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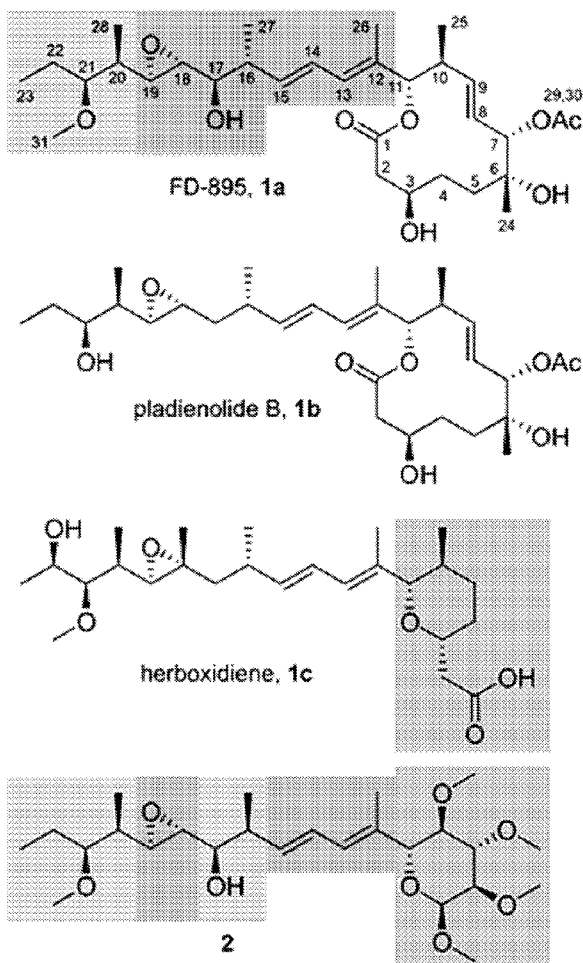
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[Continued on next page]

(54) Title: ANTI-CANCER AND SPLCE MODULATING COMPOUNDS AND METHODS

FIG. 1

(57) Abstract: There are provided *inter alia* stable anti-cancer compounds and splice modulators and methods of synthesis and use thereof.



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ANTI-CANCER AND SPLCE MODULATING COMPOUNDS AND METHODS

CROSS-REFERENCES TO RELATED APPLICATIONS

- 5 **[0001]** This application claims the benefit of U.S. Provisional Application No. 62/306,562, filed March 10, 2016, the contents of which is incorporated herein in its entirety and for all purposes.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED AS AN ASCII TEXT FILE

10

- [0002]** The Sequence Listing written in file 48537-572001WO_ST25.TXT, created on March 1, 2017, 6,280 bytes, machine format IBM-PC, MS-Windows operating system, is hereby incorporated by reference.

15

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

- [0003]** This invention was made with Government support under grant numbers NIH P01-CA081534 and NIH IRACDA K12 GM068524, awarded by National Institutes of Health. The Government has certain rights in this invention.

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BACKGROUND

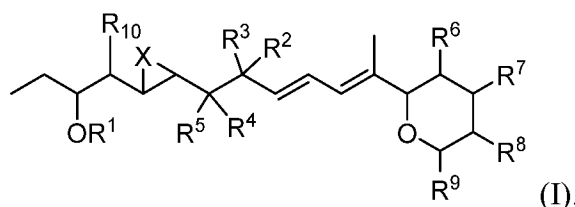
- [0004]** Splicing modulators are recognized as a new lead for the treatment of a number of diseases including cancer. There is provided herein preparation of a stable splice modulator with improved pharmacological properties. These new analogs provide benefits over known natural products (e.g., FD-895) based splice modulators including spliceostatins, pladienolides, and
25 herboxadiene as well as the current synthetic derivatives sudemycins and pladienolide analogs (i.e., E7107 or 6-deoxypladienolide B).

[0005] Solutions to the problems *inter alia* of enhanced biological activity and stability are provided herein.

SUMMARY

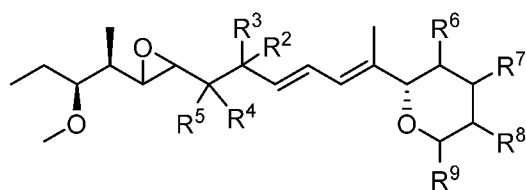
[0006] Herein are provided, *inter alia*, compounds capable of modulating or inhibiting splicing and methods of using the same.

[0007] In an aspect is provided a compound with structure of Formula (I):

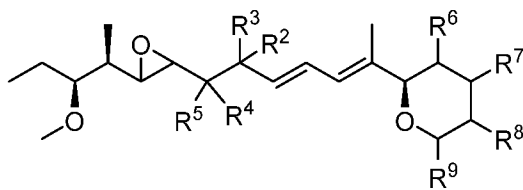


X is -O- or -C(R²⁶)(R²⁷)-. R²⁶ is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -OR²⁸, -OC(O)R²⁸, -OC(O)OR²⁸, or -OC(O)NR²⁸R²⁹. R²⁷ is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -OR³⁰, -OC(O)R³⁰, -OC(O)OR³⁰, or -OC(O)NR³⁰R³¹. R¹ is hydrogen, substituted or unsubstituted alkyl, -C(O)R¹¹, or -C(O)OR¹¹. R² is hydrogen, halogen, substituted or unsubstituted alkyl, -OR¹², -OC(O)R¹², -OC(O)OR¹², or -OC(O)NR¹²R¹³. R³ is hydrogen, halogen, substituted or unsubstituted alkyl, -OR¹⁴, -OC(O)R¹⁴, -OC(O)OR¹⁴, or -OC(O)NR¹⁴R¹⁵. R⁴ is hydrogen, halogen, substituted or unsubstituted alkyl, -OR¹⁶, -OC(O)R¹⁶, -OC(O)OR¹⁶, or -OC(O)NR¹⁶R¹⁷. R⁵ is hydrogen, halogen, substituted or unsubstituted alkyl, -OR¹⁸, -OC(O)R¹⁸, -OC(O)OR¹⁸, or -OC(O)NR¹⁸R¹⁹. R⁶ is hydrogen, -OR²⁰, -C(O)R²⁰, -C(O)OR²⁰, -OC(O)R²⁰, or -OC(O)OR²⁰. R⁷ is hydrogen, -OR²¹, -C(O)R²¹, -C(O)OR²¹, -OC(O)R²¹, or -OC(O)OR²¹. R⁸ is hydrogen, -OR²², -C(O)R²², -C(O)OR²², -OC(O)R²², or -OC(O)OR²². R⁹ is hydrogen, -OR²³, -C(O)R²³, -C(O)OR²³, -OC(O)R²³, or -OC(O)OR²³. R¹⁰ is hydrogen, substituted or unsubstituted alkyl, -OR²⁴, -OC(O)R²⁴, -OC(O)OR²⁴, or -OC(O)NR²⁴R²⁵. R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁸, R²⁹, R³⁰, and R³¹ are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0008] In embodiments, X is -O-; R¹ is hydrogen or unsubstituted C₁-C₄ alkyl; and R¹⁰ is hydrogen or unsubstituted C₁-C₄ alkyl. In embodiments, R¹ is hydrogen or -CH₃; and R¹⁰ is hydrogen or -CH₃. In embodiments, the compound having a structure of Formula (IIA):



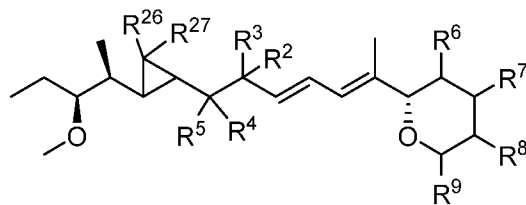
(IIA). In embodiments, the compound having a



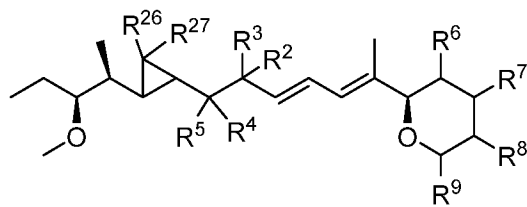
structure of Formula (IIB):

(IIB).

[0009] In embodiments, X is $-C(R^{26})(R^{27})-$; R^1 is hydrogen or unsubstituted C_1-C_4 alkyl; and R^{10} is hydrogen or unsubstituted C_1-C_4 alkyl. In embodiments, R^1 is hydrogen or $-CH_3$; and R^{10} is hydrogen or $-CH_3$. In embodiments, the compound having a structure of Formula (IIIA):



(IIIA). In embodiments, the compound having a



structure of Formula (IIIB):

(IIIB).

[0010] In embodiments, one of R^4 and R^5 is hydrogen and the other one of R^4 and R^5 is $-OH$.

In embodiments, a chiral carbon where R^4 and R^5 are attached has (S) stereochemistry. In

embodiments, a chiral carbon where R^4 and R^5 are attached has (R) stereochemistry. In

embodiments, one of R^2 and R^3 is hydrogen and the other one of R^2 and R^3 is $-CH_3$. In

embodiments, a chiral carbon where R^2 and R^3 are attached has (S) stereochemistry. In

embodiments, a chiral carbon where R^2 and R^3 are attached has (R) stereochemistry. In

embodiments, R^6 is hydrogen, $-OR^{20}$ or $-C(O)OR^{20}$; R^7 is hydrogen, $-OR^{21}$ or $-C(O)OR^{21}$; R^8 is

hydrogen, $-OR^{22}$ or $-C(O)OR^{22}$; R^9 is hydrogen, $-OR^{23}$ or $-C(O)OR^{23}$; and R^{20} , R^{21} , R^{22} , and R^{23}

are each independently hydrogen or unsubstituted C_1-C_4 alkyl. In embodiments, R^{20} , R^{21} , R^{22} ,

and R^{23} are each independently hydrogen or $-CH_3$. In embodiments, at least one of R^6 , R^7 , R^8 , and

R^9 is $-OCH_3$. In embodiments, at least two of R^6 , R^7 , R^8 , and R^9 are $-OCH_3$. In embodiments,

R^6 , R^7 , R^8 and R^9 are $-OCH_3$. In embodiments, R^6 is $-OCH_3$; R^7 is hydrogen; R^8 is hydrogen; and

R^9 is $-OCH_3$.

[0011] In another aspect provided is a pharmaceutical composition comprising a compound described herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0012] In another aspect provided is a method of treating cancer. The method includes administering to a subject in need thereof a therapeutically effective amount of a compound of described herein. In embodiments, the cancer is leukemia, lymphoma, metastatic cancer, or bone cancer. In embodiments, the cancer is chronic lymphocytic leukemia (CLL).

[0013] In another aspect provided is a method of detecting spliceosome inhibition with a test compound as described herein. The method includes (i) contacting a cell with a test compound; (ii) extracting an mRNA from said cell thereby producing an extracted mRNA; (iii) reverse transcribing said extracted mRNA using intron-specific primers thereby forming an intron cDNA; (iv) amplifying said intron cDNA thereby forming a plurality of amplified intron cDNAs; and (v) detecting the presence of said amplified intron cDNAs thereby detecting spliceosome inhibition with said test compound. In embodiments, the cell is derived from a patient. In embodiments, the cell is a cancer cell. In embodiments, the extracting in the method includes lysing the cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIG. 1 depicts structures of FD-895 (**1a**), pladienolide B (**1b**), and herboxadiene (**1c**) and carbohydrate-derived splicing modulator **2**. Compound **2** contains the terminus of **1a**, the epoxide and diene of **1a**, and a core derived from **1c**.

[0015] FIGS. 2A-2E. Models of FD-895 (**1a**), herboxadiene (**1c**) and carbohydrate-derived analog **2**. FIG. 2A) A derived solution structure of the FD-895 core motif as determined by evaluation of ^1H coupling constants and NOE interactions. NOE interactions were observed both on the top face and bottom face. Data shown was collected from ^1H , ^1H NOESY spectral data of **1a** in CDCl_3 and C_6D_6 at 23 °C. FIG. 2B) Model depicting the structure of **1a** superimposed on the surface of **1c**. FIG. 2C) Model depicting the structure of **1c** superimposed on the surface of **1a**. FIG. 2D) Models depicting the structure of **1a** superimposed on the surface of **2**. FIG. 2E) Model depicting the structure of **2** superimposed on the surface of **1a**. The structure of the core motif in **1a** was determined via NMR spectroscopy. Structures of **1b** and **1c** were modeled by energy minimization [17].

[0016] FIGS. 3A-3D. Stereoselectivity of the C12-C13 epoxidation. FIG. 3A) An expanded LC-MS trace *via* UV monitoring at 288 nm depicting the reaction product from treatment of **19** with $\text{VO}(\text{acac})_2/\text{tBuOOH}$. FIG. 3B) Comparable LC-MS trace depicting the formation of two

isomers by *m*-CBPA epoxidation. FIG. 3C) An expansion of the ¹H NMR spectra of epoxide **2** from VO(acac)₂/tBuOOH in CDCl₃. FIG. 3D) An expansion of the ¹H NMR spectra of epoxide **20** in CDCl₃ from *m*-CBPA. Traces of **2** denoted by an asterisk could not be completely removed from **20**, due to close retention times.

