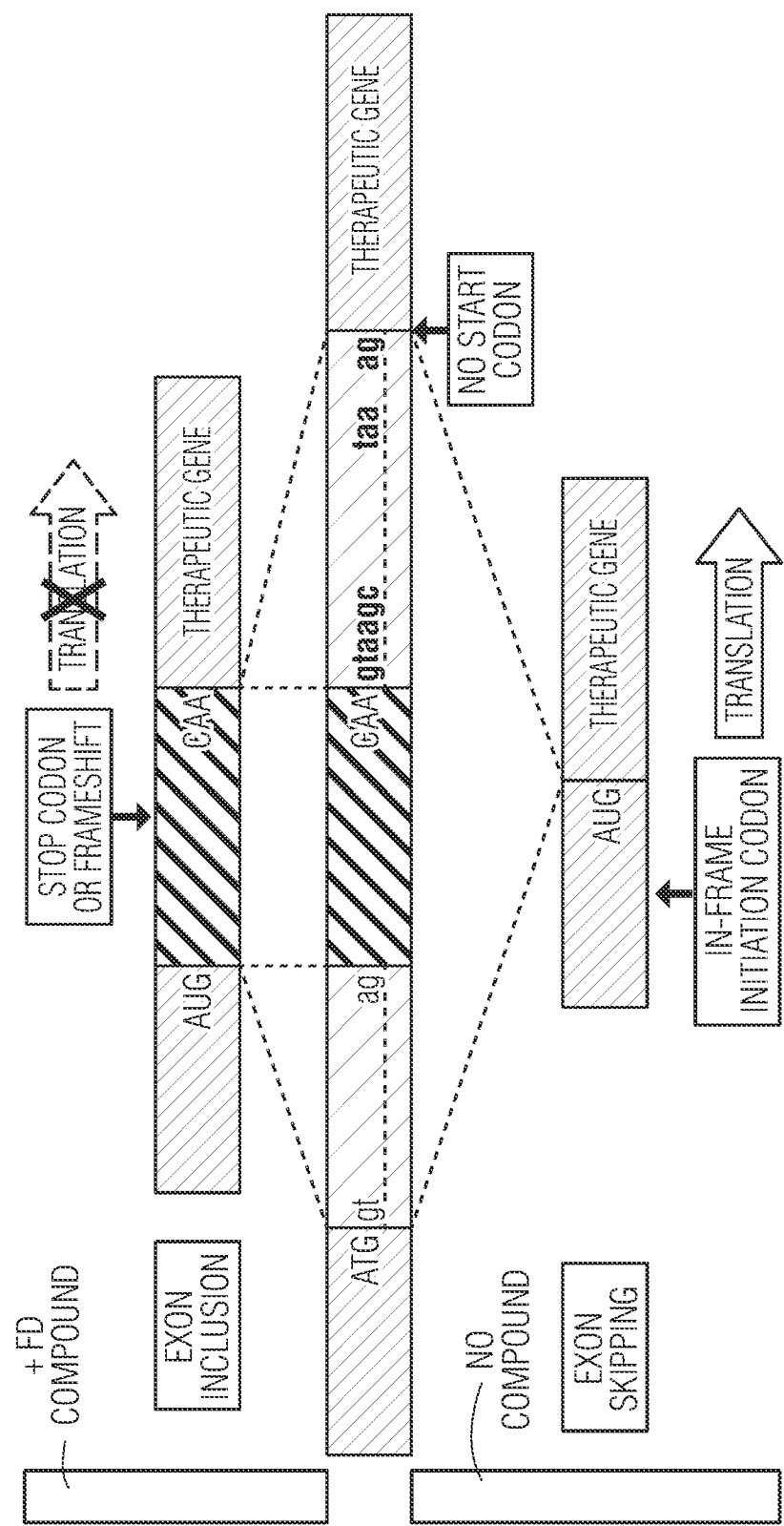


FIG. 11

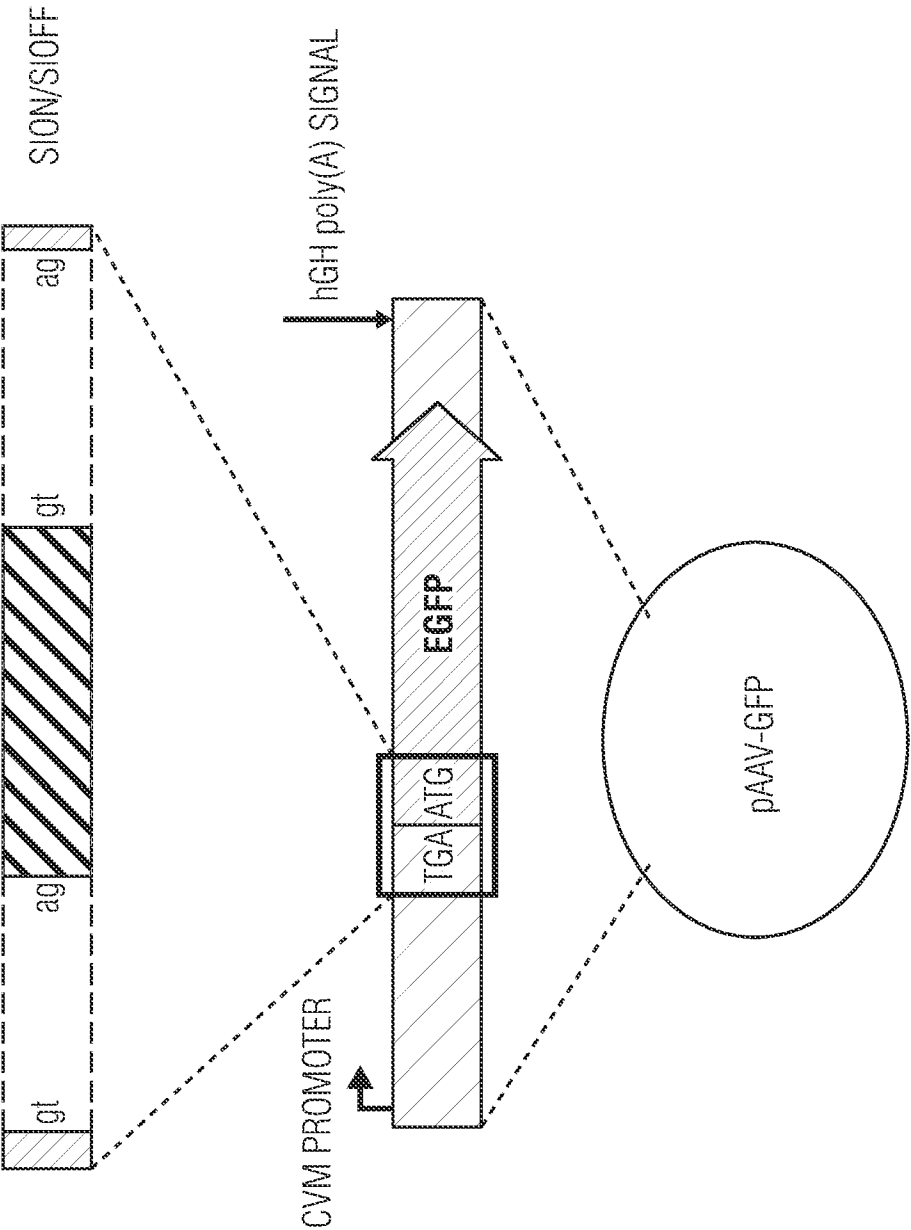


FIG. 2A

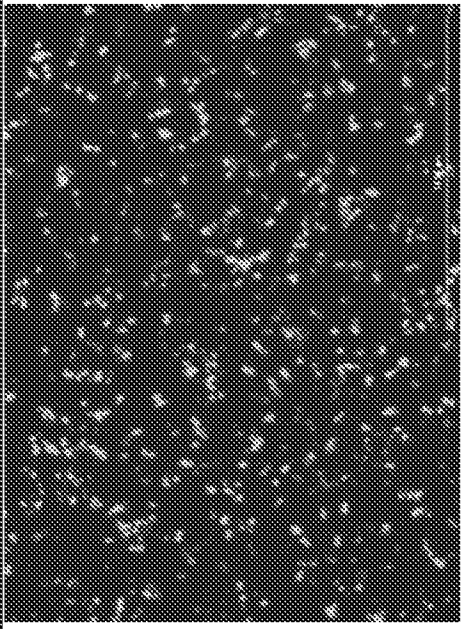
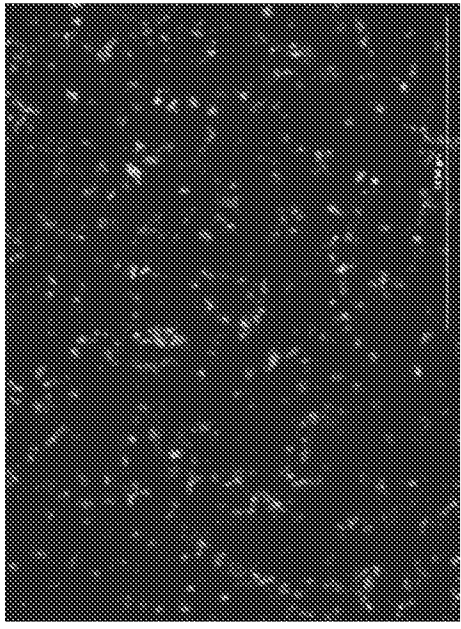
MINIGENE CASSETTE NAME	SEQ ID NO.	SEQUENCE TO REPLACE TGAATG OF PLASMID pAAV-GFP	LENGTH (NT)	COMPOUND	GFP EXPRESSION (NO COMPOUND)
POMT2 ₁₁₁₅ on (pAAV-GFP ₋ SION-1)	1	TAACAAAGGtaagtcattgacagtttgataataaat ggtacggccaccaaggggaaaattttataatgaacatttat tatttgttccagataaaaagtgaagttgttatataaaacta aataaaaagctaaattaaacccctctcatcctccacagATG CCACTTAAAAATCTGCGATCGGACGAGAAAGgttaagt ggcagtgaggagggtacctagctcaggccatgcagattaca agttottatctgacagttgactctgaacatccttggtaaa agaagaaatgttgcacatcattttctatataggataatgaca cttctcttttctaaactttatAG	351	SMA/HD, INCLUSION	
C12orf4 ₁₁₁₅ on (pAAV-GFP ₋ SION-2)	2	TGAAGACGAGgtgagccagaaacccagtgaggatgcccttt cagactgacaacccgttacacccacgacatgtacaaaagtc ctttgagtttttttataatttcagggtgatatctttttaa aacggtatgaataattttttgttttttatttttccagTCAG CACCATAAATAAACGCGCATACAAATCCACCAATATTTA TTAGTCTCTGCCATTCCCAACATCTGCTTAATACATGGAA TACACAGACAGTATCTCTTCCATTCCAGAGACGTGTTTCT AGCCAAGgttaagaaatagagcgtgataagtgccatgattc aaataagctctaggttaagacaaaatctcttgaatggtggaa tgttttcttagaaaatgggacaggaataatgaaacataa tttctttatggacttatataacccactgcttttttcttagTG	447	SMA/HD, INCLUSION	

FIG. 2B

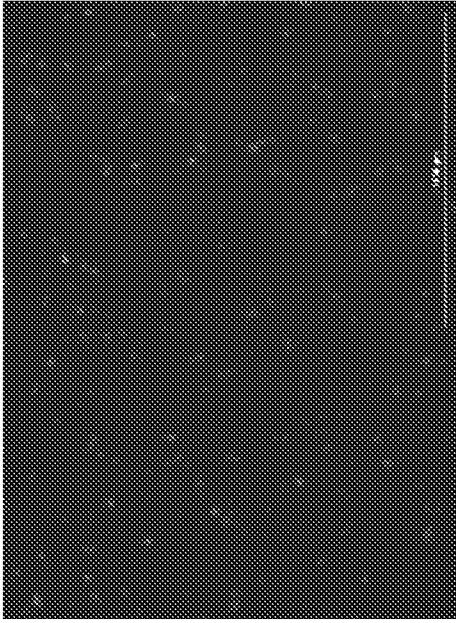
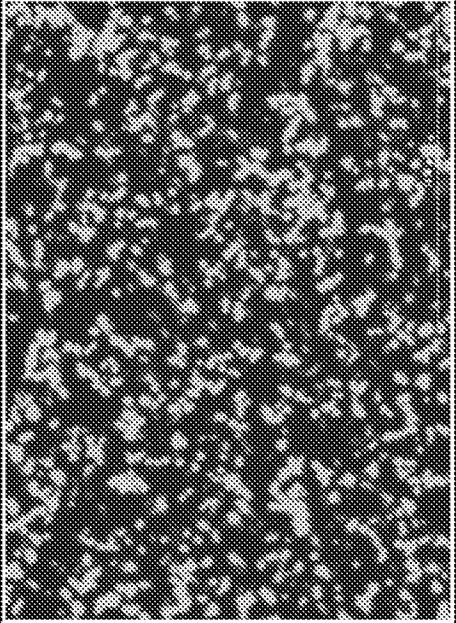
MINIGENE CASSETTE NAME	SEQ ID NO.	SEQUENCE TO REPLACE TGAATG OF PLASMID pAAV-GFP	LENGTH (NT)	COMPOUND	GFP EXPRESSION (NO COMPOUND)
HTT_149s_on (pAAV-GFP_SION-3)	3	TAACCTTGAAGGtaagaggcagctcggggcgtcagtgttgcgtggggaggggcatggggtgctgtatgcaggatgaaatatttatatggtcattctatttgactctcaaacacccctgtgagataggctctgttactccatttgacaggtgaggaaagcaaggcttagagaaatttcagtgacttgcccaggctcctctgagctaggaagtacatttggcatttgaccccaaggcctgctatccctagaacccacgctctcaaatcaactatgacagAGGCAAGCCCTGGTCTGGGAGCCCAAGCAAGCCCTCTGGCTCTGGTGGCCAGGAGCCAGGAGAGATTCTACAGGAGCCACAGCGCTGAAGAGAGAGAGGCGACAGAGtaaggggctttgtggcagagaggggactggcactttggggaaataggtgggtcaggactgaatgaatggagccatgcagagctgtccttcggaaagggcaaggcaccctggacgggtgccctcagtgccttggacggttcccaaacctgtgattcaacggttccccctaaagaaagtacagagtgggcattctgtgactcggtaacttccctttaagTC	622	SMA/HD, INCLUSION	
ZNF37BP_14S_on (pAAV-GFP_SION-4)	4	AGATAGGTCGtaagttatctatttcggctttatttaaaagatgggatggggtggggtggacaggaaacaaagcttaacatgttaagtgaactgttgacattgacacattttgttggtggcaAGTCAAGAACAGACACAGCTCGCTTGAGGACTCAGGCAGGTGTTCCTGCAATTCACACACAGAGtaagaaaaaatccgtttgctttttaaataccaaagatggttttgagaaatggacgtgtgagtatctcccttttagagatgttttgccagctgggaggtggacatttttaggcaagtacatttctcattctctttctttctttgtaagTC	335	SMA/HD, INCLUSION	

FIG. 2Bii

[illegible]

00 00000000
 01 00000000
 02 00000000
 03 00000000
 04 00000000
 05 00000000
 06 00000000
 07 00000000
 08 00000000
 09 00000000
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 11 00000000
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 246 00000

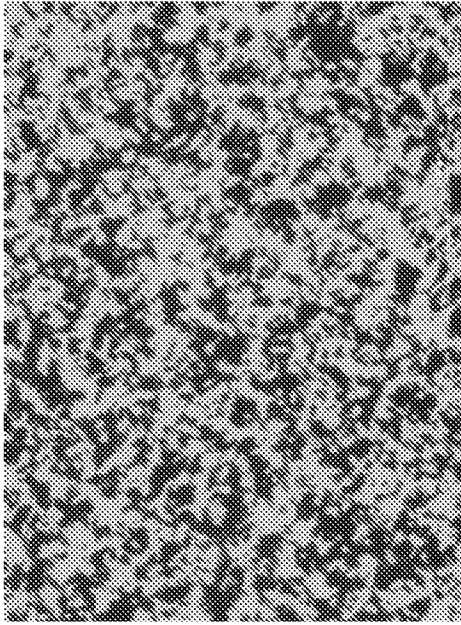
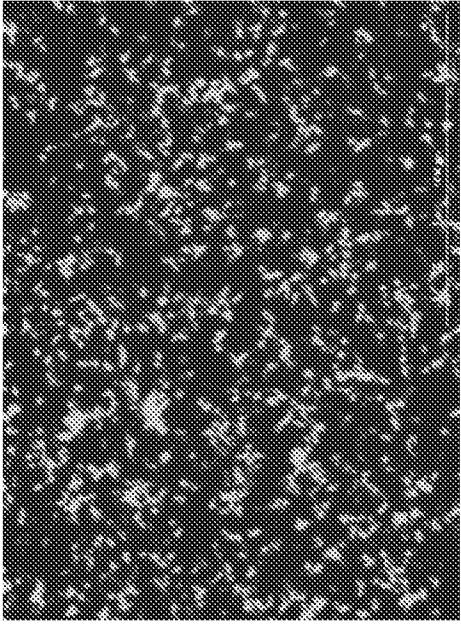
MINIGENE CASSETTE NAME	SEQ ID NO.	SEQUENCE TO REPLACE TGAATG OF PLASMID pAAV-GFP	LENGTH (NT)	COMPOUND	GFP EXPRESSION (NO COMPOUND)
ZNF207_e6s_on (pAAV-GFP -- SION-7)	7	CTAAGCCCATGgtaagaaaattcttttaattcccoctgtag gcttgcttagtaatatataactctgttaaatgattta tttgcaaaagcatcaaaactaaaatgaatatgaggtgct tgtgcccacacattttcttaaatattgtggatgtgag aggtatacaaatacacttcccactgtattttgaaaaatca cagttagattttgattttctcatacattttcacacgATTG CATCATCAGAGAAAATACACCCAGTCATTTCGGTCAA AACATgtaagcatctcattcataatgttaattcaggaggt ataatcataactgtcatttttttatgtgtgttttaattgg tatattatcagttgacttcagaaaattttcacaacttctc cacataaaacttgcaagtaattaacacaggctctctaaa gaaggaaaaagctttcactctagtgtgtttcaggcttt agccagaataatttttaattggttttatgtgttcaattaac ttaactgtttcttgaaaatttgcttttctaataag	538	FD, SKIPPING	
RPP14_e2s_on (pAAV-GFP -- SION-8)	8	CTAAGCCCATGgtaggtggaagccttccaaaagcggcgggt tgtctgggagccgtctctagtaacaaacaaaaaaac ccaaataggccaaaattctcactcaaaaactotgaaaaatagc atgtccatfggtcattttctagccctcttgaattactgtag GTGTGATCAGCCACTGGAAAAGATGCCCTGCCCTGCTGCCA CATATCAAAGAGTAGTTACAAAACCCCTTCGAGTACCA CTACATGAAGTCTGCCgtaagtttagtttcttaagttc tatttttagattacttttctaacatgaatttgaatagaatg aaatttaatatgacttttttttttttttcaacttttttag	358	FD, SKIPPING	

FIG. 2Biv

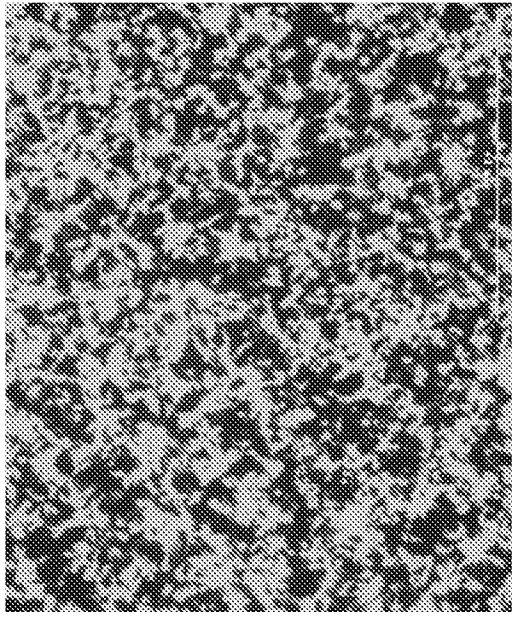
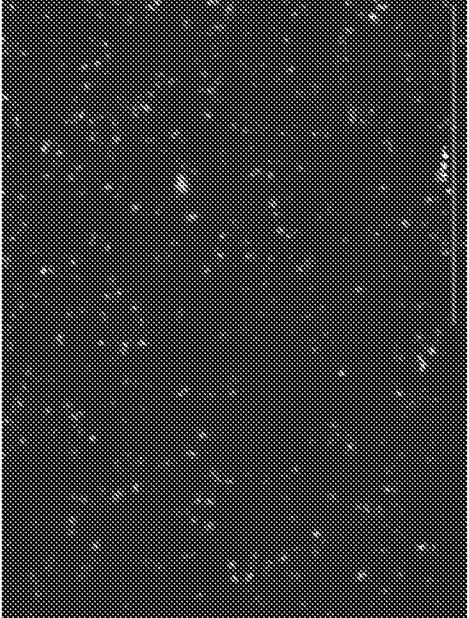
MINIGENE CASSETTE NAME	SEQ ID NO.	SEQUENCE TO REPLACE TGAATG OF PLASMID pAAV-GFP	LENGTH (NT)	COMPOUND	GFP EXPRESSION (NO COMPOUND)
HSD17B4_e3s_off (pAAV-GFP SIOFF-1)	9	TAAGCCCTGTAAGTGGTGTGTTTTTTTTTAAATCTG TAGTGATAACTGAAATACAAAAAATCTTTTAAAAAA AATTGTGTTAATCATAAATATTACATTTTCATGTATACCA TTATGCTATTTATTAAATAGTAACTTTTTTATTGTTACAG CTTCCAAAATCTATGCAATCCCTATGGAGAGATCATT TCACAAATCCAGATTCTTTTCTTCAATAATTCTTTAAAGT TCTGTTTTTCCAAAGTTATTGGCAATTTATCTATGTGAGAT GTGTAGTAATTAGAAATTCATTTTCCACACACACACACA CACATTTTGAAAGTCTAGATAAATTAATTGTTGTTGCTT GTTTTTGCATTACAG	375	FD, INCLUSION	
FANCL_e3's_off (pAAV-GFP SIOFF-2)	10	CTTAATCAGTAAGATAAGTTCAACTGGGGATCCAGGAA TTGACATGAGCAAGGTAAATAAAGACTTTCTAGTTAGTA GTAATCAATTTCTAAATCTCTTTACTCTTAAATAGAAAA CGAAGTTGGGTTTGAATGGCAATTTTATTCTCTTCTAG AAGAGGCTCTTCTCAGCAACCTTACCAATCAGCCTGT TCAGAAAGCTATCATCATCATCACTGGGAACCTCTCTTACA TTTTTCCACGAGCTGGGCGCAGACAGCTCTGCAATCAGGCA GCTGTGTGGACACCTTGTAAAGGACTTGTGCAAAATGTA CACCACTTACAGCCTTGTCTCAGATTTGTAATATTGA GACAAGAGATTGCCCCACCATTTCTAACCAGTGAGCCT TCAGTCAGAAATGATGAGTCACACTCCATAGGCTCACTGCA GAGTCAGCTTGTAGTTCTCATAGGACAGTCTCTCTAAATCTA GGAATCTTTTTTATTAGG	499	FD, SKIPPING	

FIG. 2Bv

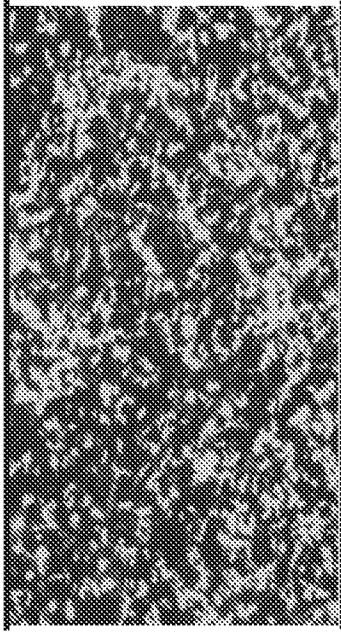
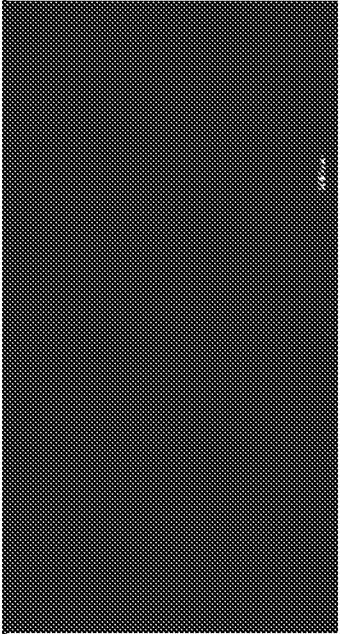
MINIGENE CASSETTE NAME	SEQ ID NO.	SEQUENCE TO REPLACE TGAATG OF PLASMID pAAV-GFP	LENGTH (NT)	COMPOUND	GFP EXPRESSION (NO COMPOUND)
POSITIVE CONTROL (pAAV-GFP)		TGAATG			
MOCK CONTROL					

FIG. 2Bvi

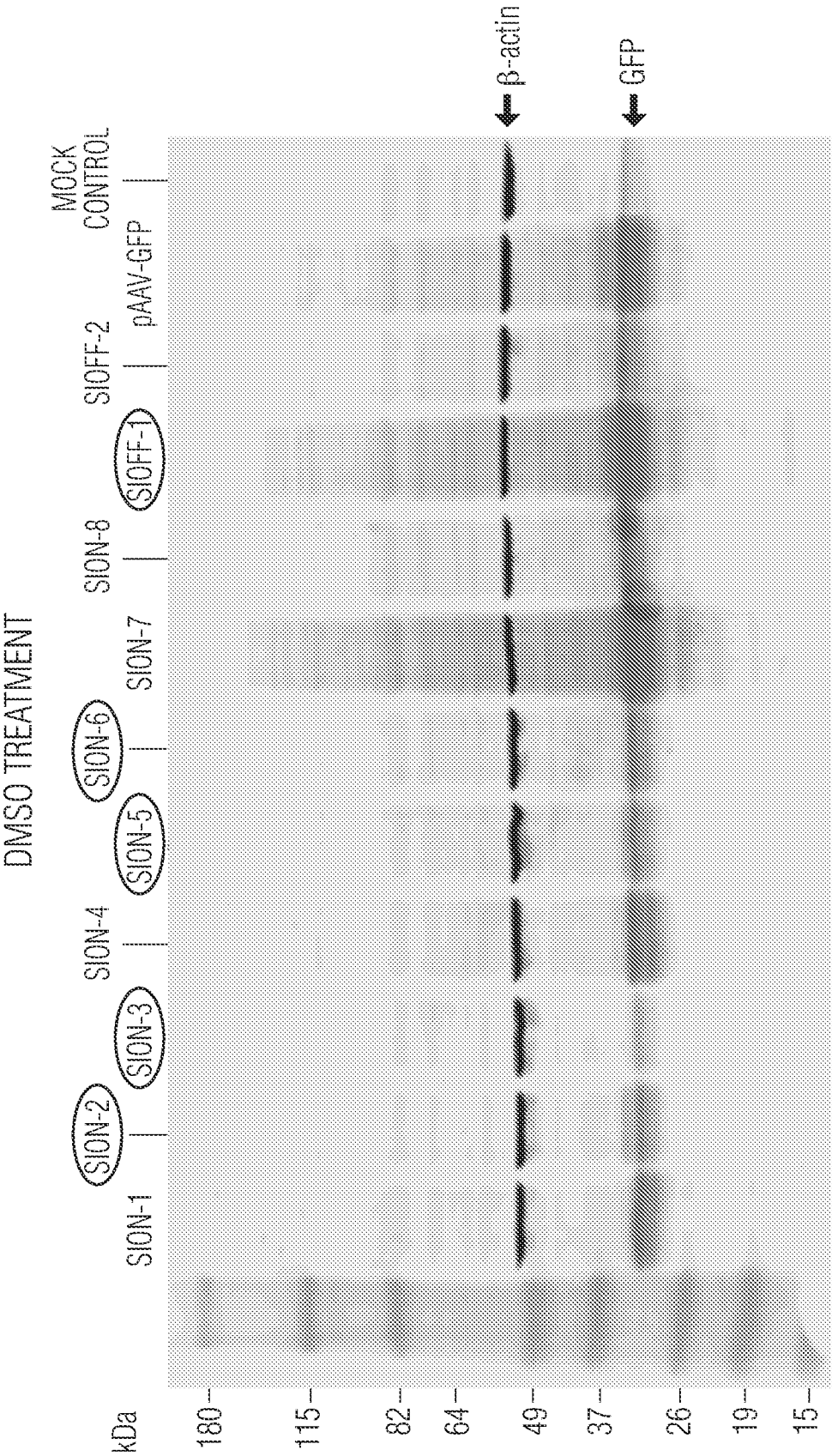


FIG. 2Ci

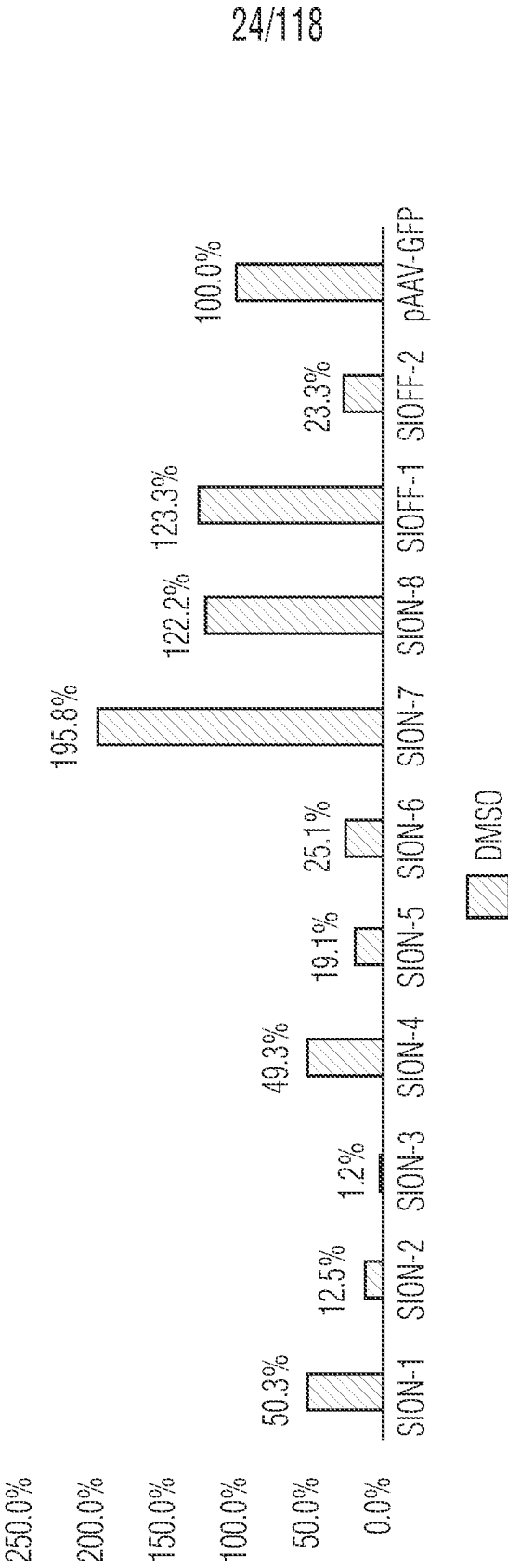


FIG. 2Cii

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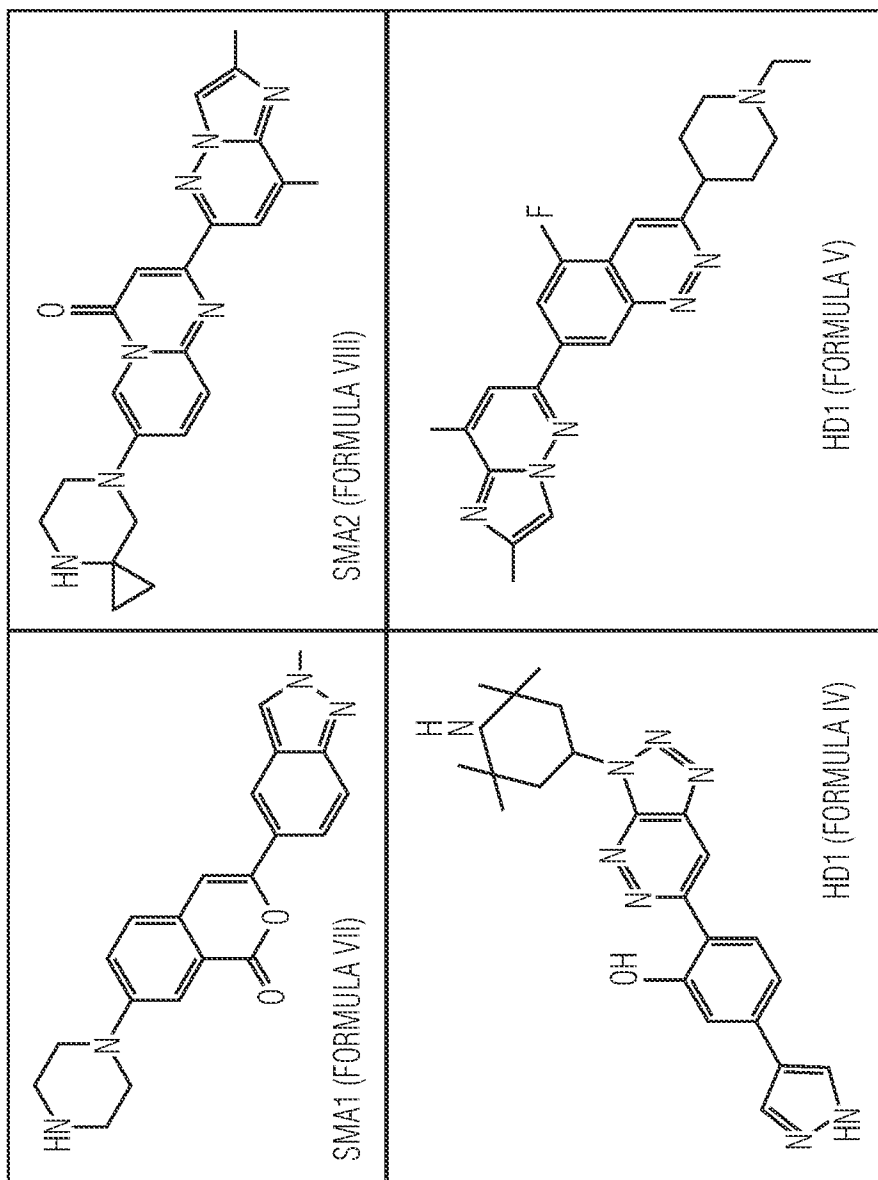
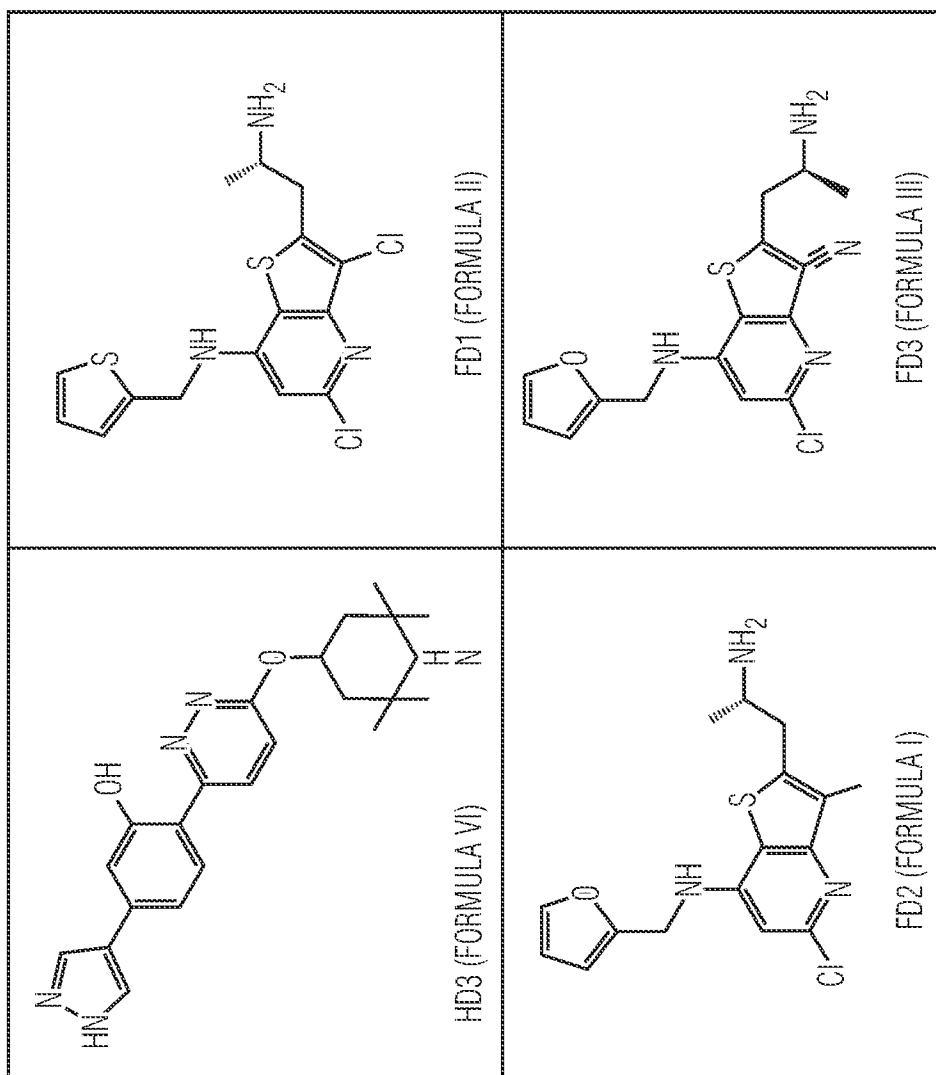