5 [0017] FIG. 4. Coupling constant analyses. NMR analysis in C₆D₆ provided a coupling pattern at C12-C13 in **2** that matched that from the corresponding FD-895 analog **1e** (green) but not analogs **1a**, **1f**, or **1g** (black) [6a,15b].

[0018] FIG. 5. Compound **2** induces splice modulation *via* intron retention (IR) comparable to FD-895 (**1a**) and pladienolide B (**1b**) in CLL-B cells. The alkene precursor **19**, which was shown
10 inactive in screening assays, did not induce IR. Genes *GAPDH* and *RNU6A* were used as unspliced and loading controls, respectively. Complementary qRT-PCR data has been provided in FIG. 8.

[0019] FIG. 6. Compound **2** modulates alternate splicing (AS) in CLL-B cells, which is comparable to FD-895 (**1a**) and pladienolide B (**1b**). The alkene precursor **19**, which was shown
15 inactive in screening assays, did not induce AS. *H2A* gene was used as unspliced loading control as depicted. S and L denote short and long isoforms, respectively.

[0020] FIGS. 7A-7B. CLL-B cells cultured either alone or with stromal cell support were treated with **1a**, **1b**, **2**, **19**, or F-ara-A for 48 h at 37 °C followed by flow cytometric analysis and determination of the % SIA, as described in the experimental section. Analyses were derived
20 from two CLL patients as indicated in the plots of FIG. 7A and FIG. 7B.

[0021] FIG. 8. The figure depicts histograms of qRT-PCR data associated with the RT-PCR data from selected genes depicted in FIG. 5. X-axis bins (left to right): control, 10 nM, 100 nM, 1000 nM. Ordering (left to right, top to bottom): *DNAJB1*, *ARF4*, *PRPF4*, *SF3A1*, *UIAF2*, *RIOK3*.

25

DETAILED DESCRIPTION

[0022] I. Definitions

[0023] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

30 [0024] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., -CH₂O- is equivalent to -OCH₂-.

[0025] The term “alkyl,” by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e., C₁-C₁₀ means one to ten carbons).

5 Alkyl is not cyclized. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds (e.g. alkene, alkyne). Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-
10 isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-). An alkyl moiety may be an alkenyl moiety. An alkyl moiety may be an alkynyl moiety. An alkyl moiety may be fully saturated.

[0026] The term “alkylene,” by itself or as part of another substituent, means, unless otherwise
15 stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, -CH₂CH₂CH₂CH₂-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term “alkenylene,” by itself or as part of another substituent,
20 means, unless otherwise stated, a divalent radical derived from an alkene.

[0027] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, or S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be
25 quaternized. The heteroatom(s) (e.g., O, N, P, S, B, As, or Si) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂, -S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, -
30 CH=CH-N(CH₃)-CH₃, -O-CH₃, -O-CH₂-CH₃, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four
35 optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five

optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

[0028] Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C}(\text{O})_2\text{R}'$ represents both $\text{C}(\text{O})_2\text{R}'$ and $-\text{R}'\text{C}(\text{O})_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as $-\text{C}(\text{O})\text{R}'$, $-\text{C}(\text{O})\text{NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}'$, and/or $-\text{SO}_2\text{R}'$. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like, it will be understood that the terms heteroalkyl and $-\text{NR}'\text{R}''$ are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like.

[0029] The terms “cycloalkyl” and “heterocycloalkyl,” by themselves or in combination with other terms, mean, unless otherwise stated, non-aromatic cyclic versions of “alkyl” and “heteroalkyl,” respectively, wherein the carbons making up the ring or rings do not necessarily need to be bonded to a hydrogen due to all carbon valencies participating in bonds with non-hydrogen atoms. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, 3-hydroxy-cyclobut-3-enyl-1,2, dione, 1H-1,2,4-triazolyl-5(4H)-one, 4H-1,2,4-triazolyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A “cycloalkylene” and a “heterocycloalkylene,” alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. A heterocycloalkyl moiety may include one ring heteroatom (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include two optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include three optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include four optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may

include five optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include up to 8 optionally different ring heteroatoms (e.g., O, N, S, Si, or P).

[0030] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term “halo(C₁-C₄)alkyl” includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0031] The term “acyl” means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0032] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term “heteroaryl” refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term “heteroaryl” includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl.

Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An “arylene” and a “heteroarylene,” alone or

as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. Non-limiting examples of aryl and heteroaryl groups include pyridinyl,

pyrimidinyl, thiophenyl, thienyl, furanyl, indolyl, benzoxadiazolyl, benzodioxolyl, benzodioxanyl, thianaphthanyl, pyrrolopyridinyl, indazolyl, quinolinyl, quinoxalinyl,

pyridopyrazinyl, quinazolinonyl, benzoisoxazolyl, imidazopyridinyl, benzofuranyl, benzothienyl, benzothiophenyl, phenyl, naphthyl, biphenyl, pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furylthienyl, pyridyl, pyrimidyl, benzothiazolyl, purinyl, benzimidazolyl, isoquinolyl, thiadiazolyl, oxadiazolyl, pyrrolyl, diazolyl, triazolyl, tetrazolyl, benzothiadiazolyl, isothiazolyl, pyrazolopyrimidinyl, pyrrolopyrimidinyl, benzotriazolyl,

benzoxazolyl, or quinolyl. The examples above may be substituted or unsubstituted and divalent radicals of each heteroaryl example above are non-limiting examples of heteroarylene. A

heteroaryl moiety may include one ring heteroatom (e.g., O, N, or S). A heteroaryl moiety may include two optionally different ring heteroatoms (e.g., O, N, or S). A heteroaryl moiety may include three optionally different ring heteroatoms (e.g., O, N, or S). A heteroaryl moiety may

include four optionally different ring heteroatoms (e.g., O, N, or S). A heteroaryl moiety may include five optionally different ring heteroatoms (e.g., O, N, or S). An aryl moiety may have a single ring. An aryl moiety may have two optionally different rings. An aryl moiety may have three optionally different rings. An aryl moiety may have four optionally different rings. A heteroaryl moiety may have one ring. A heteroaryl moiety may have two optionally different rings. A heteroaryl moiety may have three optionally different rings. A heteroaryl moiety may have four optionally different rings. A heteroaryl moiety may have five optionally different rings.

[0033] A fused ring heterocycloalkyl-aryl is an aryl fused to a heterocycloalkyl. A fused ring heterocycloalkyl-heteroaryl is a heteroaryl fused to a heterocycloalkyl. A fused ring heterocycloalkyl-cycloalkyl is a heterocycloalkyl fused to a cycloalkyl. A fused ring heterocycloalkyl-heterocycloalkyl is a heterocycloalkyl fused to another heterocycloalkyl. Fused ring heterocycloalkyl-aryl, fused ring heterocycloalkyl-heteroaryl, fused ring heterocycloalkyl-cycloalkyl, or fused ring heterocycloalkyl-heterocycloalkyl may each independently be unsubstituted or substituted with one or more of the substituents described herein.

[0034] The term “oxo,” as used herein, means an oxygen that is double bonded (“=O”) to a carbon atom.

[0035] The term “alkylsulfonyl,” as used herein, means a moiety having the formula -S(O₂)-R', where R' is a substituted or unsubstituted alkyl group as defined above. R' may have a specified number of carbons (e.g., “C₁-C₄ alkylsulfonyl”).

[0036] Each of the above terms (e.g., “alkyl,” “heteroalkyl,” “cycloalkyl,” “heterocycloalkyl,” “aryl,” and “heteroaryl”) includes both substituted and unsubstituted forms of the indicated radical.

[0037] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂N(R')(R''-NRSO₂R'), -CN, and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R'', R''', and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' group when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R'' includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term “alkyl” is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0038] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NRC(NR'R'')=NR''', S(O)R', -S(O)₂R', -S(O)₂N(R')(R'', -NRSO₂R'), -CN, -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'', R''', and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' groups when more than one of these groups is present.

[0039] Where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. For example, where a moiety herein is R^{1A}-substituted or unsubstituted alkyl, a plurality of R^{1A} substituents may be attached to the alkyl moiety wherein each R^{1A} substituent is optionally different. Where an R-substituted moiety is substituted with a plurality R substituents, each of the R-substituents may be differentiated herein using a prime symbol (') such as R', R'', etc. For example, where a moiety is R^{1A}-substituted or unsubstituted alkyl, and the moiety is substituted with a plurality of R^{1A} substituents, the plurality of R^{1A} substituents may be differentiated as R^{1A'}, R^{1A''}, R^{1A'''}, etc. In some embodiments, the plurality of R substituents is 3. In some embodiments, the plurality of R substituents is 2.

[0040] In embodiments, a compound as described herein may include multiple instances of R¹, R², and/or other substituents and variables. In such embodiments, each variable may optionally be different and be appropriately labeled to distinguish each group for greater clarity. For example, where each R^{6A} is different, they may be referred to, for example, as R^{6A.1}, R^{6A.2}, R^{6A.3}, or R^{6A.4}, respectively, wherein the definition of R^{6A} is assumed by R^{6A.1}, R^{6A.2}, R^{6A.3}, and/or R^{6A.4}. The variables used within a definition of R¹, R², and/or other variables that appear at multiple instances and are different may similarly be appropriately labeled to distinguish each group for greater clarity.

[0041] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In embodiments, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0042] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-(CRR')_q-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of

the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(C''R''R''')_d-$, where variables s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituents R, R', R'', and R''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0043] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include, oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0044] A “substituent group,” as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted

alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}(\text{O})\text{NHNH}_2$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCI}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

[0045] A “size-limited substituent” or “size-limited substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1 - C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3 - C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6 - C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0046] A “lower substituent” or “lower substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1 - C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3 - C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6 - C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0047] In embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, In embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent

group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[0048] In embodiments of the compounds herein, each substituted or unsubstituted alkyl may

5 be a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each
10 substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₂₀ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₈ cycloalkylene, each substituted or unsubstituted
15 heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0049] In embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted

20 C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a
25 substituted or unsubstituted 5 to 9 membered heteroaryl. In embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₈ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₇ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or
30 unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In embodiments, the compound is a chemical species set forth in the Examples section below.

[0050] The term “pharmaceutically acceptable salts” is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (*see, e.g., Berge et al., Journal of Pharmaceutical Science* 66:1-19 (1977)). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for the present invention. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder in 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

[0051] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

[0052] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0053] Provided herein are agents (e.g. compounds, drugs, therapeutic agents) that may be in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under select physiological conditions to provide the final agents (e.g. compounds, drugs, therapeutic agents). Additionally, prodrugs can be converted to agents (e.g. compounds, drugs, therapeutic agents) by chemical or biochemical methods in an *ex vivo* environment. Prodrugs described herein include compounds that readily undergo chemical changes under select physiological conditions to provide agents (e.g. compounds, drugs, therapeutic agents) to a biological system (e.g. in a subject, in a cell, in the extracellular space near a cell).

[0054] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0055] As used herein, the term “salt” refers to acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts.

[0056] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those which are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0057] As used herein, the term “isomers” refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0058] The term “tautomer,” as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0059] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0060] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0061] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0062] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0063] The symbol “ $\sim$ ” denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0064] The terms “treating”, or “treatment” refers to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term “treating” and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

[0065] An “effective amount” is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g. achieve the effect for which it is

administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an “therapeutically effective amount” is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a “therapeutically effective amount.” A “reduction” of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.,* Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0066] The term “associated” or “associated with” in the context of a substance or substance activity or function associated with a disease (e.g. infectious disease, hyperproliferative disease, cancer) means that the disease is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, a disease associated with infection may be treated with an agent (e.g. compound as described herein) effective as an antibiotic.

[0067] As used herein, the term "cancer" refers to all types of cancer, neoplasm, or malignant tumors found in mammals, including leukemia, carcinomas and sarcomas. Exemplary cancers include cancer of the brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus and Medulloblastoma. Additional examples include, metastatic bone cancer, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine and exocrine pancreas, and prostate cancer.

[0068] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the

type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemtic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

[0069] The term "lymphoma" refers broadly to a group of blood cell tumors that develop from cells of the immune system found in lymph, i.e. lymphocytes (e.g. natural killer cells (NK cells), T cells, and B cells). Lymphoma is typically classified into Hodgkin's lymphomas (HL) and the non-Hodgkin lymphomas (NHL) or based on whether it develops in B-lymphocytes (B-cells) or T-lymphocytes (T-cells). Exemplary lymphomas (Hodgkin's lymphomas and non-Hodgkin's lymphomas) that may be treated with a compound or method provided herein include, for example, nodular-sclerosis classical Hodgkin lymphoma, mixed cellularity classical Hodgkin lymphoma, lymphocyte-rich classical Hodgkin lymphoma, lymphocyte-depleted classical Hodgkin lymphoma, aggressive NHL, transformed NHL, indolent NHL, relapsed NHL, refractory NHL, low grade non-Hodgkin's Lymphoma, follicular lymphoma, large cell lymphoma, B-cell lymphoma, T-cell lymphoma, Mantle cell lymphoma, Burkitt's lymphoma, NK cell lymphoma, diffuse large B-cell lymphoma, and acute lymphoblastic lymphoma.

[0070] "Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

[0071] The terms "DNA" and "RNA" refer to deoxyribonucleic acid and ribonucleic acid, respectively.

[0072] Where a method disclosed herein refers to "amplifying" a nucleic acid, the term "amplifying" refers to a process in which the nucleic acid is exposed to at least one round of extension, replication, or transcription in order to increase (e.g., exponentially increase) the number of copies (including complimentary copies) of the nucleic acid. The process can be iterative including multiple rounds of extension, replication, or transcription. Various nucleic acid amplification techniques are known in the art, such as PCR amplification or rolling circle amplification.

[0073] A "primer" as used herein refers to a nucleic acid that is capable of hybridizing to a complimentary nucleic acid sequence in order to facilitate enzymatic extension, replication or transcription.

[0074] The words "complementary" or "complementarity" refer to the ability of a nucleic acid in a polynucleotide to form a base pair with another nucleic acid in a second polynucleotide. For example, the sequence 3'-A-G-T-C-5' is complementary to the sequence 3'-G-A-C-T-5'. Complementarity may be partial, in which only some of the nucleic acids match according to base pairing, or complete, where all the nucleic acids match according to base pairing.

[0075] The terms "identical" or percent "identity," in the context of two or more nucleic acids, refer to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection. *See e.g.*, the NCBI web site at ncbi.nlm.nih.gov/BLAST. Such sequences are then said to be "substantially identical." This definition also refers to, or may be applied to, the complement of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

[0076] A variety of methods of specific DNA and RNA measurements that use nucleic acid hybridization techniques are known to those of skill in the art (*see*, Sambrook, *Id.*). Some methods involve electrophoretic separation (*e.g.*, Southern blot for detecting DNA, and Northern

blot for detecting RNA), but measurement of DNA and RNA can also be carried out in the absence of electrophoretic separation (*e.g.*, quantitative PCR, dot blot, or array).

[0077] The sensitivity of the hybridization assays may be enhanced through use of a nucleic acid amplification system that multiplies the target nucleic acid being detected. Amplification can also be used for direct detection techniques. Examples of such systems include the polymerase chain reaction (PCR) system and the ligase chain reaction (LCR) system. Other methods include the nucleic acid sequence based amplification (NASBA, Canguene, Mississauga, Ontario) and Q Beta Replicase systems. These systems can be used to directly identify mutants where the PCR or LCR primers are designed to be extended or ligated only when a selected sequence is present. Alternatively, the selected sequences can be generally amplified using, for example, nonspecific PCR primers and the amplified target region later probed for a specific sequence indicative of a mutation. It is understood that various detection probes, including Taqman® and molecular beacon probes can be used to monitor amplification reaction products in real time.

[0078] The terms “spliceosome” or “spliceosomal” are used according to their common and ordinary meaning and refer to the component or complex in a cell involved in removal of introns from transcribed pre-mRNA. A spliceosome may include a complex of small nuclear RNA (snRNA) and protein subunits.

[0079] The term “splicing” is used according to its common and ordinary meaning and refer to a process in a cell involved in removal of introns from transcribed pre-mRNA. During the splicing, the removal of introns and joining of exons from nascent pre-mRNA occur simultaneously or sequentially. Splicing plays an important role in human biology and its relevance in developing and proliferation of cancer cells.

[0080] As defined herein, the term “inhibition”, “inhibit”, “inhibiting” and the like in reference to a protein-inhibitor interaction means negatively affecting (*e.g.*, decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In some embodiments, inhibition refers to reduction of a disease or symptoms of disease. In some embodiments, inhibition refers to a reduction in the activity of a particular protein or nucleic acid target. In some embodiment, inhibition of the invention refers to an inhibition upon a splicing process in a cell, preferably in a cancer cell, using an inhibitor (*e.g.*, antagonist, antibodies, RNAi molecules or small molecules). Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein or protein complex (*e.g.* spliceosome).

[0081] A “test compound” as used herein refers to an experimental compound as described herein that can be used in a screening process to identify activity, non-activity, or other modulation of a particularized biological target or pathway.

[0082] The term “modulation”, “modulate”, or “modulator” are used in accordance with their plain ordinary meaning and refer to the act of changing or varying one or more properties.

“Modulator” refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule. “Modulation” refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a biological target, to modulate means to change by increasing or decreasing a property or function of the biological target or the amount of the biological target.

[0083] “Contacting” is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0084] The term “contacting” may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway.

[0085] As used herein, “biomolecule” is used in its customary sense and refers to a molecule found in nature or derivatives thereof, including macromolecules such as proteins, carbohydrates, lipids, and nucleic acids, as well as small molecules such as primary metabolites, secondary metabolites, and natural products. A biomolecule may be present as a moiety attached to the remainder of a compound. A biomolecule includes but is not limited to nucleic acids (e.g. DNA and RNA), peptide nucleic acids, sugars, peptides, proteins, antibodies, lipids, small molecule affinity ligands e.g. inhibitors, biotin and haptens.

[0086] As used herein, “carbohydrate” is used in its customary sense and refers to a molecule found in nature or derivatives thereof, which comprises carbon (C), hydrogen (H) and oxygen (O) atoms and typically containing polyhydroxy aldehydes, ketones, alcohols, acids, simple derivatives thereof and polymeric forms from monomeric units (monosaccharides). A monosaccharide is used in its customary sense and refers to a basic building block of carbohydrates or disaccharide containing two units of the monosaccharides. The monosaccharide can have either linear form or cyclic (ring) form and contains at least three carbons, at least four

carbons, at least five carbons, or at least six carbons. The monosaccharide as used in the invention can have a 5 to 7 membered, or preferably, 6-membered ring structure. In addition, the monosaccharide may be chemically modified, for example, by removing or adding hydrogen, oxo, halogen, -OH, -NH₂, -COOH, -CONH₂, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0087] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0088] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0089] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or

transdermal). Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.*

5 **[0090]** By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compound of the invention can be administered alone or can be co-administered to the patient. Co-administration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the
10 preparations can also be combined, when desired, with other active substances (*e.g.* to reduce metabolic degradation).

[0091] The compositions disclosed herein can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder,
15 dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, *etc.*, suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained
20 release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions disclosed herein can also be delivered as microspheres for slow
25 release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, *e.g.*, Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, *e.g.*, Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the
30 compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.*, by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery
35 of the compositions of the present invention into the target cells in vivo. (See, *e.g.*, Al-

Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions can also be delivered as nanoparticles.

[0092] Pharmaceutical compositions may include compositions wherein the active ingredient (e.g. compounds described herein, including embodiments or examples) is contained in a therapeutically effective amount, *i.e.*, in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, *inter alia*, on the condition being treated. When administered in methods to treat a disease, such compositions will contain an amount of active ingredient effective to achieve the desired result, e.g., modulating the activity of a target molecule, and/or reducing, eliminating, or slowing the progression of disease symptoms.

[0093] The dosage and frequency (single or multiple doses) administered to a mammal can vary depending upon a variety of factors, for example, whether the mammal suffers from another disease, and its route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated, kind of concurrent treatment, complications from the disease being treated or other health-related problems. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds of Applicants' invention. Adjustment and manipulation of established dosages (e.g., frequency and duration) are well within the ability of those skilled in the art.

[0094] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0095] As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0096] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of

the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0097] An “agonist,” as used herein, refers to a compound capable of detectably increasing the expression or activity of a given protein or receptor. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100% or more in comparison to a control in the absence of the agonist. In embodiments, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or more higher than the expression or activity in the absence of the agonist.

[0098] The term “antagonist” refers to a substance capable of detectably lowering expression or activity of a given protein. The antagonist can inhibit expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100% or less in comparison to a control in the absence of the antagonist. In embodiments, the inhibition is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, or more than the expression or activity in the absence of the antagonist.

[0099] The term “nucleic acid” refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single-, double- or multiple-stranded form, or complements thereof. The term “polynucleotide” refers to a linear sequence of nucleotides. The term “nucleotide” typically refers to a single unit of a polynucleotide, *i.e.*, a monomer. Nucleotides can be ribonucleotides, deoxyribonucleotides, or modified versions thereof. Examples of polynucleotides contemplated herein include single and double stranded DNA, single and double stranded RNA (including siRNA), and hybrid molecules having mixtures of single and double stranded DNA and RNA. Nucleic acids can be linear or branched. For example, nucleic acids can be a linear chain of nucleotides or the nucleic acids can be branched, *e.g.*, such that the nucleic acids comprise one or more arms or branches of nucleotides. Optionally, the branched nucleic acids are repetitively branched to form higher ordered structures such as dendrimers and the like.

[0100] Nucleic acids, including nucleic acids with a phosphothioate backbone can include one or more reactive moieties. As used herein, the term reactive moiety includes any group capable of reacting with another molecule, *e.g.*, a nucleic acid or polypeptide through covalent, non-covalent or other interactions. By way of example, the nucleic acid can include an amino acid reactive moiety that reacts with an amino acid on a protein or polypeptide through a covalent, non-covalent or other interaction.

[0101] The terms also encompass nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphodiester derivatives including, *e.g.*, phosphoramidate, phosphorodiamidate, phosphorothioate (also known as phosphothioate), phosphorodithioate, phosphonocarboxylic acids, phosphonocarboxylates, phosphonoacetic acid, phosphonoformic acid, methyl phosphonate, boron phosphonate, or O-methylphosphoroamidite linkages (see Eckstein, OLIGONUCLEOTIDES AND ANALOGUES: A PRACTICAL APPROACH, Oxford University Press); and peptide nucleic acid backbones and linkages. Other analog nucleic acids include those with positive backbones; non-ionic backbones, modified sugars, and non-ribose backbones (*e.g.* phosphorodiamidate morpholino oligos or locked nucleic acids (LNA)), including those described in U.S. Patent Nos. 5,235,033 and 5,034,506, and Chapters 6 and 7, ASC Symposium Series 580, *Carbohydrate Modifications in Antisense Research*, Sanghui & Cook, eds. Nucleic acids containing one or more carbocyclic sugars are also included within one definition of nucleic acids. Modifications of the ribose-phosphate backbone may be done for a variety of reasons, *e.g.*, to increase the stability and half-life of such molecules in physiological environments or as probes on a biochip. Mixtures of naturally occurring nucleic acids and analogs can be made; alternatively, mixtures of different nucleic acid analogs, and mixtures of naturally occurring nucleic acids and analogs may be made. In embodiments, the internucleotide linkages in DNA are phosphodiester, phosphodiester derivatives, or a combination of both.

[0102] A "labeled nucleic acid or oligonucleotide" is one that is bound, either covalently, through a linker or a chemical bond, or noncovalently, through ionic, van der Waals, electrostatic, or hydrogen bonds to a label such that the presence of the nucleic acid may be detected by detecting the presence of the detectable label bound to the nucleic acid. Alternatively, a method using high affinity interactions may achieve the same results where one of a pair of binding partners binds to the other, *e.g.*, biotin, streptavidin. In embodiments, the phosphorothioate nucleic acid or phosphorothioate polymer includes a detectable label, as disclosed herein and generally known in the art.

[0103] The word "expression" or "expressed" as used herein in reference to a gene means the transcriptional and/or translational product of that gene. The level of expression of a DNA molecule in a cell may be determined on the basis of either the amount of corresponding mRNA that is present within the cell or the amount of protein encoded by that DNA produced by the cell. The level of expression of non-coding nucleic acid molecules (*e.g.*, siRNA) may be

detected by standard PCR or Northern blot methods well known in the art. *See, Sambrook et al., 1989 Molecular Cloning: A Laboratory Manual, 18.1-18.88.*

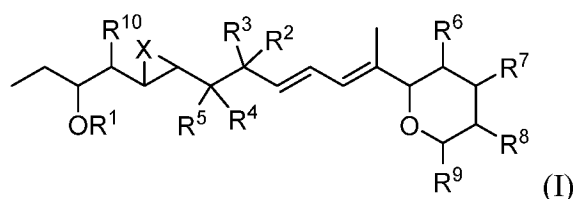
[0104] The term "recombinant" when used with reference, *e.g.*, to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all. Transgenic cells and plants are those that express a heterologous gene or coding sequence, typically as a result of recombinant methods.