FIG. 3Ai



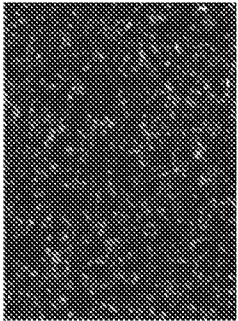
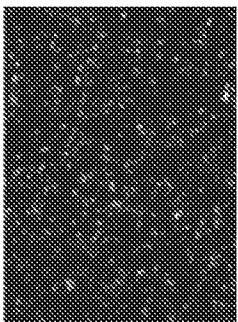
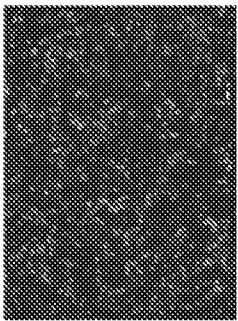
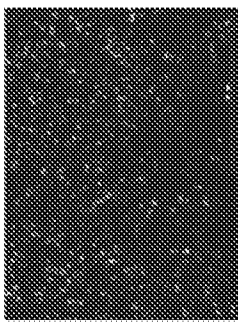
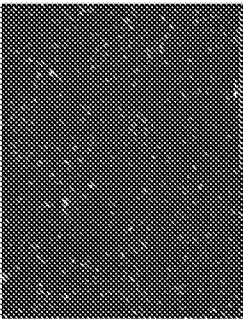
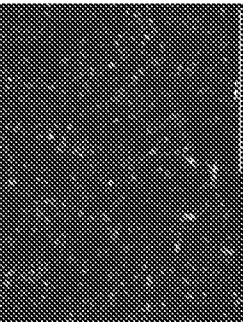
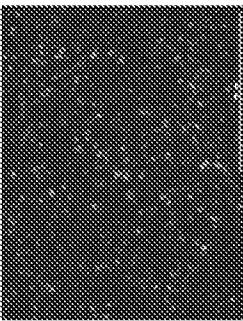
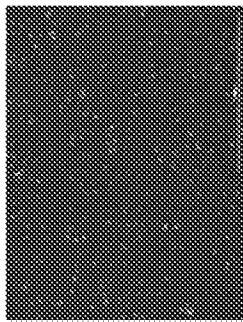
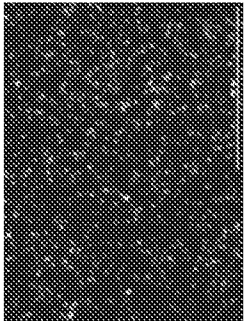
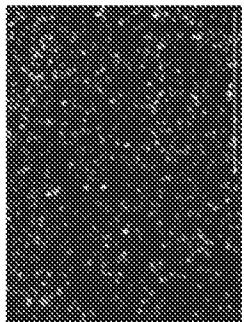
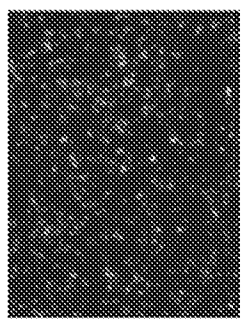
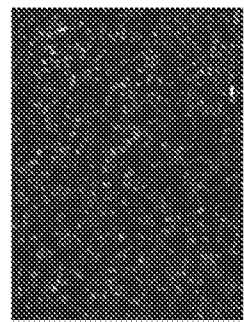
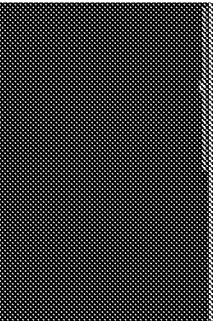
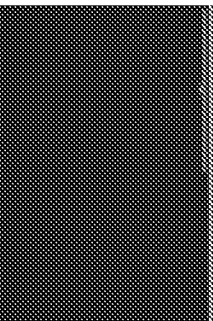
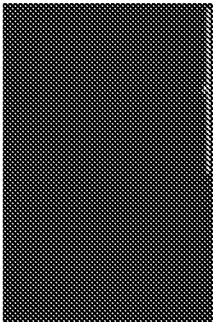
VECTOR				
COMPOUND:	SMA1 (1µM)	SMA2 (1µM)	HD1 (1µM)	DMSO
SION-2				
SION-3				
POSITIVE CONTROL (pAAV-GFP)				
MOCK CONTROL				

FIG. 3Bi

VECTOR				
COMPOUND:	HD2 (1µM)	HD3 (1µM)	DMSO	
SION-2				
SION-3				
POSITIVE CONTROL (pAAV-GFP)				
MOCK CONTROL				

FIG. 3Bii

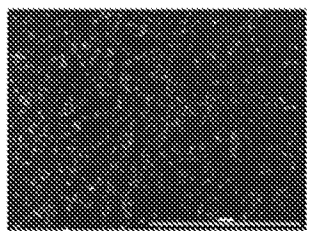
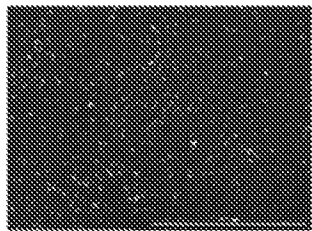
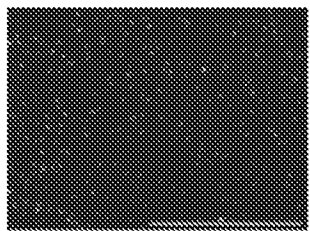
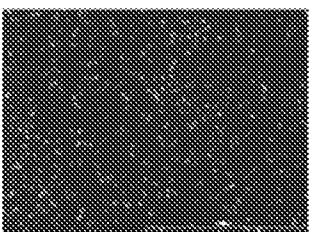
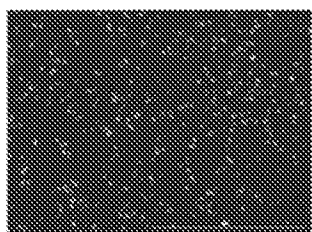
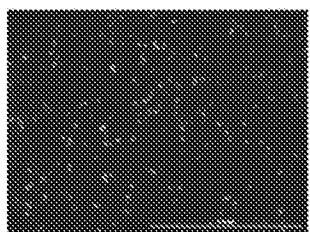
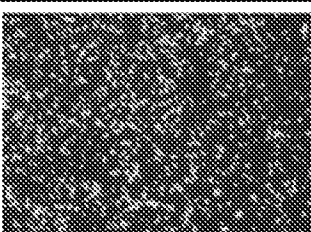
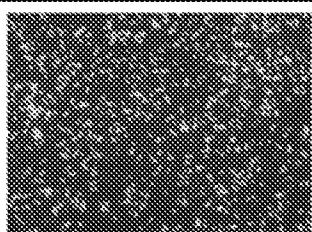
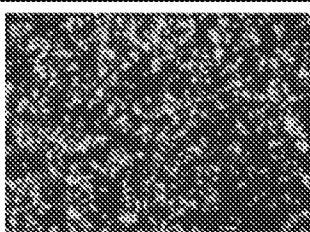
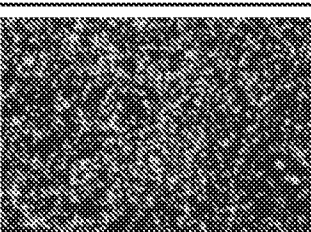
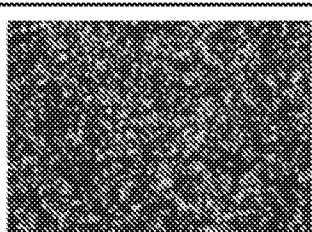
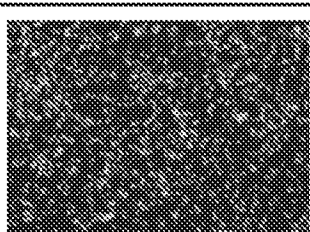
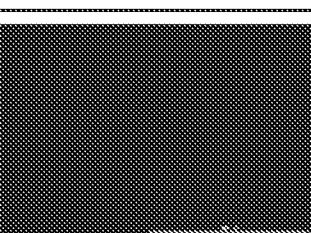
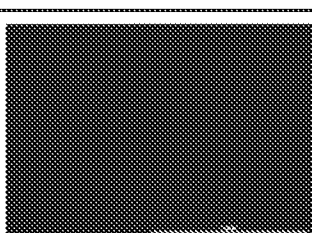
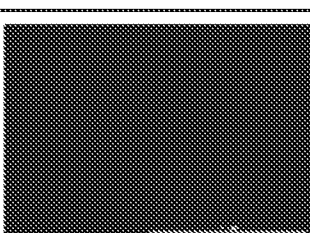
VECTOR	COMPOUND:	FD1 (1µM)	FD2 (1µM)	DMSO
	SION-5			
	SION-6			
	SIOFF-1			
	POSITIVE CONTROL (pAAV-GFP)			
	MOCK CONTROL			

FIG. 3Biii

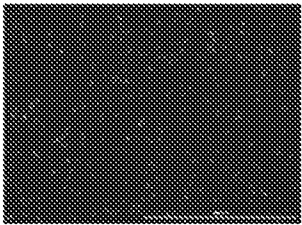
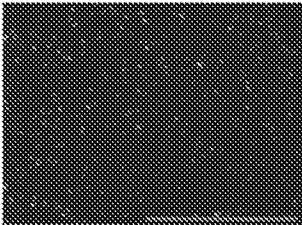
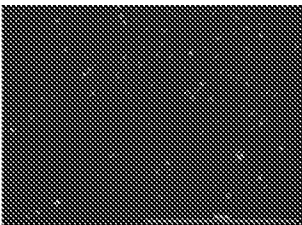
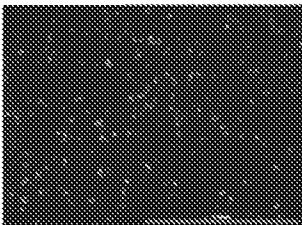
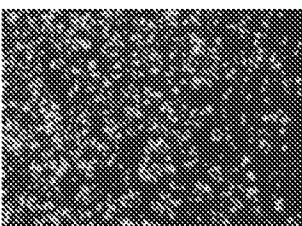
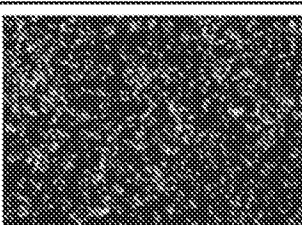
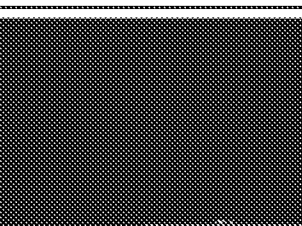
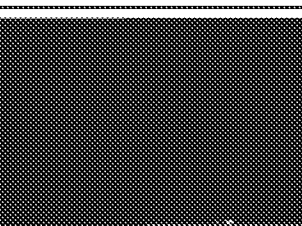
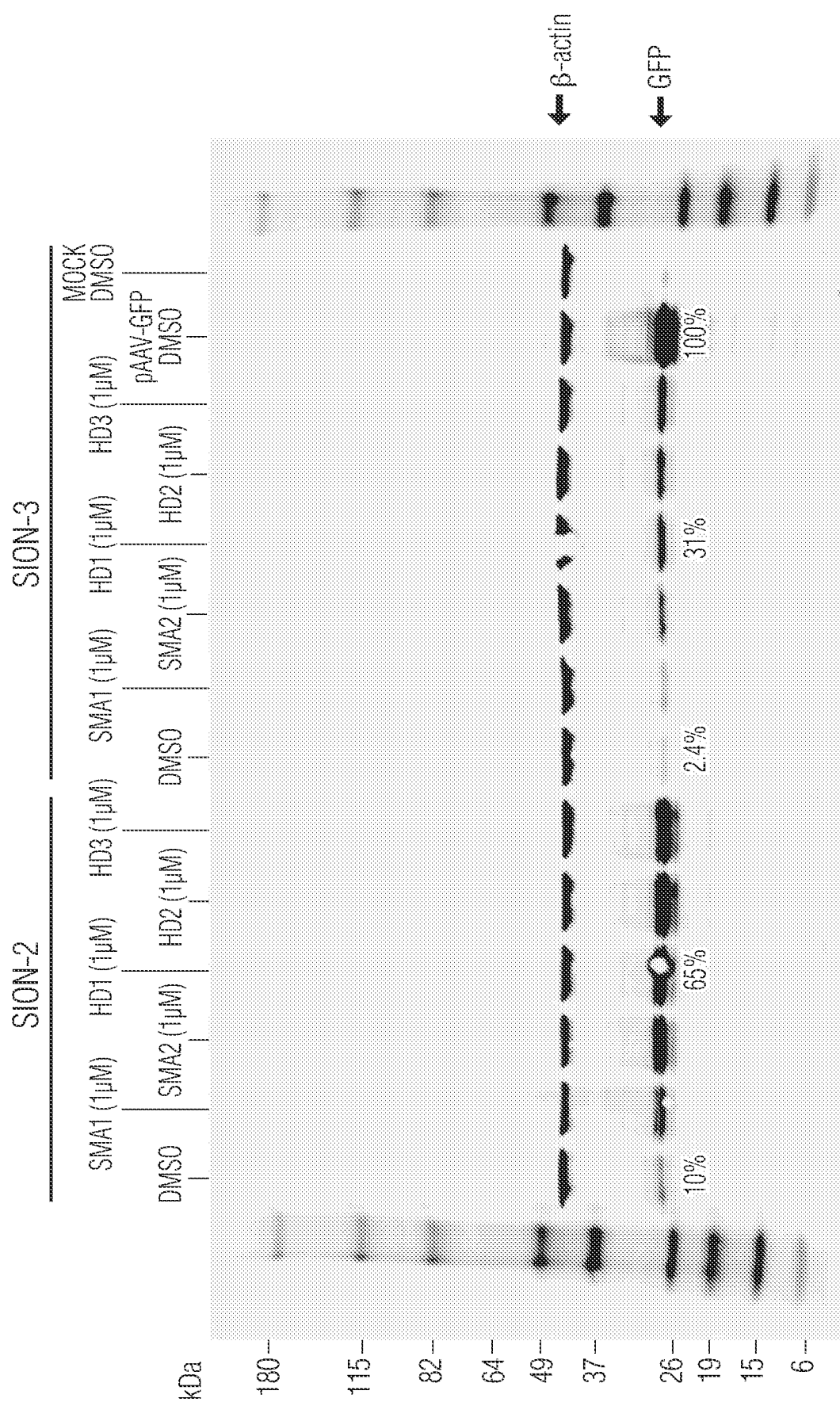
VECTOR	COMPOUND:	FD3 (1µM)	DMSO
	SION-5		
	SION-6		
	SIOFF-1		
	POSITIVE CONTROL (pAAV-GFP)		
	MOCK CONTROL		

FIG. 3Biv



AA
44
or
GG
LL

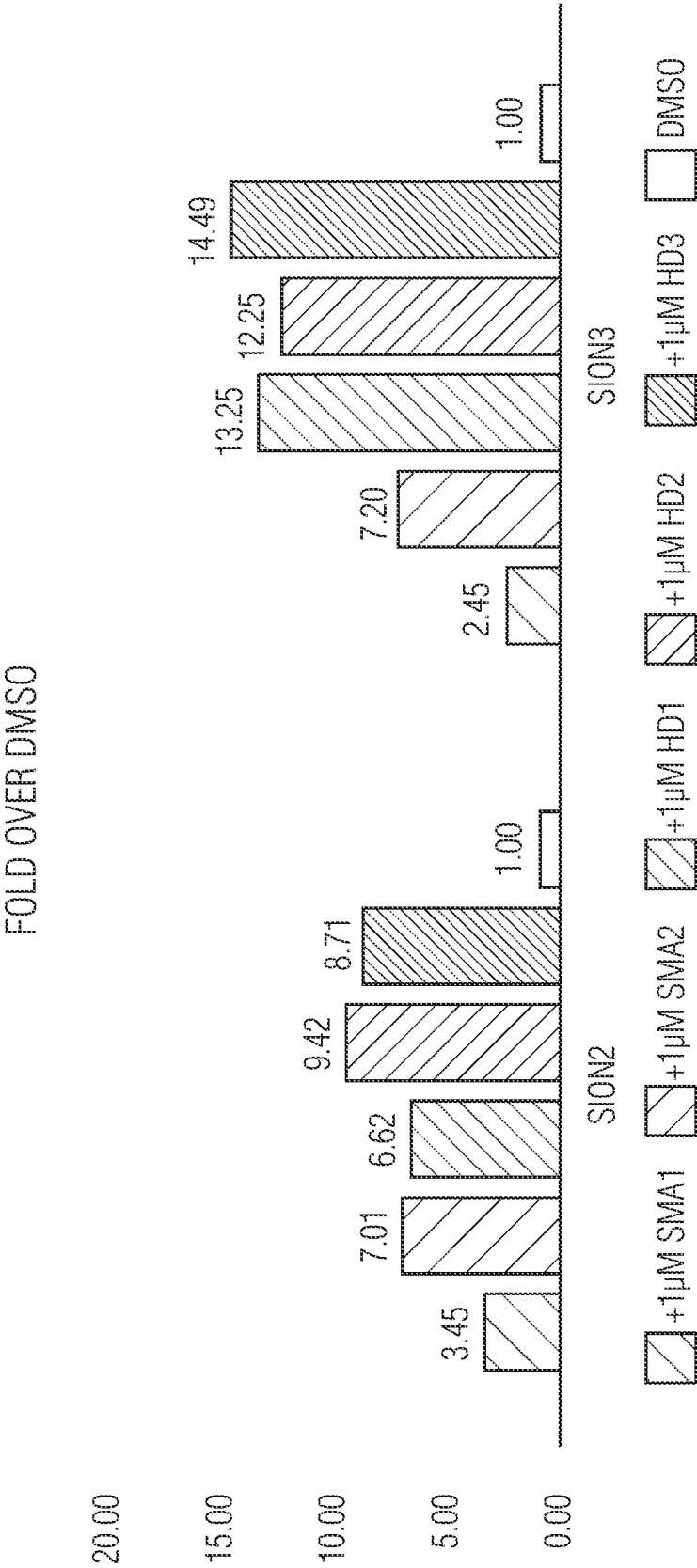


FIG. 4B

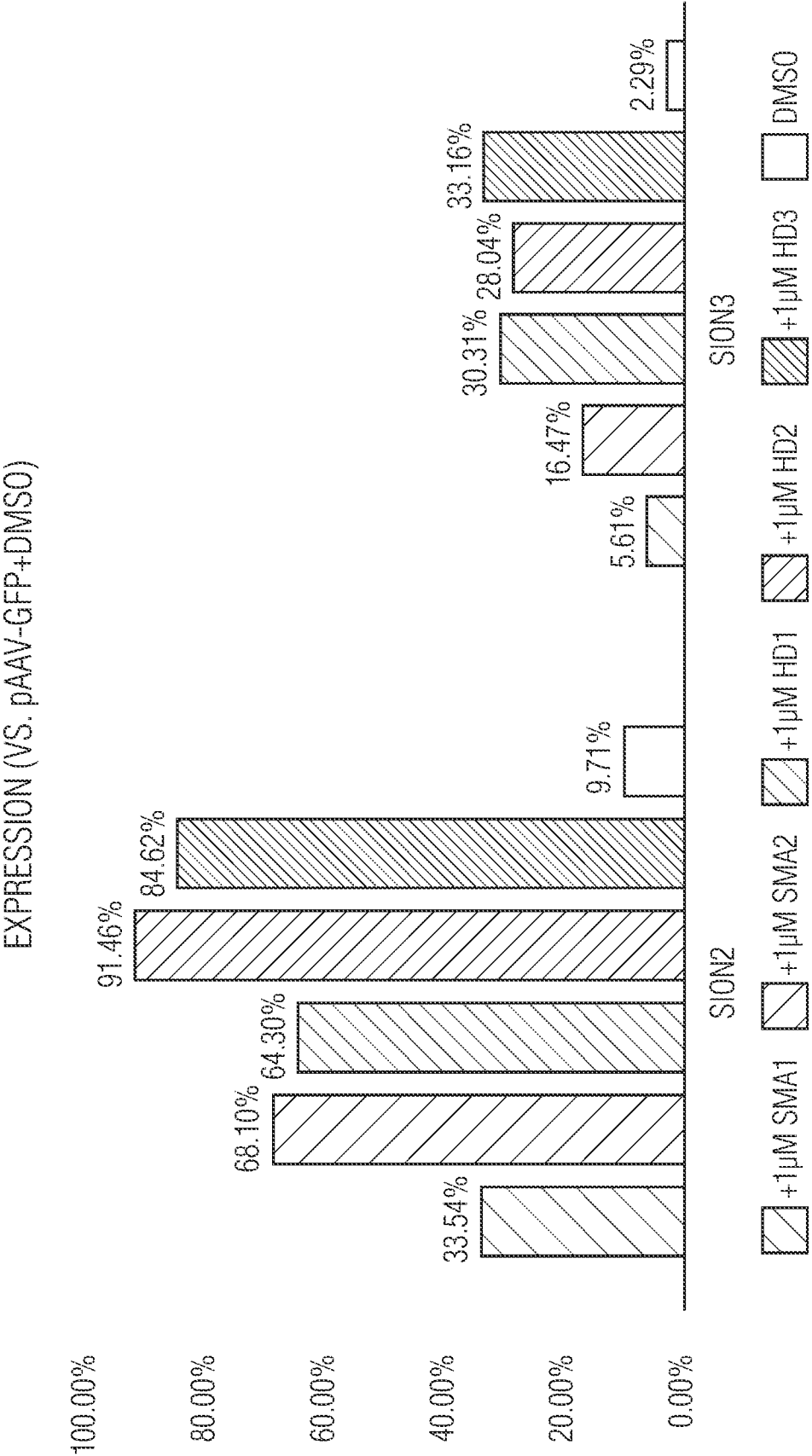


FIG. 4C

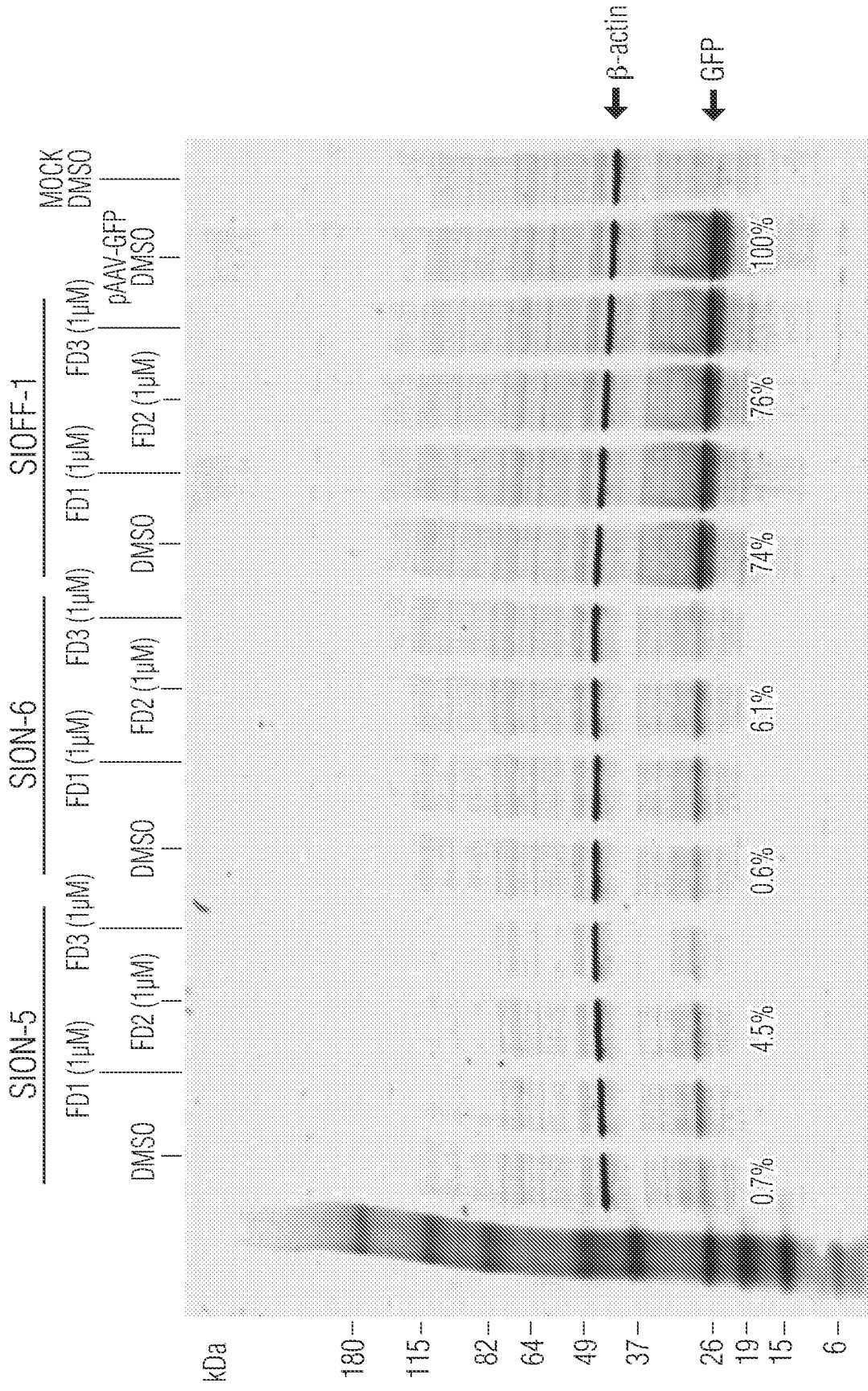


FIG. 4D

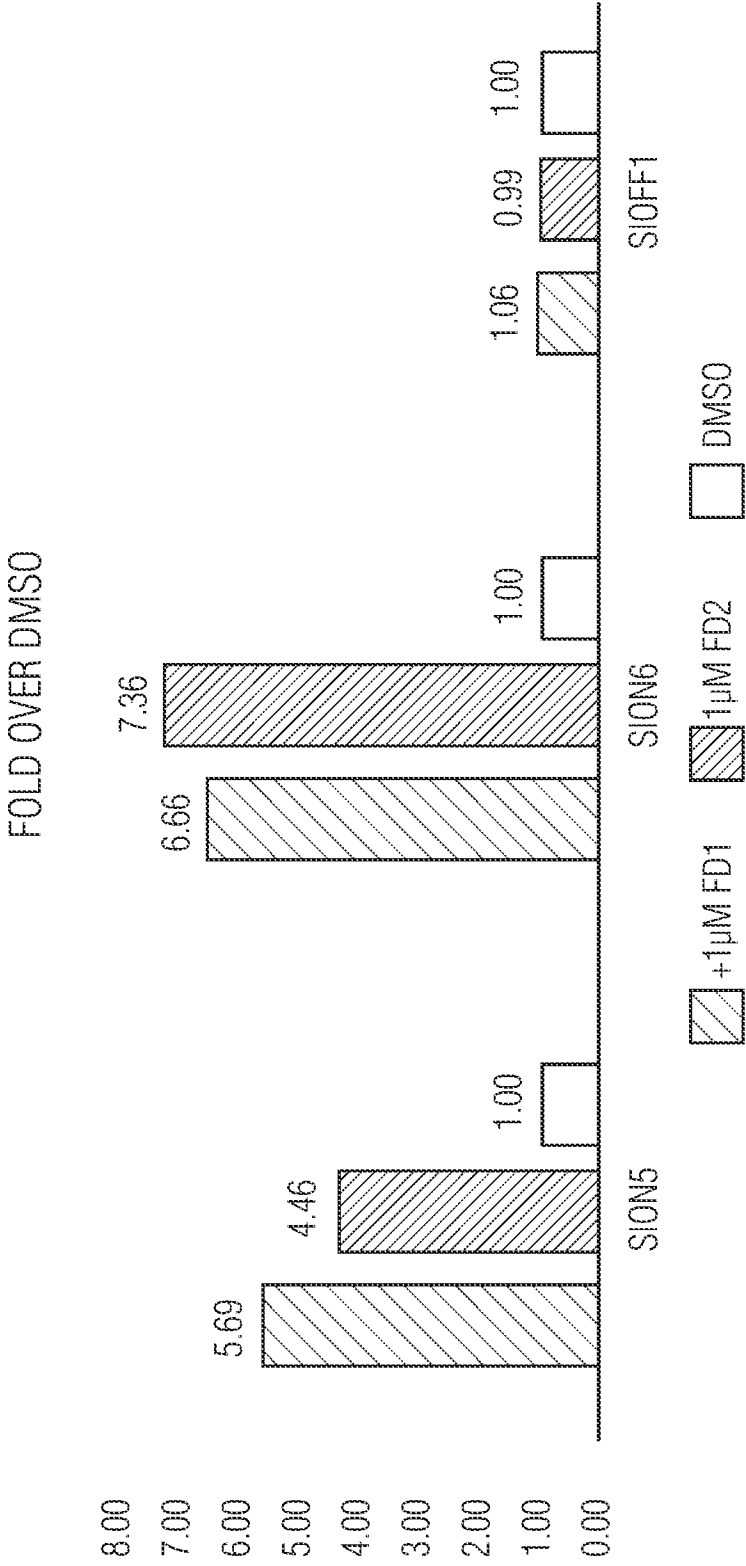


FIG. 4E

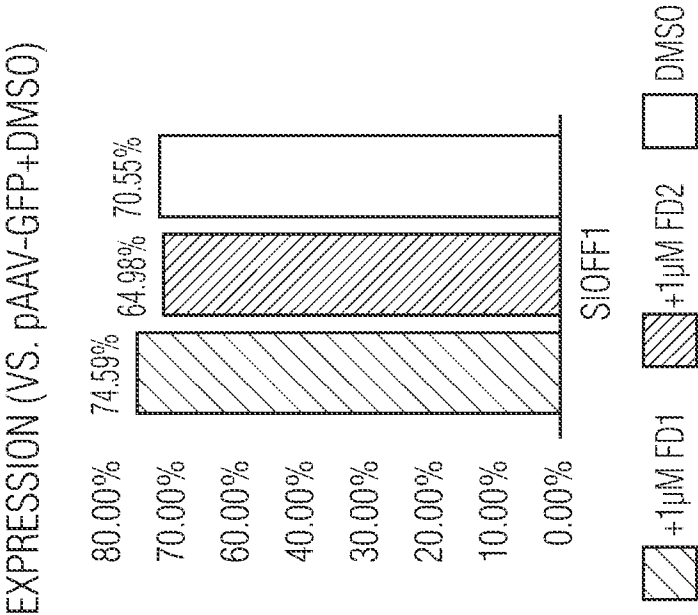
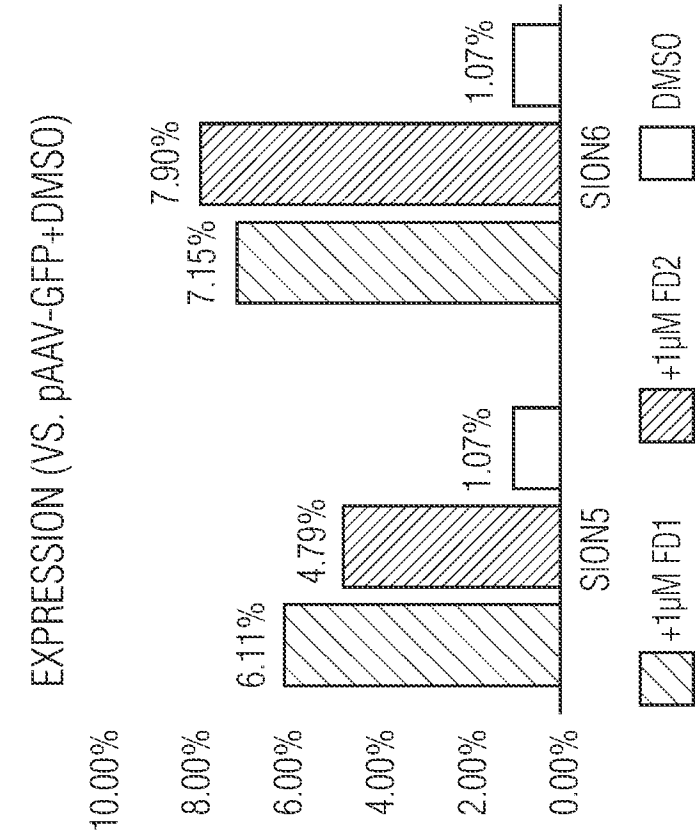


FIG. 4G



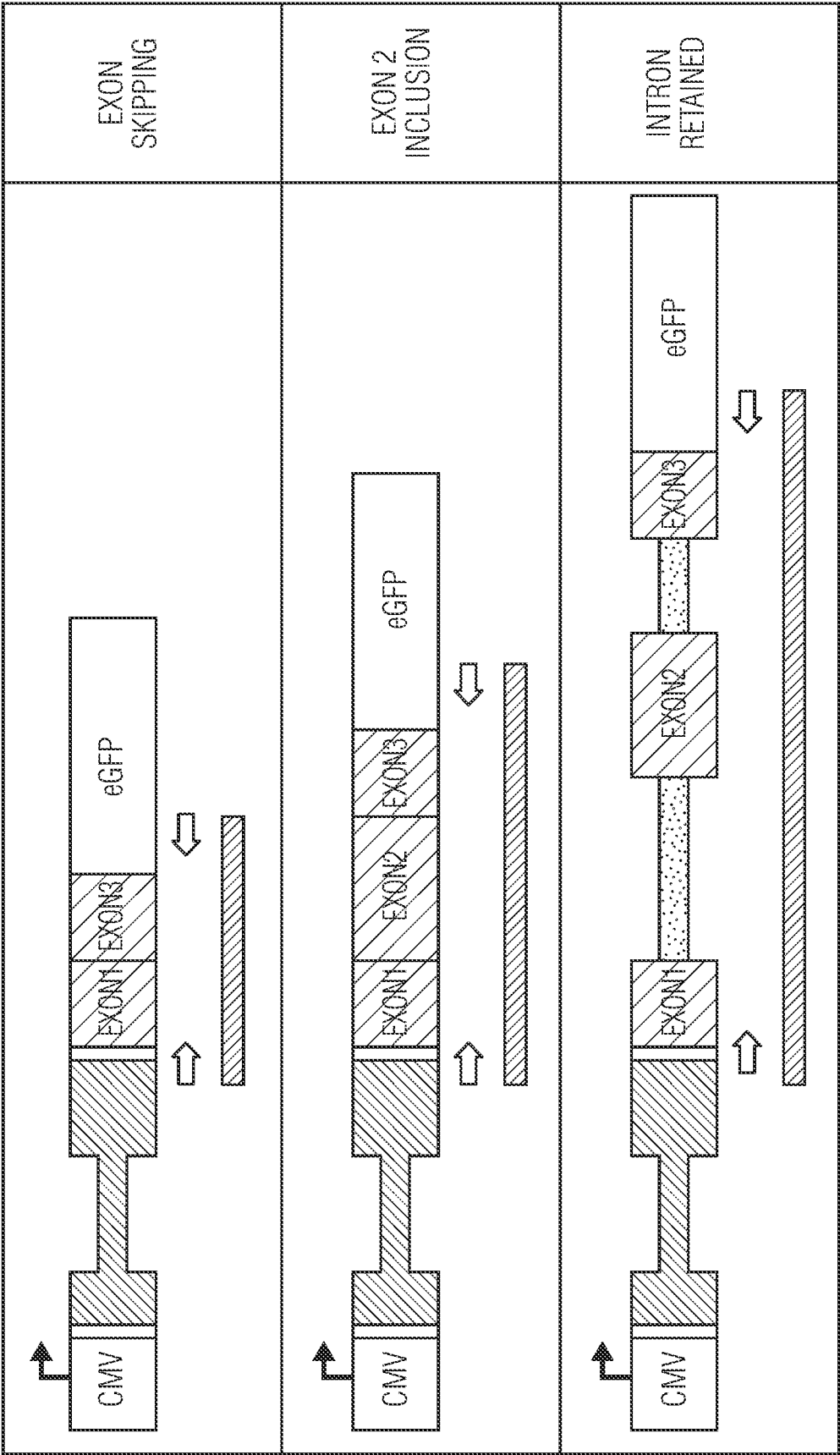


FIG. 5A

CONSTRUCT	BASED ON	TYPE	SMSM COMPOUND	SHORT (EXON SKIPPING)	LONG (EXON INCLUSION)	INTRON RETAINED
SION1	POMT2	incl	SMA/HD	80	119	419
SION2	C12orf4	incl	SMA/HD	80	215	515
SION3	HTT	incl	SMA/HD	80	195	690
SION4	ZNF37BP	incl	SMA/HD	80	143	403
SION5	HSD17B4	incl	FD	80	145	445
SION6	IKBKAP	incl	FD	80	154	690
SION7	ZNF207	skip	FD	78	126	606
SION8	RPP14	skip	FD	78	176	426
SIOFF1	HSD17B4	incl	FD	78	143	443
SIOFF2	FANCI	skip	FD	79	267	567
GFP contr		NA	NA	74	74	74