[0105] The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C₁-C₂₀ alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C₁-C₂₀ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0106] Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

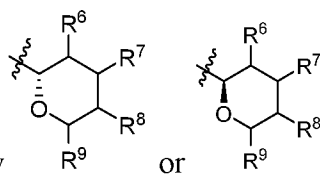
[0107] II. Compounds

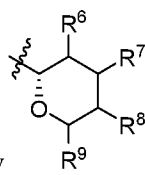
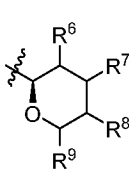
[0108] In one aspect, provided is a compound with structure of Formula (I):

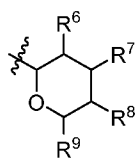


X is $-O-$ or $-C(R^{26})(R^{27})-$. R^{26} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, $-OR^{28}$, $-OC(O)R^{28}$, $-OC(O)OR^{28}$, or $-OC(O)NR^{28}R^{29}$. R^{27} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, $-OR^{30}$, $-OC(O)R^{30}$, $-OC(O)OR^{30}$, or $-OC(O)NR^{30}R^{31}$. R^1 is hydrogen, substituted or unsubstituted alkyl, $-C(O)R^{11}$, or $-C(O)OR^{11}$. R^2 is hydrogen, halogen, substituted or unsubstituted alkyl, $-OR^{12}$, $-OC(O)R^{12}$, $-OC(O)OR^{12}$, or $-OC(O)NR^{12}R^{13}$. R^3 is hydrogen, halogen, substituted or unsubstituted alkyl, $-OR^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{14}$, or $-OC(O)NR^{14}R^{15}$. R^4 is hydrogen, halogen, substituted or unsubstituted alkyl, $-OR^{16}$, $-OC(O)R^{16}$, $-OC(O)OR^{16}$, or $-OC(O)NR^{16}R^{17}$. R^5 is hydrogen, halogen, substituted or unsubstituted alkyl, $-OR^{18}$, $-OC(O)R^{18}$, $-OC(O)OR^{18}$, or $-OC(O)NR^{18}R^{19}$. R^6 is hydrogen, $-OR^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, or $-OC(O)OR^{20}$. R^7 is hydrogen, $-OR^{21}$, $-C(O)R^{21}$, $-C(O)OR^{21}$, $-OC(O)R^{21}$, or $-OC(O)OR^{21}$. R^8 is hydrogen, $-OR^{22}$, $-C(O)R^{22}$, $-C(O)OR^{22}$, $-OC(O)R^{22}$, or $-OC(O)OR^{22}$. R^9 is hydrogen, $-OR^{23}$, $-C(O)R^{23}$, $-C(O)OR^{23}$, $-OC(O)R^{23}$, or $-OC(O)OR^{23}$. R^{10} is hydrogen, substituted or unsubstituted alkyl, $-OR^{24}$, $-OC(O)R^{24}$, $-OC(O)OR^{24}$, or $-OC(O)NR^{24}R^{25}$. R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{28} , R^{29} , R^{30} , and R^{31} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

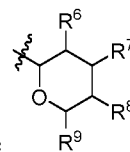
[0109] In embodiments, the 6-membered ring structure in the compound may be a monosaccharide or a derivative thereof. In embodiments, the monosaccharide has a structure,



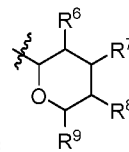
which is represented by  or . In embodiments, the compound is derived or synthesized from a monosaccharide having a 6-membered ring structure such as hexose sugar ($C_6H_{12}O_6$) including, but not limited thereto, allose, maltose, glucose, mannose, gulose, galactose, talose and iodose. In embodiments, the compound is derived or synthesized from a monosaccharide having a 6-membered ring structure such as a deoxy sugar lacking a hydroxyl group or oxygen at least one hydroxy position of the hexose sugar or the monosaccharide. Examples of the deoxy sugar include, but not limited to, deoxygalactose, deoxyglucose, deoxymannose, fucose, rhamnose and derivatives thereof. In embodiments, the compound is derived or synthesized from an acidic monosaccharide having a 6-membered ring structure, such as an acidic sugar containing at least one acidic group (e.g. carboxyl group) at least one hydroxy position of the hexose sugar or the monosaccharide. Examples of the acidic sugar include, but not limited to, uronic acid, glucuronic acid and derivatives thereof. In embodiments, the



moiety in the compound has (D) or (L) configuration, which may be originated from

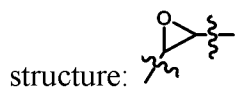


the monosaccharide used for modification or synthesis thereof. In embodiments, the



moiety in the compound has (D) configuration. In embodiments, the moiety in the compound has (L) configuration.

- 5 **[0110]** In embodiments, X is -O-. In embodiments, X together with the atoms attached thereto forms “oxirane-diyl” which refers, in the usual and customary sense, to a divalent moiety with



. In embodiments, X together with the atoms attached thereto forms



. In embodiments, X together with the atoms attached thereto forms

embodiment, X together with the atoms attached thereto forms

- 10 **[0111]** In embodiments, X is -C(R²⁶)(R²⁷)-. In embodiments, X is -C(R²⁶)(R²⁷)-, wherein R²⁶ and R²⁷ are independently hydrogen, or substituted or unsubstituted alkyl, wherein R²⁶ and R²⁷ are independently hydrogen, or substituted or unsubstituted C¹-C⁴ alkyl, wherein R²⁶ and R²⁷ are independently hydrogen or -CH₃, or R²⁶ and R²⁷ are hydrogen. In embodiments, X is -CH₂-.

[0112] In embodiments, X together with the atoms attached thereto forms substituted or

- 15 unsubstituted “cyclopropane”, to a divalent moiety with structure:

together with the atoms attached thereto forms , or

together with the atoms attached thereto forms

atoms attached thereto forms

[0113] In embodiments, R^1 is hydrogen, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), $-C(O)R^{11}$, or $-C(O)OR^{11}$. In embodiments, R^1 is hydrogen, substituted or unsubstituted C_1 - C_4 alkyl, $-OH$, $-OCH_3$, $-C(O)H$, $-C(O)CH_3$, $-C(O)OH$, or $-C(O)OCH_3$. In embodiments, R^1 is hydrogen, unsubstituted C_1 - C_4 alkyl, $-OH$, -

5 OCH_3 , $-C(O)H$, $-C(O)CH_3$, $-C(O)OH$, or $-C(O)OCH_3$. In embodiments, R^1 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-OH$, $-OCH_3$, $-C(O)H$, $-C(O)CH_3$, $-C(O)OH$, or $-C(O)OCH_3$. In embodiments, R^1 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-OH$, or $-OCH_3$. In embodiments, R^1 is hydrogen, $-CH_3$ or $-CH_2CH_3$. In embodiments, R^1 is hydrogen. In embodiments, R^1 is $-CH_3$. In embodiments, R^1 is $-CH_2CH_3$.

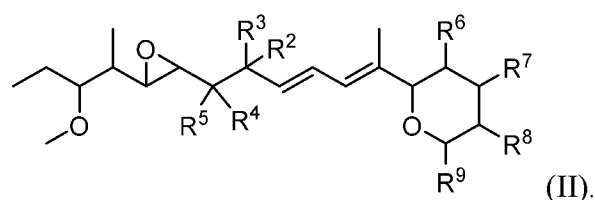
[0114] In embodiments, a chiral carbon where $-OR^1$ is attached has (S) stereochemistry. In
10 embodiments, a chiral carbon where $-OR^1$ is attached has (R) stereochemistry.

[0115] In embodiments, R^{10} is hydrogen, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), $-OR^{24}$, $-OC(O)R^{24}$, $-OC(O)OR^{24}$, or $-OC(O)NR^{24}R^{25}$. In embodiments, R^{10} is hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, OH , -

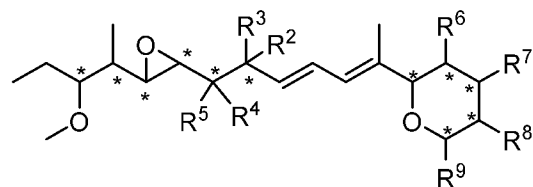
15 OCH_3 , $-OC(O)H$, $-OC(O)CH_3$, $-OC(O)OH$, $-OC(O)OCH_3$, $-OC(O)NH_2$, or $-OC(O)NHCH_3$. In embodiments, R^{10} is hydrogen, substituted or unsubstituted C_1 - C_4 alkyl, $-OH$, $-OCH_3$, $-OC(O)H$, $-OC(O)CH_3$, $-OC(O)OH$, or $-OC(O)OCH_3$. In embodiments, R^{10} is hydrogen, unsubstituted C_1 - C_4 alkyl, $-OH$, $-OCH_3$, $-OC(O)H$, or $-OC(O)CH_3$. In embodiments, R^{10} is hydrogen, $-CH_3$, $-CH_2CH_3$, $-OH$, or $-OCH_3$. In
20 embodiments, R^{10} is hydrogen, $-CH_3$, or $-CH_2CH_3$. In embodiments, R^{10} is hydrogen. In embodiments, R^{10} is $-CH_3$. In embodiments, R^{10} is $-CH_2CH_3$.

[0116] In embodiments, when R^{10} is not hydrogen, a chiral carbon where R^{10} is attached has (S) stereochemistry. In embodiments, when R^{10} is not hydrogen, a chiral carbon where R^{10} is attached has (R) stereochemistry.

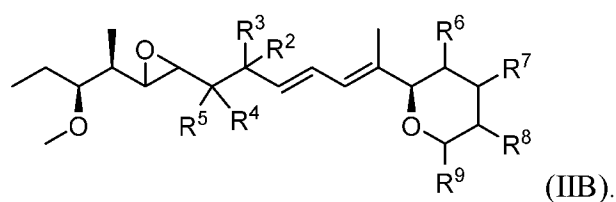
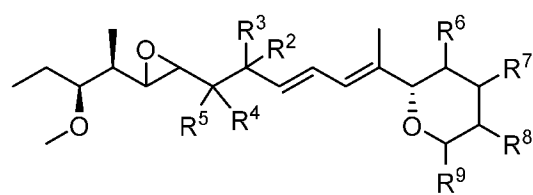
25 **[0117]** In embodiments, X is $-O-$; R^1 is hydrogen or unsubstituted C_1 - C_4 alkyl; and R^{10} is hydrogen or unsubstituted C_1 - C_4 alkyl. In embodiments, X is $-O-$; R^1 is hydrogen, $-CH_3$, or $-CH_2CH_3$; and R^{10} is hydrogen, $-CH_3$, or $-CH_2CH_3$. In embodiments, X is $-O-$; R^1 is hydrogen or $-CH_3$; and R^{10} is hydrogen or $-CH_3$. In embodiments, X is $-O-$; R^1 is hydrogen; and R^{10} is hydrogen. In embodiments, X is $-O-$; R^1 is hydrogen; and R^{10} is $-CH_3$. In embodiments, X is $-O-$; R^1 is $-CH_3$; and R^{10} is hydrogen. In embodiments, X is $-O-$; R^1 is $-CH_3$; and R^{10} is $-CH_3$. In
30 embodiments, the compound has a structure of Formula (II):



[0118] In embodiments, the compounds of Formula (II) may have chiral centers denoted by a "*" in the following structure, where stereochemical modification or variation can be made:

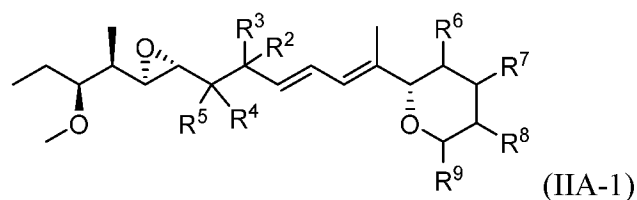


5 [0119] In embodiments, the compound has a structure of Formula (IIA) or Formula (IIB).

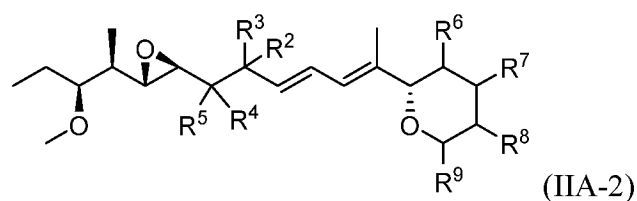


In embodiments, the compound has the structure of Formula (IIA). In embodiments, the compound has the structure of Formula (IIB).

[0120] In embodiments, the compound has a structure of Formula (IIA-1) or Formula (IIA-2).

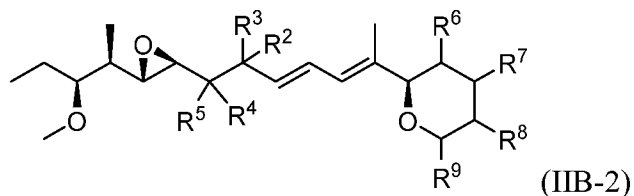
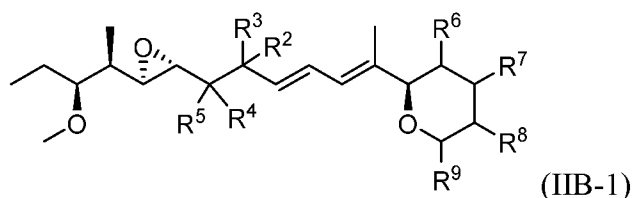


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In embodiments, the compound has a structure of Formula (IIA-1). In embodiments, the compound has a structure of Formula (IIA-2).

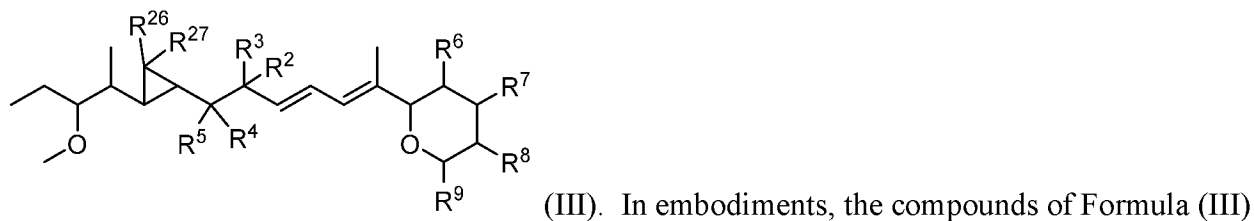
[0121] In embodiments, the compound has a structure of Formula (IIB-1) or Formula (IIB-2).



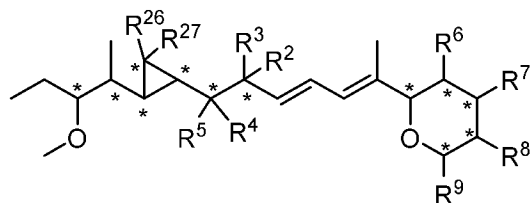
In embodiments, the compound has a structure of Formula (IIB-1). In embodiments, the compound has a structure of Formula (IIB-2).

- 5 **[0122]** In embodiments, X is $-\text{C}(\text{R}^{26})(\text{R}^{27})-$; R^1 is hydrogen or unsubstituted C_1 - C_4 alkyl; and R^{10} is hydrogen or unsubstituted C_1 - C_4 alkyl. In embodiments, X is $-\text{C}(\text{R}^{26})(\text{R}^{27})-$; R^1 is hydrogen, $-\text{CH}_3$, or $-\text{CH}_2\text{CH}_3$; and R^{10} is hydrogen, $-\text{CH}_3$, or $-\text{CH}_2\text{CH}_3$. In embodiments, X is $-\text{C}(\text{R}^{26})(\text{R}^{27})-$; R^1 is hydrogen or $-\text{CH}_3$; and R^{10} is hydrogen or $-\text{CH}_3$. In embodiments, X is $-\text{C}(\text{R}^{26})(\text{R}^{27})-$; R^1 is hydrogen; and R^{10} is hydrogen. In embodiments, X is $-\text{C}(\text{R}^{26})(\text{R}^{27})-$; R^1 is hydrogen; and R^{10} is $-\text{CH}_3$. In embodiments, X is $-\text{C}(\text{R}^{26})(\text{R}^{27})-$; R^1 is $-\text{CH}_3$; and R^{10} is hydrogen. In embodiments, X is $-\text{C}(\text{R}^{26})(\text{R}^{27})-$; R^1 is $-\text{CH}_3$; and R^{10} is $-\text{CH}_3$.
- 10

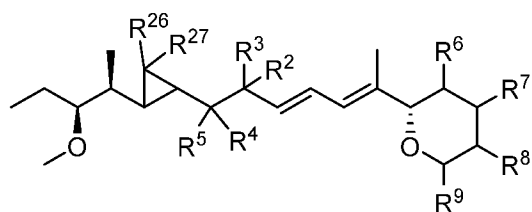
[0123] In embodiments, the compound has a structure of Formula (III),



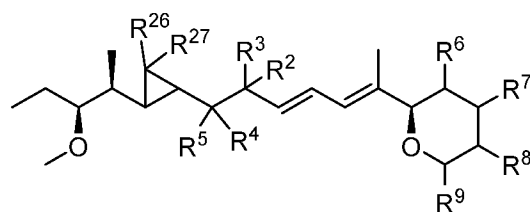
- may have chiral centers denoted by a "*" in the following structure, where stereochemical modification or variation can be made:
- 15



[0124] In embodiments, the compound has a structure of Formula (IIIA) or Formula (IIIB).



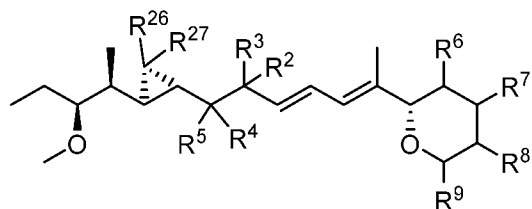
(IIIA)



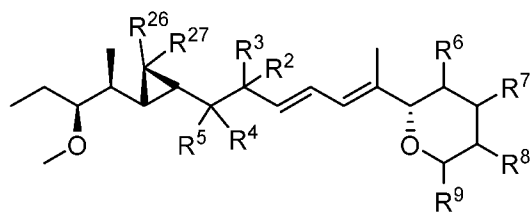
(IIIB).

In embodiments, the compound has the structure of Formula (IIIA). In embodiments, the compound has the structure of Formula (IIIB).

[0125] In embodiments, the compound has a structure of Formula (IIIA-1) or Formula (IIIA-2).



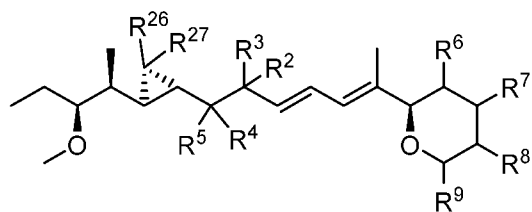
(IIIA-1)



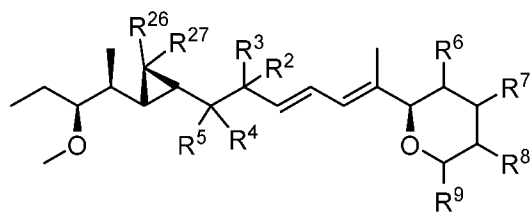
(IIIA-2)

In embodiments, the compound has a structure of Formula (IIIA-1). In embodiments, the compound has a structure of Formula (IIIA-2).

[0126] In embodiments, the compound has a structure of Formula (IIIB-1) or Formula (IIIB-2).



(IIIB-1)



(IIIB-2)

In embodiments, the compound has a structure of Formula (IIIB-1). In embodiments, the compound has a structure of Formula (IIIB-2).

[0127] In embodiments, R^{26} is hydrogen, halogen (e.g. -F, -Cl, or -Br), substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted aryl (e.g. phenyl), -OH, -OCH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂, or -OC(O)NHCH₃. In embodiments, R^{26} is

hydrogen, halogen (e.g. -F, -Cl, or -Br), substituted or unsubstituted C₁-C₄ alkyl, -OH, -OCH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂, or -OC(O)NHCH₃. In embodiments, R²⁶ is hydrogen, halogen (e.g. -F, -Cl, or -Br), substituted or unsubstituted C₁-C₄ alkyl, -OH, or -OCH₃. In embodiments, R²⁶ is hydrogen, halogen (e.g. -F, -Cl, or -Br), unsubstituted C₁-C₄ alkyl, -OH, or -OCH₃. In embodiments, R²⁶ is hydrogen, halogen (e.g. -F, -Cl, or -Br), -CH₃, -CH₂CH₃, -OH, or -OCH₃. In embodiments, R²⁶ is hydrogen. In embodiments, R²⁶ is -F, -Cl, or -Br. In embodiments, R²⁶ is -CH₃ or -CH₂CH₃. In embodiments, R²⁶ is -OH, or -OCH₃.

[0128] In embodiments, R²⁷ is hydrogen, halogen (e.g. -F, -Cl, or -Br), substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted aryl (e.g. phenyl), -OH, -OCH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂, or -OC(O)NHCH₃. In embodiments, R²⁷ is hydrogen, halogen (e.g. -F, -Cl, or -Br), substituted or unsubstituted C₁-C₄ alkyl, -OH, -OCH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂, or -OC(O)NHCH₃. In embodiments, R²⁷ is hydrogen, halogen (e.g. -F, -Cl, or -Br), substituted or unsubstituted C₁-C₄ alkyl, -OH, or -OCH₃. In embodiments, R²⁷ is hydrogen, halogen (e.g. -F, -Cl, or -Br), unsubstituted C₁-C₄ alkyl, -OH, or -OCH₃. In embodiments, R²⁷ is hydrogen, halogen (e.g. -F, -Cl, or -Br), -CH₃, -CH₂CH₃, -OH, or -OCH₃. In embodiments, R²⁷ is hydrogen. In embodiments, R²⁷ is -F, -Cl, or -Br. In embodiments, R²⁷ is -CH₃ or -CH₂CH₃. In embodiments, R²⁷ is -OH, or -OCH₃.

[0129] In embodiments, the chiral carbon where R²⁶ and R²⁷ are attached has (S) stereochemistry. In embodiments, the chiral carbon where R²⁶ and R²⁷ are attached has (R) stereochemistry.

[0130] In embodiments, one of R⁴ and R⁵ is hydrogen and the other one of R⁴ and R⁵ is not hydrogen. In embodiments, R⁴ is hydrogen and R⁵ is substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -OR¹⁸, -OC(O)R¹⁸, -OC(O)OR¹⁸, or -OC(O)NR¹⁸R¹⁹ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R⁴ is hydrogen and R⁵ is substituted or unsubstituted C₁-C₆ alkyl, or -OR¹⁸. In embodiments, R⁴ is hydrogen and R⁵ is substituted or unsubstituted C₁-C₄ alkyl, or -OH, -OCH₃, -OCH₂CH₃. In embodiments, R⁴ is hydrogen and R⁵ is -CH₃, -OH, -OCH₃, or -OCH₂CH₃. In embodiments, R⁴ is hydrogen and R⁵ is -CH₃ or -OH. In embodiments, R⁴ is hydrogen and R⁵ is -OH.

[0131] In embodiments, R⁵ is hydrogen and R⁴ is substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -OR¹⁶, -OC(O)R¹⁶, -OC(O)OR¹⁶, or -OC(O)NR¹⁶R¹⁷ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -

OC(O)NHCH₃). In embodiments, R⁵ is hydrogen and R⁴ is substituted or unsubstituted C₁-C₆ alkyl, or -OR¹⁶. In embodiments, R⁵ is hydrogen and R⁴ is substituted or unsubstituted C₁-C₄ alkyl, or -OH, -OCH₃, -OCH₂CH₃. In embodiments, R⁵ is hydrogen and R⁴ is -CH₃, -OH, -OCH₃, or -OCH₂CH₃. In embodiments, R⁵ is hydrogen and R⁴ is -CH₃ or -OH. In embodiments, R⁵ is hydrogen and R⁴ is -OH. In embodiments, R⁵ is hydrogen and R⁴ is -CH₃.

[0132] In embodiments, the chiral carbon where R⁴ and R⁵ are attached has (S) stereochemistry. In embodiments, the chiral carbon where R⁴ and R⁵ are attached has (R) stereochemistry.

[0133] In embodiments, one of R² and R³ is hydrogen and the other one of R² and R³ is not hydrogen. In embodiments, R² is hydrogen and R³ is substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -OR¹⁴, -OC(O)R¹⁴, -OC(O)OR¹⁴, or -OC(O)NR¹⁴R¹⁵ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R² is hydrogen and R³ is substituted or unsubstituted C₁-C₆ alkyl, or -OR¹⁴ (e.g. -OH, -OCH₃, or -OCH₂CH₃). In embodiments, R² is hydrogen and R³ is C₁-C₄ unsubstituted alkyl. In embodiments, R² is hydrogen and R³ is -CH₃ or -CH₂CH₃. In embodiments, R² is hydrogen and R³ is -CH₃.

[0134] In embodiments, R³ is hydrogen and R² is substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -OR¹², -OC(O)R¹², -OC(O)OR¹², or -OC(O)NR¹²R¹³ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R³ is hydrogen and R² is substituted or unsubstituted C₁-C₆ alkyl, or -OR¹² (e.g. -OH, -OCH₃, or -OCH₂CH₃). In embodiments, R³ is hydrogen and R² is C₁-C₄ unsubstituted alkyl. In embodiments, R³ is hydrogen and R² is -CH₃ or -CH₂CH₃. In embodiments, R³ is hydrogen and R² is -CH₃.