FIG. 5B

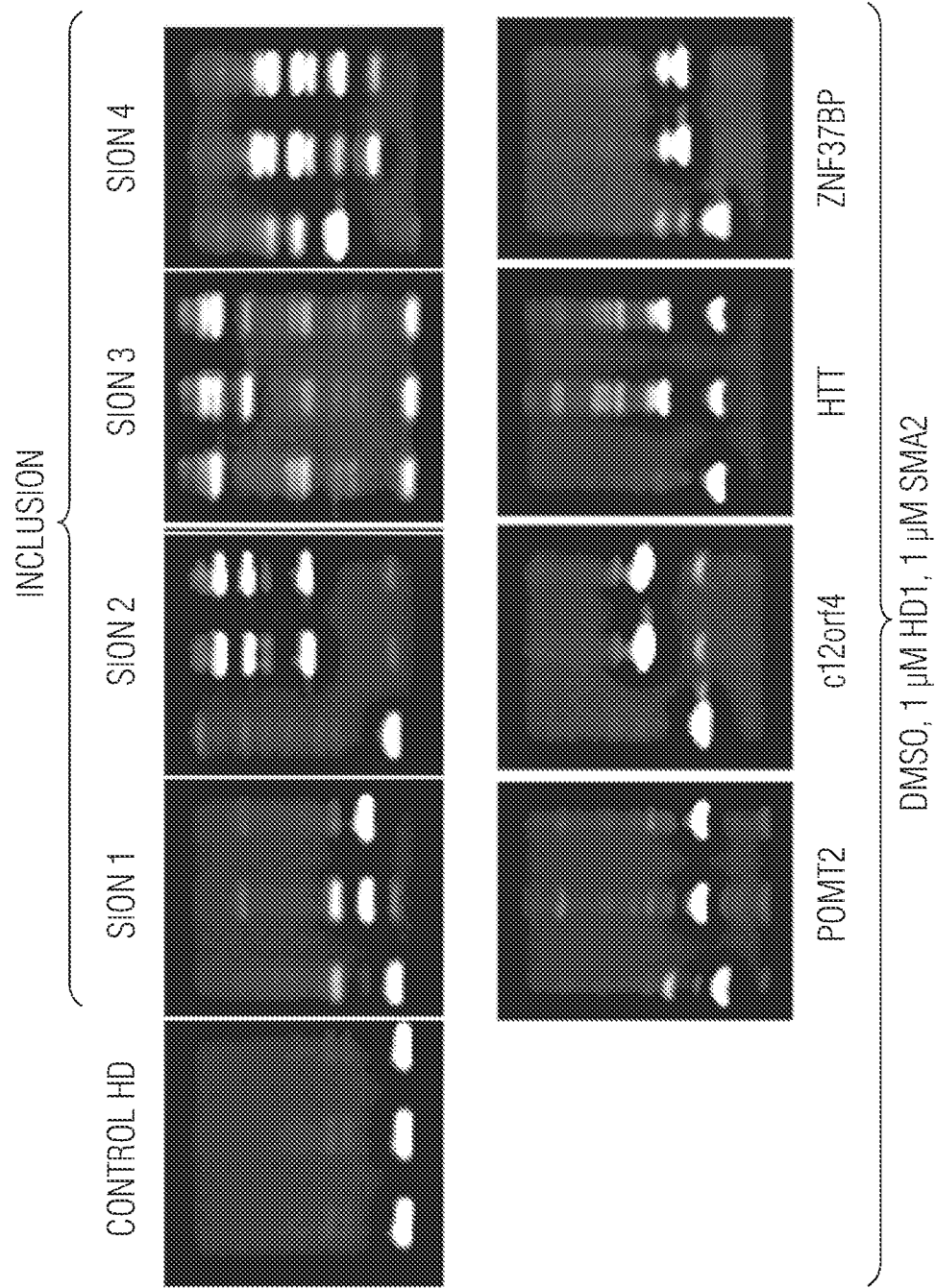


FIG. 5Ci

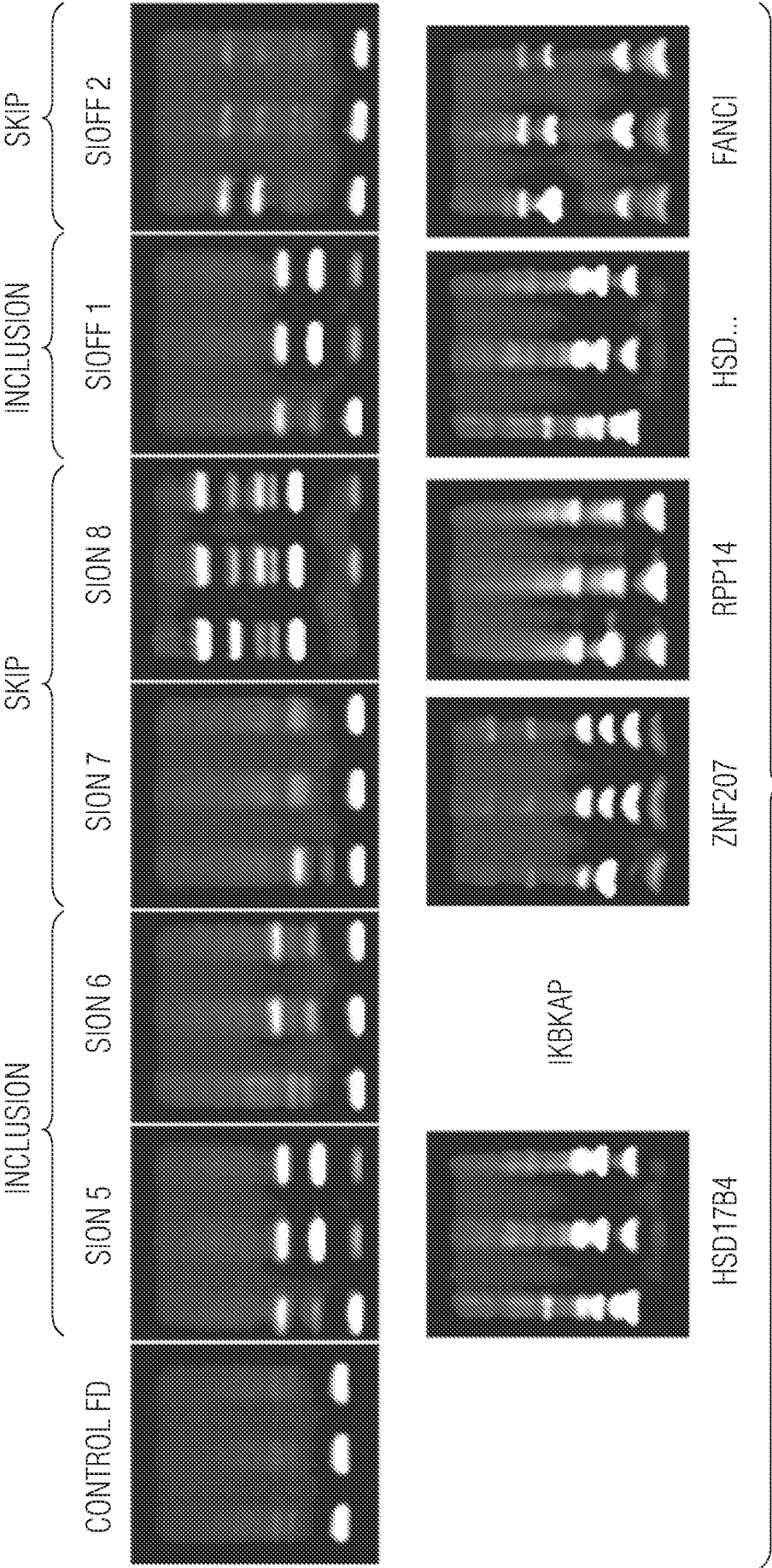


FIG. 50i

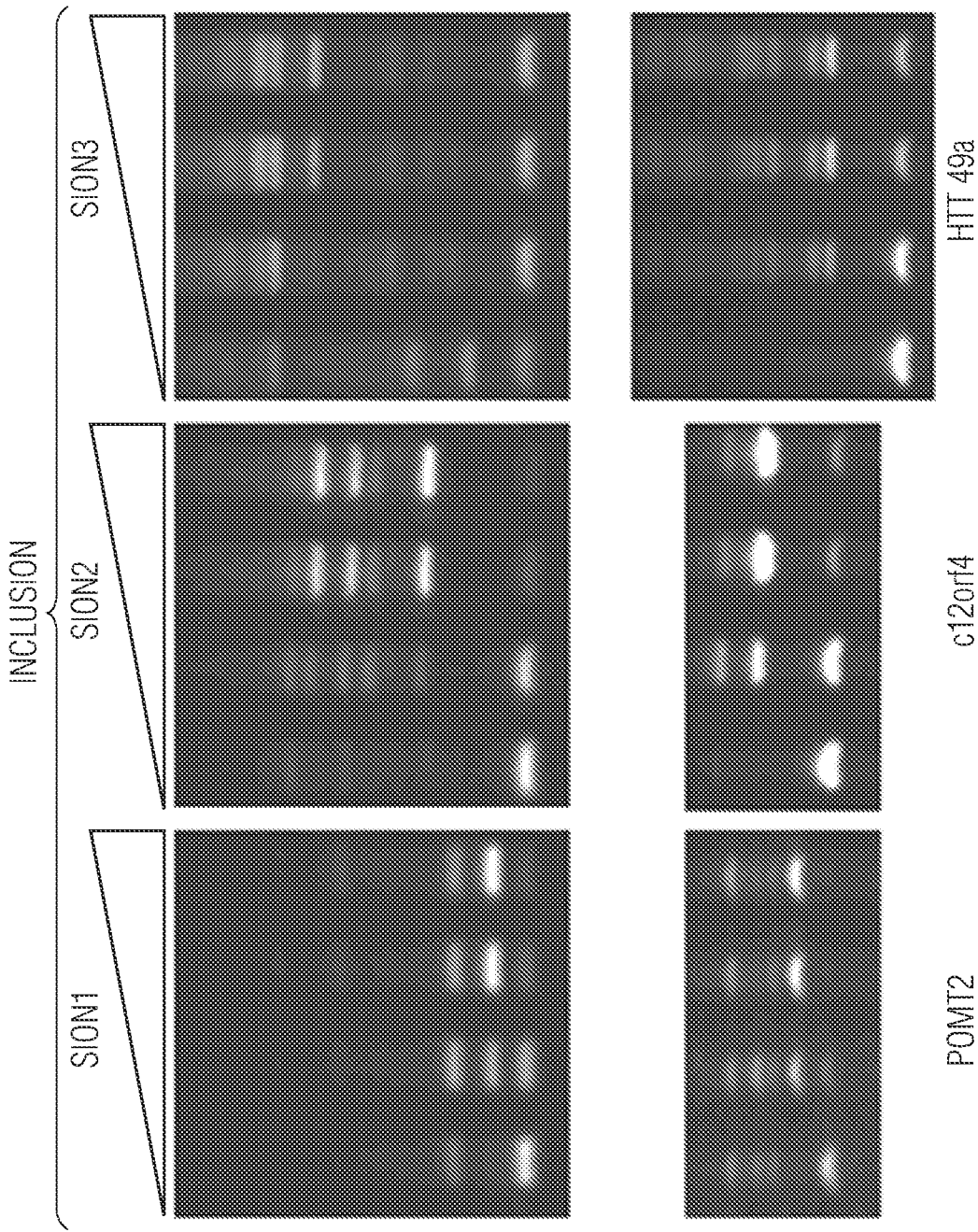


FIG. 5Di

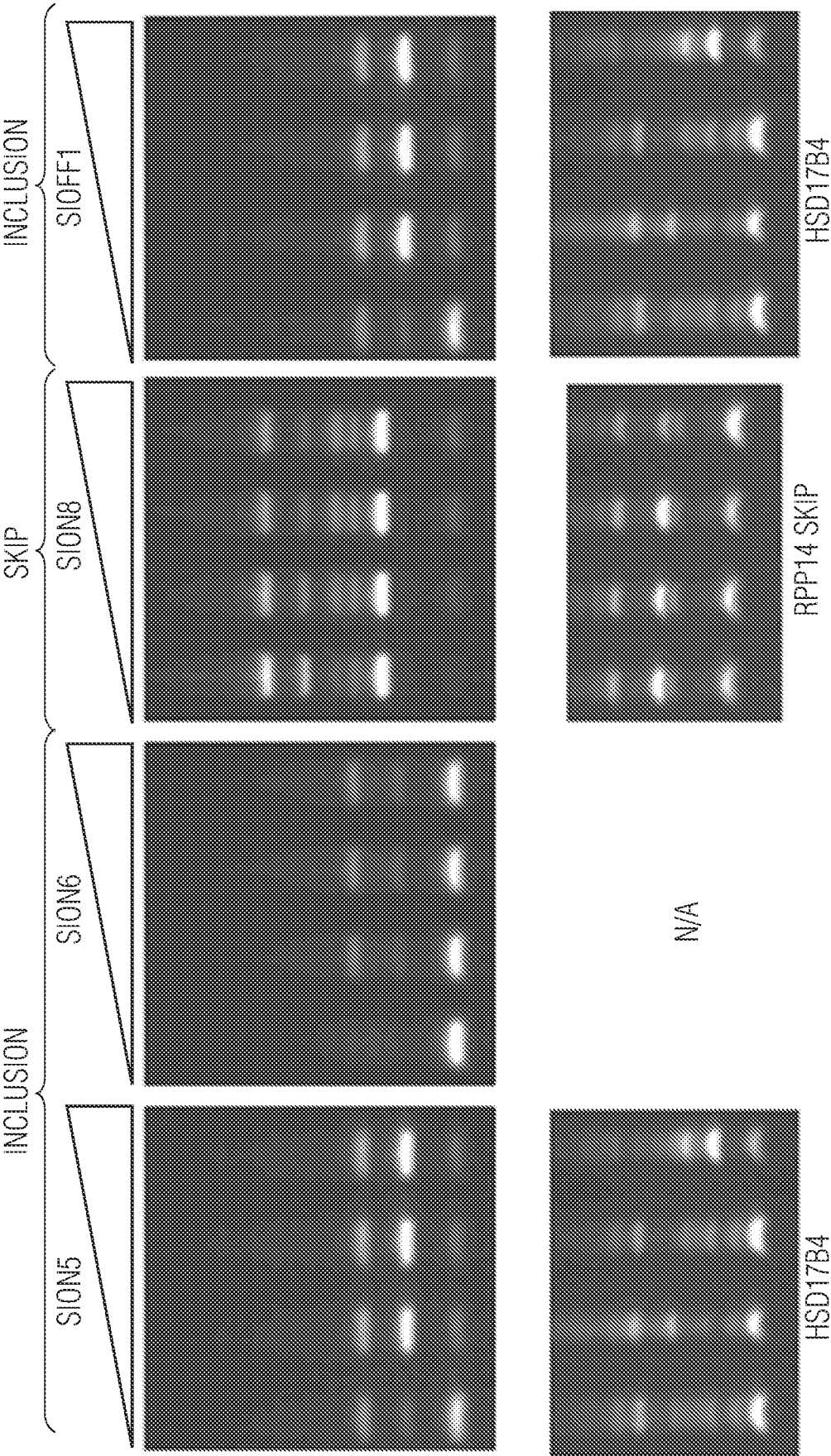


FIG. 5Dii

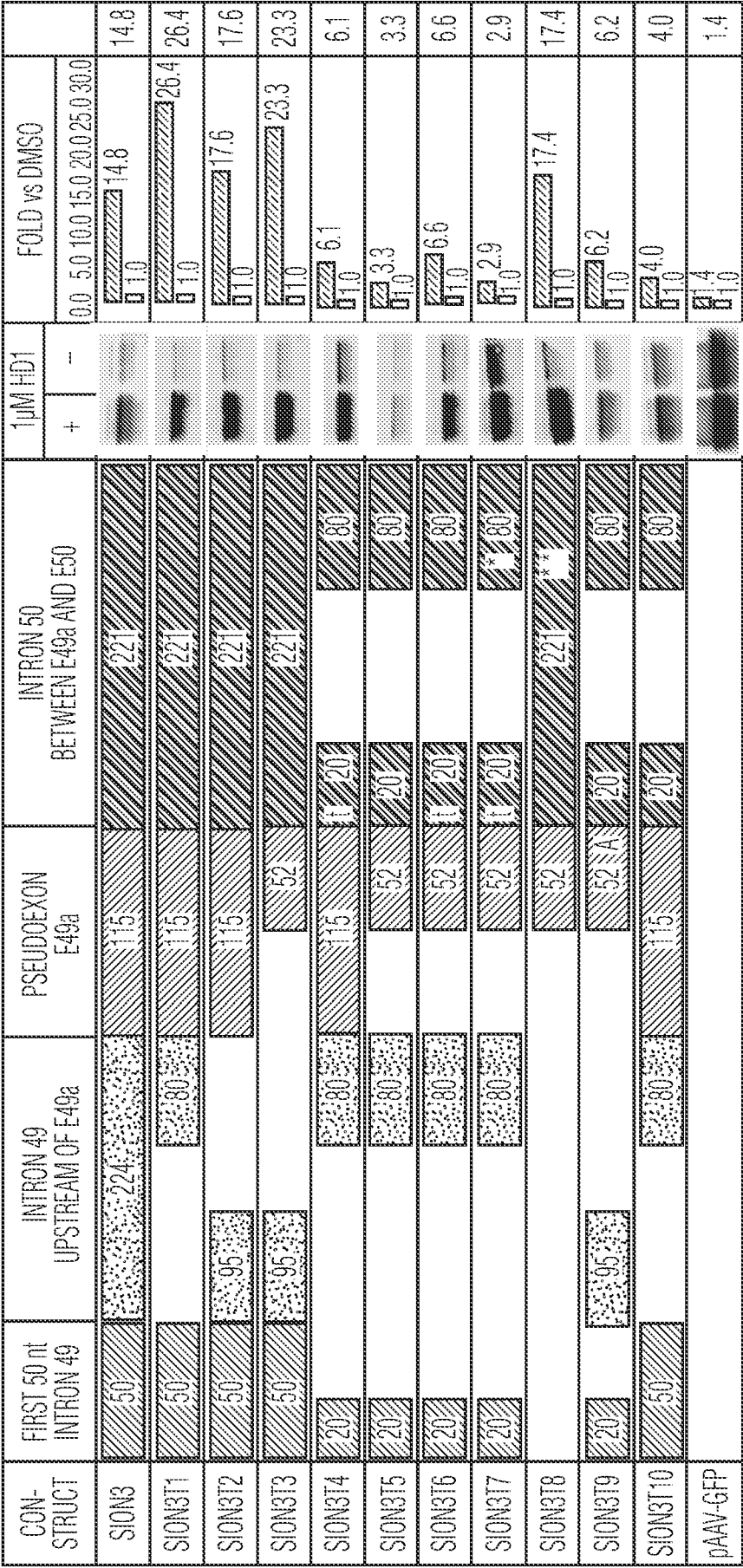


FIG. 6A

MINIGENE ID	SEQUENCE TO REPLACE TGAATG OF PLASMID PAAV-GFP	SEQ ID NO:	TOTAL LENGTH (NT)	MIDDLE EXON SIZE (NT)
SION3	AAACCCCTGACGgtaagaggcagctcgggagctcagtgctgtggtgggaggggcatggggtgctgtatgcagga tgaaatactttatatgcgtcatcttatttgactctcacaaacccctgtgagataggctctgttactcccatttg acagggtgaggaagcaaggcttagagaatttcagtgacttgcccaggctcctctgagctagggaagtagccattct ggcatttgaaccccaaggcctgtctatccctaggaaacccacgctctcaaatccaacctatgacaggAGGCAAGCCCTG GTGCTGTGGAGCCCCAAGGAAGAGCCTCTGGCTGGTGGCCACGTAGCCAGGAGAGATTCTACAGGAGCCC ACAGCGCTGAAGGAGAGAGAGGACAGCAGgtaagggggctttgtggcagagaggggactggcactttggggaat aggtgggtcaggactgaatgtaattggagccatgtcagagctgtccttcttggaagggcaagggcacctggacgcg ctgccccctcagtgctttggacggttcacaaactgtgattcacacggcttccccctaaacggaaggtacacgagtggg cattctgtgactcgggtacttccctttaagTC	98	622	115
SION3T1	AAACCCCTGACGgtaagaggcagctcgggagctcagtgctgtggtgggaggggcatggggtaggaagtagcca ttctggcatttgaacccaaggcctgctatccctaggaaacccacgctctcaaatccaacctatgacaggAGGCAAGC CCTGGTGTGTGGGAGCCCCAAGGAAGAGCCTCTGGCTGGTGGCCACGTAGCCAGGAGAGATTCTACAGGA GCCCCACAGCGCTGAAGGAGAGAGAGGACAGCAGgtaagggggctttgtggcagagaggggactggcactttggg gaataggtgggtcaggactgaatgtaattggagccatgtcagagctgtccttcttggaagggcaagggcacctgga cgcgctgccccctcagtgctttggacggttcacaaactgtgattcacacggcttccccctaaacggaaggtacacgag tgggcattctgtgactcgggtacttccctttaagTC	99	478	115

FIG. 6Bi

MINIGENE ID	SEQUENCE TO REPLACE IGAATG OF PLASMID PAAV-GFP	SEQ ID NO.	TOTAL LENGTH (NT)	MIDDLE EXON SIZE (NT)
SION3T2	AAACCCCTGACGtaagaggcagctcgggagctcagtggtgtgtgggaggggcatggggtgctgtatgcagga tgaataactttatatgcgtcatcttatttgactctcaaacccctgtgagataggctctgttactcccatttg acagGTGAGCCAGCCCTGGTGCTGTGGGAGCCCAAGGAAGAGCCTCTGGCCTGGTGGCCACGTAGCCCAGGA GAGATTCTACAGGAGCCACAGCCCTGAAGGAGAGAGAGCCAGCAGGtaaggggggtttgtggcagagaggg gactggcactttggggaaatagggtgggtcaggactgaatgtaatggagccatgtcagagctgtccttcttggaagg gcaagggcacctggacgcgtgccccctcagtgcttttgacgggttccacaaactgtgattcacaagggttccccctaa acgaagggtacacgagtgggcattctgtgactcggtaacttccctttagTGTG	100	493	118
SION3T3	AAACCCCTGACGtaagaggcagctcgggagctcagtggtgtgtgggaggggcatggggtgctgtatgcagga tgaataactttatatgcgtcatcttatttgactctcaaacccctgtgagataggctctgttactcccatttg acagGTGAGGAGAGATTCTACAGGAGCCCAAGCCTGAAGGAGAGAGAGCCAGCAGGtaaggggggtttgt ggcagagaggggactggcactttggggaatagggtgggtcaggactgaatgtaatggagccatgtcagagctgtc cttctggaaggggcaaggccacctggacgcgtgccccctcagtgcttttgacgggttccacaaactgtgattcacaac ggcttccccctaaacgaagggtacacgagtgggcattctgtgactcggtaacttccctttagTGTG	100	430	55

FIG. 6Bii

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MINIGENE ID	SEQUENCE TO REPLACE TGAATG OF PLASMID PAAV-GFP	SEQ ID NO:	TOTAL LENGTH (NT)	MIDDLE EXON SIZE (NT)
S10N314	AACCTTGAAGgtaaaggcagctcgggagcctaggaagtagccattcttgccatttgaaacccaaggcctgctatc cctagaacccacgctctcaaatccaacctatgacagAGGCAAGCCCTGGTGGTGGAGCCCAAGGAAGAGC ACAgtaaagtgggctttgtggcaggttccacaactgtgattcacacggcttcccctaaacgaaggtacacgagtggtg gcattctgtgactcggctacttcccccttagTG	102	327	115
S10N315	AACCTTGAAGgtaaaggcagctcgggagcctaggaagtagccattcttgccatttgaaacccaaggcctgctatc cctagaacccacgctctcaaatccaacctatgacagAGGAGAGATTTCTACAGGAGCCCAACAGCGCTGAAGGAG AGAGAGGCAGCAGAgtaaagggggtttgtggcaggttccacaactgtgattcacacggcttcccctaaacgaaggt tacacgagtggtgactcgtgactcgttcccccttagTG	103	264	52
S10N316	AACCTTGAAGgtaaaggcagctcgggagcctaggaagtagccattcttgccatttgaaacccaaggcctgctatc cctagaacccacgctctcaaatccaacctatgacagAGGAGAGATTTCTACAGGAGCCCAACAGCGCTGAAGGAG AGAGAGGCAGCAGAgtaaagtggggtttgtggcaggttccacaactgtgattcacacggcttcccctaaacgaaggt tacacgagtggtgactcgtgactcgttcccccttagTG	104	264	52
S10N317	AACCTTGAAGgtaaaggcagctcgggagcctaggaagtagccattcttgccatttgaaacccaaggcctgctatc cctagaacccacgctctcaaatccaacctatgacagGGAGAGATTTCTACAGGAGCCCAACAGCGCTGAAGGAGA GAGAGGCAGCAGAgtaaagtggggtttgtggcaggttccacaactgtgatggcacaacgggttcccctaaacgaaggt tacacgagtggtgactcgtgactcgttcccccttagTG	105	264	51

FIG. 6Biii

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MINIGENE ID	SEQUENCE TO REPLACE TGAATG OF PLASMID PAIV-GFP	SEQ ID NO:	TOTAL LENGTH (NT)	MIDDLE EXON SIZE (NT)
SION3T8	AAACCTTGAAGAGGAGAGATTCTACAGGAGCCACAGCCGCTGAAGGAGAGAGAGCCAGCAAGgttaaggggctt tgtggcagagaggggactggcaactttggggaataggtgggtcaggactgaatgtaatggtggagagccatgtcaga gctgtccttctgtgaagggaaggacacctggacgcgtgccccctcagtgctttggacgggtccacaactgtgat ggcacacacgggcttccccctgaacgaagggtacacgagtgggcattctgtgactcgtcggtacttcccccttagTG	106	289	52
SION3T9	AAACCTTGAAGgttaagagggcagctcgggagctgctgtatgcaggatgaaataactttatatgcgtcatcttatttg actctcaaacacccctgtgagataggctctgttactcccatttgacagGTGAGGAGAGATTTCTACAGGAGCCCC ACAGCCGCTGAAGGAGAGAGAGAGCCAGCAAGgttaaggggctttgtggcaggttccacaactgtgattcacacggc ttccccctaaacgaagggtacacgagtgggcattctgtgactcgtcggtacttcccccttagTG	107	279	55
SION3T10	AAACCTTGAAGgttaagagggcagctcgggagctcagtgctgtgtgggaggggcatggggctaggaagtagcca ttctggcatttgaaccacaaggcctgctatccctcagaacccacgcctctcaaatccaacctatgacagAGGCAAGC CCTGGTGTGTGGGAGCCCAAGGAGAGAGCCCTCTGGCCCTGGTGGCCACGTAGCCCAAGGAGAGATTTCTACAGGA GCCCCACAGCCGCTGAAGGAGAGAGAGAGCCAGCAAGgttaaggggctttgtggcaggttccacaactgtgattcaca cgggttccccctaaacgaagggtacacgagtgggcattctgtgactcgtcggtacttcccccttagTG	108	357	115

FIG. 6Biv

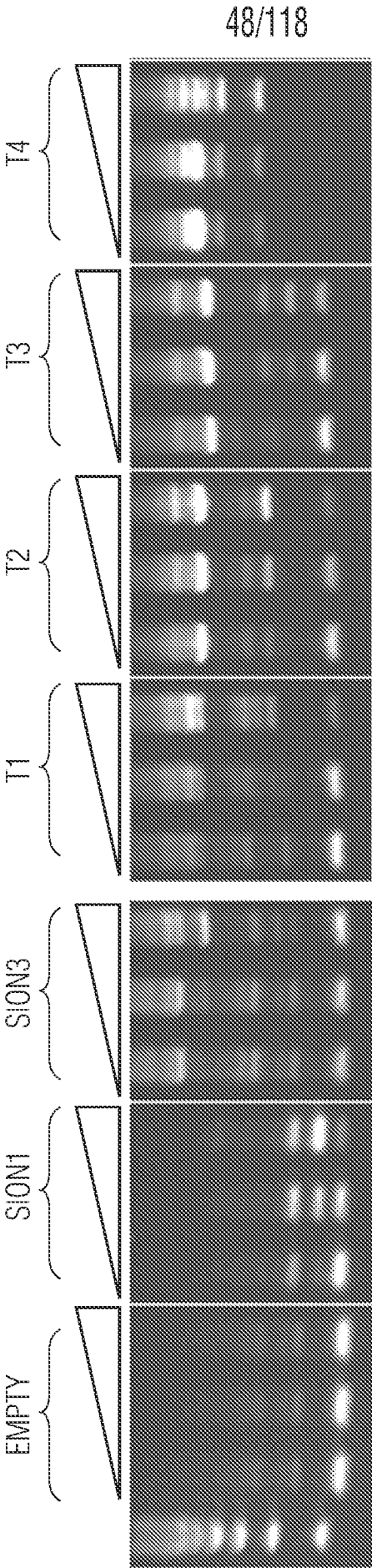


FIG. 6Ci

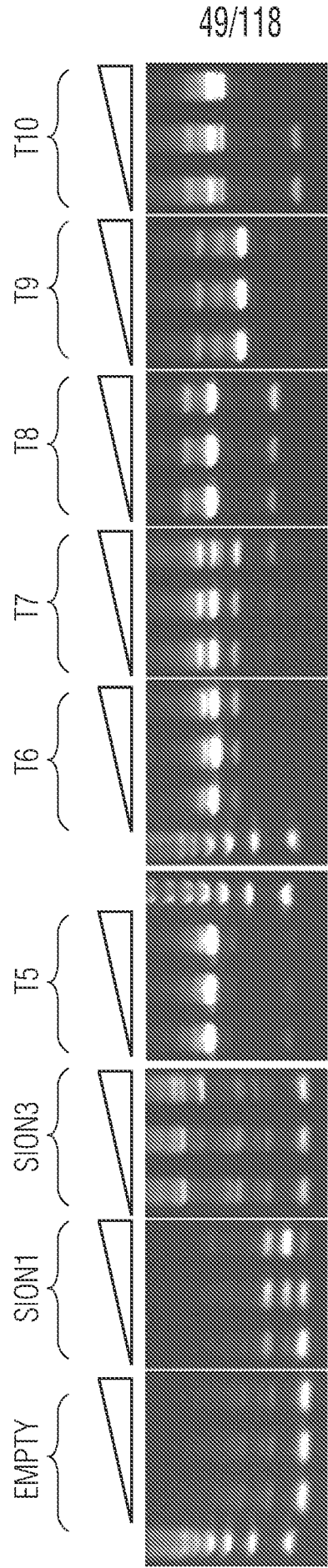


FIG. 6Cii

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SEQUENCE ID	SHORT (SKIP)	LONG (INCL)	INTR RET
pAAV-GFP	74	74	74
SION1	80	119	419
SION3	80	195	690
SION3T1	86	201	552
SION3T2	86	201	567
SION3T3	86	138	504
SION3T4	86	201	401
SION3T5	86	138	338
SION3T6	86	138	338
SION3T7	86	138	338
SION3T8	86	138	363
SION3T9	86	138	353
SION3T10	86	201	431

FIG. 6Ciii

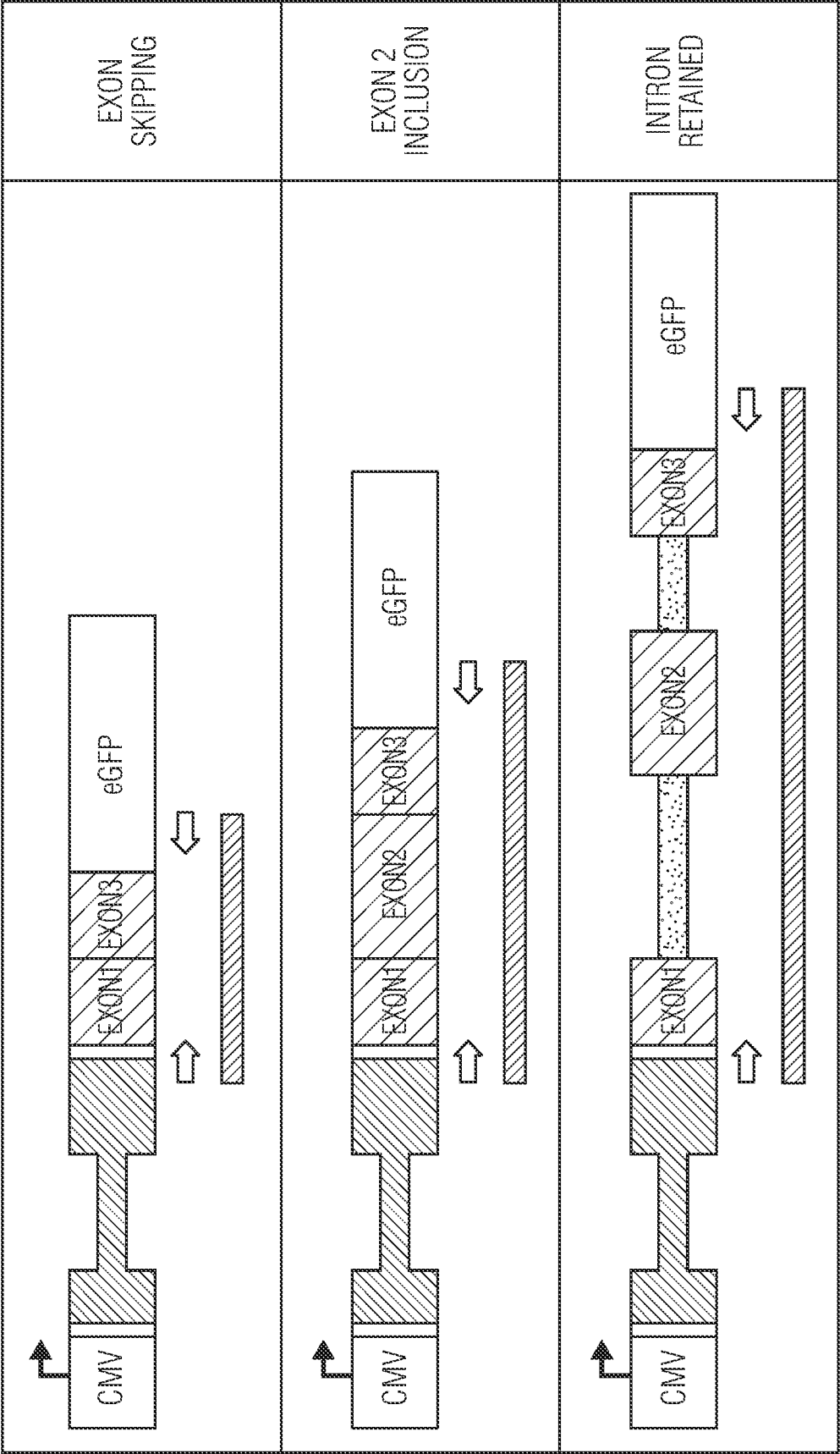


FIG. 6Civ

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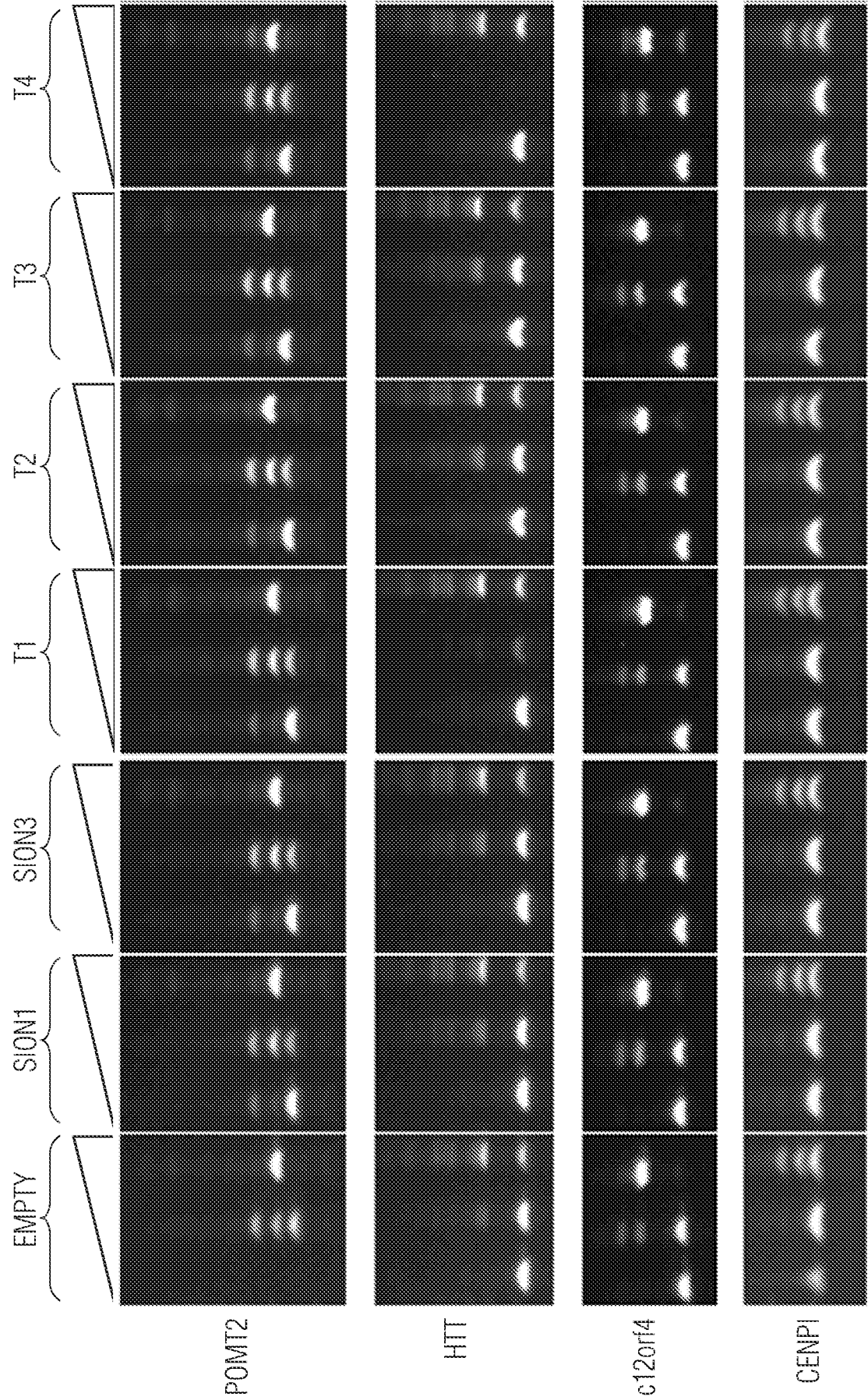