[0135] In embodiments, the chiral carbon where R² and R³ are attached has (S) stereochemistry. In embodiments, the chiral carbon where R² and R³ are attached has (R) stereochemistry.

[0136] In embodiments, R⁶ is hydrogen, -OR²⁰, -C(O)R²⁰, -C(O)OR²⁰, -OC(O)R²⁰, or -OC(O)OR²⁰. In embodiments, R⁶ is hydrogen, -OR²⁰, -C(O)R²⁰, or -C(O)OR²⁰. In embodiments, R⁶ is hydrogen, -OR²⁰, or -C(O)OR²⁰. In embodiments, R⁶ is hydrogen. In embodiments, R⁶ is -OR²⁰. In embodiments, R⁶ is -C(O)OR²⁰.

[0137] In embodiments, R²⁰ is independently hydrogen, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or

unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{20} is independently hydrogen, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, or substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{20} is independently hydrogen, substituted or unsubstituted C_1 - C_4 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^{20} is independently hydrogen, or substituted or unsubstituted C_1 - C_4 alkyl. In embodiments, R^{20} is substituted or unsubstituted C_1 - C_2 alkyl. In embodiments, R^{20} is unsubstituted C_1 - C_2 alkyl. In embodiments, R^{20} is $-CH_3$ or $-CH_2CH_3$. In embodiments, R^{20} is hydrogen.

10 **[0138]** In embodiments, R^6 is hydrogen, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)H$, $-C(O)CH_3$, $-C(O)OH$, $-C(O)OCH_3$, $-OC(O)H$, $-OC(O)CH_3$, $-OC(O)OH$, or $-OC(O)OCH_3$. In embodiments, R^6 is hydrogen, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)H$, $-C(O)CH_3$, $-C(O)OH$, $-C(O)OCH_3$, $-OC(O)H$, or $-OC(O)CH_3$. In embodiments, R^6 is hydrogen, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)H$, $-C(O)CH_3$, $-C(O)OH$, or $-C(O)OCH_3$. In embodiments, R^6 is hydrogen, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)H$, or $-C(O)CH_3$. In embodiments, R^6 is hydrogen, $-OH$, or $-OCH_3$. In embodiments, R^6 is hydrogen. In embodiments, R^6 is $-OH$. In embodiments, R^6 is $-OCH_3$. In embodiments, R^6 is $-C(O)H$. In embodiments, R^6 is $-C(O)CH_3$. In embodiments, R^6 is $-C(O)OH$. In embodiments, R^6 is $-C(O)OCH_3$.

20 **[0139]** In embodiments, the chiral carbon where R^6 is attached has (S) stereochemistry. In embodiments, the chiral carbon where R^6 is attached has (R) stereochemistry.

[0140] In embodiments, R^7 is hydrogen, $-OR^{21}$, $-C(O)R^{21}$, $-C(O)OR^{21}$, $-OC(O)R^{21}$, or $-OC(O)OR^{21}$. In embodiments, R^7 is hydrogen, $-OR^{21}$, $-C(O)R^{21}$, or $-C(O)OR^{21}$. In embodiments, R^7 is hydrogen, $-OR^{21}$, or $-C(O)OR^{21}$. In embodiments, R^7 is hydrogen. In embodiments, R^7 is $-OR^{21}$. In embodiments, R^7 is $-C(O)OR^{21}$.

[0141] In embodiments, R^{21} is independently hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{21} is independently hydrogen, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, or substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{21} is independently hydrogen, substituted or unsubstituted C_1 - C_4 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^{21} is independently hydrogen, or

substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R²¹ is substituted or unsubstituted C₁-C₂ alkyl. In embodiments, R²¹ is unsubstituted C₁-C₂ alkyl. In embodiments, R²¹ is -CH₃ or -CH₂CH₃. In embodiments, R²¹ is hydrogen.

[0142] In embodiments, R⁷ is hydrogen, -OH, -OCH₃, -OCH₂CH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, or -OC(O)OCH₃. In embodiments, R⁷ is hydrogen, -OH, -OCH₃, -OCH₂CH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -OC(O)H, or -OC(O)CH₃. In embodiments, R⁷ is hydrogen, -OH, -OCH₃, -OCH₂CH₃, -C(O)H, -C(O)CH₃, -C(O)OH, or -C(O)OCH₃. In embodiments, R⁷ is hydrogen, -OH, -OCH₃, -OCH₂CH₃, -C(O)H, or -C(O)CH₃. In embodiments, R⁷ is hydrogen, -OH, or -OCH₃. In embodiments, R⁷ is hydrogen. In embodiments, R⁷ is -OH. In embodiments, R⁷ is -OCH₃. In embodiments, R⁷ is -C(O)H. In embodiments, R⁷ is -C(O)CH₃. In embodiments, R⁷ is -C(O)OH. In embodiments, R⁷ is -C(O)OCH₃.

[0143] In embodiments, the chiral carbon where R⁷ is attached has (S) stereochemistry. In embodiments, the chiral carbon where R⁷ is attached has (R) stereochemistry.

[0144] In embodiments, R⁸ is hydrogen, -OR²², -C(O)R²², -C(O)OR²², -OC(O)R²², or -OC(O)OR²². In embodiments, R⁸ is hydrogen, -OR²², -C(O)R²², or -C(O)OR²². In embodiments, R⁸ is hydrogen, -OR²², or -C(O)OR²². In embodiments, R⁸ is hydrogen. In embodiments, R⁸ is -OR²². In embodiments, R⁸ is -C(O)OR²².

[0145] In embodiments, R²² is independently hydrogen, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R²² is independently hydrogen, substituted or unsubstituted C₁-C₄ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, or substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R²² is independently hydrogen, substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R²² is independently hydrogen, substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R²² is substituted or unsubstituted C₁-C₂ alkyl. In embodiments, R²² is unsubstituted C₁-C₂ alkyl. In embodiments, R²² is -CH₃ or -CH₂CH₃. In embodiments, R²² is hydrogen.

[0146] In embodiments, R⁸ is hydrogen, -OH, -OCH₃, -OCH₂CH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, or -OC(O)OCH₃. In embodiments, R⁸ is hydrogen, -OH, -OCH₃, -

OCH₂CH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -OC(O)H, or -OC(O)CH₃. In
embodiments, R⁸ is hydrogen, -OH, -OCH₃, -OCH₂CH₃, -C(O)H, -C(O)CH₃, -C(O)OH,
or -C(O)OCH₃. In embodiments, R⁸ is hydrogen, -OH, -OCH₃, -OCH₂CH₃, -C(O)H,
or -C(O)CH₃. In embodiments, R⁸ is hydrogen, -OH, or -OCH₃. In embodiments, R⁸ is
5 hydrogen. In embodiments, R⁸ is -OH. In embodiments, R⁸ is -OCH₃. In embodiments, R⁸
is -C(O)H. In embodiments, R⁸ is -C(O)CH₃. In embodiments, R⁸ is -C(O)OH. In
embodiments, R⁸ is -C(O)OCH₃.

[0147] In embodiments, the chiral carbon where R⁸ is attached has (S) stereochemistry. In
embodiments, the chiral carbon where R⁸ is attached has (R) stereochemistry.

10 [0148] In embodiments, R⁹ is hydrogen, -OR²³, -C(O)R²³, -C(O)OR²³, -OC(O)R²³,
or -OC(O)OR²³. In embodiments, R⁹ is hydrogen, -OR²³, -C(O)R²³, or -C(O)OR²³. In
embodiments, R⁹ is hydrogen, -OR²³, or -C(O)OR²³. In embodiments, R⁹ is hydrogen. In
embodiments, R⁹ is -OR²³. In embodiments, R⁹ is -C(O)OR²³.

[0149] In embodiments, R²³ is independently hydrogen, substituted or unsubstituted C₁-C₆
15 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-
C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or
unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In
embodiments, R²³ is independently hydrogen, substituted or unsubstituted C₁-C₄ alkyl,
substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆
20 cycloalkyl, or substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments,
R²³ is independently hydrogen, substituted or unsubstituted C₁-C₄ alkyl, or substituted or
unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R²³ is independently hydrogen, or
substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R²³ is substituted or unsubstituted C₁-
C₂ alkyl. In embodiments, R²³ is unsubstituted C₁-C₂ alkyl. In embodiments, R²³ is -CH₃ or -
25 CH₂CH₃. In embodiments, R²³ is hydrogen.

[0150] In embodiments, R⁹ is hydrogen, -OH, -OCH₃, -
OCH₂CH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH,
or -OC(O)OCH₃. In embodiments, R⁹ is hydrogen, -OH, -OCH₃, -
OCH₂CH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -OC(O)H, or -OC(O)CH₃. In
30 embodiments, R⁹ is hydrogen, -OH, -OCH₃, -OCH₂CH₃, -C(O)H, -C(O)CH₃, -C(O)OH,
or -C(O)OCH₃. In embodiments, R⁹ is hydrogen, -OH, -OCH₃, -OCH₂CH₃, -C(O)H,
or -C(O)CH₃. In embodiments, R⁹ is hydrogen, -OH, or -OCH₃. In embodiments, R⁹ is
hydrogen. In embodiments, R⁹ is -OH. In embodiments, R⁹ is -OCH₃. In embodiments, R⁹

is -C(O)H. In embodiments, R⁹ is -C(O)CH₃. In embodiments, R⁹ is -C(O)OH. In embodiments, R⁹ is -C(O)OCH₃.

[0151] In embodiments, the chiral carbon where R⁹ is attached has (S) stereochemistry. In embodiments, the chiral carbon where R⁹ is attached has (R) stereochemistry.

5 [0152] In embodiments, R²⁰, R²¹, R²², and R²³ are each independently hydrogen, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R²⁰, R²¹, R²², and R²³ are each independently hydrogen, or substituted or
10 unsubstituted C₁-C₆ alkyl. In embodiments, R²⁰, R²¹, R²², and R²³ are each independently hydrogen or substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R²⁰, R²¹, R²², and R²³ are each independently hydrogen or unsubstituted C₁-C₄ alkyl. In embodiments, R²⁰, R²¹, R²², and R²³ are each independently hydrogen or unsubstituted C₁-C₂ alkyl. In embodiments, R²⁰, R²¹, R²², and R²³ are each independently hydrogen, -CH₃ or -CH₂CH₃. In embodiments, R²⁰, R²¹, R²², and R²³ are each independently hydrogen, or -CH₃. In embodiments, R²⁰, R²¹, R²², and R²³ are hydrogen. In embodiments, R²⁰, R²¹, R²², and R²³ are -CH₃.

[0153] In embodiments, at least one of R⁶, R⁷, R⁸, and R⁹ is -OCH₃. In embodiments, R⁶, R⁷ and R⁸ are hydrogen and R⁹ is -OCH₃. In embodiments, R⁶, R⁷ and R⁹ are hydrogen and R⁸ is -OCH₃. In embodiments, R⁶, R⁸ and R⁹ are hydrogen and R⁷ is -OCH₃. In embodiments, R⁷, R⁸ and R⁹ are hydrogen and R⁶ is -OCH₃. In embodiments, at least one of R⁶, R⁷, R⁸, and R⁹ is hydrogen. In embodiments, R⁶, R⁷ and R⁸ are -OCH₃ and R⁹ is hydrogen. In embodiments, R⁶, R⁷ and R⁹ are -OCH₃ and R⁸ is hydrogen. In embodiments, R⁶, R⁸ and R⁹ are -OCH₃ and R⁷ is hydrogen. In embodiments, R⁷, R⁸ and R⁹ are -OCH₃ and R⁶ is hydrogen. In embodiments, at least two of R⁶, R⁷, R⁸, and R⁹ are hydrogen. In embodiments, R⁶ and R⁷ are -OCH₃ and R⁸ and R⁹ are hydrogen. In embodiments, R⁶ and R⁸ are -OCH₃ and R⁷ and R⁹ are hydrogen. In
25 embodiments, R⁶ and R⁹ are -OCH₃ and R⁷ and R⁸ are hydrogen. In embodiments, R⁷ and R⁸ are -OCH₃ and R⁶ and R⁹ are hydrogen. In embodiments, R⁸ and R⁹ are -OCH₃ and R⁶ and R⁷ are hydrogen. In embodiments, R⁶, R⁷, R⁸ and R⁹ are -OCH₃. In embodiments, R⁶, R⁷, R⁸ and R⁹ are hydrogen. In embodiments, at least one of R⁶, R⁷, R⁸ and R⁹ is -OH. In embodiments, at least two
30 of R⁶, R⁷, R⁸ and R⁹ are -OH. In embodiments, at least one of R⁶, R⁷, R⁸ and R⁹ is hydrogen. In embodiments, at least two of R⁶, R⁷, R⁸ and R⁹ are hydrogen.