FIG. 6Di

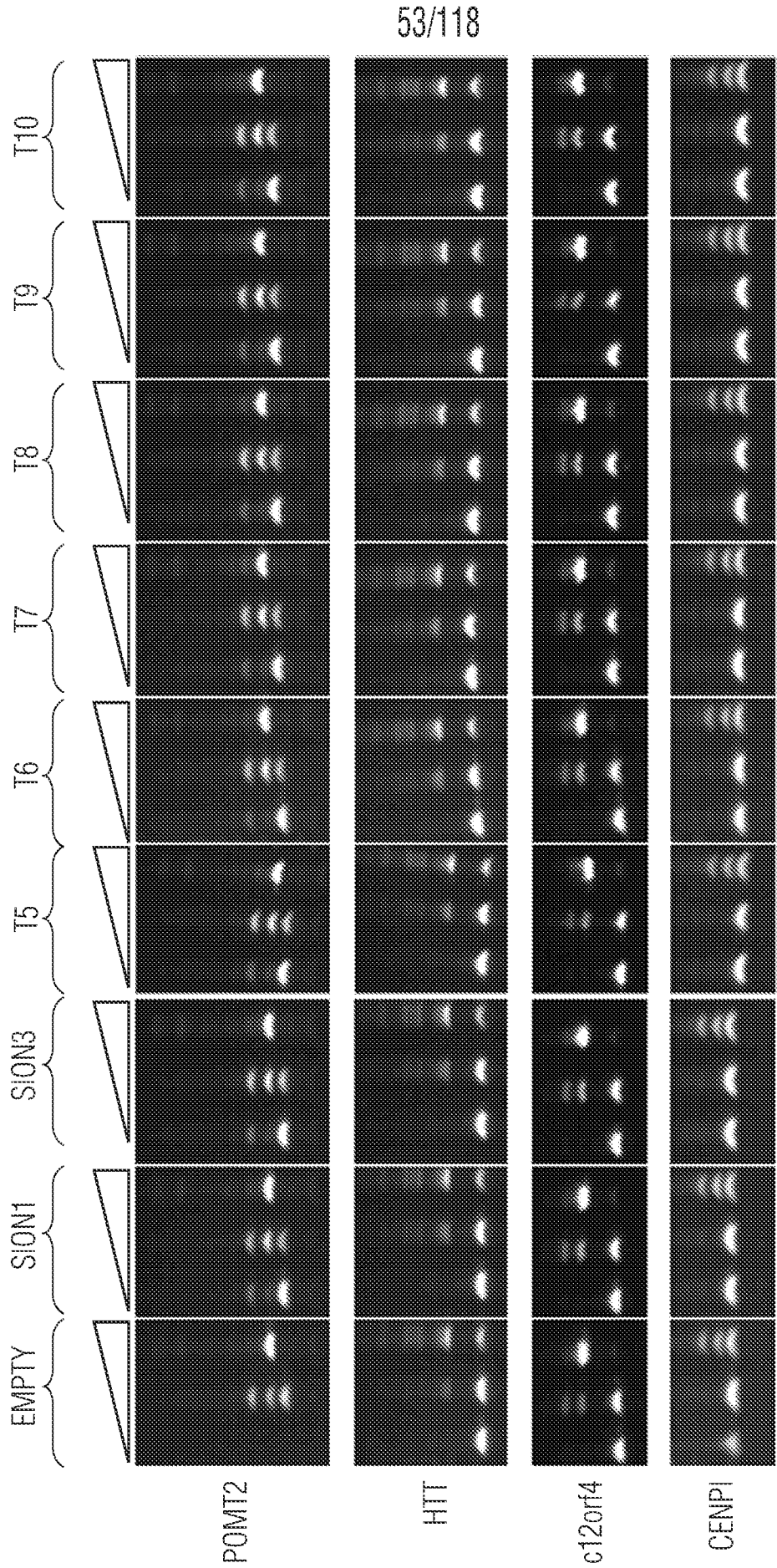


FIG. 6Dii

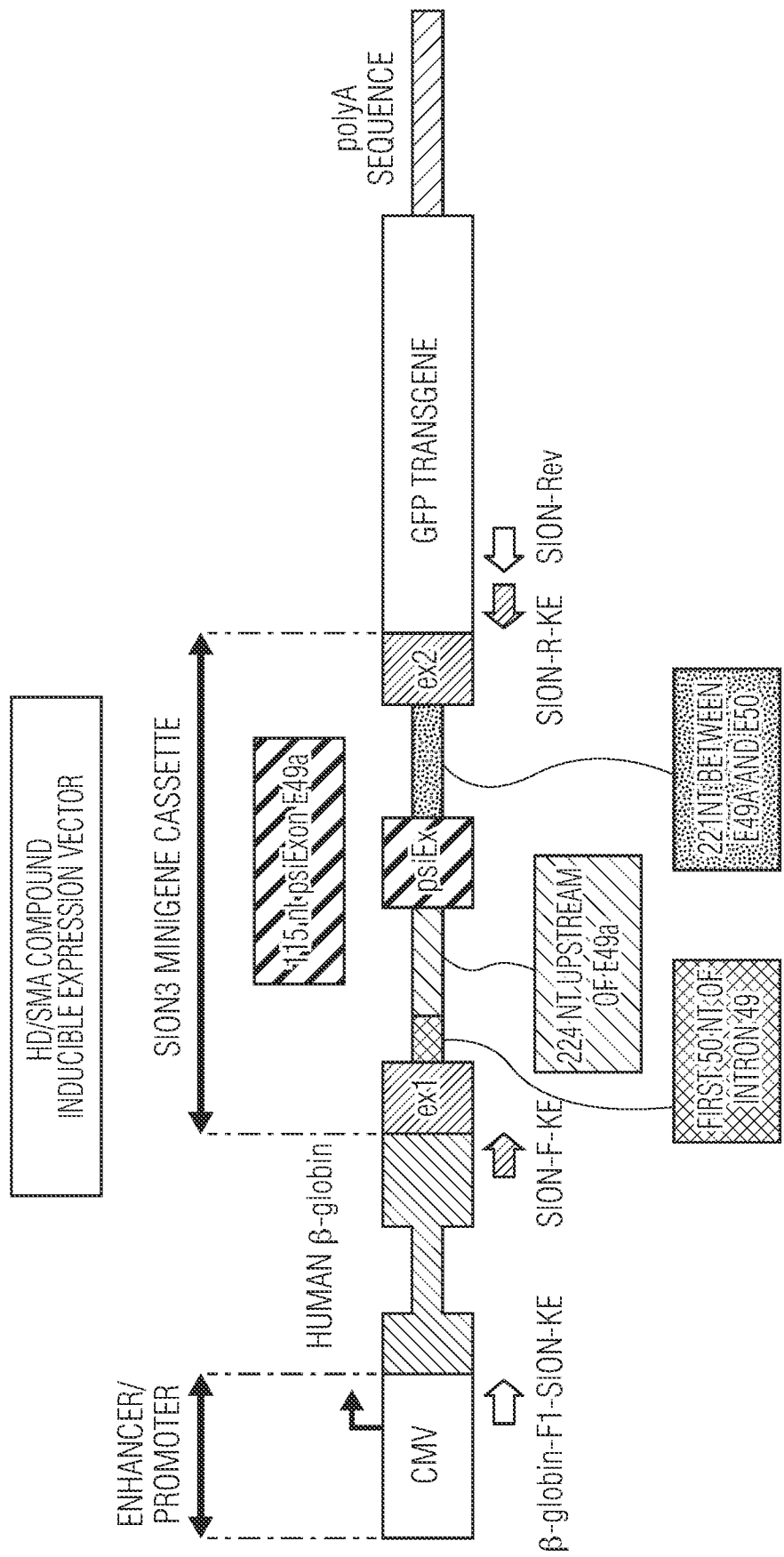


FIG. 7A

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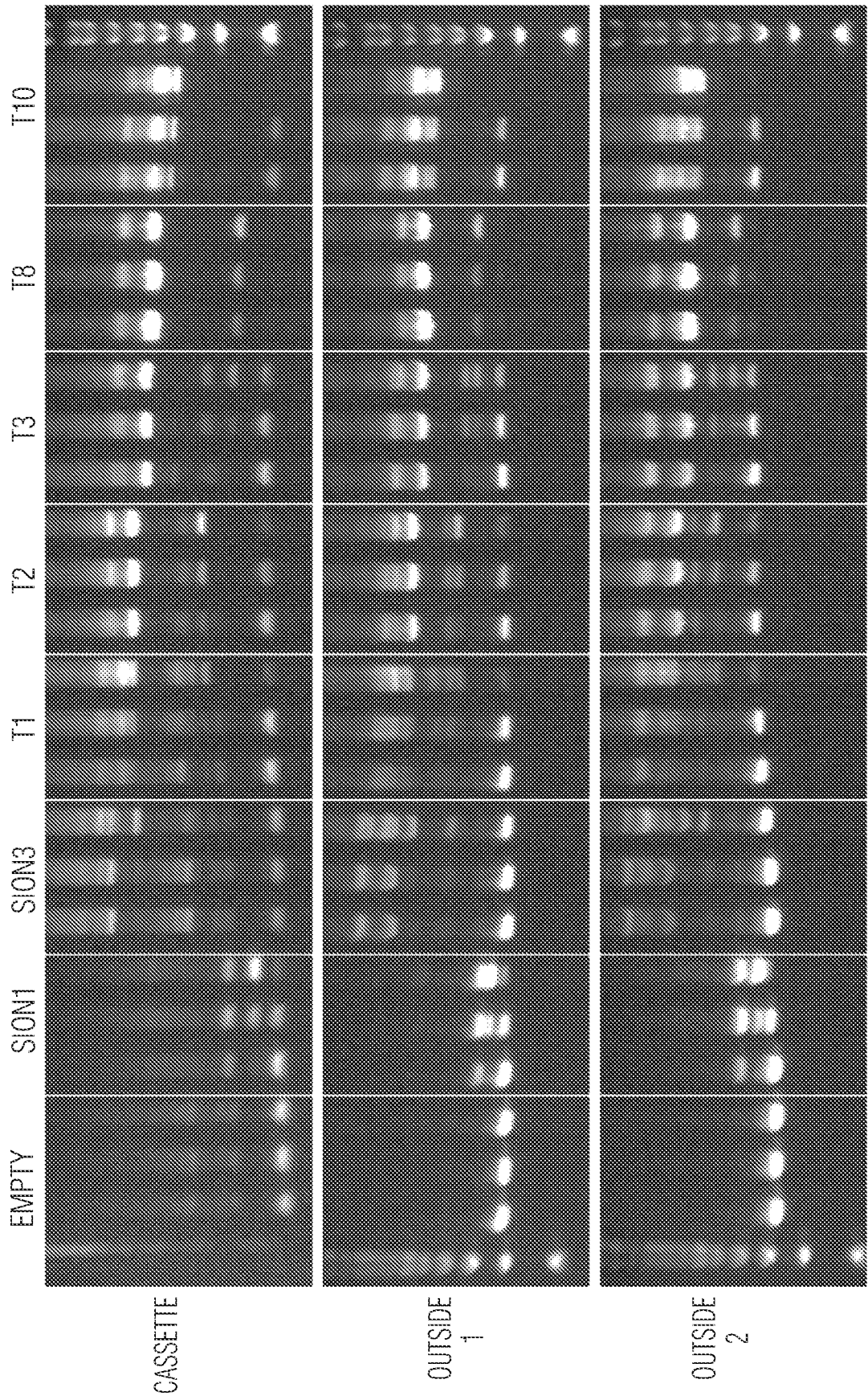


FIG. 7B

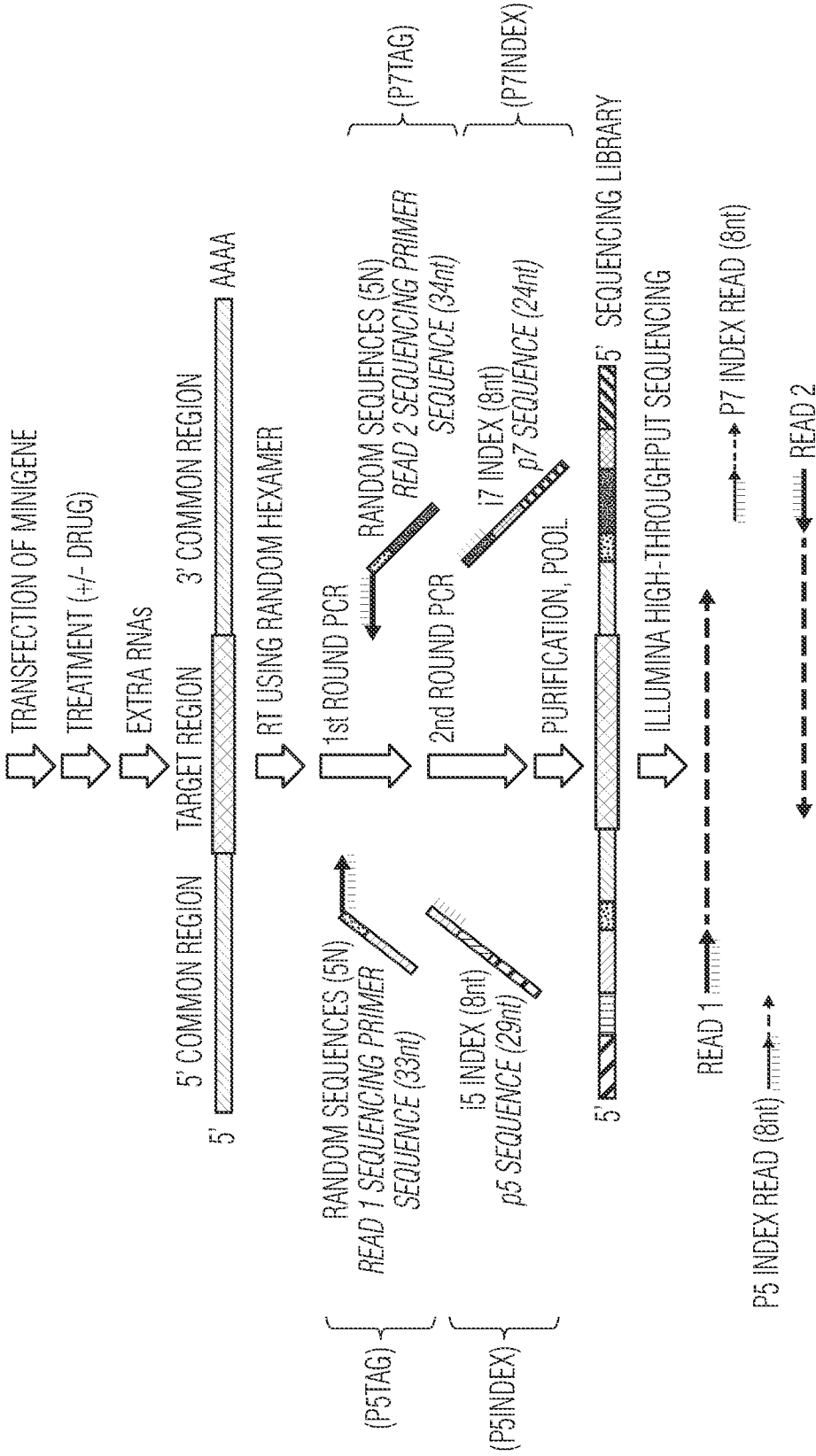


FIG. 8A

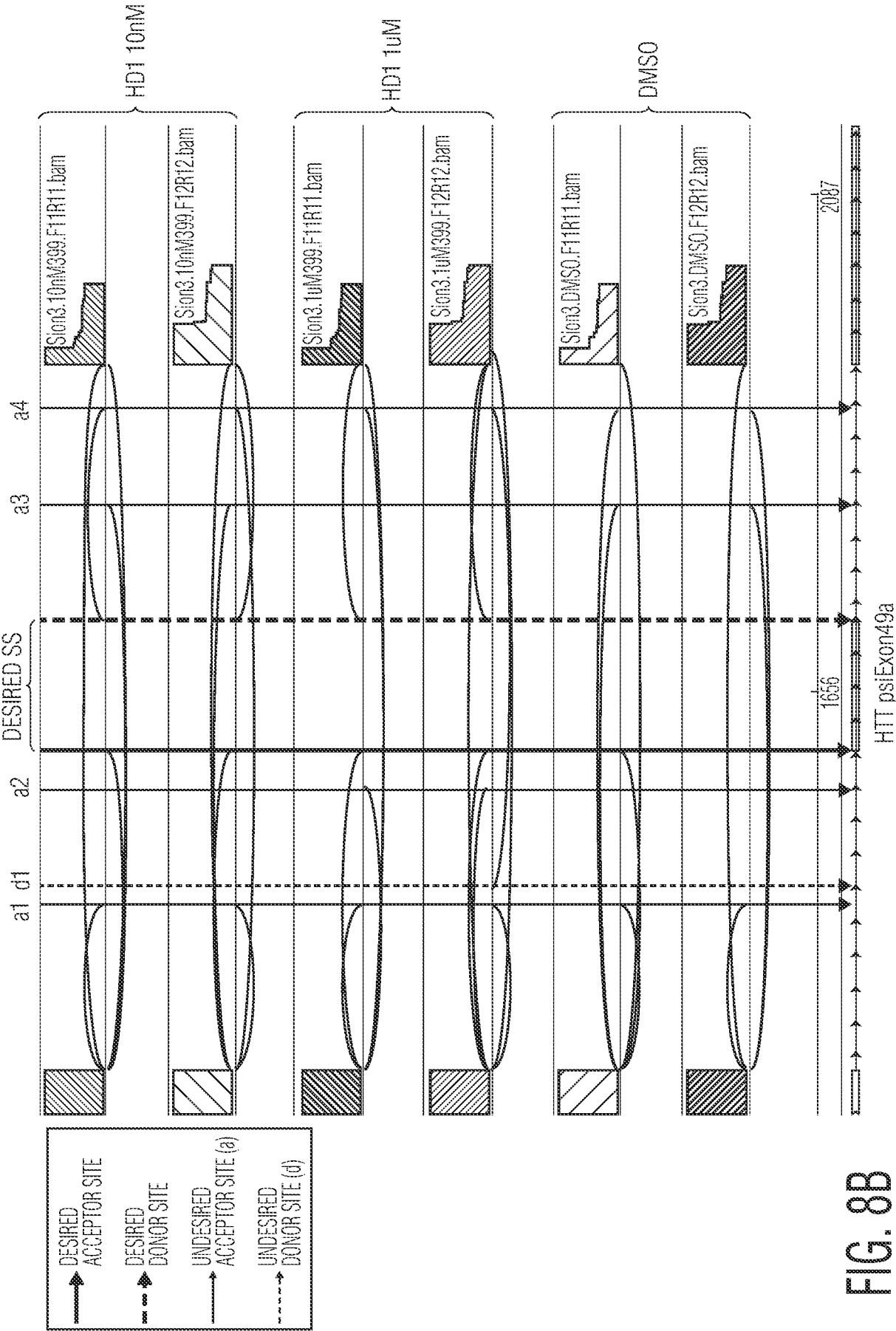
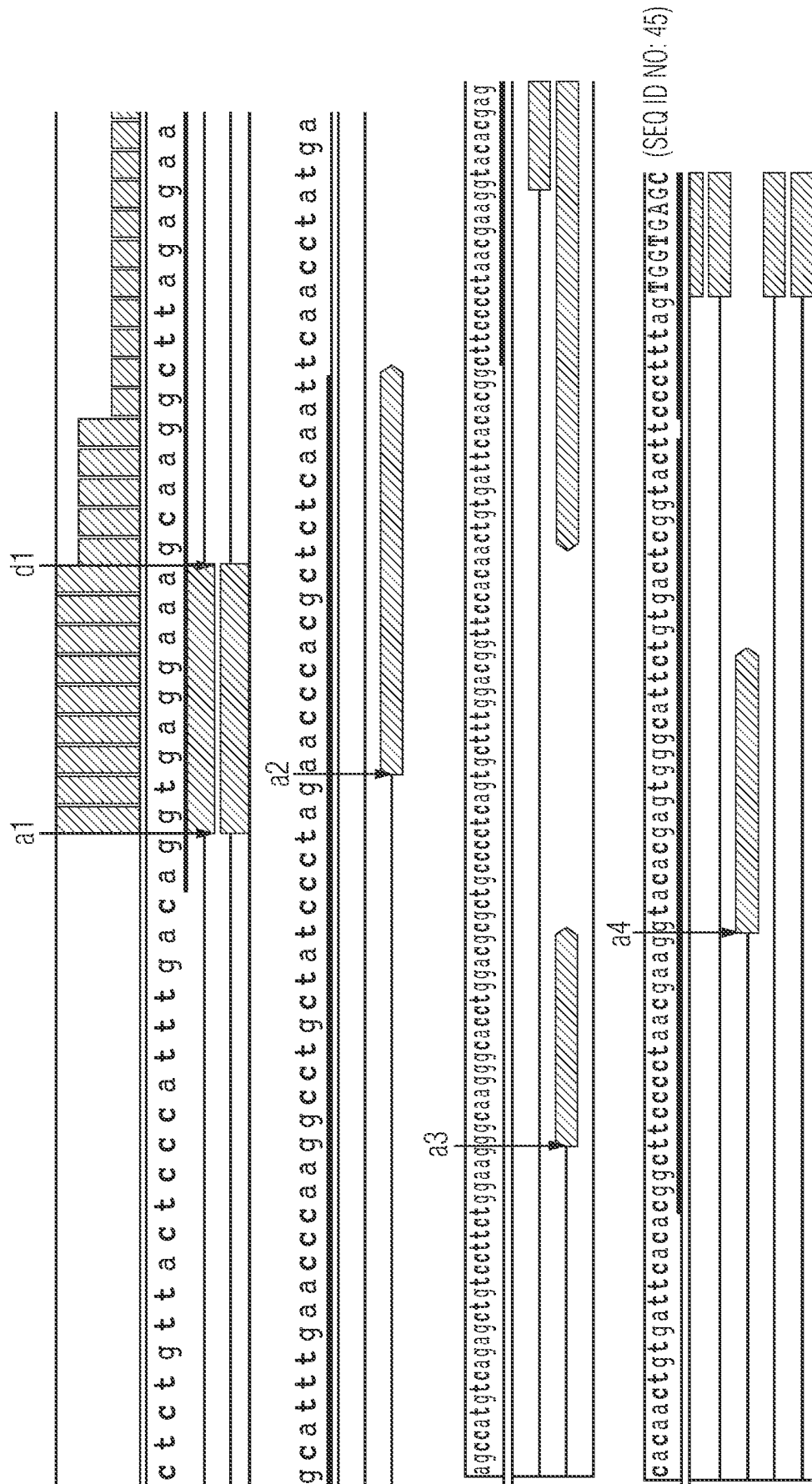


FIG. 8B



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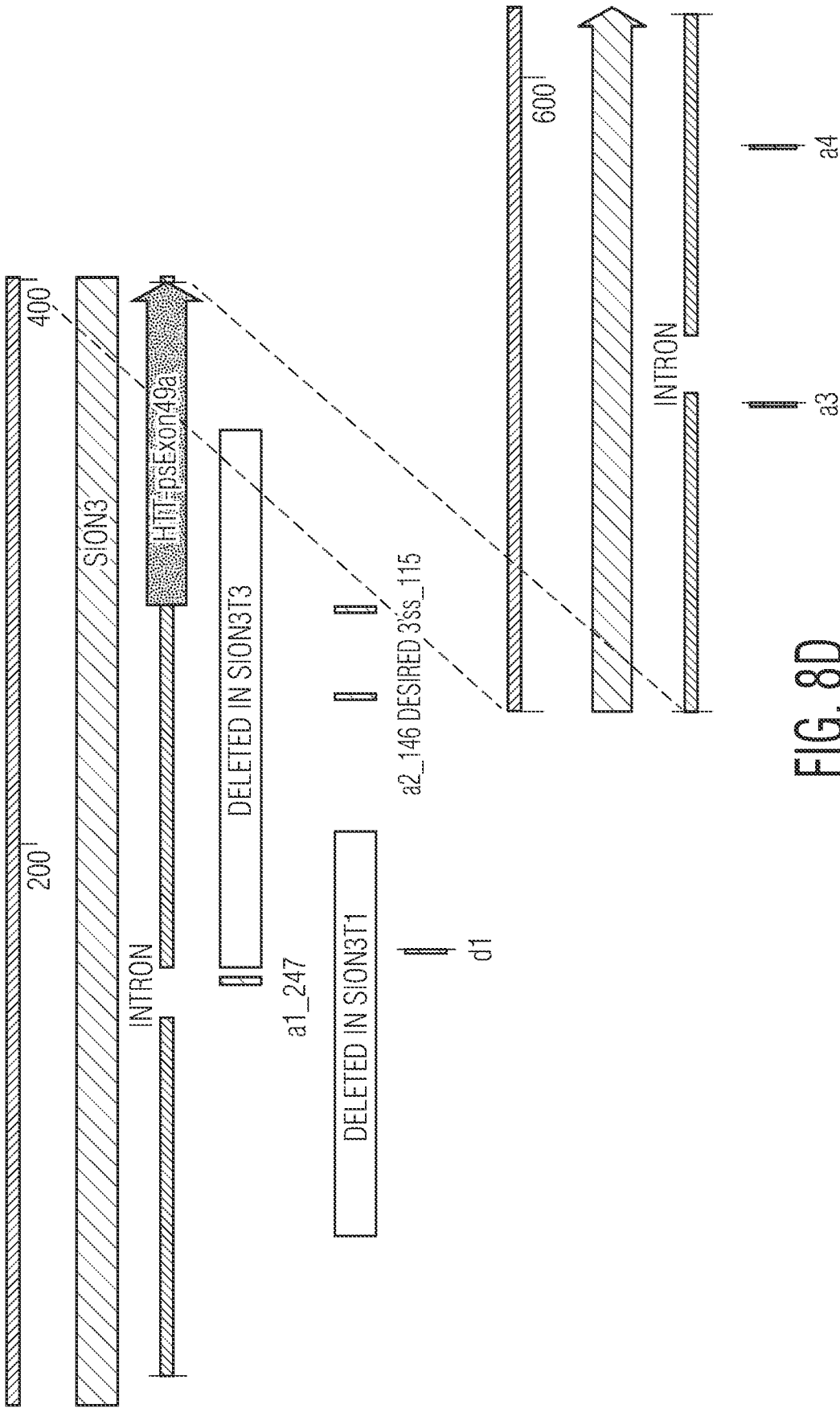


FIG. 8D

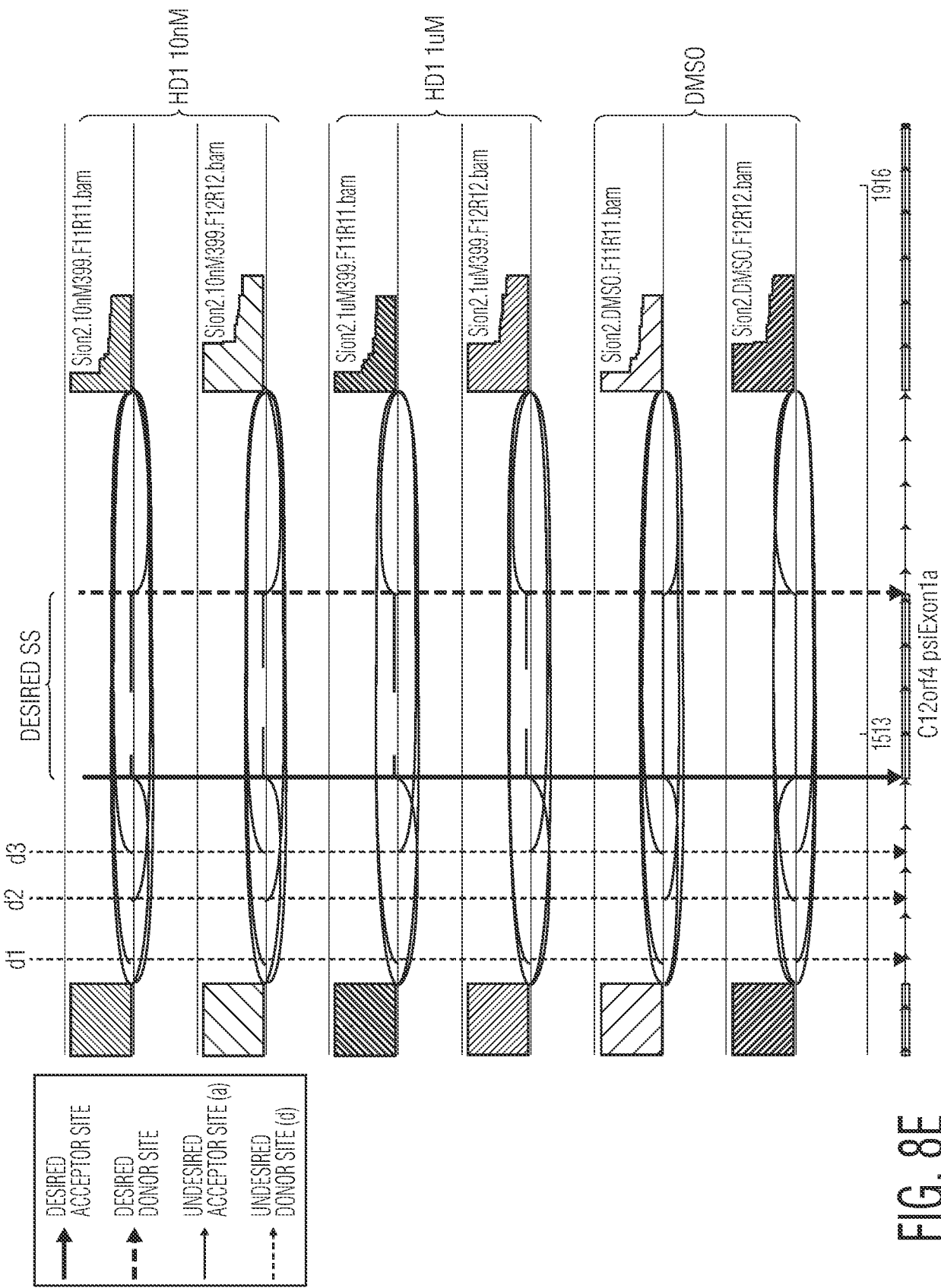
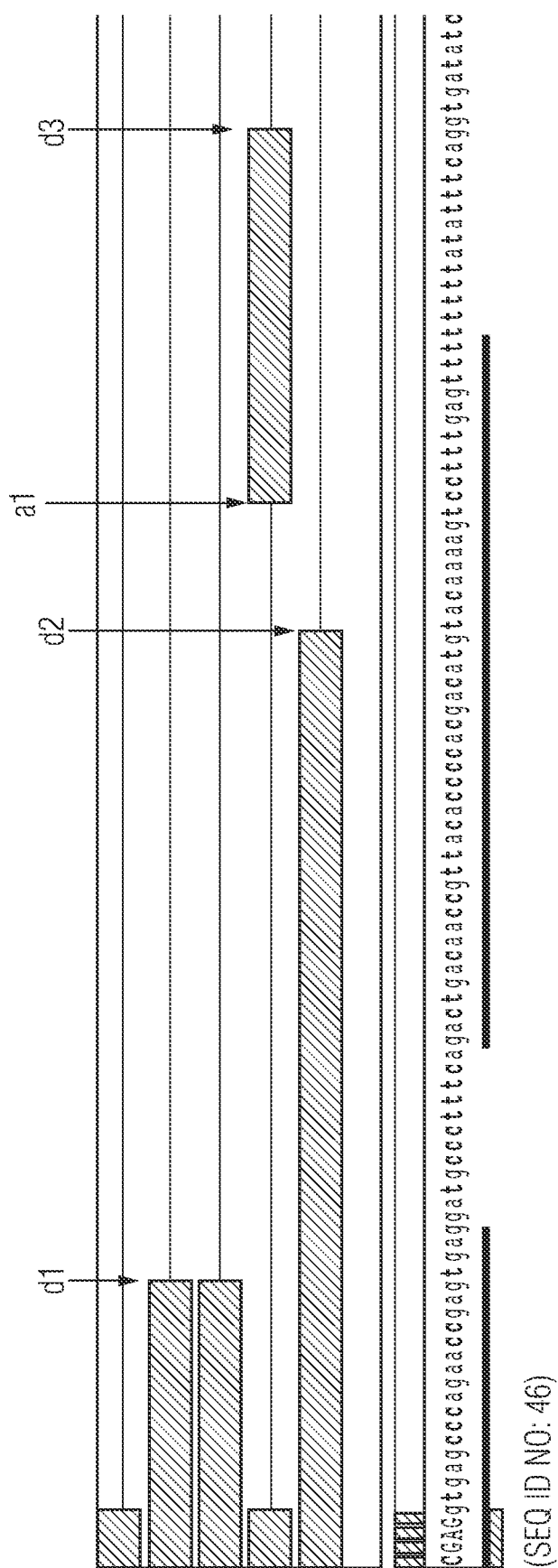


FIG. 8E



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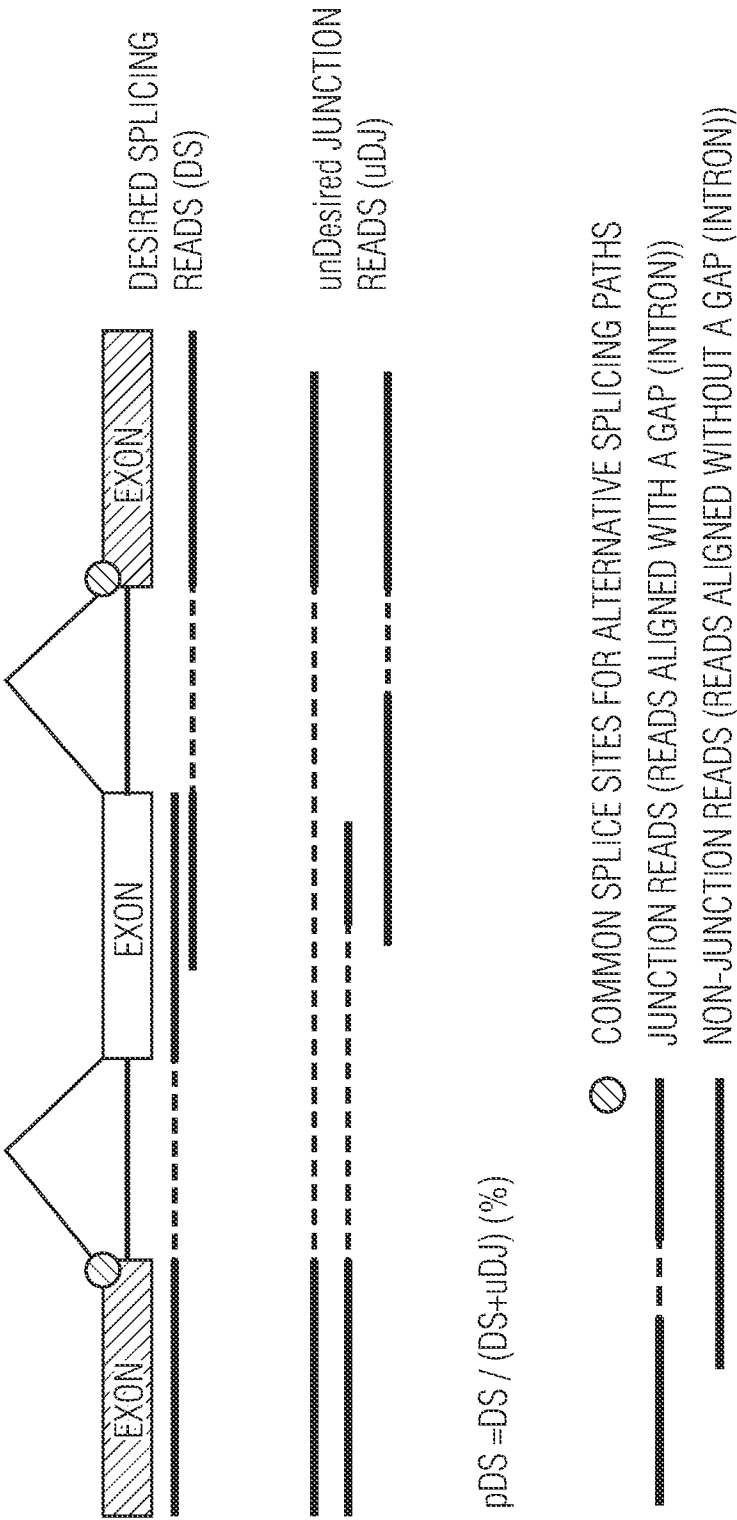


FIG. 8G

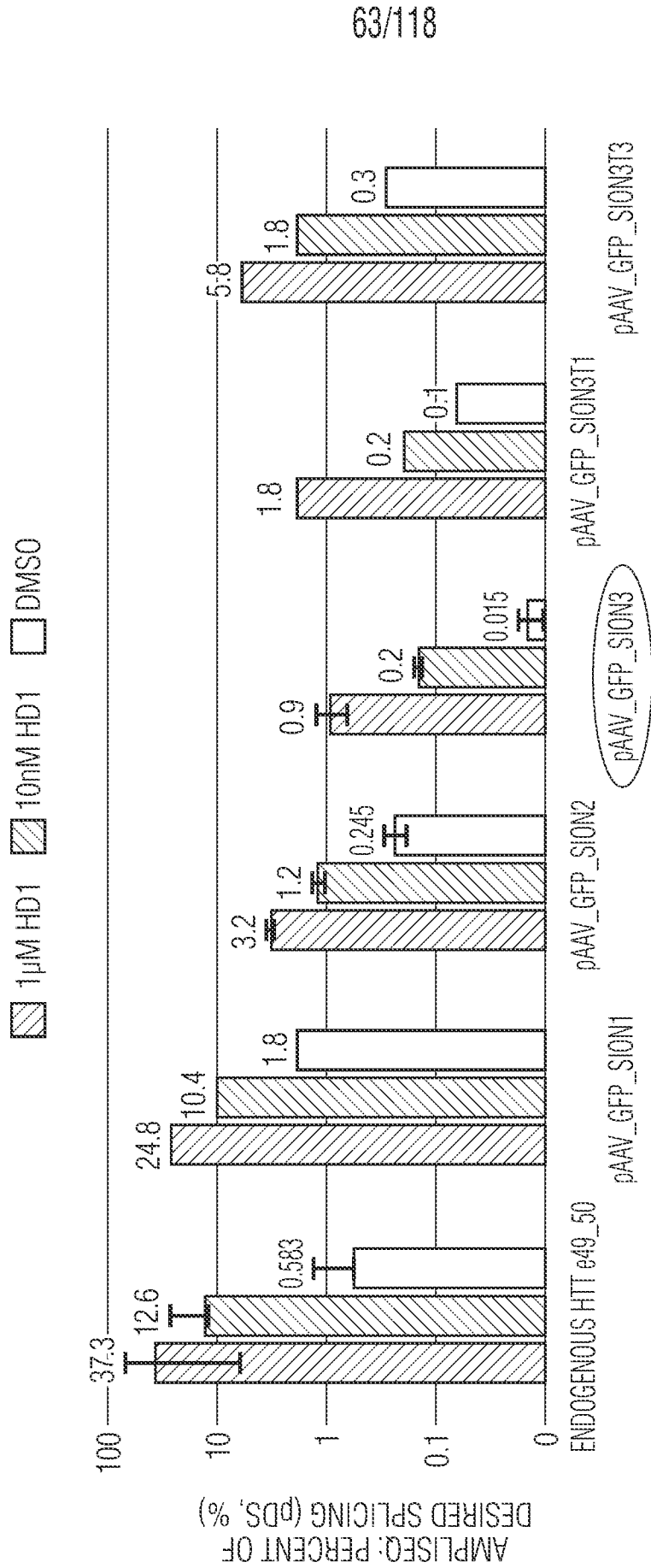


FIG. 8H

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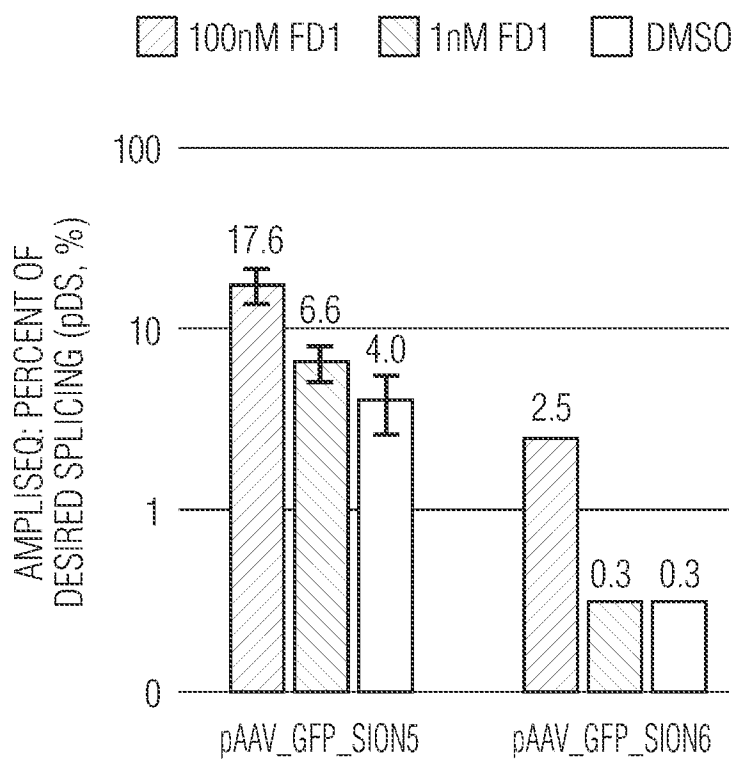
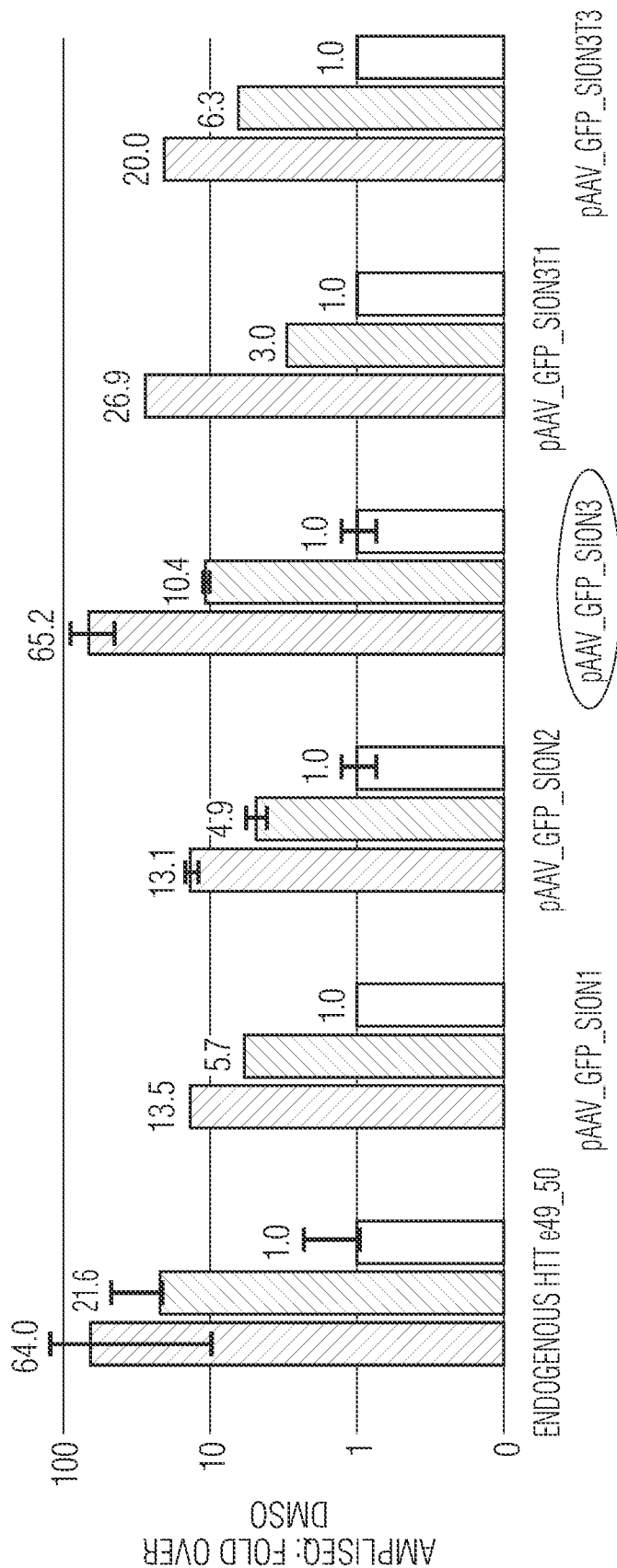


FIG. 8I

1 μ M HD1 10nM HD1 DMSO

1000



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FIG. 8J

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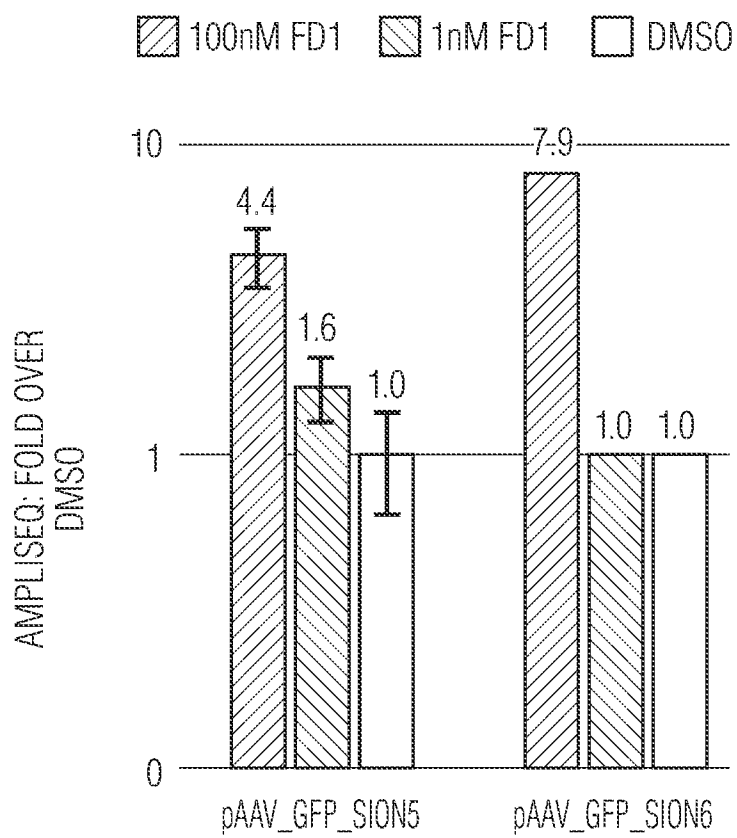


FIG. 8K

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SEQ ID NO.	MINIGENE CASSETTE ID	PARENT MINIGENE CASSETTE ID	MUTATE CRYPTIC SS	MUTATE CG, ATG TATA, SS	COMPOUND TOTAL LENGTH MIDDLE EXON SIZE	MINIGENE CASSETTE NUCLEOTIDE SEQUENCE
47	ON3m1	SION3	YES	NO	SMA/HD (INCLUSION) 622 115	TAACCTTTGAAGGtaagaggagcagctcgaggagctcagtggtgtgtgggagggggcagtggggtgctgtatgca ggatgaaataactttatatggtcatctctatttgaactctcaaacccccctgtgagataggctctgtttactcc catttgactggtgaggaaccaaaggcttagagaaattcagtgacttgccagggtccctctgagctagggaagt agccattctggcatttgaacccaaggcctgctatcccttgaacccacgctctcaaatccaacctatgacag TAGGCAAGCCCTGGTCTGTGGAGAGCCCAAGCAAGAGCCCTGTGGCCCTGGTGGCCAGCTAGCCCAAGGAGAGA TTTCTACAGGAGCCCAAGCCCTGTGAAGCAGAGAGAGCCAGAGGtaaggggctttgtggcagagagggg actggcaactttggggaataggtgggtcaggactgaatgtaatggagccatgtcagagctgtccctctggat aggcaagggcacccggacgcctgcccctcagtgctttggacgggtccacaaactgtgattcacacggcttc ccctaacgactgtacacgagtggggaattctgtgactcgtggtacttccctttaagTg
48	ON3m2	SION3	YES	YES	SMA/HD (INCLUSION) 622 115	TAACCTTTGAAGGtaagaggagcagctttggagctcagtggtgtgtgggagggggcaggggtgctgtttgca agttgaaataactttggttgtttcaacttggttgactctcaaacccccctaaagatataggtctctgtttactcc caattgactgaaggaggaaccaaaggcttagagaaattcagtgacttgcccagggtccctctgagctagggaagt agccaatctggcaagggaaccaaaggcctgctatcccttgaacccacgctctcaaatccaacctatgacag TAGGCAAGCCCTGGTCTGTGGAGAGCCCAAGCAAGAGCCCTGTGGCCCTGGTGGCCAGCTAGCCCAAGGAGAGA TTTTTACAGGAGCCCAAGCTCTGTGAAGCAGAGAGAGCCAGAGGtaaggggctttgtggcagagagggg attggcattttggggaataagtggggtcaggattgattgtaattggagccaaagtcaggtgttttttggat aagcaagggtctcaggattttctgcccctcaatgctttggattgtccacaaactgtgattcaacattgtctc ccctaacgactgtacacgagtggggaattctgtgactcgtggtacttccctttaagTg

FIG. 9A

SEQ ID NO.	MINIGENE CASSETTE ID	PARENT MINIGENE CASSETTE ID	MUTATE CRYPTIC SS	MUTATE CG, ATG TATA, SS	COMPOUND TOTAL LENGTH- MIDDLE EXON SIZE	MINIGENE CASSETTE NUCLEOTIDE SEQUENCE
49	T1m2	SION3T1	YES	YES	SMA/HD (INCLUSION) 478 115	AACCCCTGACGgttaagagggcagctttggagctcagtggttgctgtggggagggggggaaggggctaggaagtagccaatotggcaagggaaccccaagcctgtctatcccttgaaacccaagctctcaaaattcaacctatacaagAGGCAAGCCCTGGTGTGTGGGAGCCCCCAAGGAAGAGCCTCTGGCTTGGTGGCCAAATTAGCCCAAGSACAGATTTTTACAGAGCCCCACACACTTCTGAAGGACAGACAGAGGGCAGCAGGtaagggggtttgtgtggcagagaggggat tggcattttggggaataaagtgggtcaggattgattgattggagccaaagtcagagttgttttttttggataa gcaaggggtttctggattttctgccccctcaatgctttggattgttcccaaaactgtgattcaacattgtctcccc ctcaagcattgtacacgagtgggcattctgtgactcgttacttccctttatGTC
50	T3m2	SION3T3	YES	YES	SMA/HD (INCLUSION) 430 55	AACCCCTGACGgttaagagggcagctttggagctcagtggttgctgtggggagggggggaaggggtgtgtgtttgga aattgaaataactttgggtgttttaacttatttgactctcacaaccccctgtgagataggtctgttactcc catttgacagctGACGACAGACATTTTACAGGAGCCCAACAGCTCTCTGAAGGACAGACAGCCAGCAGCAGgttaagg gggctttgtggcagagaggggattggcattttggggaataagtggttcaggattgattgtattggagccaa gtccagagttgtttttttggataaagcaagggtctctggattttctgccccctcaatgctttggattgtttccac aactgtgattcaccattgtctccccctaacgactgtacacagatgggcattctgtgactcgttacttcccttt aGTC
51	ON1m2	SION1		YES	SMA/HD (INCLUSION) 351 39	TAAACAAAGGgttaagtcacatttgcaagtttggataaaggaattgaaattggccaccaaggggaaaaaccttaaggt tgaaccttaagtgtgggttcocagabaaaaagagagtggttattataaaaaactaaaaagctaaaaattaaac ccctctcatcctccacagATGTCGACCCCAAAAAATCTGCTTTTGGGAGCAGAAAGgttaagtgggcagtgga ggaggtttttotagctcagggccaaagcagattacaagttcttatcctgacaattgactctgaacattcttga aagaagaagaattgtttgcacatcatctttctatataggatcatgacacttctcttttcttaactctatagTGC

895

L

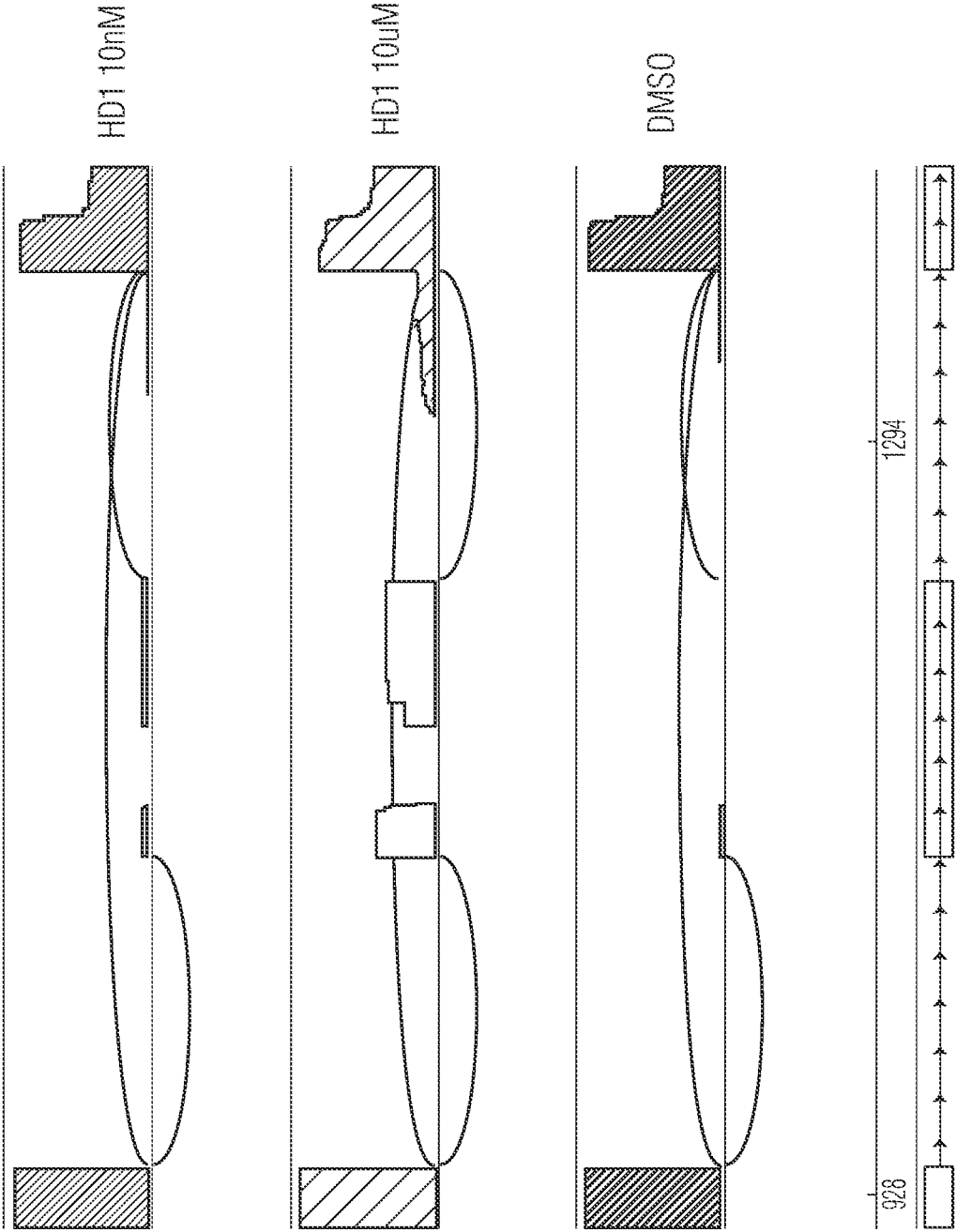
SEQ ID NO:	MINIGENE CASSETTE ID	PARENT MINIGENE CASSETTE ID	MUTATE CRYPTIC SS	MUTATE CG, ATG TATA, SS	COMPOUND TOTAL LENGTH MIDDLE EXON SIZE	MINIGENE CASSETTE NUCLEOTIDE SEQUENCE
52	ON2m1	SION2	YES	NO	SMA/HD (INCLUSION) 447 135	TGAAGACGAGgtgagcccaagaccgaggaggatgcccttccagactgacaaacggttaacccccagacatctacaaaactcccttgagtttttttatatttcaggcgatatcttttaataaacggtatgaataattttttgttttttattttttccatgagccaccataaaataaaacggccatagcaatccacacattttattagttctTGGCAATTCGCAACATCCTGCCCTAATACATGCAATACAGACAGTATCCTCCACTCCAGAGAGACTGTTTCTACCCCAAGgttaagaaatagagcgtgataagtgcctgattccaaataagtcctaggtcctagacacaaatctctgaatggtggaatgttttcttagaaatgggacagcaataatgaacacataattttctttatggacttataacctaactgctttttgttttagTg
53	ON2m2	SION2	YES	YES	SMA/HD (INCLUSION) 447 135	TGAAGACGAGgtgagcccaagacccttagggaggttgcccttccaaactgacaaacttttaacccccaatacaaactacaaaactcccttgagtttttggtaggttccaggttatatatcttttaataaacggtatgaataattttttgttttttattttttccatgagccaccacaaagaaaattTCCAAAAGATCCACACAAAATGCTTGGGTCTTGGCAATTCGCAACATCCTGCCCTAATACAAAATAACAGACAGTATCCTCCACTCCAGAGAGACTGTTTCTACCCCAAGgttaagaaatagagtttgataaagtgcctagattccaggaagtcctaggtcctagacacaaatctctgaatggtggaatgttttcttaaaattgggacacacataatgaacacataattttctttatggacttataacctaactgctttttgttttagTg

FIG. 9C

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SEQ ID NO.	MINIGENE CASSETTE ID	PARENT MINIGENE CASSETTE ID	MUTATE CRYPTIC SS	MUTATE CG, ATG TATA, SS	COMPOUND TOTAL LENGTH MIDDLE EXON SIZE	MINIGENE CASSETTE NUCLEOTIDE SEQUENCE
54	ON6m2	SION6		YES	FD (INCLUSION) 622 74	<u>TGA</u><u>AATTACAG</u>gtaagctgggtttttcagacaagatagatagttgattgtcaatcagccaatcaaggaggt ggtgatacaggctgtgacacaaaaggctcaaaagttaaatttttttgaaaaatcaagataaggatagagaaca acaagattotgtataaaaaagtgttgatttgggagagttgtggttaatttttgtgaaaaattaaaaaaattg gtgtatccctggctattttaaatgtttttctacttaattaaaaatgttactgcttttaatttttaag<u>ATGCCA</u> <u>AGGGGAAA</u><u>ACTTAGAA</u><u>GTGTTCAACA</u><u>ATTAGCCCTGCTTTTAGCCACAGATTTTGAAGTGTTCACACAA</u>gta agcgccattgtactgtttgttactagttagttgtgtgatttgggtgtgaagacataaagtatttggttacaa tttttagaaccccaagaatttgaaaagccctcaatacttatatcaacaatcaaatcttataaaaactottttt tttttggaaaacttggtttttttatttggatataaattgaattgtatcaaatgaaacccaagctgggccccaa ggagctcagtttttgggaatatotttttctattttttctctgtcttctcaca<u>gTG</u>
55	ON6m3	SION6		YES	SMA/HD (INCLUSION) 622 74	<u>TGA</u><u>AATTACAG</u>gtaagctgggtttttcagacaagatagatagttgattgtcaatcagccaatcaaggaggt ggtgatacaggctgtgacacaaaaggctcaaaagttaaatttttttgaaaaatcaagataaggatagagaaca acaagattotgtataaaaaagtgttgatttgggagagttgtggttaatttttgtgaaaaattaaaaaaattg gtgtatccctggctattttaaatgtttttctacttaattaaaaatgttactgcttttaatttttaag<u>ATGCCA</u> <u>AGGGGAAA</u><u>ACTTAGAA</u><u>GTGTTCAACA</u><u>ATTAGCCCTGCTTTTAGCCACAGATTTTGAAGTGTTCACACAA</u>gta agcgccattgtactgtttgttactagttagttgtgtgatttgggtgtgaagacataaagtatttggttacaa tttttagaaccccaagaatttgaaaagccctcaatacttatatcaacaatcaaatcttataaaaactottttt tttttggaaaacttggtttttttatttggatataaattgaattgtatcaaatgaaacccaagctgggccccaa ggagctcagtttttgggaatatotttttctattttttctctgtcttctcaca<u>gTG</u>

FIG. 9D



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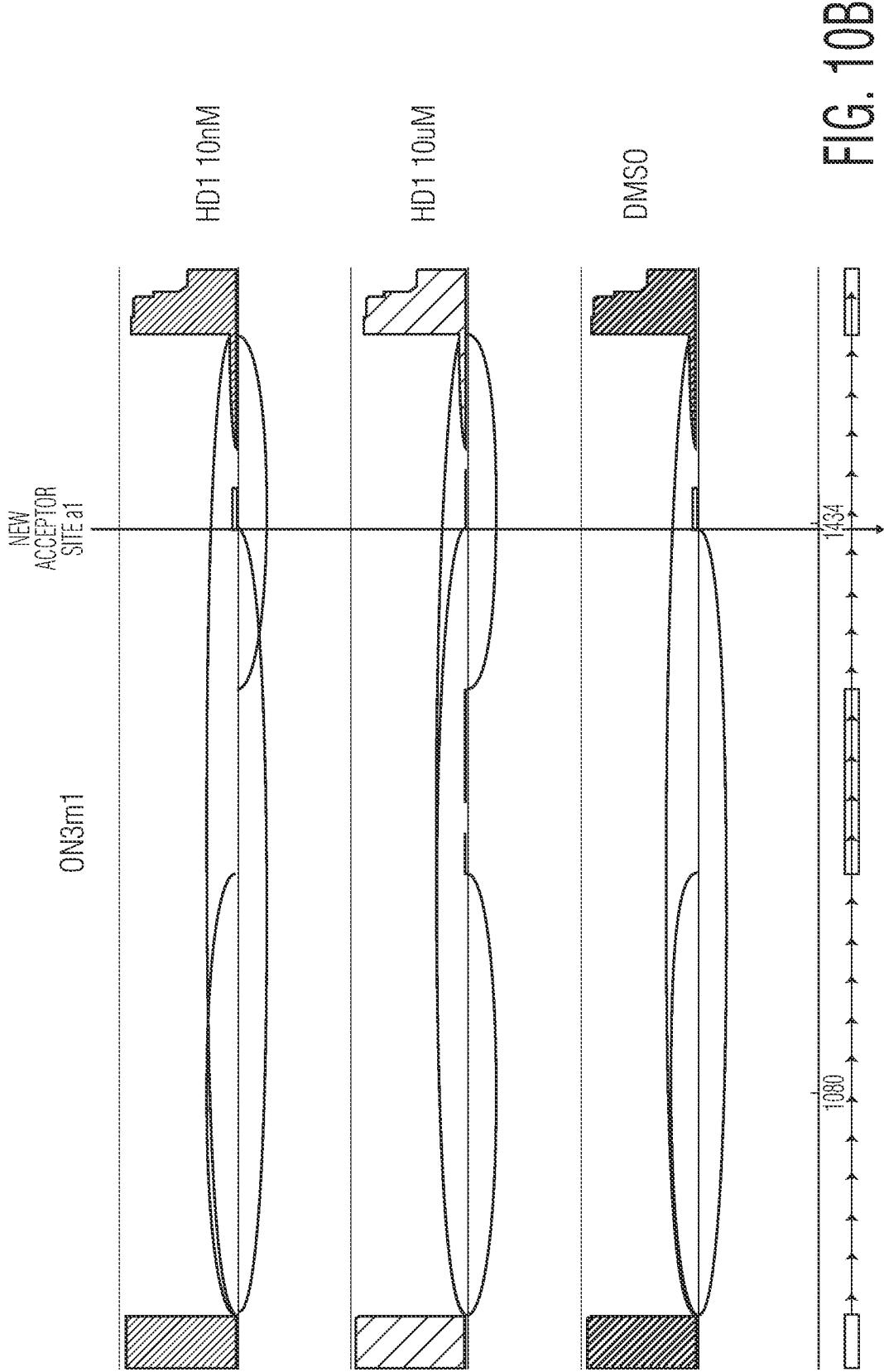


FIG. 10B

ON2m1

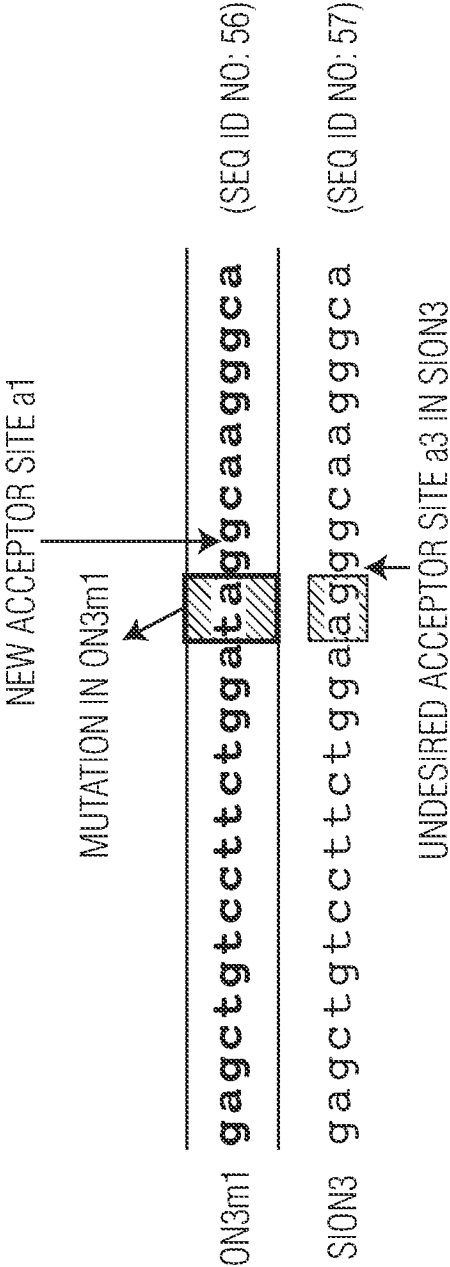


FIG. 10C

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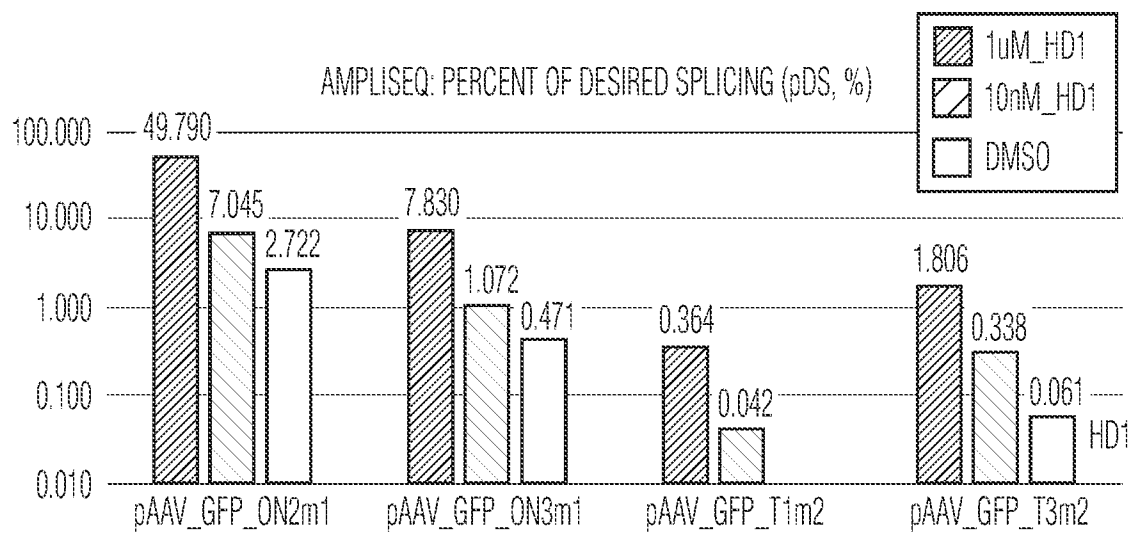


FIG. 10D

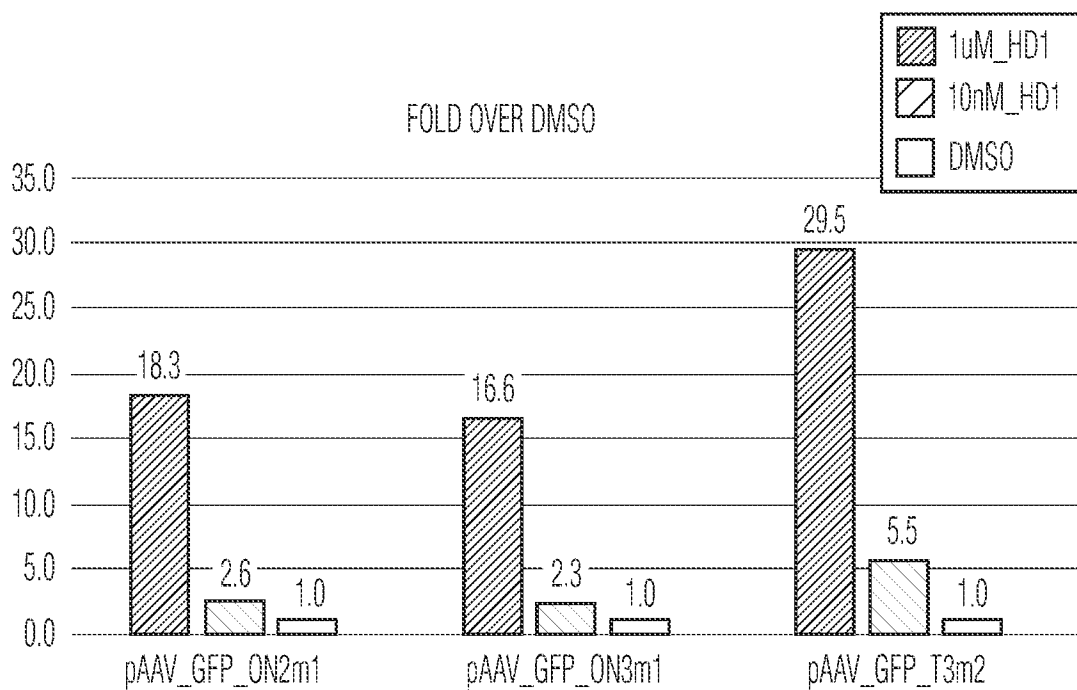


FIG. 10E

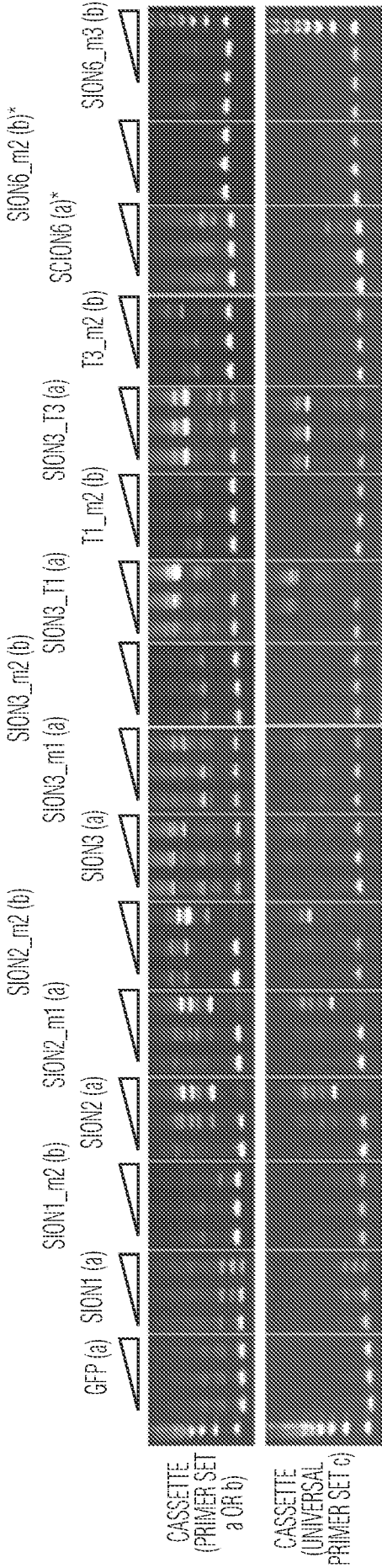


FIG. 11A

CASSETTE	PRIMER	SEQ ID NO	NUCLEOTIDE SEQUENCE
CASSETTE a:	SION-F-KE	(SEQ ID NO: 58)	5'-GGCAAAGAAATTGGGATTCGAACAT-3'
	SION-R-KE	(SEQ ID NO: 59)	5'-CACCCCGGTGACAGCTC-3'
CASSETTE b:	SION-F-mut	(SEQ ID NO: 60)	5'-GGCAAAGAAATTGGGATTTTAACAA-3'
	SION-R-KE	(SEQ ID NO: 59)	5'-CACCCCGGTGACAGCTC-3'
CASSETTE c:	SION-F-uni	(SEQ ID NO: 61)	5'-TTGGCAAAGAAATTGGGATT-3'
	SION-R-KE	(SEQ ID NO: 59)	5'-CACCCCGGTGACAGCTC-3'

FIG. 11B

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PLASMID	PRIMER SET a, b		PRIMER SET c	
	SKIP	INCL.	SKIP	INCL.
GFP	74	74	77	77
SION1	80	119	83	122
ON1m2	86	125	89	128
SION2	80	215	83	218
ON2m1	86	221	89	224
ON2m2	86	221	89	224
SION3	80	195	83	198
ON3m1	86	201	89	204
ON3m2	86	201	89	204
SION3T1	86	201	89	204
T1m2	86	201	89	204
SION3T3	86	138	89	141
T3m2	86	138	89	141
SION6	80	154	83	157
ON6m2	86	160	89	163
ON6m3	86	160	89	163

FIG. 11C

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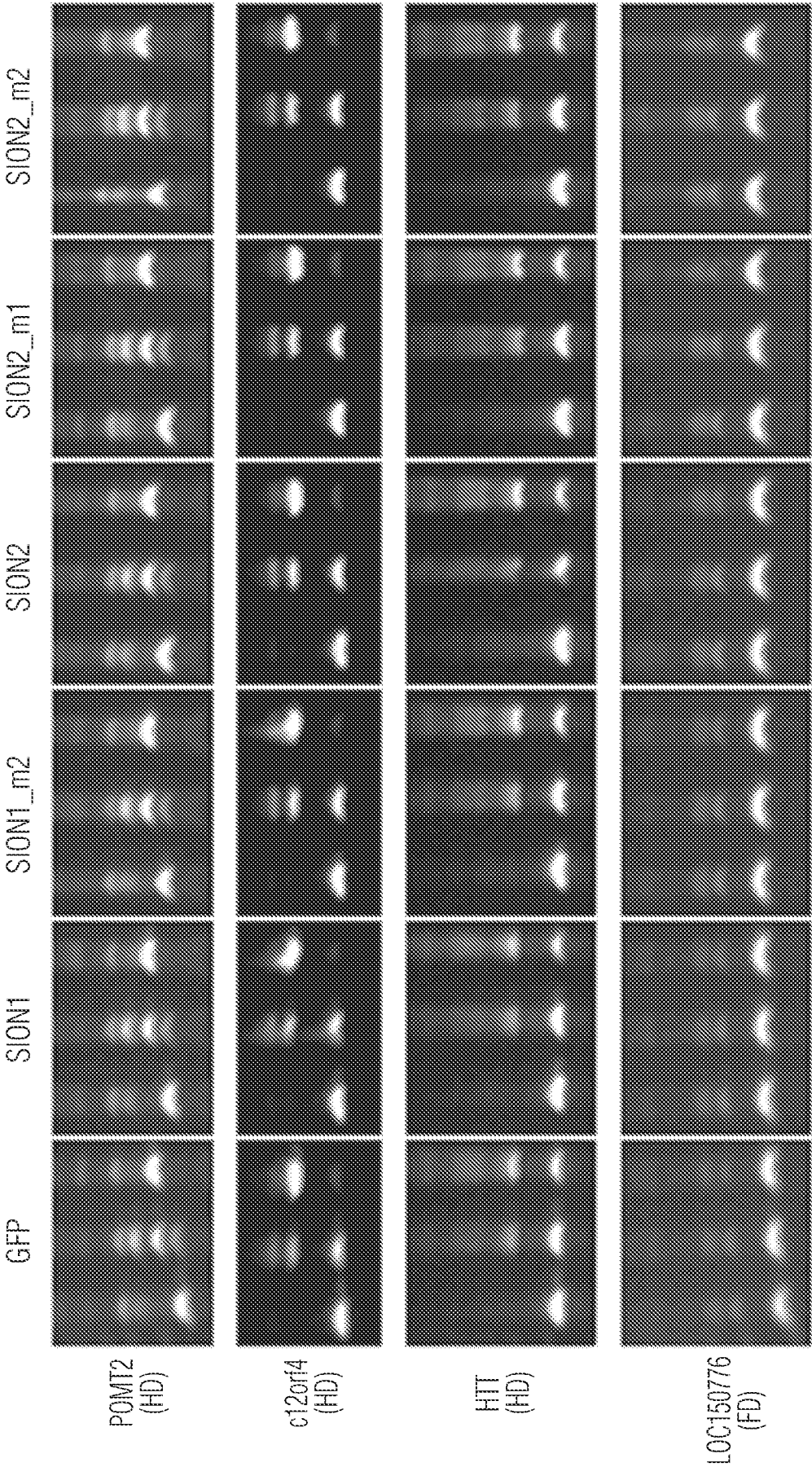


FIG. 11Di

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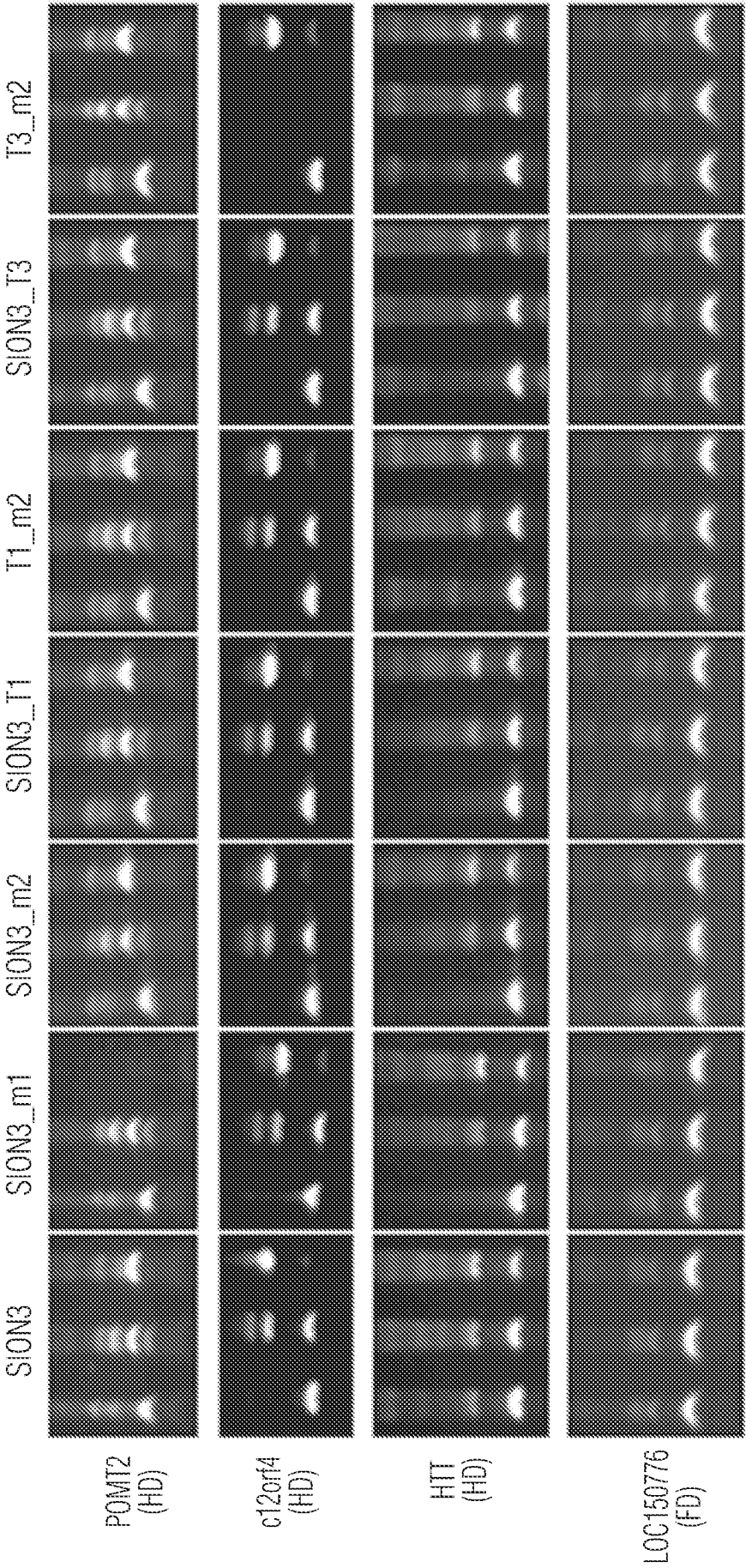


FIG. 11Dii

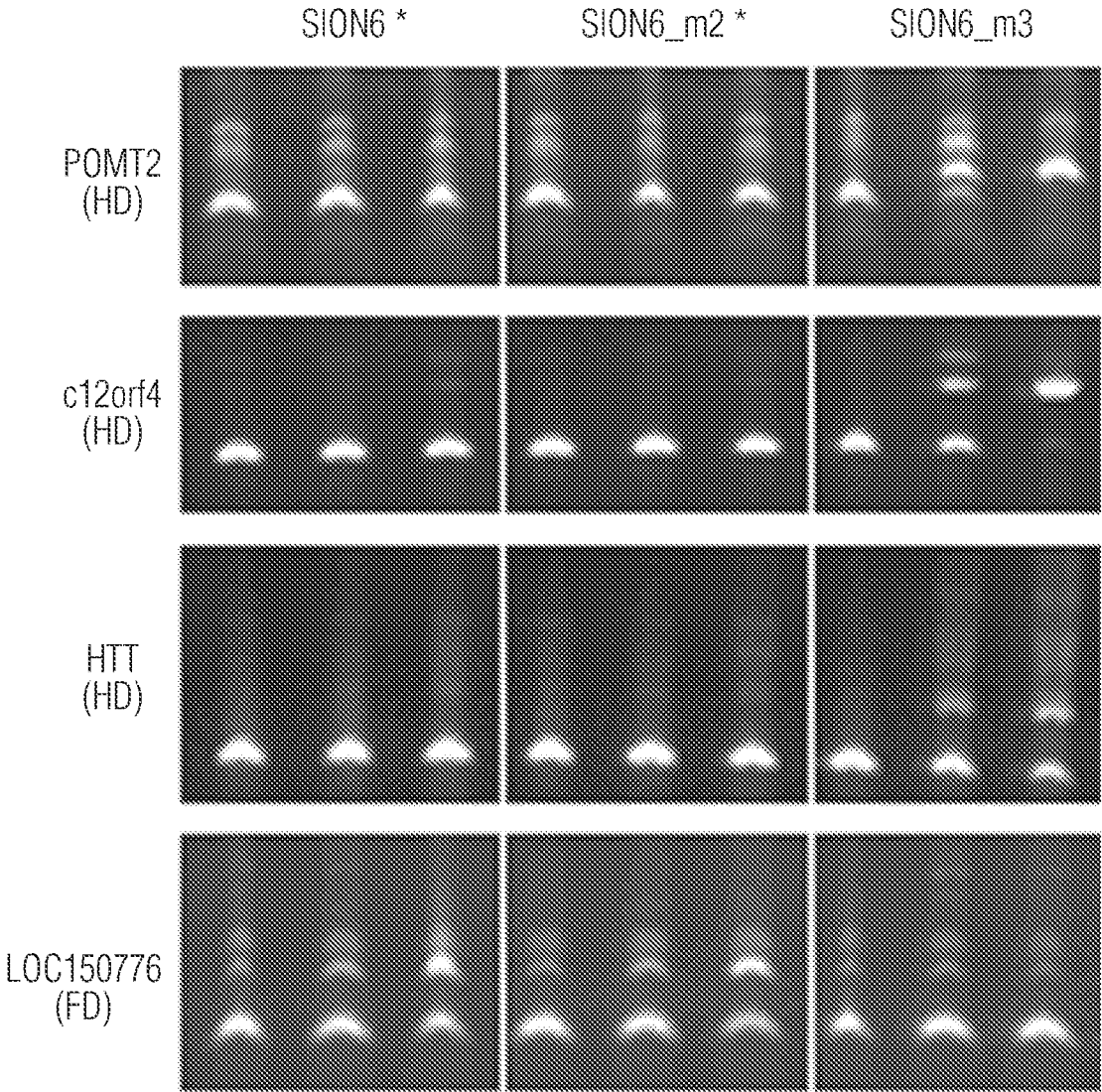


FIG. 11Diii

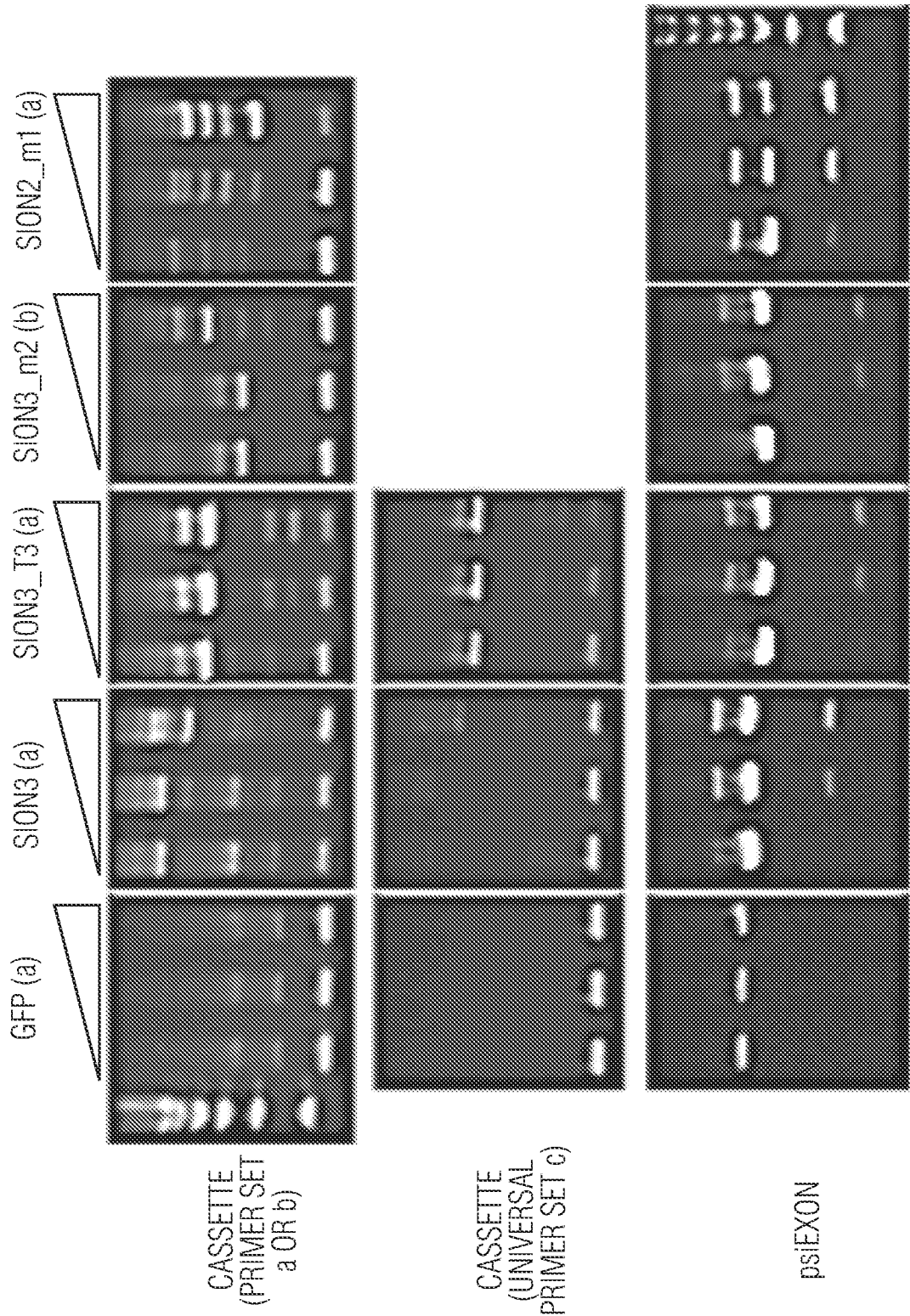
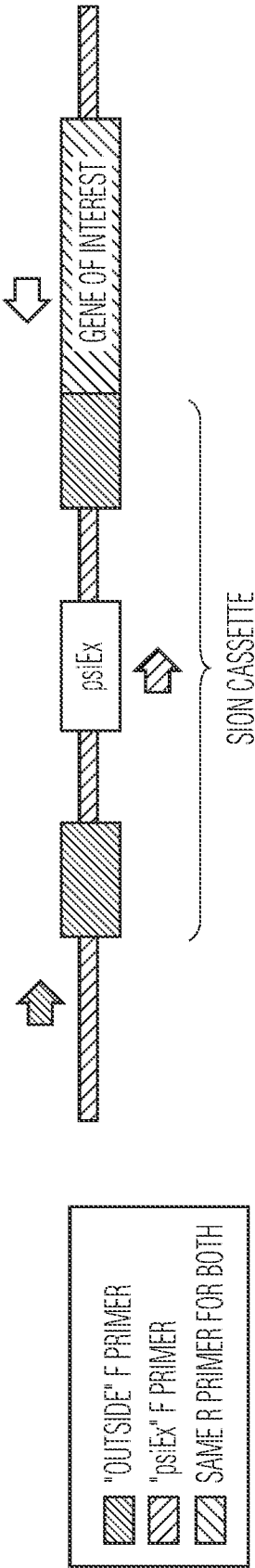
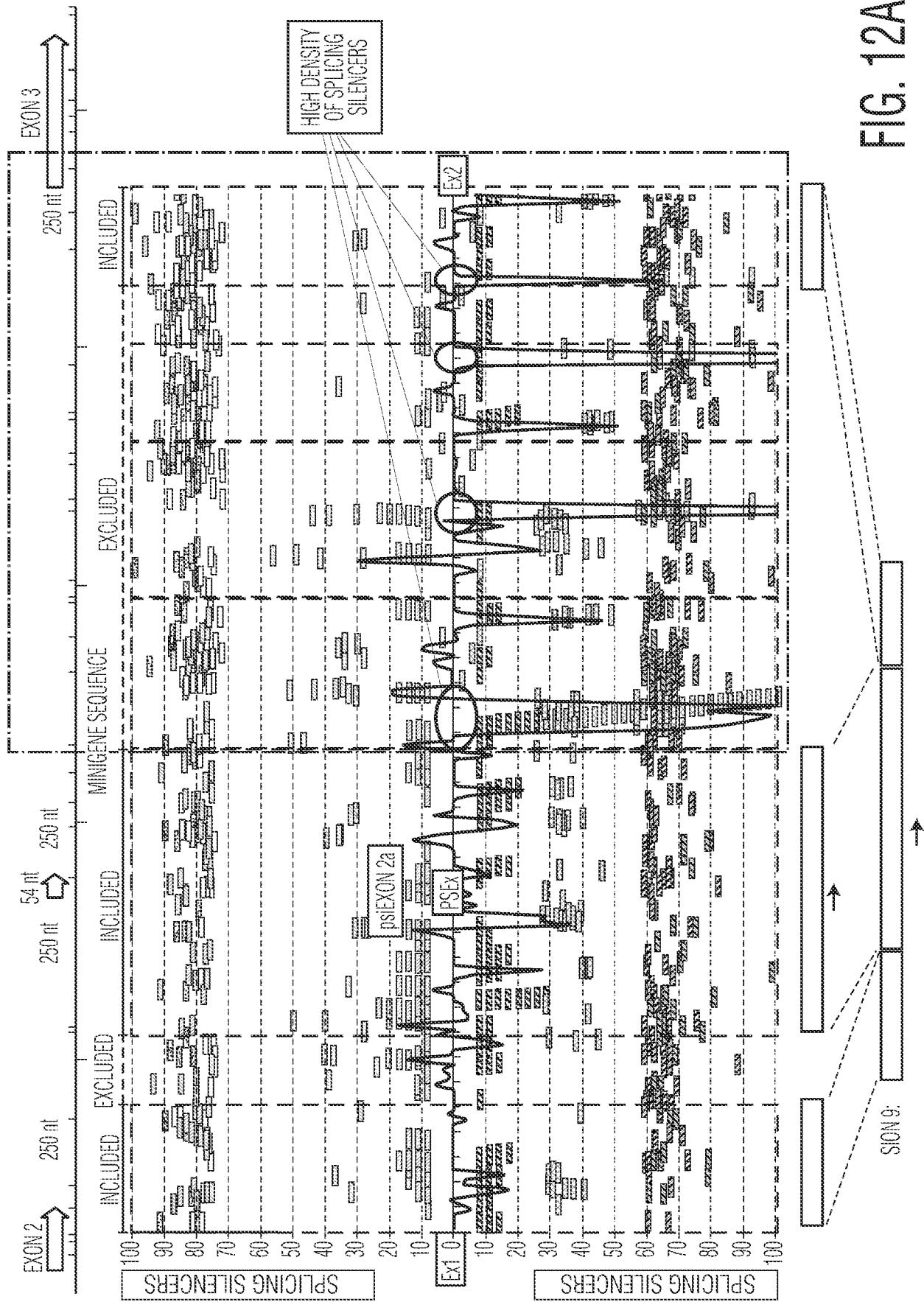


FIG. 11E



SEQUENCE ID	OUTSIDE (SPECIFIC)					OUTSIDE (UNIVERSAL)					psiExon	
	psiEx skip (SHORT)	psiEx incl (LONG)	UPSTR INTRON RETENTION	DOWNSTR INTRON RETENTION	BOTH INTRON RETENTION	AMPLICON psiEx skip (SHORT)	AMPLICON psiEx incl (LONG)	UPSTR INTRON RETENTION	DOWNSTR INTRON RETENTION	BOTH INTRON RETENTION	AMPLICON (psiEx/GFP)	INTRON RETENTION
GFP	74	74	NA	NA	NA	77	77	NA	NA	NA	NA	NA
SION3	80	195	469	416	690	83	198	472	419	693	130	351
SION3T3	86	138	278	359	499	89	141	281	362	502	74	295
T3m2	86	138	278	359	499	89	141	281	362	502	71	292
ON2m1	86	221	371	371	521	89	224	374	374	524	117	267

FIG. 11F



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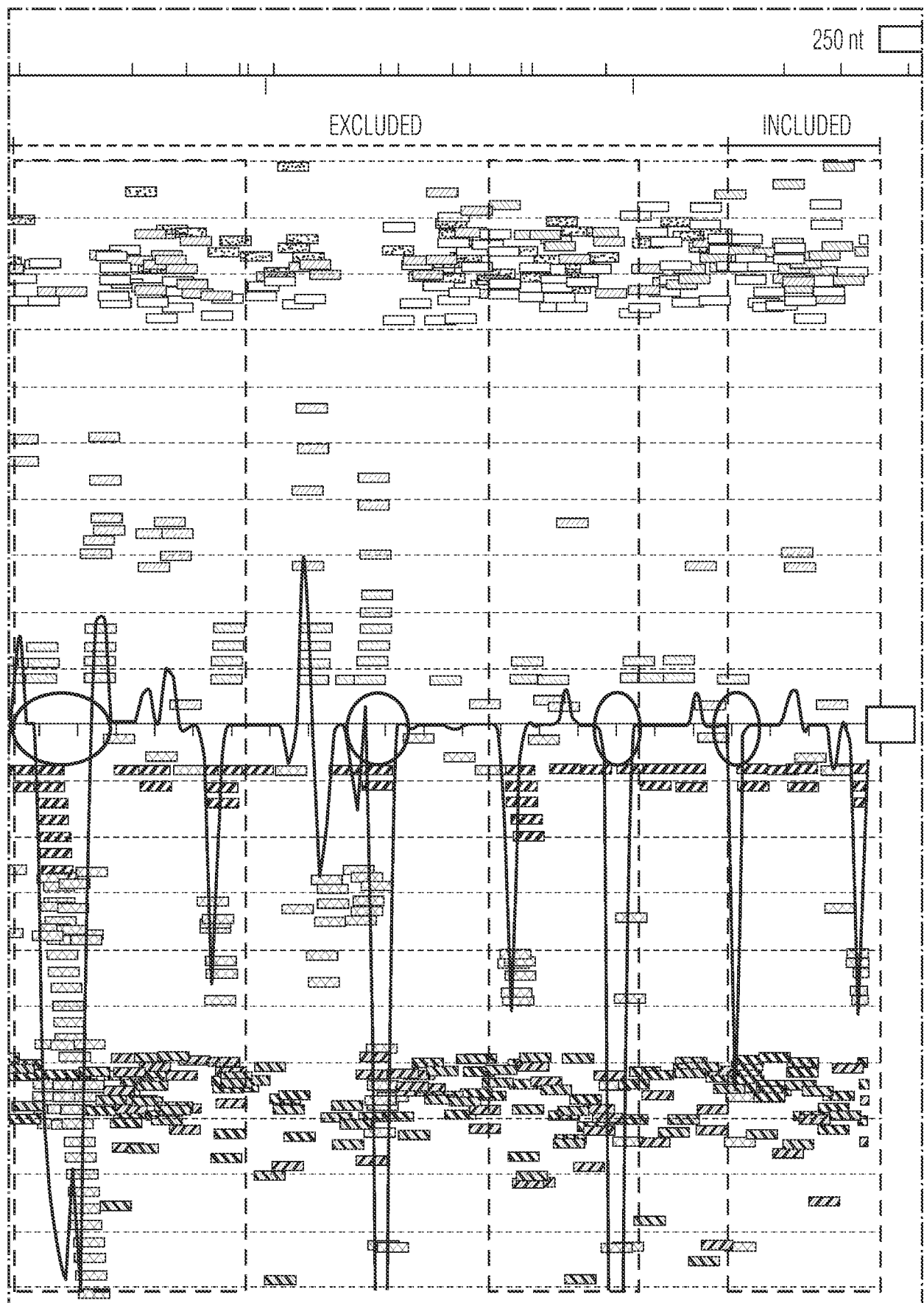


FIG. 12Aii

TAGTTTCTGgtaagttctctgtaccatcttttgaaattttaagtgaattaacatatottgcttagtctctgtgcaggaaatgttttccatttat ATCAAAAGACcattcaagagagcaatggtagaaaactttaaaaattcacttaattatgtatagaacgaatcagagaacacgtcctttacaaaaaggtaaata	END EXON2 SION 9 (250 nt.) (SEQ ID NO: 71)	100
gacaaaaacagttgttggtaaatgtaaacaaattcaaatattagatgaggtggttaagttctggtgcattatctgttacctatttcagatgcatttccttagt ctgtttgtcaacaaccatttacatttgtttaagtttaactctactccacaattcaagaccacgtaatagacaatggataaagtcctacgtaaaaggatca	SION 10 (50 nt.) (SEQ ID NO: 72) SION 9 (250 nt.) (SEQ ID NO: 71)	200
tcacaaaattgtgtaatgattctgtgcagggcacactttcttggtgctgtacctagtgctggttggctgtgaagagatagaacttttgatatgagaga agtgtttaacacattactaagaacagtcctgtgaaaagaaccgacgaatggatcacggaccaaacccagaaactctctatcttgaaaacatactctct	SION 9 (250 nt.) (SEQ ID NO: 71) SION 9 (250 nt.) (SEQ ID NO: 73)	300
aaagggaaaatgcagtttaggtaggagtgctgtcgtatagaacacagataatttgcttacgtttaccatgtggggaataattttgtgaagatggattaa ttttcccttttacgtcaaatccatccctcacgacagcgtatctttgtctattaaacgaatgcaaatggtacacccttataaaaaacattttctacctaatt	SION 9 (250 nt.) (SEQ ID NO: 73)	400
ggctaggtttgaattgtgtgaaatttcaaatattggattaggaaatacaaaagttactgaaagtgaggtactaatgtttataaaaaaactttttctgtg ccgatccaaaacttaacacactttaaaagttataacctaatccttttatgtttcaatgacttcaactccatgattacaaaatattttatttttgaaaaagaac	SION 9 (250 nt.) (SEQ ID NO: 73) SION 10 (100 nt.) (SEQ ID NO: 74)	500

325

ccatttgagATTTAACATTTTGAGTCAATCCCAAGTAATGCAGGAGTTTCATGATTGTTAGAGtaagacataaattttgttgaggtttaactotgaata	SION 9 (250 nt.) (SEQ ID NO: 75)	SION 9 (250 nt.) (SEQ ID NO: 76)	600
ggtaaagctCTAAATTGTAAAAACTCAGTTAGGTTCAATTACGTCCTCCCAAGTACTAACACATCTcattotgtattaacaacaactccaattgagacttat	SION 9 (250 nt.) (SEQ ID NO: 75)	SION 9 (250 nt.) (SEQ ID NO: 76)	700
cttaatgtggtactgaatacttaatgtggtactgagaggcagcctaactgaccacacagcattcataatttcattgttgatttttctctgatcctcattat	SION 9 (250 nt.) (SEQ ID NO: 75)	SION 9 (250 nt.) (SEQ ID NO: 76)	800
gaattacaccatgacttatgaattacaccatgacttccgtcggattgactggtgtgtcgtgaagtataaagtaacaacaataaaaagagactaggagtaata	SION 9 (250 nt.) (SEQ ID NO: 75)	SION 9 (250 nt.) (SEQ ID NO: 76)	900
SION 10 (50 nt.) (SEQ ID NO: 77)			
ggctcttcctgcggggttgagttctcatttgggtaatttagttattcttctgctgcatttgatttaaggaaatacgtatatgggaatttggagatttgtgac	SION 10 (50 nt.) (SEQ ID NO: 77)	SION 10 (50 nt.) (SEQ ID NO: 77)	600
ccgagaaggacgcccaactcagaagtaaacccattaaatcaataagaaaacgacgtaaacctaattcctttatgcataatacccttaaacctctaaacactg	SION 10 (50 nt.) (SEQ ID NO: 77)	SION 10 (50 nt.) (SEQ ID NO: 77)	700
tgacttcaactatgtagtggcacagtcttggtctcacagcaacctctacctcctgggttcaaggattctcctgccttagcctcccgagtagctgggattac	SION 10 (50 nt.) (SEQ ID NO: 77)	SION 10 (50 nt.) (SEQ ID NO: 77)	800
actgaagtgatacatcacctgtcagaaccgagtgctgttgagatggaggaccacaagttcgcctaagaggacggaatcggagggtcatcgaccctaagt	SION 10 (50 nt.) (SEQ ID NO: 77)	SION 10 (50 nt.) (SEQ ID NO: 77)	900
SION 9 (250 nt.) (SEQ ID NO: 78)			
SION 9 (250 nt.) (SEQ ID NO: 76)			

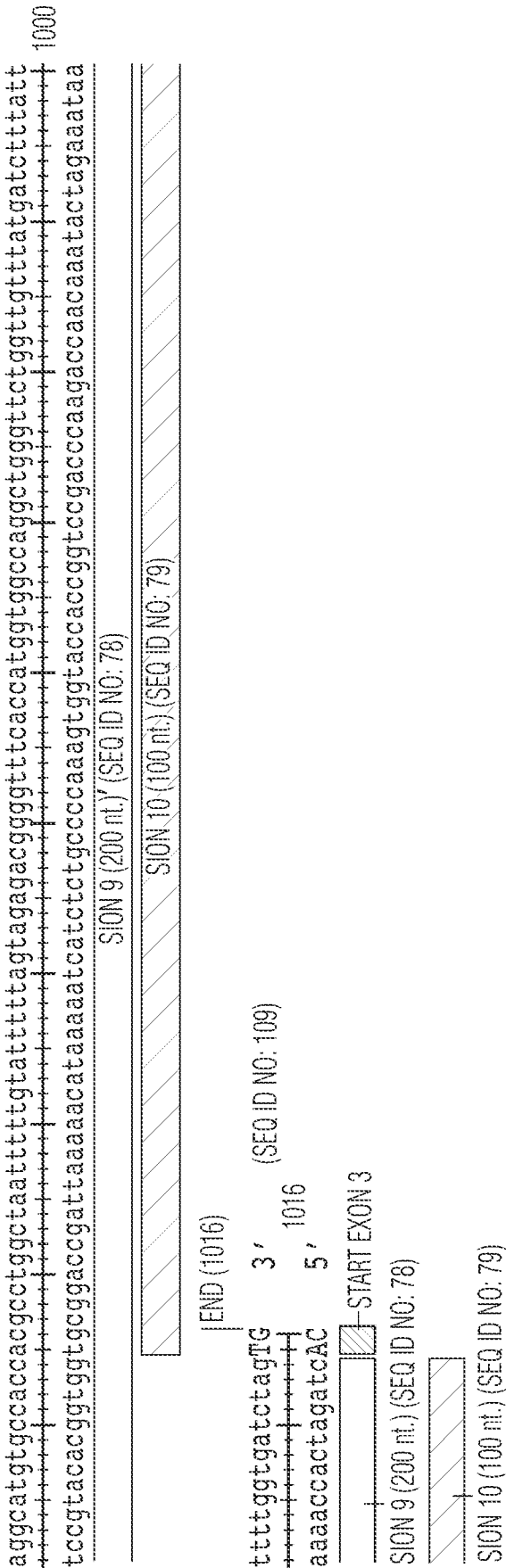


FIG. 12Biii

MINIGENE CASSETTE ID	SEQ ID NO:	SEQUENCE TO REPLACE TGAATG OF PLASMID PAAV-GFP	COMPOUND	INDUCED SPLICING	TOTAL LENGTH (NT)	MIDDLE EXON LENGTH (NT)
SION2m1	52	TAACAAAGGtaagtcaatttcaggttggataaaggaattgaaattggcaccaggggaaaaact taagttgaaccttaagtgggtccagataaaaaagagagttgttatataaaactaaaaaagc taattaaacccctcctccacagTGTCCACCCAAAATCTGTTTGGCAGCAGAAAG gtaagtggcagtgaagggtttctagctcaggccaagcagattacaagttcttattcctgacaat tgactctgaacattcttgaaaaaagaagaattgttgccatctctttctatataggataatgacact tctcttttctaactttctagTGC	SMA/HD	INCLUSION	447	135
	64	TAGTTTCTGtaagtctctctgttaccatcttttgaaattttaagtgaatttaatacatatcttgc ttagctctctgtgcaggaaatgtttccatttatgacaaaacagttgttgtaaatgaaacaatt caattatgagatgaggttaagtctctgggcatttatctgttacctatttcagatgcatttcccta gttacaaaaattgttaagtctctgtcagggcacactttctctggctgttacctagtgcctgggt ttgggtcttgaagagatgaacttttgtatgagagaaaaagggaaaatgcagtttaggtaggagtg ctgctgcatagaaaacagataattgtcttaagtttaccatgtggggaatatttttgtaaagatgga ttaaggctaggtttgaattgttgaaatttcaaatattggattagaaaatacaaaqttactgaaaag tgaggtactaatgtttataaaaaataaaaaactttttcttgccatttccagTATTTAACATTTTGGAGTC AATCCAACTAATGCCAGCGGTTCAATGATTTGCTTACGtaagacataattttgttgaggtttaactc tgaatacttaattgtggtactgaatacttaagtgggtactgagagggcagcctaactgaacacacagc attcattattcattgtttattttctctgtatcctcattatgtggtcttctcctgcgggttgagtcttc atttgggtaattttagttattctttgtgcatttgatttaaggaaaacgltatatgggaatttggaga tttgbactgacttcaactatgtagtggcagctcttggctcacagaaacctctacctcctgggttc aaggagttctcctgccttagcctccgagtagctgggtattacagcatgtgccaccagcctggct aatttttgtatttttttagagagacgggtttccaccatgggtggccgggtgggttctgtgtttta gaattcttttattttttgtgtatctagTGC	SMA/HD	INCLUSION	1016	54

FIG. 12Ci

MINIGENE CASSETTE ID	SEQ ID NO:	SEQUENCE TO REPLACE TGAATG OF PLASMID PAAV-GFP	COMPOUND	INDUCED SPLICING	TOTAL LENGTH (NT)	MIDDLE EXON LENGTH (NT)
SION10	65	CACTTTTCTGtaagttctctgtaccatcttttgaaattttaagtgaaattaatacatagaattg tgtgaaatttcaaatatttgattaggaatacaaaagttaactgaaagtcaggtaactaatgtttataa aataaaaaacttttcttggcaatttgcagATTTAACTTTTGAATCAATCCAACTAATGCAGAGG TTCAATGATTCGTTACAGtaagacataattttgttgaggtttaactctgaataacttaattgtggtact acgcctggctaatttttgatatttttagtagagaggggttcaccatggtggccaggctgggttct ggttgtttatgatctttatttttttggtgatctatCTG	SMA/HD	INCLUSION	366	54

FIG. 12Cii

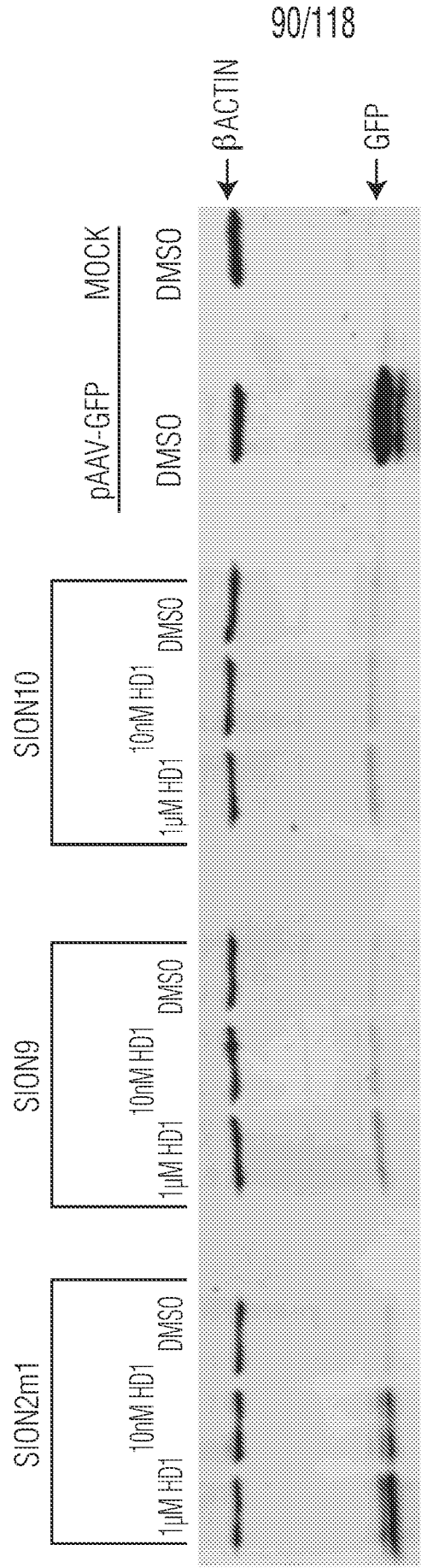


FIG. 12D

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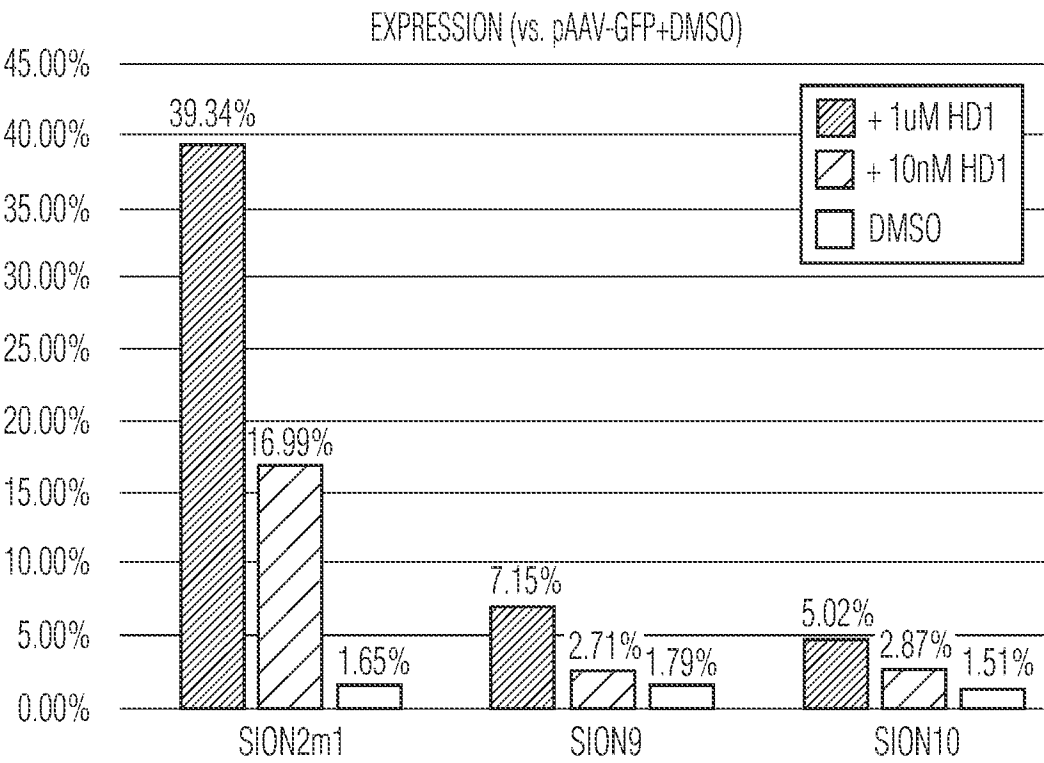


FIG. 12Ei

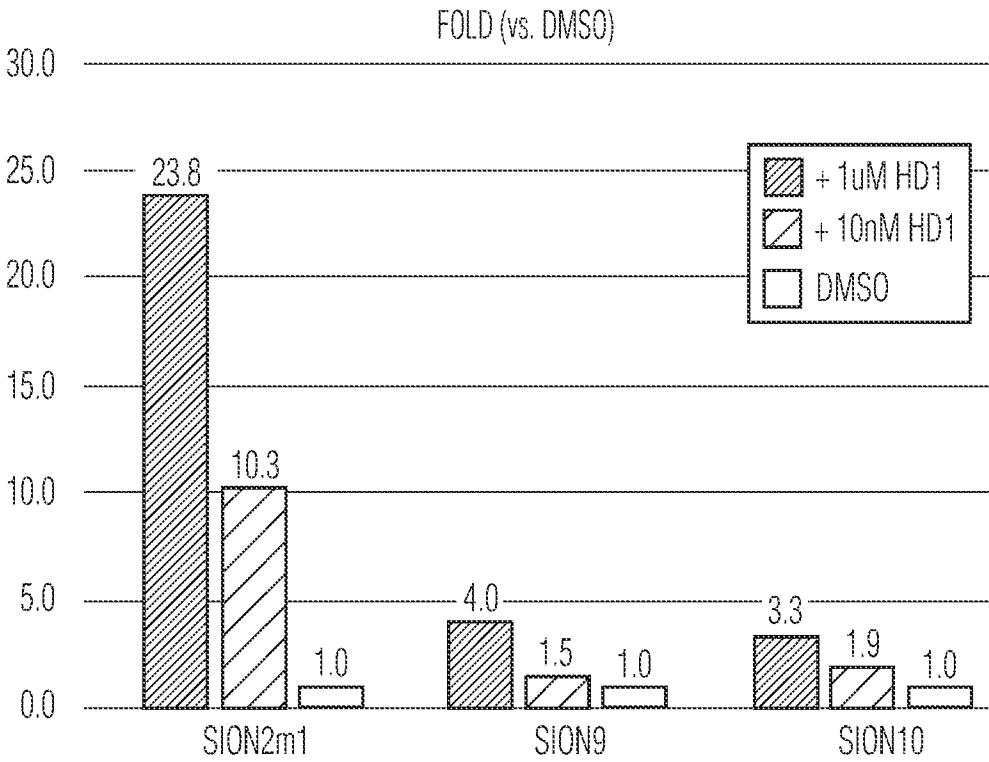


FIG. 12Eii

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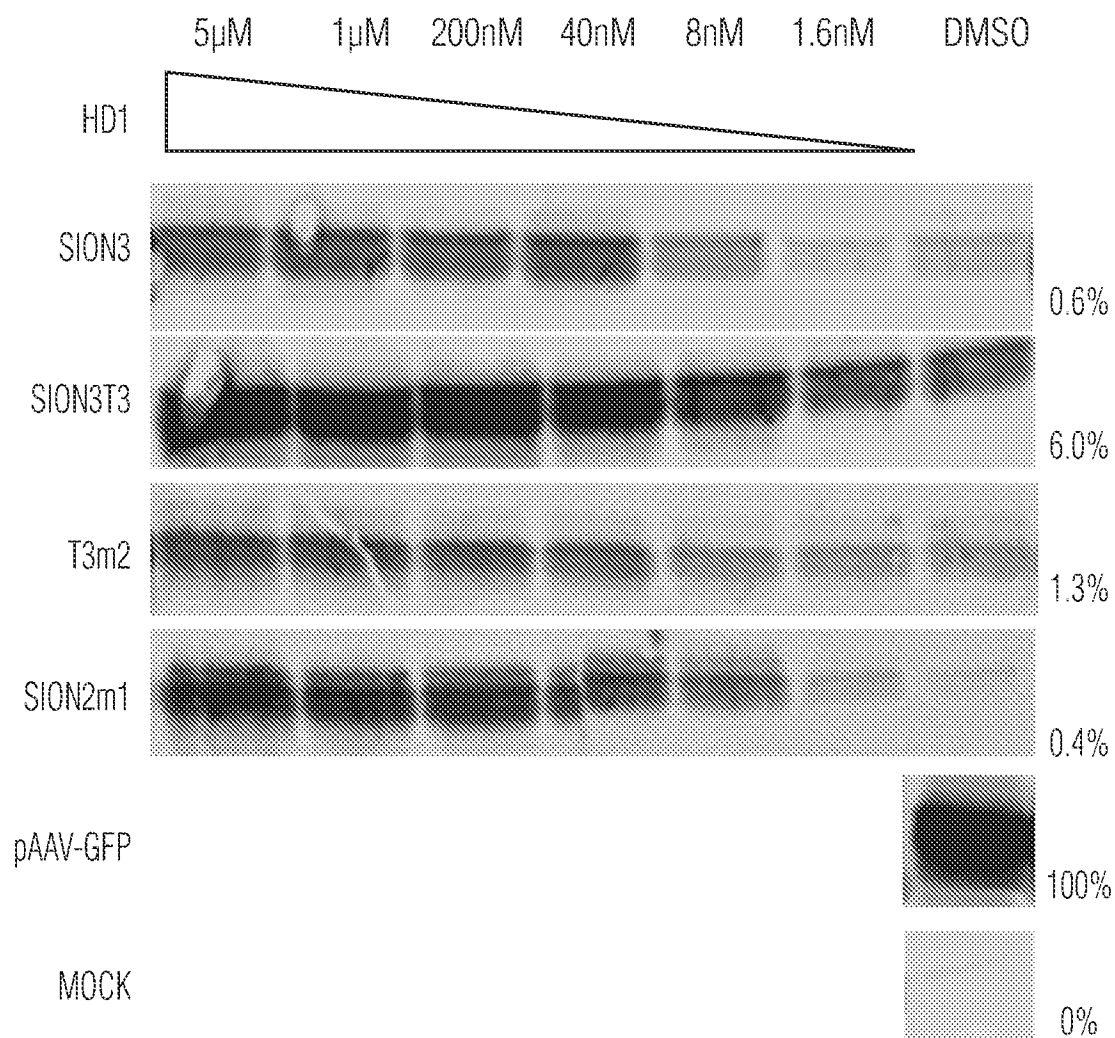


FIG. 13A

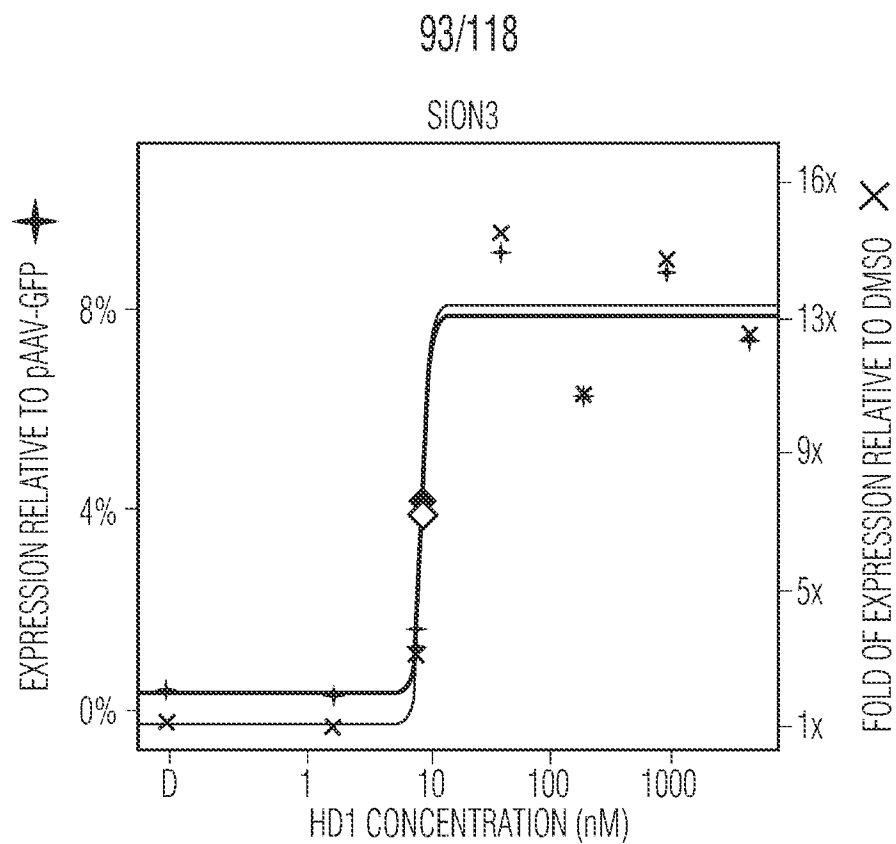


FIG. 13B

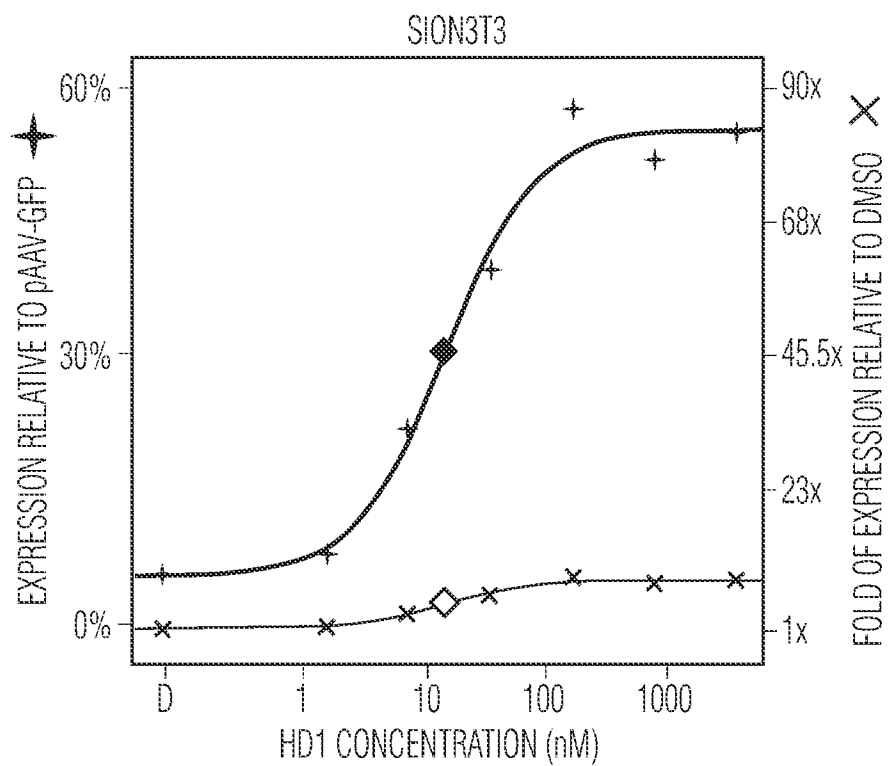


FIG. 13C

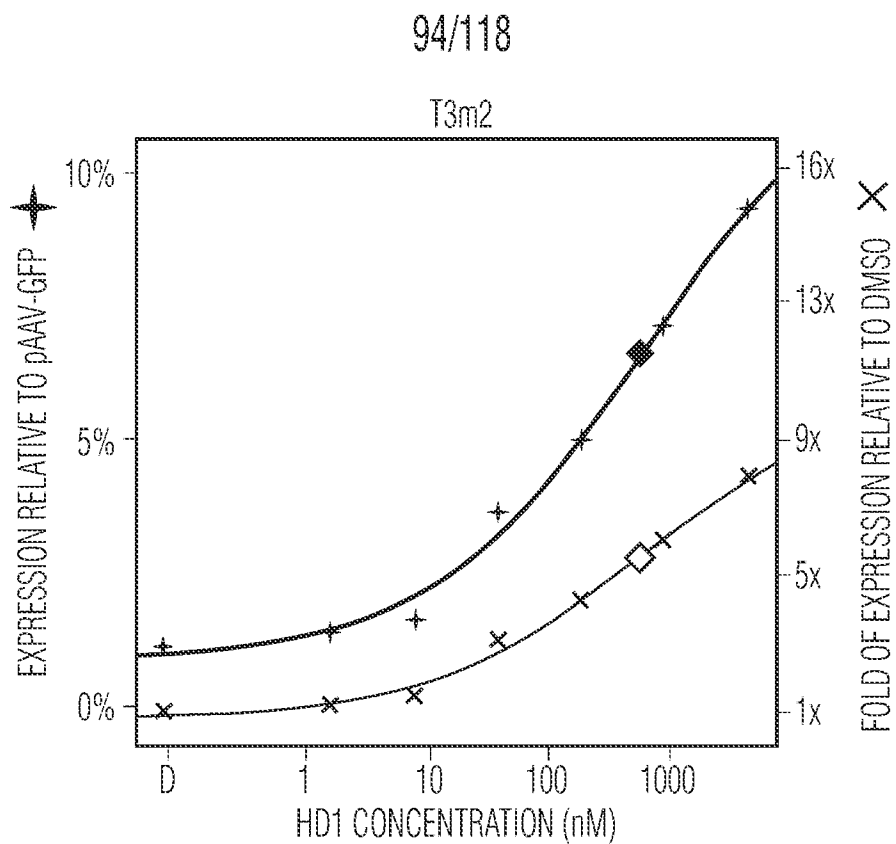


FIG. 13D

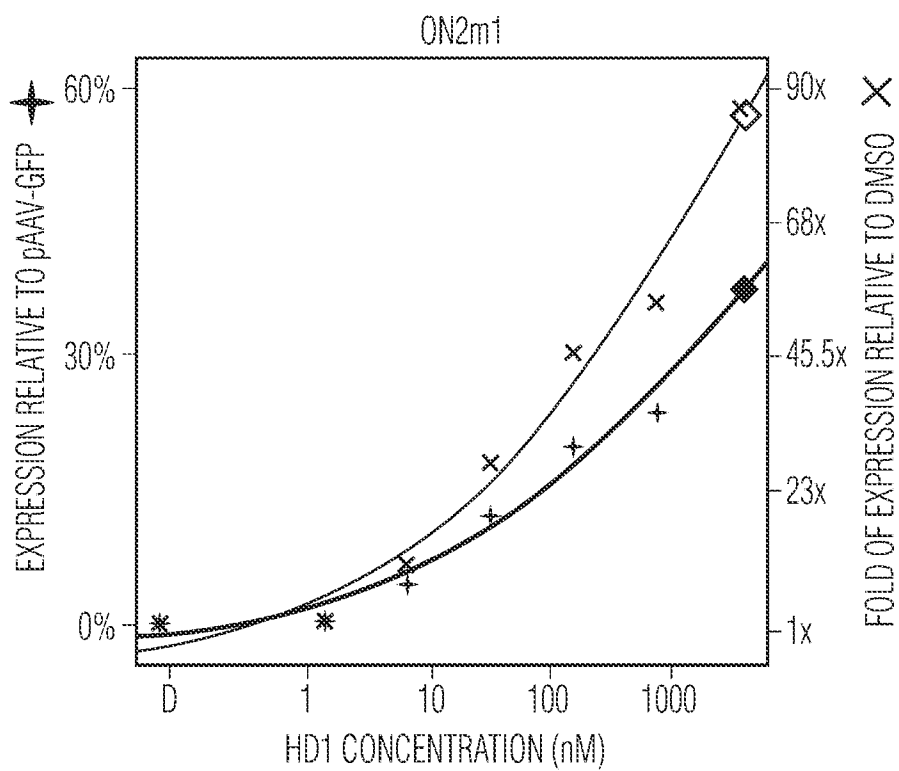


FIG. 13E

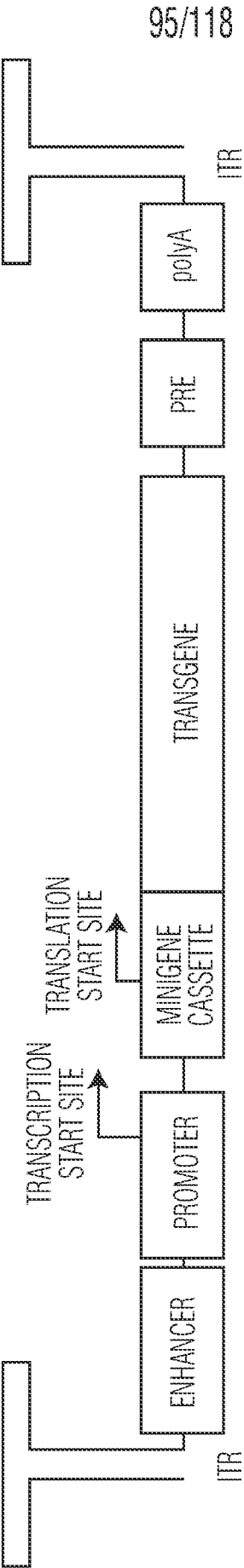


FIG. 14A

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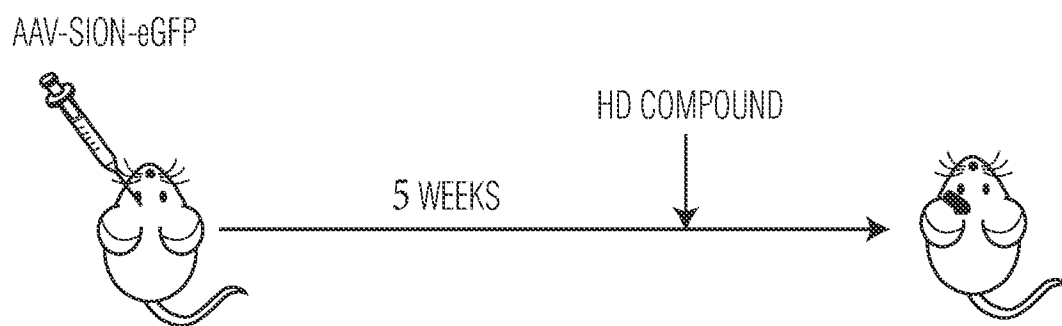


FIG. 14B

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GROUP	NUMBER OF MICE	VIRUS	VIRUS DOSE (vg/MOUSE)	DOSE CONCENTRATION (vg/ML)	VOLUME (μ L)	DRUG	DOSE	TIME OF EUTHANASIA (POST LAST DOSE OF COMPOUND)	MICE TESTED
1	8	VEHICLE	--	--	4	--	--	DAY 14,	1-1, 1-2, 1-5, 1-6
2	8	AAV9-GFP	1.44E10	3.59E12	4	--	--	DAY 14,	2-1, 2-2, 2-4, 2-5
3	8	AAV9- SION2m1	1.44E10	3.59E12	4	VEHICLE	0, QDx14	DAY 14, 4h POST DOSE	3-1, 3-2, 3-3, 3-4, 3-5
4	5	AAV9- SION2m1	1.44E10	3.59E12	4	HD1	20, QDx3	DAY 4, 4h POST DOSE	4-1, 4-2, 4-3, 4-4, 4-5
5	5	AAV9- SION2m1	1.44E10	3.59E12	4	HD1	20, QDx7	DAY 7, 4h POST DOSE	5-1, 5-2, 5-3, 5-4, 5-5
6	5	AAV9- SION2m1	1.44E10	3.59E12	4	HD1	20, QDx14	DAY 14, 4h POST DOSE	6-1, 6-2, 6-3, 6-4, 6-5
7	5	AAV9- SION2m1	1.44E10	3.59E12	4	HD3	10, QDx3	DAY 4, 4h POST DOSE	7-1, 7-2, 7-3, 7-4, 7-5
8	5	AAV9- SION2m1	1.44E10	3.59E12	4	HD3	10, QDx7	DAY 7, 4h POST DOSE	8-1, 8-2, 8-3, 8-4, 8-5
9	8	AAV9- SION2m1	1.44E10	3.59E12	4	HD3	10, QDx14	DAY 14, 4h POST DOSE	9-1, 9-2, 9-5, 9-6

FIG. 14C

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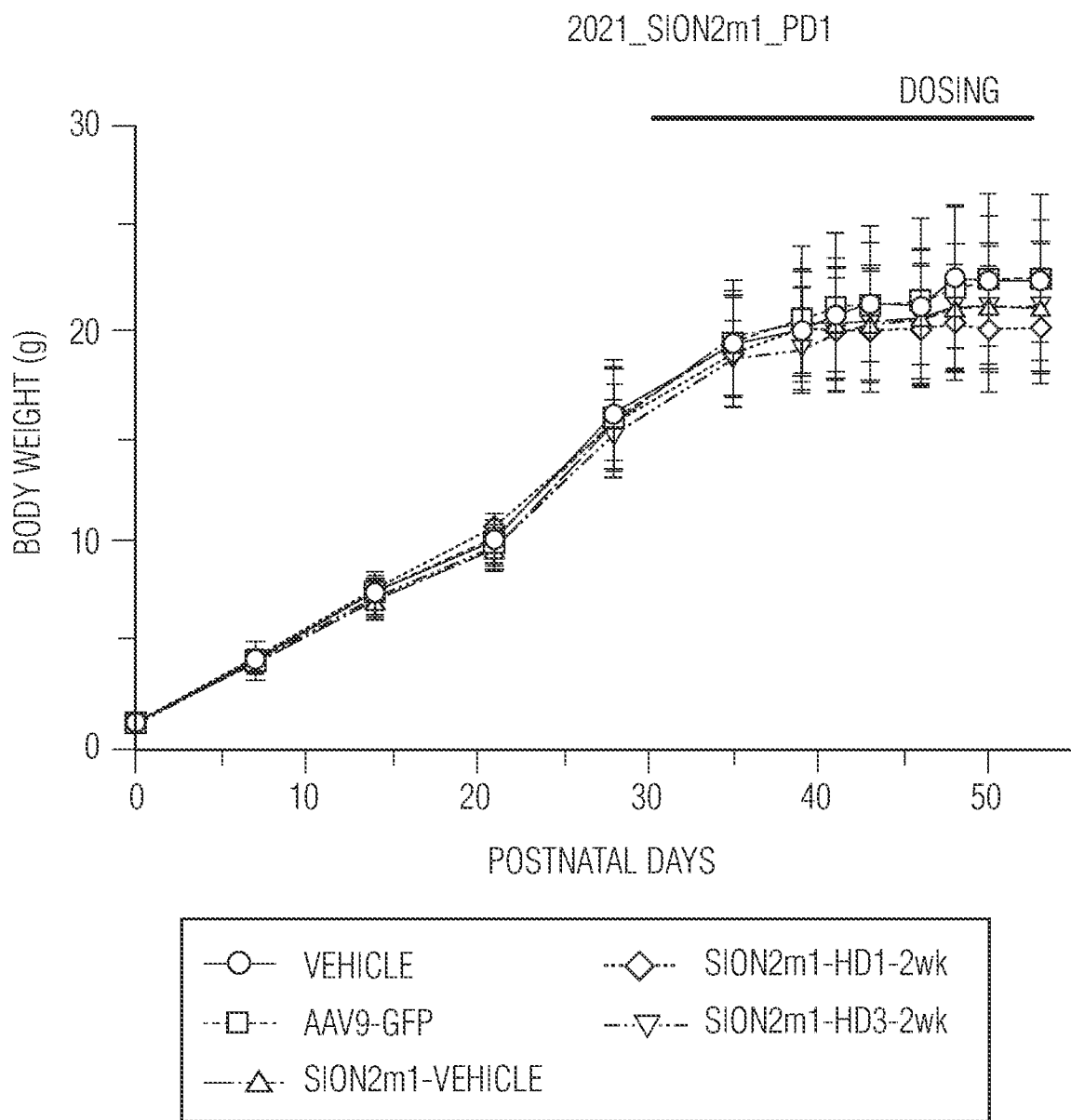


FIG. 14D

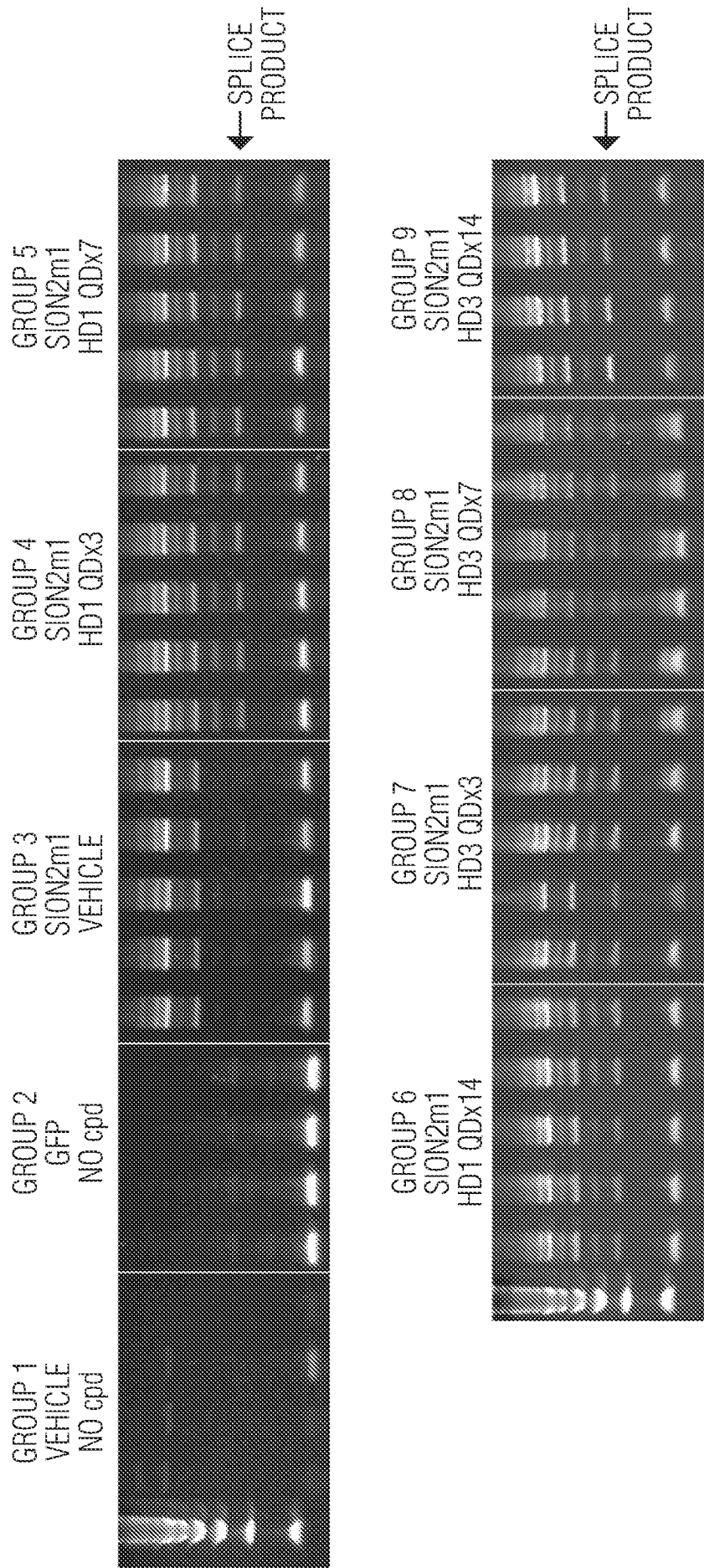
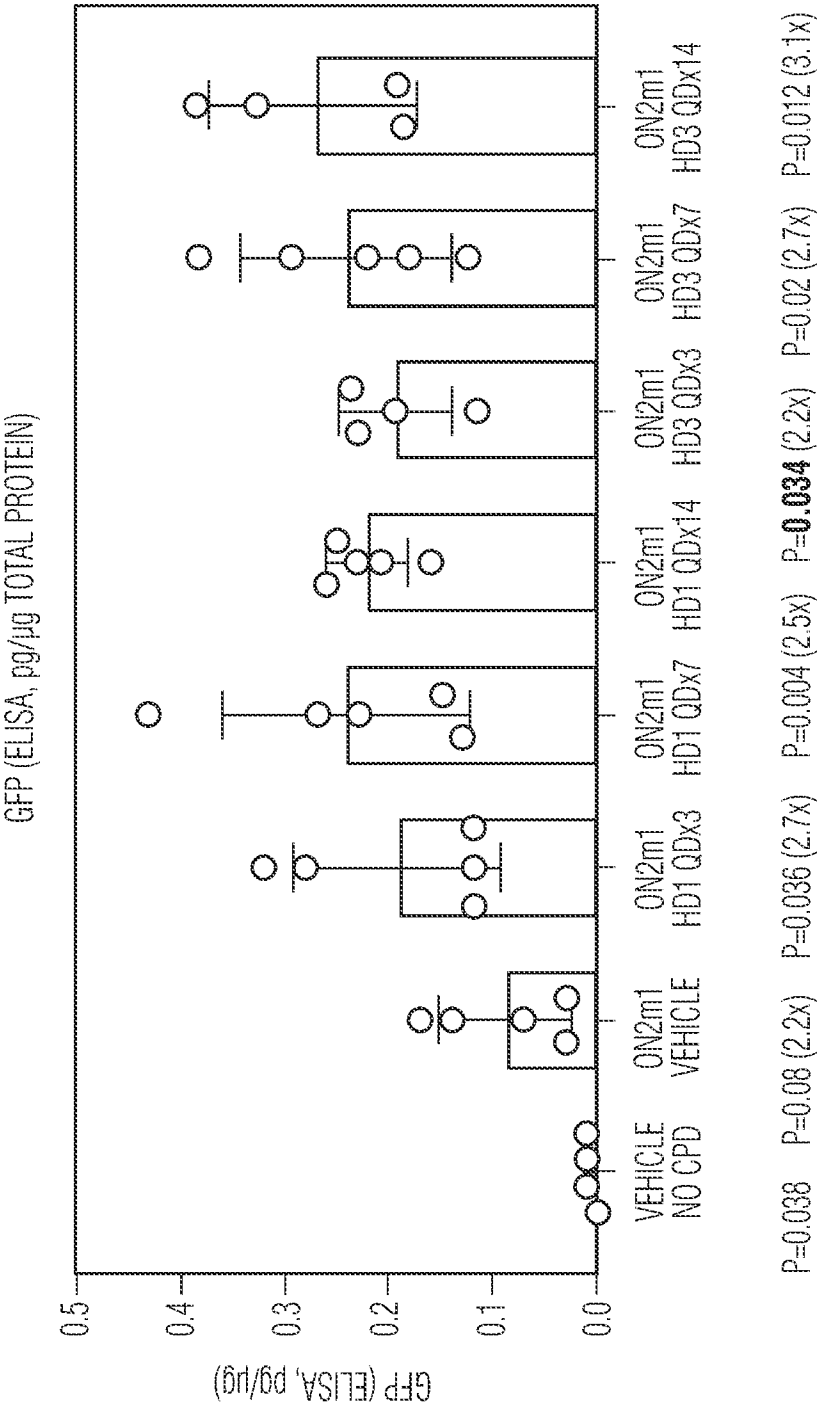


FIG. 14E



- P-VALUES ARE BASED ON UN-PAIRED t-TEST
- SAMPLE 7-2 WAS REMOVED (LOW AAV DNA DETECTION)

FIG. 14Fi

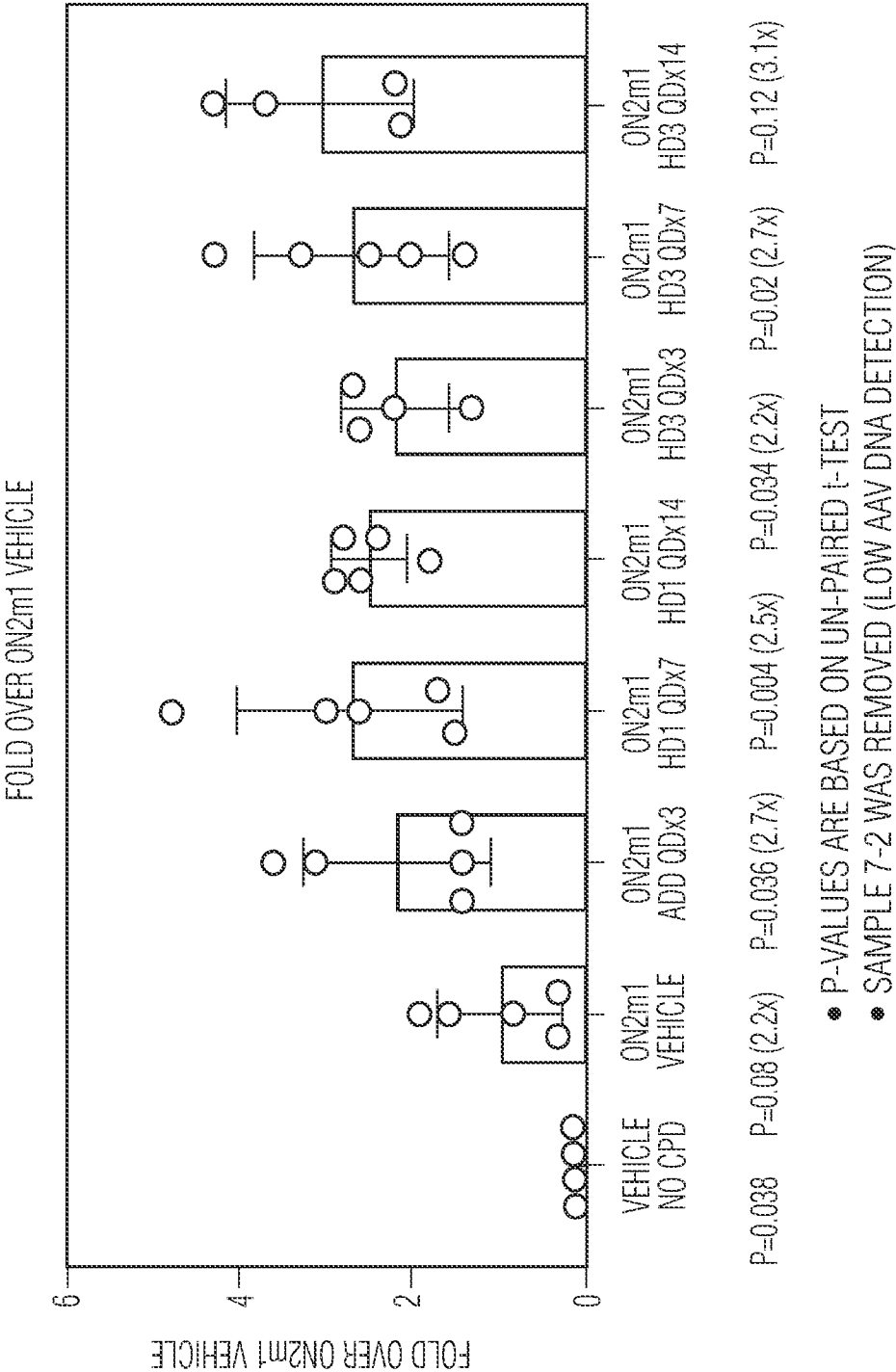


FIG. 14Fii

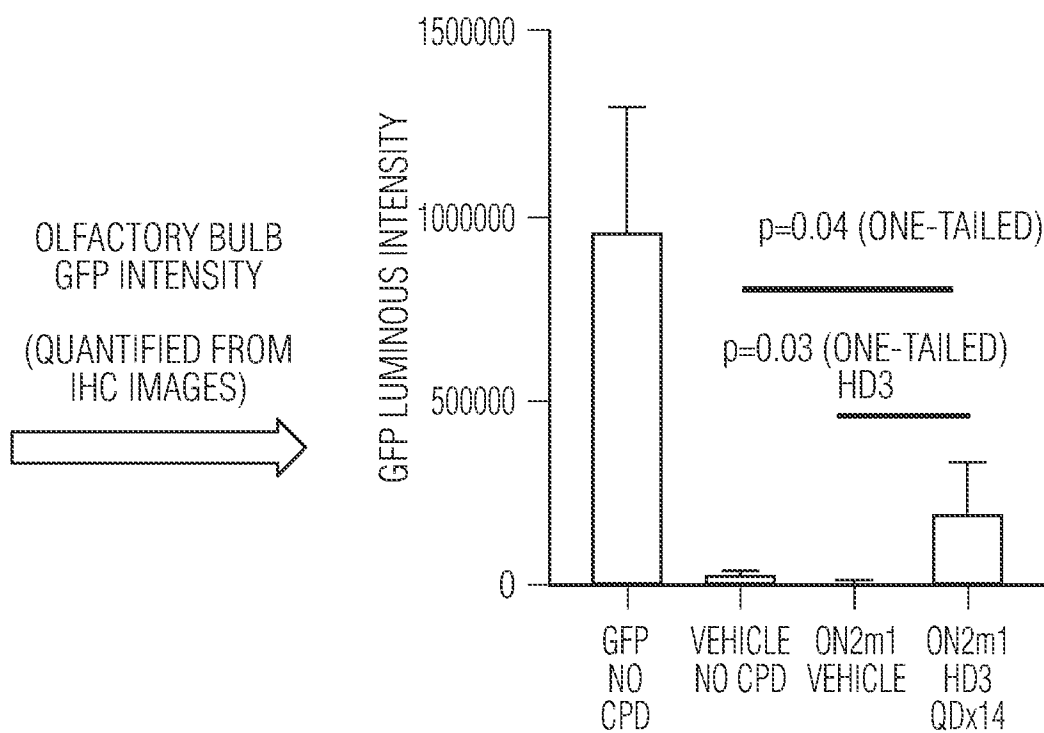
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- SION2m1+ HD3 10mg/kg, 14 DAYS
- LOW LEVEL OF GFP EXPRESSION SEEN THROUGHOUT THE BRAIN
- SOME ENHANCEMENT OF SIGNAL IN OLFACTORY BULB
- NOTE: FLUORESCENCE INTENSITY DEPENDS ON BRAIN SECTION

FIG. 14Gi

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	FOLD OVER CONTROL	HD3 CONCENTRATION
IN VITRO	11.27	200nM
ELISA (WHOLE BRAIN)	3.1	7572 $\pm$ 426 ng/g
IHC (ONLY OB)	21.1	7572 $\pm$ 426 ng/g

FIG. 14Gii

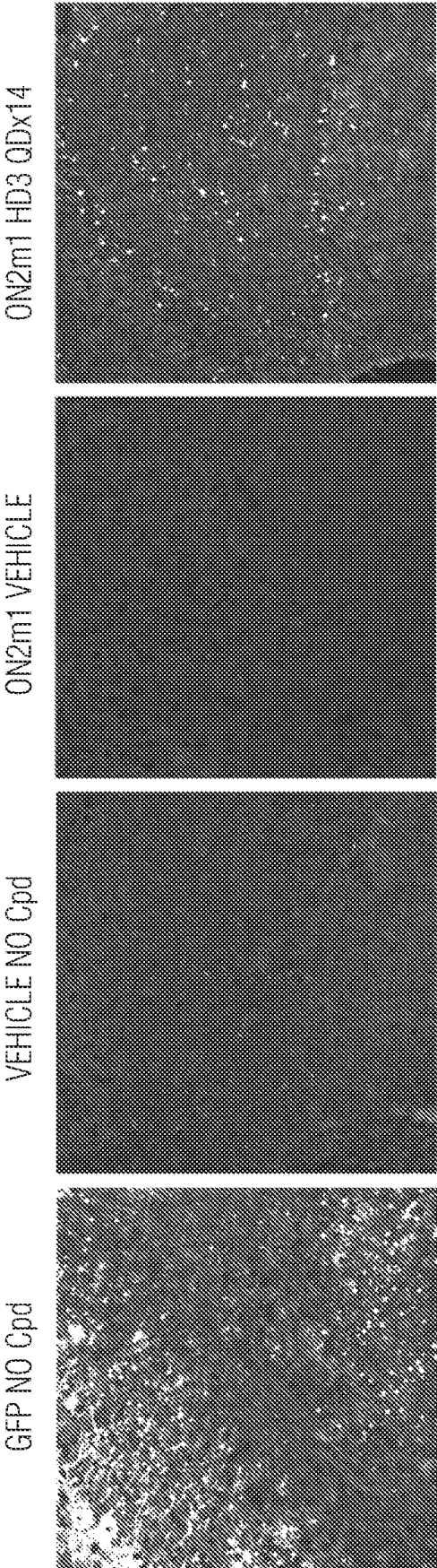


FIG. 14H

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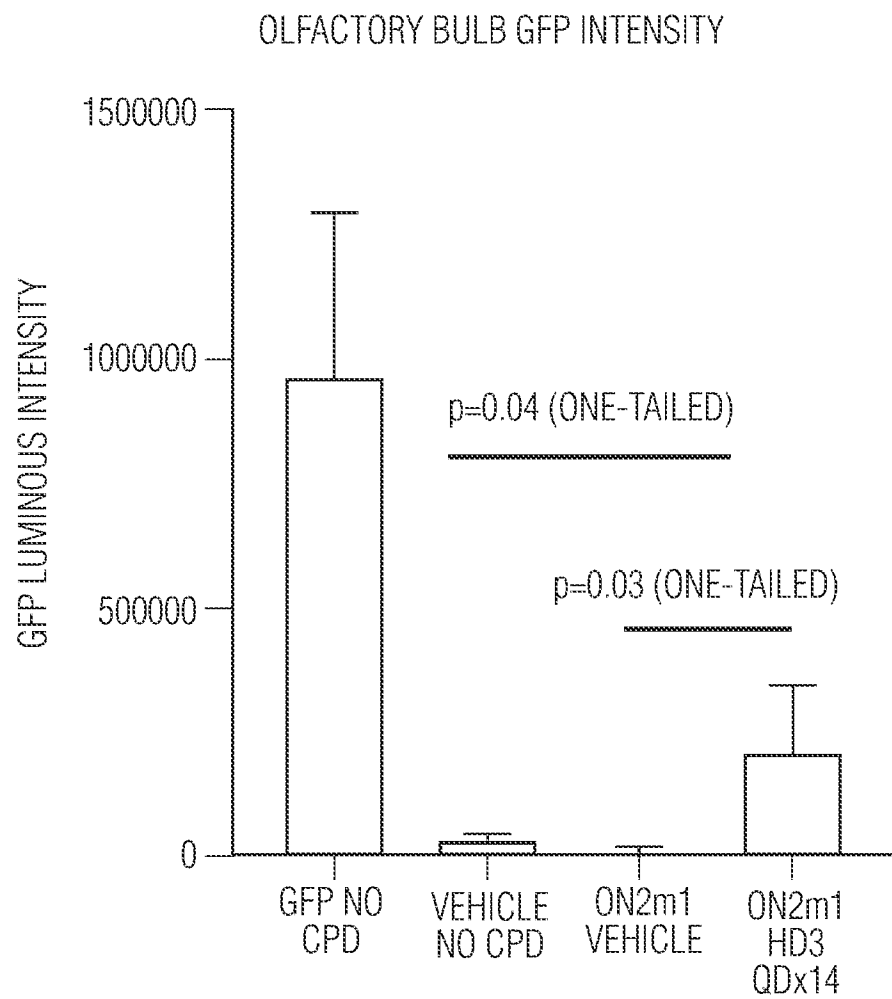


FIG. 14Ii

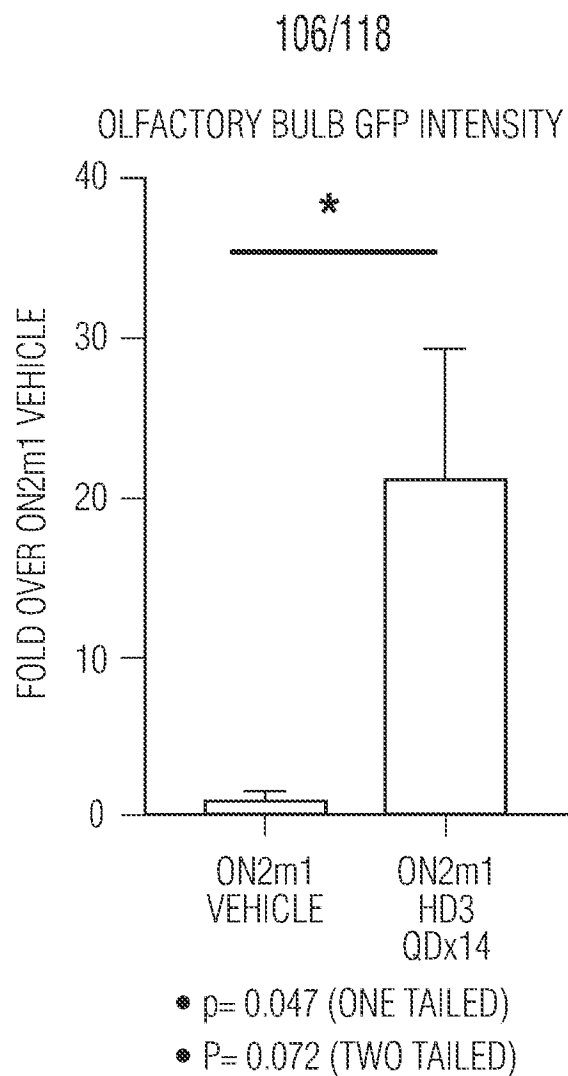


FIG. 14Iii

	FOLD OVER SION2m1 VEHICLE
SION2m1+HD3 QDx14	21
GFP NO CPD	98.4

FIG. 14Iiii

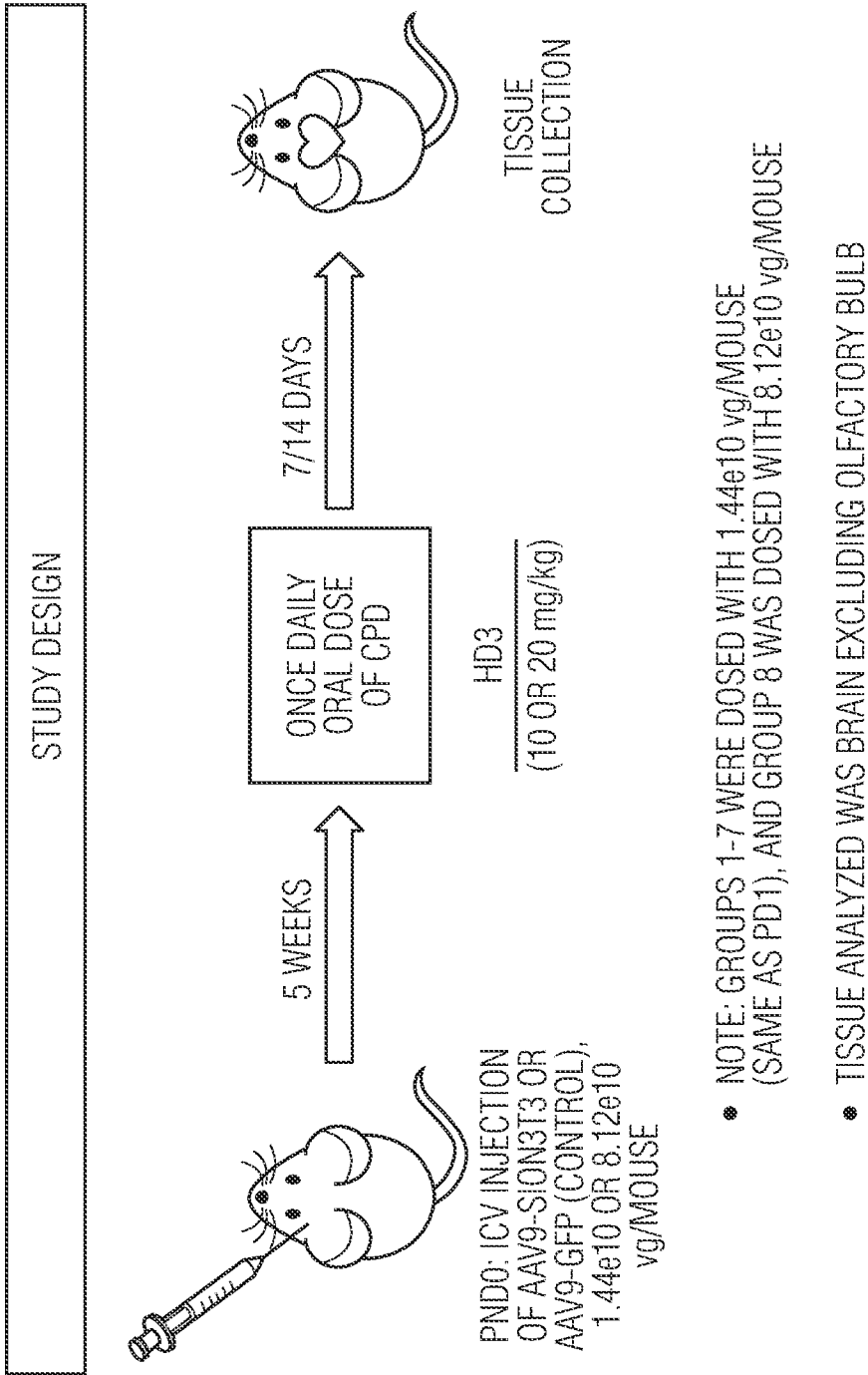
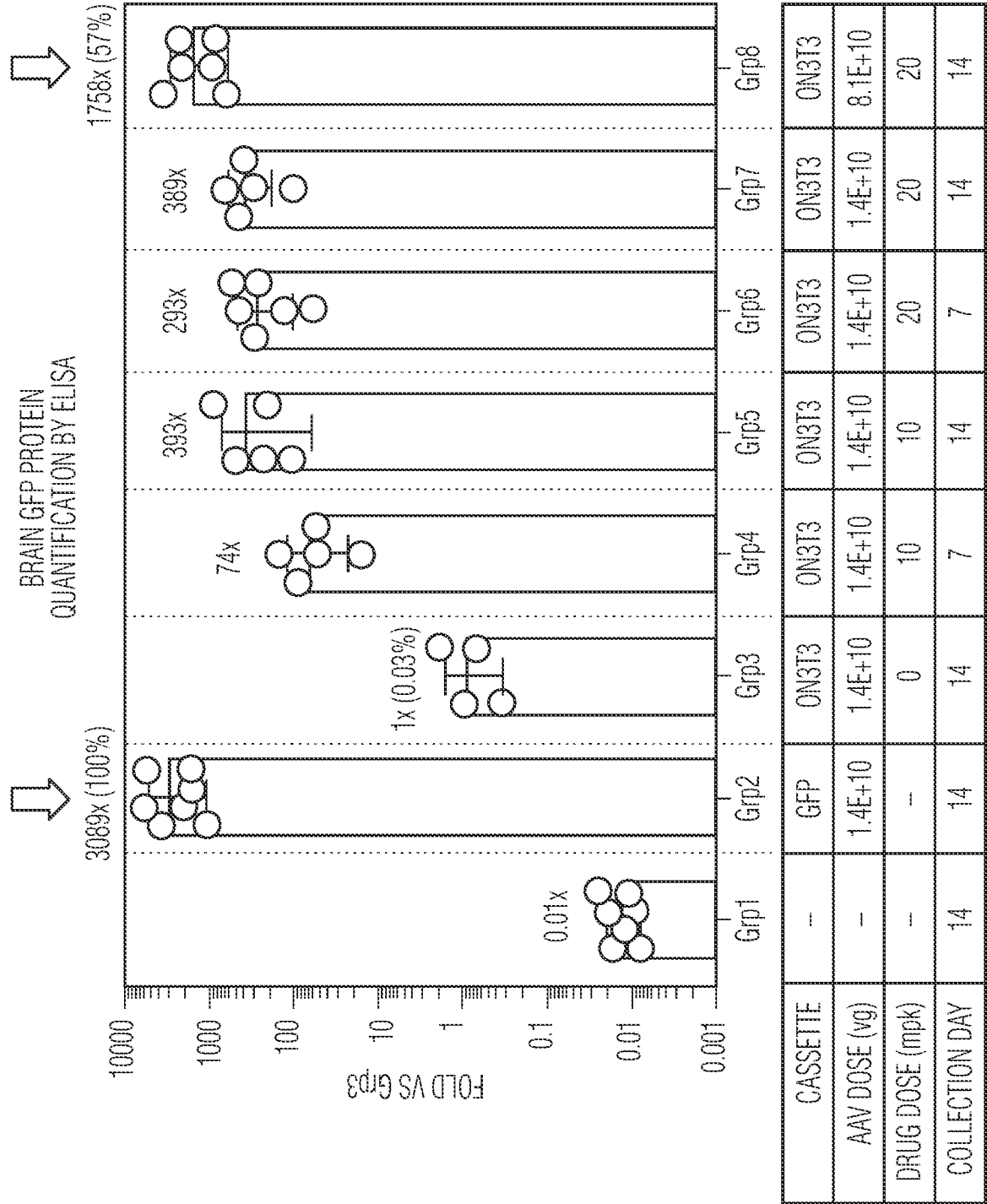


FIG. 15A

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GROUP	NUMBER OF MICE	VIRUS	VIRUS DOSE (vg/MOUSE)	DOSE CONCENTRATION (vg/ML)	VOLUME (μL)	DRUG	DRUG DOSE	TIME OF EUTHANASIA (POST LAST DOSE OF COMPOUND)	DESCRIPTION
1	13	VEHICLE	—	—	4	—	—	DAY 14,	VEH NO CPD
2	12	AAV9-GFP	1.44E+10	3.59E+12	4	—	—	DAY 14,	GFP NO CPD
3	8	AAV9-SION3T3	1.44E+10	3.59E+12	4	VEHICLE	0, QDx14	DAY 14, 4h POST DOSE	ON3T3 VEH
4	9	AAV9-SION3T3	1.44E+10	3.59E+12	4	HD3	10, QDx7	DAY 7, 4h POST DOSE	ON3T3 HD3 10mpk 7d
5	9	AAV9-SION3T3	1.44E+10	3.59E+12	4	HD3	10, QDx14	DAY 14, 4h POST DOSE	ON3T3 HD3 10mpk 14d
6	8	AAV9-SION3T3	1.44E+10	3.59E+12	4	HD3	20, QDx7	DAY 7, 4h POST DOSE	ON3T3 HD3 20mpk 7d
7	9	AAV9-SION3T3	1.44E+10	3.59E+12	4	HD3	20, QDx14	DAY 14, 4h POST DOSE	ON3T3 HD3 20mpk 14d
8	11	AAV9-SION3T3	8.12E+10	2.03E+13	4	HD3	20, QDx14	DAY 14, 4h POST DOSE	HIGH DOSE ON3T3 HD3 20mpk 14d

FIG. 15B



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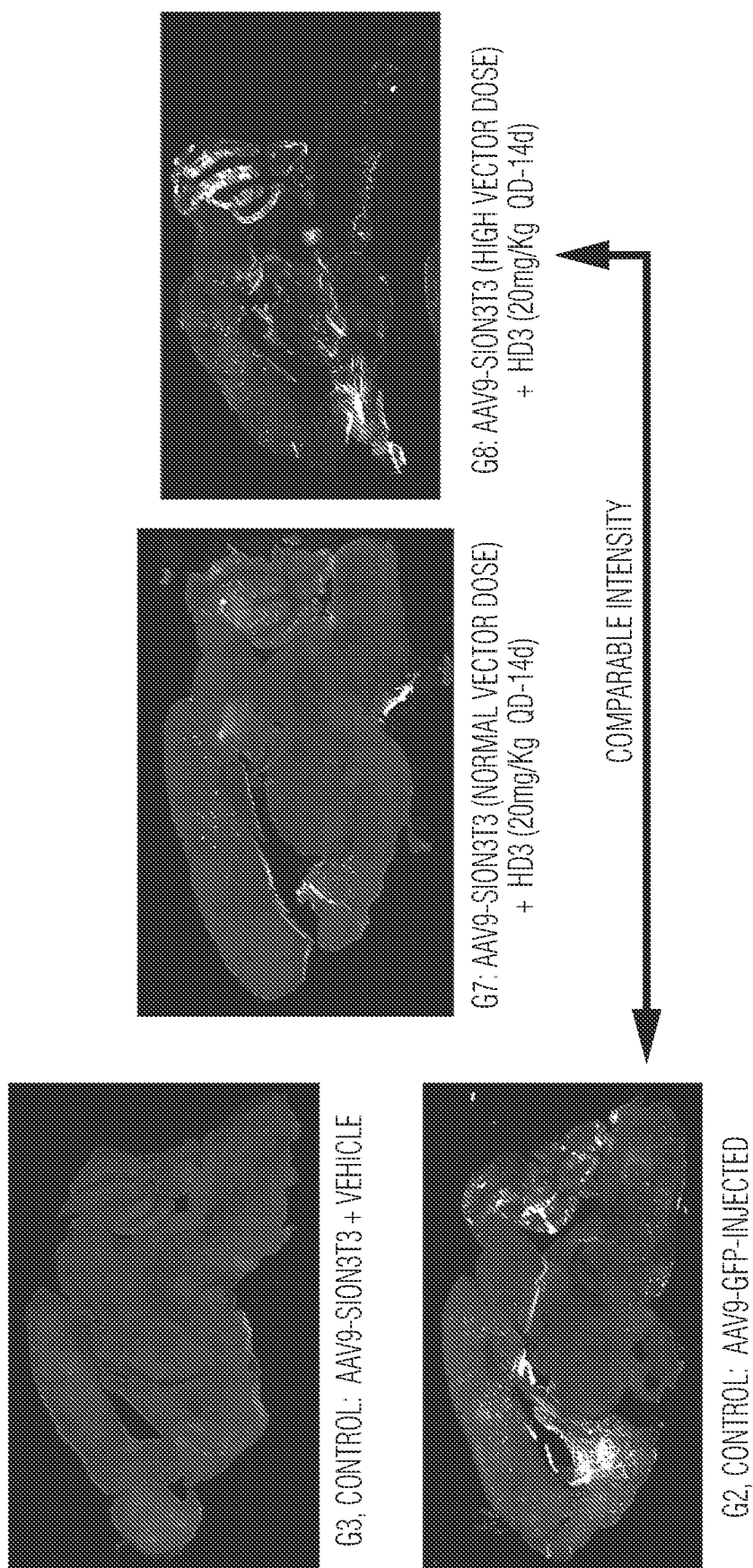


FIG. 15D

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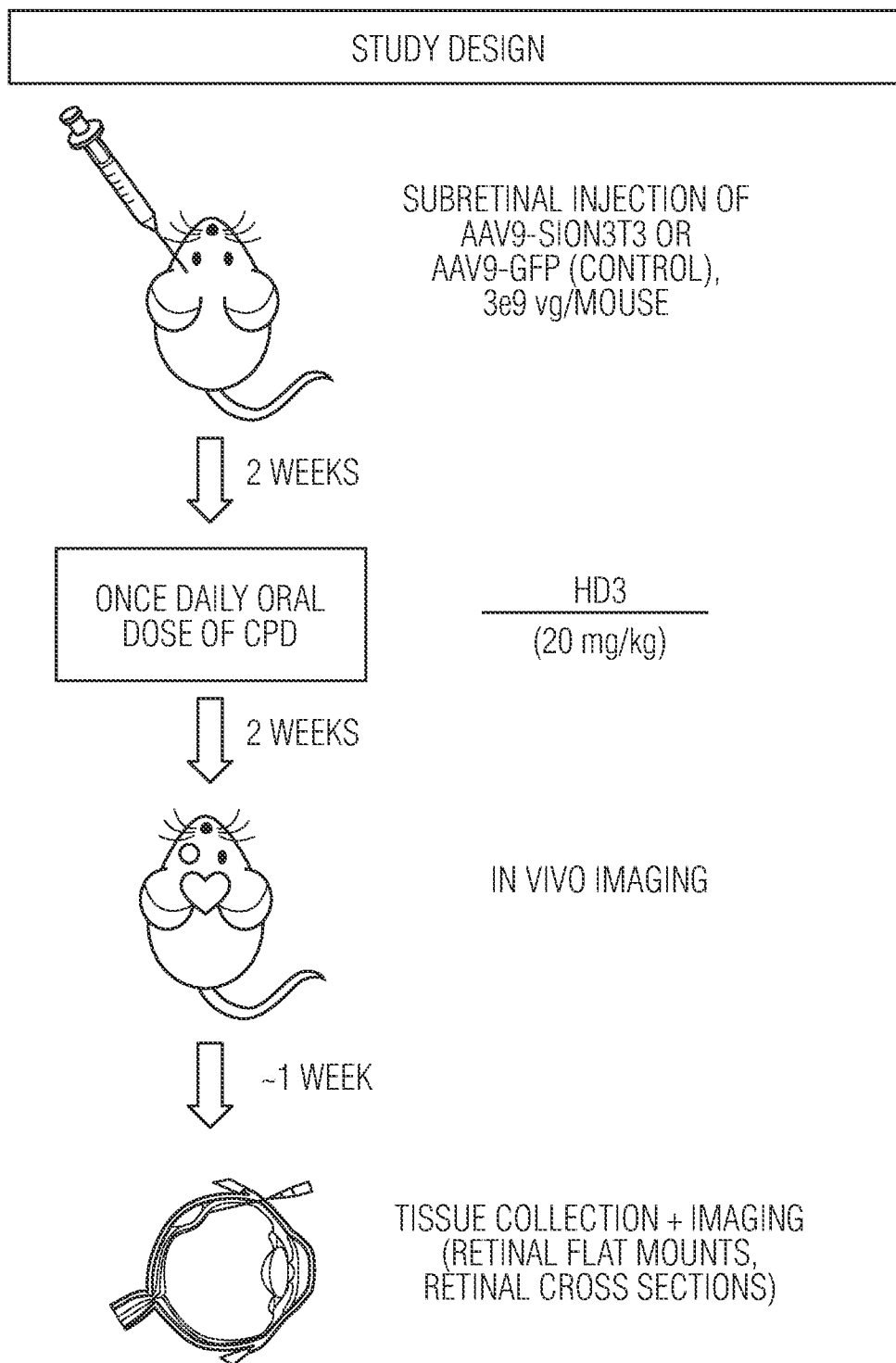


FIG. 16A

GROUP	MOUSE MODEL	AAV DOSE (vg/EYE)	ORAL DOSING POST TWO WEEKS OF INJ., (HD3)	NUMBER OF MICE/GROUP #	FUNDUS IMAGING	ASSAYS AT 4-5 WEEKS POST SUBRETINAL INJECTION (TENTATIVE)%
1	C57BL/6J	VEHICLE	VEHICLE	06	AROUND 4 WEEKS POST SUBRETINAL INJECTION	• qPCR & RT-PCR FOR GFP (DNA AND RNA) • GFP IMAGING IN RETINAL SECTIONS
2	C57BL/6J	3e+10 ⁹ (AAV9-CMV-GFP)	—	06		
3	C57BL/6J	3e+10 ⁹ (AAV9-CMV-SION3T3)	VEHICLE; QD x7-14d*	10		
4	C57BL/6J	3e+10 ⁹ (AAV9-CMV-SION3T3)	20mg/kg (10mi/kg); QD x7-14d*	10		

FIG. 16B

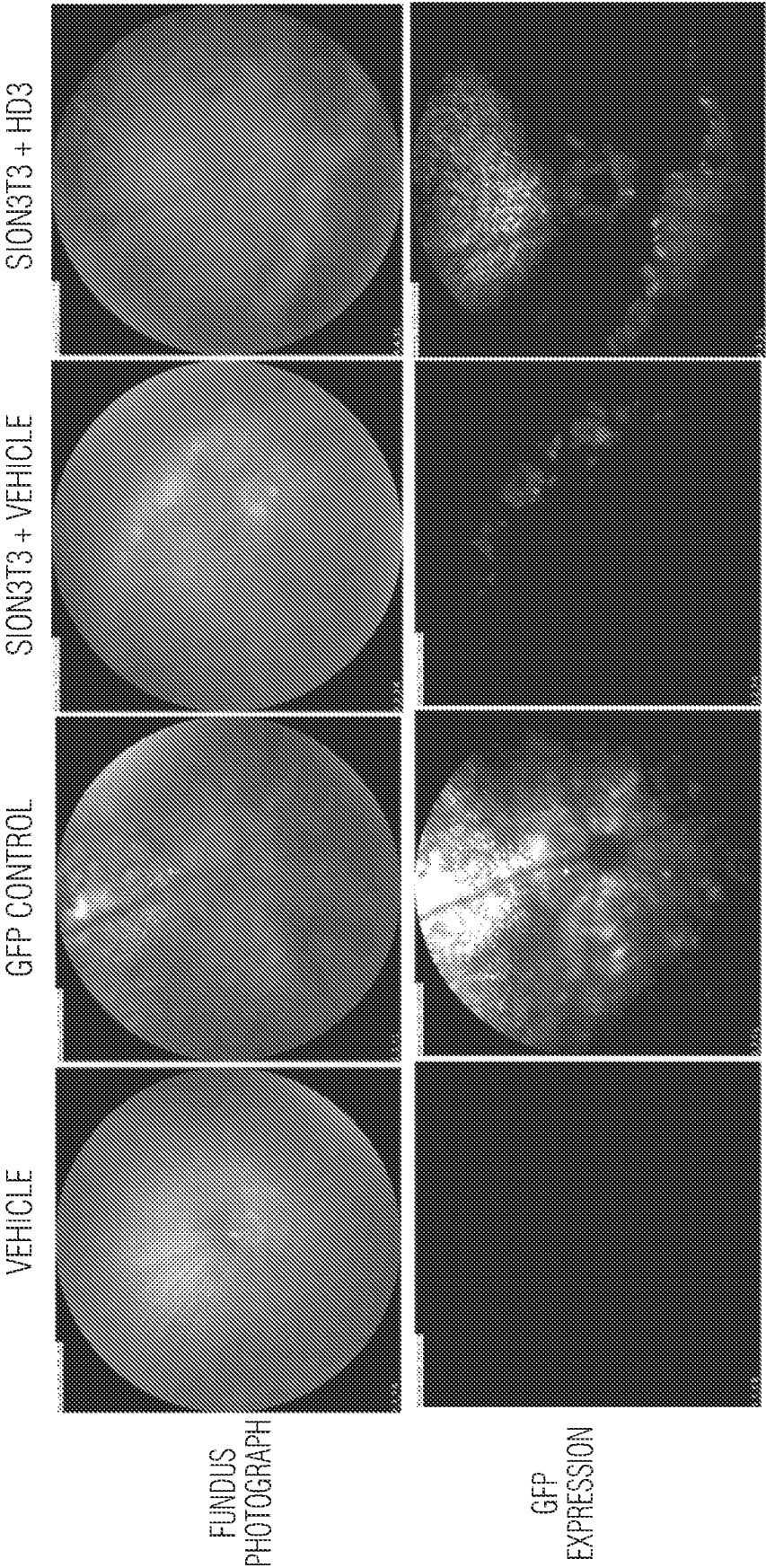


FIG. 16C

CMV-SION3T3 + HD3

CMV-SION3T3 + VEHICLE

CMV GFP VEHICLE

VEHICLE

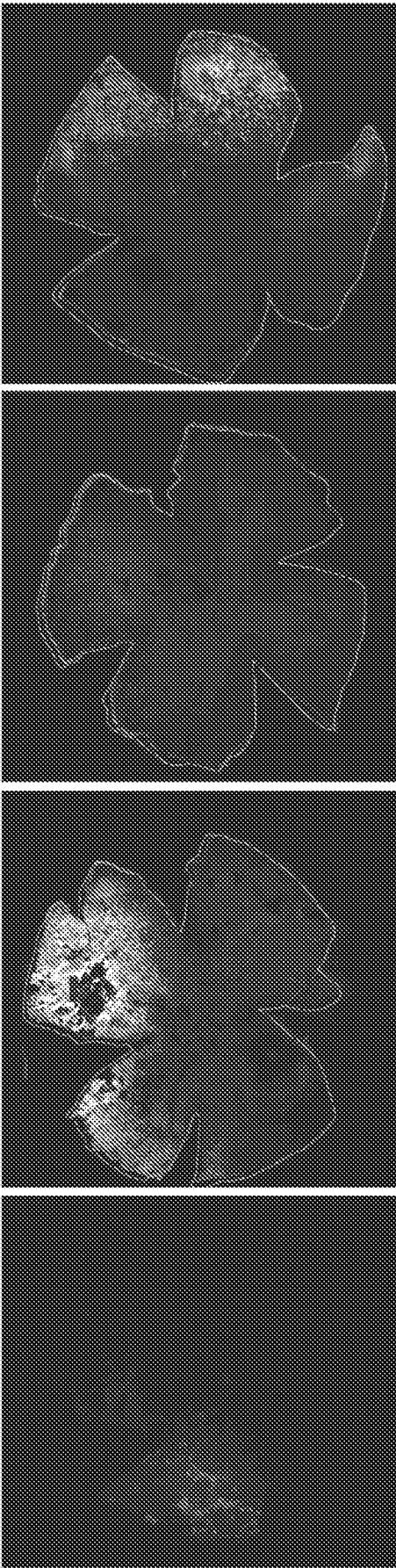


FIG. 16D

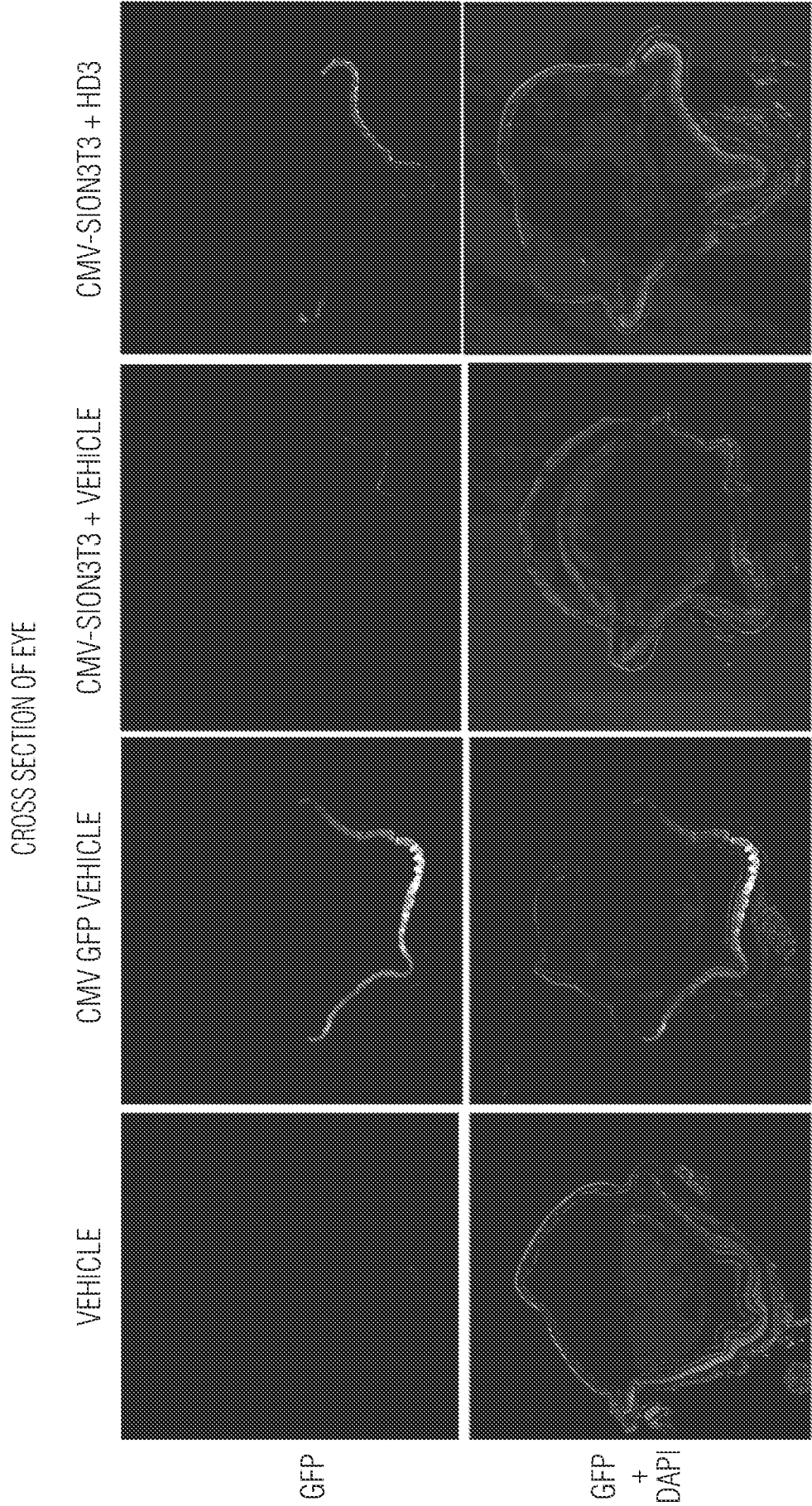


FIG. 16E

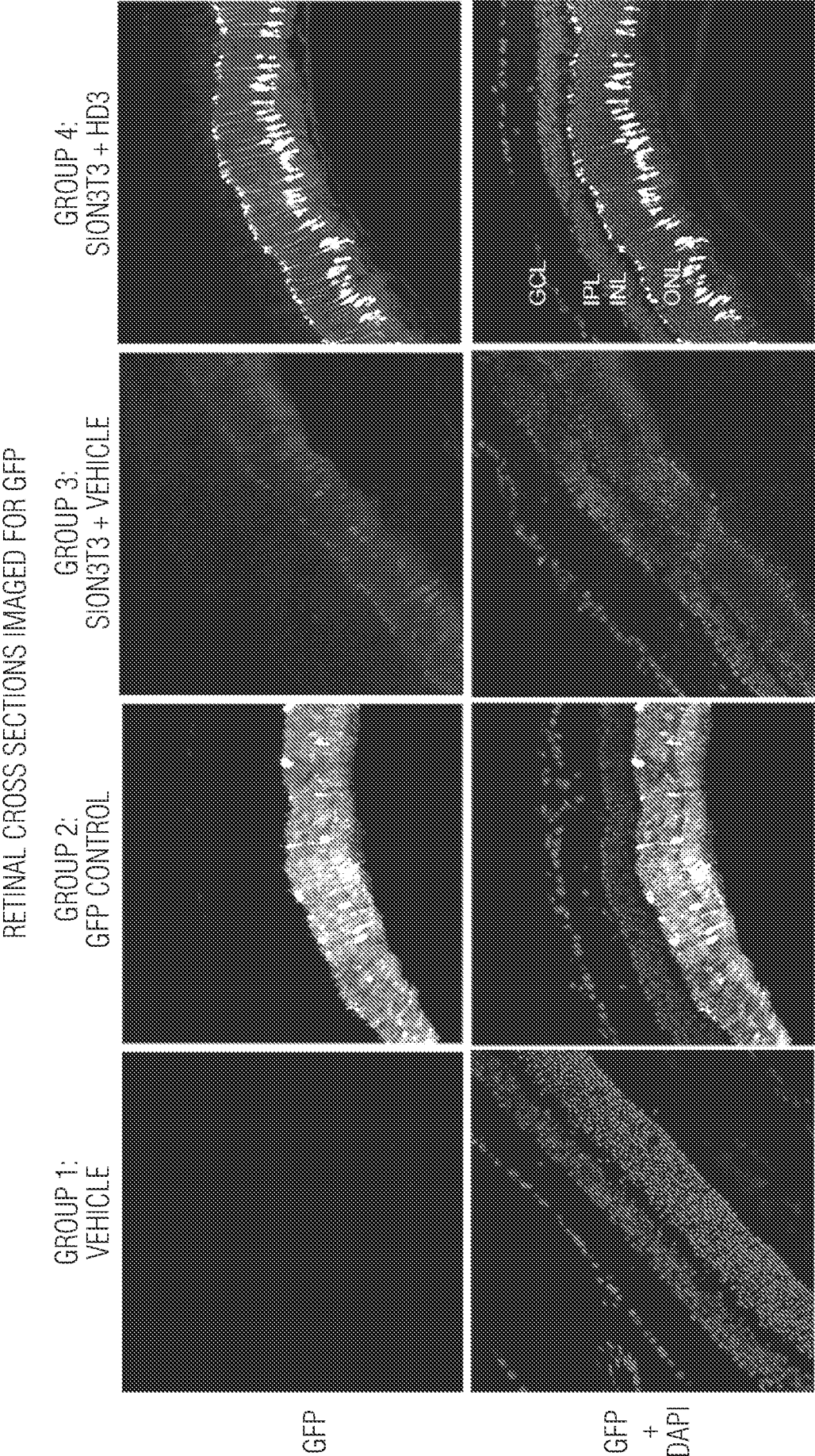
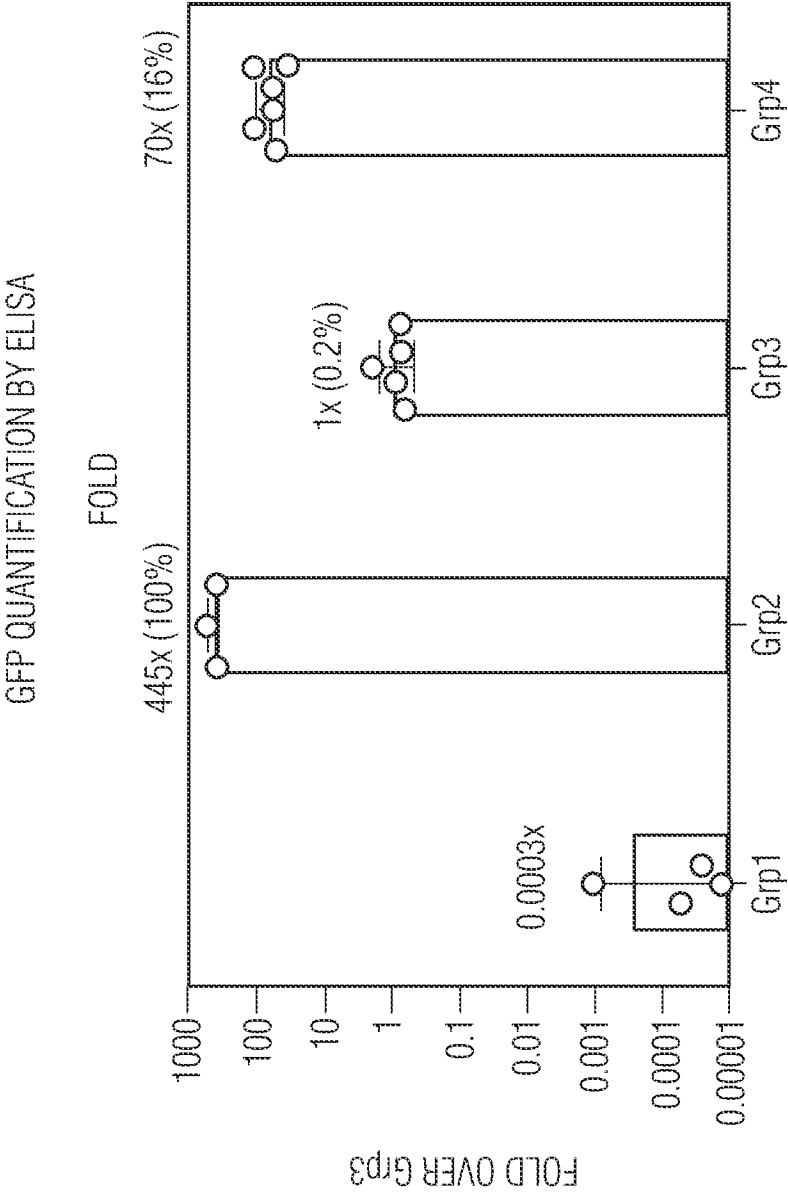


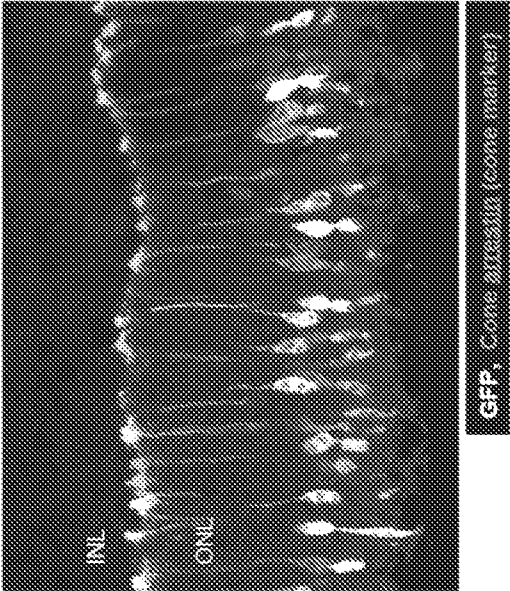
FIG. 16Fi



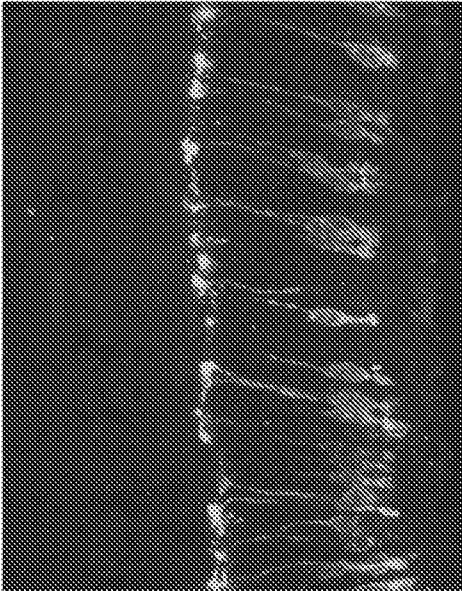
CASSETTE	—	GFP	ON3T3
AAV DOSE (vg)	—	3E + 9	3E + 9
DRUG DOSE (mpk)	0	—	20

FIG. 16Fii

GROUP 4:
SION3T3 + HD3



GROUP 3:
SION3T3 + VEHICLE



GROUP 2:
GFP CONTROL



FIG. 16G

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/021872

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12N 15/11; C12N 15/52; C12N 15/63 (2022.01)

CPC - C12N 15/8209; C12N 15/8213; C12N 15/8216; C12N 15/8217 (2022.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

see Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

see Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2020/0370043 A1 (PTC THERAPEUTICS INC.) 26 November 2020 (26.11.2020) entire document	1-13, 14a, 14b, 24, 25, 27, 31
Y	US 2006/0128020 A1 (CALOS) 15 June 2006 (15.06.2006) entire document	1-13, 14a, 14b, 31
Y	WO 2020/084035 A1 (INSTITUT CURIE et al) 30 April 2020 (30.04.2020) entire document	5
Y	US 2018/0305705 A1 (GENE STREAM PTY LTD) 25 October 2018 (25.10.2018) entire document	7-13, 24, 25, 27
Y	US 2010/0233685 A1 (STOILOV et al) 16 September 2010 (16.09.2010) entire document	12, 13, 14b
A	US 2006/0134681 A1 (BECKMANN et al) 22 June 2006 (22.06.2006) entire document	1-13, 14a, 14b, 15-27, 28a, 28b, 29-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"D" document cited by the applicant in the international application	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"E" earlier application or patent but published on or after the international filing date	"&" document member of the same patent family
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 07 June 2022	Date of mailing of the international search report JUN 27 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Taina Matos Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/021872

Box No. 1 **Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/021872

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 32-35, 36a, 36b, 37
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.