[0154] In embodiments, R¹ is hydrogen, R^{1A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -C(O)R¹¹, or -C(O)OR¹¹, (e.g. -C(O)H, -C(O)CH₃, -C(O)OH, or -C(O)OCH₃). In embodiments, R¹ is hydrogen, R^{1A}-substituted or unsubstituted C₁-C₆

alkyl, $-C(O)R^{11}$, or $-C(O)OR^{11}$ (e.g. $-C(O)H$, $-C(O)CH_3$, $-C(O)OH$, or $-C(O)OCH_3$). In embodiments, R^1 is hydrogen, R^{1A} -substituted or unsubstituted C_1 - C_4 alkyl, $-C(O)H$, $-C(O)CH_3$, $-C(O)OH$, or $-C(O)OCH_3$. In embodiments, R^1 is hydrogen, unsubstituted C_1 - C_4 alkyl, $-C(O)H$, $-C(O)CH_3$, $-C(O)OH$, or $-C(O)OCH_3$.

- 5 **[0155]** R^{1A} is independently oxo, halogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, $-OCX^{1A}_3$, $-OCH_2X^{1A}$, $-OCHX^{1A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, R^{1B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{1B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{1B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{1B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{1B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{1B} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{1A} is
- 10 independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{1A} is independently oxo, halogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, $-OCX^{1A}_3$, $-OCH_2X^{1A}$, $-OCHX^{1A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-CI_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{1B} -substituted or unsubstituted C_1 - C_6 alkyl, R^{1B} -substituted or unsubstituted 2 to 6 membered
- 25 heteroalkyl, R^{1B} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{1B} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{1B} -substituted or unsubstituted phenyl, or R^{1B} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-CI_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$,
- 30

–ONH₂, –NHC(O)NHNH₂, –NHC(O)NH₂, –NH₂SO₂H, –NHC(O)H, –NHC(O)OH, –NHOH, –OCF₃, –OCCl₃, –OCBr₃, –OCl₃, –OCHF₂, –OCHCl₂, –OCHBr₂, –OCHI₂, –OCH₂F, –OCH₂Cl, –OCH₂Br, –OCH₂I, unsubstituted C₁–C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃–C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0156] In embodiments, R² is hydrogen, halogen (e.g. –F, –Cl, –Br, or –I), R^{2A}-substituted or unsubstituted alkyl (e.g., C₁–C₈, C₁–C₆, C₁–C₄, or C₁–C₂), –OR¹², –OC(O)R¹², –OC(O)OR¹², or –OC(O)NR¹²R¹³ (e.g. –OH, –OCH₃, –OCH₂CH₃, –OC(O)H, –OC(O)CH₃, –OC(O)OH, –OC(O)OCH₃, –OC(O)NH₂ or –OC(O)NHCH₃). In embodiments, R² is hydrogen, halogen (e.g. –F, –Cl, –Br, or –I), unsubstituted alkyl (e.g., C₁–C₈, C₁–C₆, C₁–C₄, or C₁–C₂), –OR¹², –OC(O)R¹², –OC(O)OR¹², or –OC(O)NR¹²R¹³ (e.g. –OH, –OCH₃, –OCH₂CH₃, –OC(O)H, –OC(O)CH₃, –OC(O)OH, –OC(O)OCH₃, –OC(O)NH₂ or –OC(O)NHCH₃). In embodiments, R² is hydrogen, halogen, R^{2A}-substituted or unsubstituted C₁–C₆ alkyl, –OR¹², –OC(O)R¹², –OC(O)OR¹², or –OC(O)NR¹²R¹³ (e.g. –OH, –OCH₃, –OCH₂CH₃, –OC(O)H, –OC(O)CH₃, –OC(O)OH, –OC(O)OCH₃, –OC(O)NH₂ or –OC(O)NHCH₃). In embodiments, R² is hydrogen, halogen (e.g. –F, –Cl, –Br, or –I), R^{2A}-substituted or unsubstituted C₁–C₄ alkyl, –OH, –OCH₃, –OCH₂CH₃, –OC(O)H, –OC(O)CH₃, –OC(O)OH, –OC(O)OCH₃, –OC(O)NH₂ or –OC(O)NHCH₃. In embodiments, R² is hydrogen, halogen (e.g. –F, –Cl, –Br, or –I), unsubstituted C₁–C₄ alkyl, –OH, –OCH₃, –OCH₂CH₃, –OC(O)H, –OC(O)CH₃, –OC(O)OH, –OC(O)OCH₃, –OC(O)NH₂ or –OC(O)NHCH₃.

[0157] R^{2A} is independently oxo, halogen, –CX^{2A}₃, –CHX^{2A}₂, –CH₂X^{2A}, –OCX^{2A}₃, –OCH₂X^{2A}, –OCHX^{2A}₂, –CN, –OH, –NH₂, –COOH, –CONH₂, –NO₂, –SH, –SO₃H, –SO₄H, –SO₂NH₂, –NHNH₂, –ONH₂, –NHC(O)NHNH₂, –NHC(O)NH₂, –NH₂SO₂H, –NHC(O)H, –NHC(O)–OH, –NHOH, R^{2B}-substituted or unsubstituted alkyl (e.g., C₁–C₈, C₁–C₆, C₁–C₄, or C₁–C₂), R^{2B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{2B}-substituted or unsubstituted cycloalkyl (e.g., C₃–C₈, C₃–C₆, C₄–C₆, or C₅–C₆), R^{2B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{2B}-substituted or unsubstituted aryl (e.g., C₆–C₁₂, C₆–C₁₀, or phenyl), or R^{2B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{2A} is independently –F, –Cl, –Br, or –I. In embodiments, R^{2A} is independently oxo, halogen, –CX^{2A}₃, –CHX^{2A}₂, –CH₂X^{2A}, –OCX^{2A}₃, –OCH₂X^{2A}, –OCHX^{2A}₂, –CN, –OH, –NH₂, –COOH, –CONH₂, –NO₂, –SH, –SO₃H, –SO₄H, –SO₂NH₂, –NHNH₂, –ONH₂, –NHC(O)NHNH₂, –NHC(O)NH₂, –NH₂SO₂H, –NHC(O)H, –NHC(O)–OH, –NHOH, unsubstituted alkyl (e.g., C₁–C₈, C₁–C₆, C₁–C₄,

or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{2A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{2B}-substituted or unsubstituted C₁-C₆ alkyl, R^{2B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{2B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{2B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2B}-substituted or unsubstituted phenyl, or R^{2B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{2A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0158] In embodiments, R³ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{3A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -OR¹⁴, -OC(O)R¹⁴, -OC(O)OR¹⁴, or -OC(O)NR¹⁴R¹⁵ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R³ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -OR¹⁴, -OC(O)R¹⁴, -OC(O)OR¹⁴, or -OC(O)NR¹⁴R¹⁵ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R³ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{3A}-substituted or unsubstituted C₁-C₆ alkyl, -OR¹⁴, -OC(O)R¹⁴, -OC(O)OR¹⁴, or -OC(O)NR¹⁴R¹⁵ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R³ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{3A}-substituted or unsubstituted C₁-C₄ alkyl, -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃. In embodiments, R³ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), unsubstituted

C₁-C₄ alkyl, -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃.

[0159] R^{3A} is independently oxo, halogen, -CX^{3A}₃, -CHX^{3A}₂, -CH₂X^{3A}, -OCX^{3A}₃, -OCH₂X^{3A}, -OCHX^{3A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂,
 5 -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, R^{3B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{3B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{3B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{3B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{3B}-substituted or
 10 unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{3B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{3A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{3A} is independently oxo, halogen, -CX^{3A}₃, -CHX^{3A}₂, -CH₂X^{3A}, -OCX^{3A}₃, -OCH₂X^{3A}, -OCHX^{3A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂,
 15 -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4
 20 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂,
 25 -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{3B}-substituted or unsubstituted C₁-C₆ alkyl, R^{3B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{3B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{3B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{3B}-substituted or unsubstituted phenyl, or R^{3B}-substituted or
 30 unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{3A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -

OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0160] In embodiments, R⁴ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{4A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -OR¹⁶, -OC(O)R¹⁶, -OC(O)OR¹⁶, or -OC(O)NR¹⁶R¹⁷ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R⁴ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -OR¹⁶, -OC(O)R¹⁶, -OC(O)OR¹⁶, or -OC(O)NR¹⁶R¹⁷ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R⁴ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{4A}-substituted or unsubstituted C₁-C₆ alkyl, -OR¹⁶, -OC(O)R¹⁶, -OC(O)OR¹⁶, or -OC(O)NR¹⁶R¹⁷ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R⁴ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{4A}-substituted or unsubstituted C₁-C₄ alkyl, -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃. In embodiments, R⁴ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), unsubstituted C₁-C₄ alkyl, -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃.

[0161] R^{4A} is independently oxo, halogen, -CX^{4A}₃, -CHX^{4A}₂, -CH₂X^{4A}, -OCX^{4A}₃, -OCH₂X^{4A}, -OCHX^{4A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, R^{4B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{4B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{4B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{4B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{4B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{4B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{4A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{4A} is independently oxo, halogen, -CX^{4A}₃, -CHX^{4A}₂, -CH₂X^{4A}, -OCX^{4A}₃, -OCH₂X^{4A}, -OCHX^{4A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),

unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCL₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{4B}-substituted or unsubstituted C₁-C₆ alkyl, R^{4B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{4B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{4B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{4B}-substituted or unsubstituted phenyl, or R^{4B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{4A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCL₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0162] In embodiments, R⁵ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{5A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -OR¹⁸, -OC(O)R¹⁸, -OC(O)OR¹⁸, or -OC(O)NR¹⁸R¹⁹ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R⁵ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -OR¹⁸, -OC(O)R¹⁸, -OC(O)OR¹⁸, or -OC(O)NR¹⁸R¹⁹ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R⁵ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{5A}-substituted or unsubstituted C₁-C₆ alkyl, -OR¹⁸, -OC(O)R¹⁸, -OC(O)OR¹⁸, or -OC(O)NR¹⁸R¹⁹ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R⁵ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{5A}-substituted or unsubstituted C₁-C₄ alkyl, -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃. In embodiments, R⁵ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), unsubstituted C₁-C₄ alkyl, -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃. In embodiments, R⁵ is hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), unsubstituted C₁-C₄ alkyl, -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃.

[0163] R^{5A} is independently oxo, halogen, $-CX^{5A}_3$, $-CHX^{5A}_2$, $-CH_2X^{5A}$, $-OCX^{5A}_3$, $-OCH_2X^{5A}$, $-OCHX^{5A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, R^{5B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{5B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{5B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{5B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{5B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{5B} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{5A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{5A} is independently oxo, halogen, $-CX^{5A}_3$, $-CHX^{5A}_2$, $-CH_2X^{5A}$, $-OCX^{5A}_3$, $-OCH_2X^{5A}$, $-OCHX^{5A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{5A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{5B} -substituted or unsubstituted C_1 - C_6 alkyl, R^{5B} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{5B} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{5B} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{5B} -substituted or unsubstituted phenyl, or R^{5B} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{5A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl,

unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

- [0164]** In embodiments, R¹⁰ is independently hydrogen, R^{10A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), -OR²⁴, -OC(O)R²⁴, -OC(O)OR²⁴, or -OC(O)NR²⁴R²⁵ (e.g., -OH, -OCH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂, or -OC(O)NHCH₃). In embodiments, R¹⁰ is independently hydrogen, R^{10A}-substituted or unsubstituted C₁-C₆ alkyl, -OR²⁴, -OC(O)R²⁴, -OC(O)OR²⁴, or -OC(O)NR²⁴R²⁵ (e.g., -OH, -OCH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂, or -OC(O)NHCH₃). In embodiments, R¹⁰ is independently hydrogen, R^{10A}-substituted or unsubstituted C₁-C₄ alkyl, OH, -OCH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -OC(O)H, -OC(O)CH₃, -OC(O)NH₂, or -OC(O)NHCH₃. In embodiments, R¹⁰ is independently hydrogen, unsubstituted C₁-C₄ alkyl, -OH, -OCH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂, or -OC(O)NHCH₃.
- [0165]** R^{10A} is independently oxo, halogen, -CX^{10A}₃, -CHX^{10A}₂, -CH₂X^{10A}, -OCX^{10A}₃, -OCH₂X^{10A}, -OCHX^{10A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, R^{10B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{10B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{10B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{10B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{10B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{10B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{10A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{10A} is independently oxo, halogen, -CX^{10A}₃, -CHX^{10A}₂, -CH₂X^{10A}, -OCX^{10A}₃, -OCH₂X^{10A}, -OCHX^{10A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{10A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

- SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{10B}-substituted or unsubstituted C₁-C₆ alkyl, R^{10B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{10B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{10B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{10B}-substituted or unsubstituted phenyl, or R^{10B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{10A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.
- [0166]** In embodiments, R¹¹ is independently hydrogen, R^{11A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{11A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{11A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{11A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{11A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{11A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹¹ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹¹ is independently hydrogen, R^{11A}-substituted or unsubstituted C₁-C₆ alkyl, R^{11A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{11A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{11A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{11A}-substituted or unsubstituted phenyl, or R^{11A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹¹ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0167] R^{11A} is independently oxo, halogen, $-CX^{11A}_3$, $-CHX^{11A}_2$, $-CH_2X^{11A}$, $-OCX^{11A}_3$, $-OCH_2X^{11A}$, $-OCHX^{11A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, R^{11B} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{11B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{11B} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{11B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{11B} -substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or R^{11B} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{11A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{11A} is independently oxo, halogen, $-CX^{11A}_3$, $-CHX^{11A}_2$, $-CH_2X^{11A}$, $-OCX^{11A}_3$, $-OCH_2X^{11A}$, $-OCHX^{11A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{11A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{11B} -substituted or unsubstituted C_1-C_6 alkyl, R^{11B} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{11B} -substituted or unsubstituted C_3-C_6 cycloalkyl, R^{11B} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{11B} -substituted or unsubstituted phenyl, or R^{11B} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{11A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, unsubstituted C_1-C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl,

unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0168] In embodiments, R¹² is independently hydrogen, R^{12A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{12A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{12A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{12A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{12A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{12A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹² is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹² is independently hydrogen, R^{12A}-substituted or unsubstituted C₁-C₆ alkyl, R^{12A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{12A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{12A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{12A}-substituted or unsubstituted phenyl, or R^{12A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹² is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0169] R^{12A} is independently oxo, halogen, -CX^{12A}₃, -CHX^{12A}₂, -CH₂X^{12A}, -OCX^{12A}₃, -OCH₂X^{12A}, -OCHX^{12A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, R^{12B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{12B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{12B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{12B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{12B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{12B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{12A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{12A} is independently oxo, halogen, -CX^{12A}₃, -CHX^{12A}₂, -CH₂X^{12A}, -OCX^{12A}₃, -OCH₂X^{12A}, -OCHX^{12A}₂, -CN,

- OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),
- 5 unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{12A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -
- 10 CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{12B}-substituted or unsubstituted C₁-C₆ alkyl, R^{12B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{12B}-substituted or unsubstituted
- 15 C₃-C₆ cycloalkyl, R^{12B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{12B}-substituted or unsubstituted phenyl, or R^{12B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{12A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -
- 20 OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.
- 25 **[0170]** In embodiments, R¹³ is independently hydrogen, R^{13A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{13A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{13A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{13A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5
- 30 membered, or 5 to 6 membered), R^{13A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{13A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹³ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5
- 35 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted

heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹³ is independently hydrogen, R^{13A}-substituted or unsubstituted C₁-C₆ alkyl, R^{13A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{13A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{13A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{13A}-substituted or unsubstituted phenyl, or R^{13A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹³ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0171] R^{13A} is independently oxo, halogen, -CX^{13A}₃, -CHX^{13A}₂, -CH₂X^{13A}, -OCX^{13A}₃, -OCH₂X^{13A}, -OCHX^{13A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, R^{13B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{13B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{13B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{13B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{13B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{13B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{13A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{13A} is independently oxo, halogen, -CX^{13A}₃, -CHX^{13A}₂, -CH₂X^{13A}, -OCX^{13A}₃, -OCH₂X^{13A}, -OCHX^{13A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{13A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{13B}-substituted or unsubstituted C₁-C₆ alkyl,

R^{13B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{13B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{13B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{13B}-substituted or unsubstituted phenyl, or R^{13B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{13A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0172] In embodiments, R¹⁴ is independently hydrogen, R^{14A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{14A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{14A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{14A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{14A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{14A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁴ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁴ is independently hydrogen, R^{14A}-substituted or unsubstituted C₁-C₆ alkyl, R^{14A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{14A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{14A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{14A}-substituted or unsubstituted phenyl, or R^{14A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹⁴ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0173] R^{14A} is independently oxo, halogen, -CX^{14A}₃, -CHX^{14A}₂, -CH₂X^{14A}, -OCX^{14A}₃, -OCH₂X^{14A}, -OCHX^{14A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -

SO_2NH_2 , $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}=\text{(O)NHNH}_2$, $-\text{NHC}=\text{(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC}=\text{(O)H}$, $-\text{NHC(O)-OH}$, $-\text{NHOH}$, $\text{R}^{14\text{B}}$ -substituted or unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, $\text{C}_1\text{-C}_4$, or $\text{C}_1\text{-C}_2$), $\text{R}^{14\text{B}}$ -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), $\text{R}^{14\text{B}}$ -substituted or unsubstituted cycloalkyl (e.g., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, $\text{C}_4\text{-C}_6$, or $\text{C}_5\text{-C}_6$), $\text{R}^{14\text{B}}$ -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), $\text{R}^{14\text{B}}$ -substituted or unsubstituted aryl (e.g., $\text{C}_6\text{-C}_{12}$, $\text{C}_6\text{-C}_{10}$, or phenyl), or $\text{R}^{14\text{B}}$ -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $\text{X}^{14\text{A}}$ is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$. In embodiments, $\text{R}^{14\text{A}}$ is independently oxo, halogen, $-\text{CX}^{14\text{A}}_3$, $-\text{CHX}^{14\text{A}}_2$, $-\text{CH}_2\text{X}^{14\text{A}}$, $-\text{OCX}^{14\text{A}}_3$, $-\text{OCH}_2\text{X}^{14\text{A}}$, $-\text{OCHX}^{14\text{A}}_2$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}=\text{(O)NHNH}_2$, $-\text{NHC}=\text{(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC}=\text{(O)H}$, $-\text{NHC(O)-OH}$, $-\text{NHOH}$, unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, $\text{C}_1\text{-C}_4$, or $\text{C}_1\text{-C}_2$), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, $\text{C}_4\text{-C}_6$, or $\text{C}_5\text{-C}_6$), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., $\text{C}_6\text{-C}_{12}$, $\text{C}_6\text{-C}_{10}$, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $\text{R}^{14\text{A}}$ is independently oxo, halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC(O)NHNH}_2$, $-\text{NHC(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC(O)H}$, $-\text{NHC(O)OH}$, $-\text{NHOH}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCI}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $\text{R}^{14\text{B}}$ -substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, $\text{R}^{14\text{B}}$ -substituted or unsubstituted 2 to 6 membered heteroalkyl, $\text{R}^{14\text{B}}$ -substituted or unsubstituted $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{R}^{14\text{B}}$ -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, $\text{R}^{14\text{B}}$ -substituted or unsubstituted phenyl, or $\text{R}^{14\text{B}}$ -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, $\text{R}^{14\text{A}}$ is independently oxo, halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC(O)NHNH}_2$, $-\text{NHC(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC(O)H}$, $-\text{NHC(O)OH}$, $-\text{NHOH}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCI}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, unsubstituted $\text{C}_1\text{-C}_6$ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted $\text{C}_3\text{-C}_6$ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0174] In embodiments, R^{15} is independently hydrogen, R^{15A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{15A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{15A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{15A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{15A} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{15A} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{15} is independently hydrogen, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{15} is independently hydrogen, R^{15A} -substituted or unsubstituted C_1 - C_6 alkyl, R^{15A} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{15A} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{15A} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{15A} -substituted or unsubstituted phenyl, or R^{15A} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{15} is independently hydrogen, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3 - C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0175] R^{15A} is independently oxo, halogen, $-CX^{15A}_3$, $-CHX^{15A}_2$, $-CH_2X^{15A}$, $-OCX^{15A}_3$, $-OCH_2X^{15A}$, $-OCHX^{15A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, R^{15B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{15B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{15B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{15B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{15B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{15B} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{15A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{15A} is independently oxo, halogen, $-CX^{15A}_3$, $-CHX^{15A}_2$, $-CH_2X^{15A}$, $-OCX^{15A}_3$, $-OCH_2X^{15A}$, $-OCHX^{15A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$,

unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{15A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{15B}-substituted or unsubstituted C₁-C₆ alkyl, R^{15B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{15B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{15B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{15B}-substituted or unsubstituted phenyl, or R^{15B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{15A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0176] In embodiments, R¹⁶ is independently hydrogen, R^{16A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{16A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{16A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{16A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{16A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{16A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁶ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl

(e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{16} is independently hydrogen, R^{16A} -substituted or unsubstituted C_1 - C_6 alkyl, R^{16A} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{16A} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{16A} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{16A} -substituted or unsubstituted phenyl, or R^{16A} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{16} is independently hydrogen, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3 - C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0177] R^{16A} is independently oxo, halogen, $-CX^{16A}_3$, $-CHX^{16A}_2$, $-CH_2X^{16A}$, $-OCX^{16A}_3$, $-OCH_2X^{16A}$, $-OCHX^{16A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, R^{16B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{16B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{16B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{16B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{16B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{16B} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{16A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{16A} is independently oxo, halogen, $-CX^{16A}_3$, $-CHX^{16A}_2$, $-CH_2X^{16A}$, $-OCX^{16A}_3$, $-OCH_2X^{16A}$, $-OCHX^{16A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{16A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{16B} -substituted or unsubstituted C_1 - C_6 alkyl, R^{16B} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{16B} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{16B} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{16B} -

substituted or unsubstituted phenyl, or R^{16B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{16A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

- 10 **[0178]** In embodiments, R¹⁷ is independently hydrogen, R^{17A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{17A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{17A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{17A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{17A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{17A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁷ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁷ is independently hydrogen, R^{17A}-substituted or unsubstituted C₁-C₆ alkyl, R^{17A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{17A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{17A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{17A}-substituted or unsubstituted phenyl, or R^{17A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹⁷ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0179] R^{17A} is independently oxo, halogen, -CX^{17A}₃, -CHX^{17A}₂, -CH₂X^{17A}, -OCX^{17A}₃, -OCH₂X^{17A}, -OCHX^{17A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NH₂SO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, R^{17B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-

C_2), R^{17B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{17B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{17B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{17B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{17B} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{17A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{17A} is independently oxo, halogen, $-CX^{17A}_3$, $-CHX^{17A}_2$, $-CH_2X^{17A}$, $-OCX^{17A}_3$, $-OCH_2X^{17A}$, $-OCHX^{17A}_2$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{17A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{17B} -substituted or unsubstituted C_1 - C_6 alkyl, R^{17B} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{17B} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{17B} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{17B} -substituted or unsubstituted phenyl, or R^{17B} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{17A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3 - C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0180] In embodiments, R^{18} is independently hydrogen, R^{18A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{18A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{18A} -

substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{18A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{18A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{18A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁸ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁸ is independently hydrogen, R^{18A}-substituted or unsubstituted C₁-C₆ alkyl, R^{18A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{18A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{18A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{18A}-substituted or unsubstituted phenyl, or R^{18A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹⁸ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0181] R^{18A} is independently oxo, halogen, -CX^{18A}₃, -CHX^{18A}₂, -CH₂X^{18A}, -OCX^{18A}₃, -OCH₂X^{18A}, -OCHX^{18A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, R^{18B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{18B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{18B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{18B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{18B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{18B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{18A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{18A} is independently oxo, halogen, -CX^{18A}₃, -CHX^{18A}₂, -CH₂X^{18A}, -OCX^{18A}₃, -OCH₂X^{18A}, -OCHX^{18A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl

- (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{18A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{18B}-substituted or unsubstituted C₁-C₆ alkyl, R^{18B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{18B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{18B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{18B}-substituted or unsubstituted phenyl, or R^{18B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{18A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.
- [0182]** In embodiments, R¹⁹ is independently hydrogen, R^{19A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{19A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{19A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{19A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{19A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{19A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁹ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁹ is independently hydrogen, R^{19A}-substituted or unsubstituted C₁-C₆ alkyl, R^{19A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{19A}-substituted or unsubstituted

C₃-C₆ cycloalkyl, R^{19A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{19A}-substituted or unsubstituted phenyl, or R^{19A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹⁹ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0183] R^{19A} is independently oxo, halogen, -CX^{19A}₃, -CHX^{19A}₂, -CH₂X^{19A}, -OCX^{19A}₃, -OCH₂X^{19A}, -OCHX^{19A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, R^{19B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{19B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{19B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{19B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{19B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{19B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{19A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{19A} is independently oxo, halogen, -CX^{19A}₃, -CHX^{19A}₂, -CH₂X^{19A}, -OCX^{19A}₃, -OCH₂X^{19A}, -OCHX^{19A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{19A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{19B}-substituted or unsubstituted C₁-C₆ alkyl, R^{19B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{19B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{19B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{19B}-substituted or unsubstituted phenyl, or R^{19B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{19A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -

CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂,
 -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -
 OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -
 OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl,
 5 unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted
 phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0184] In embodiments, R²⁰ is independently hydrogen, R^{20A}-substituted or unsubstituted alkyl
 (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{20A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{20A}-
 10 substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{20A}-substituted or
 unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5
 membered, or 5 to 6 membered), R^{20A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or
 phenyl), or R^{20A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10
 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²⁰ is independently
 15 hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl
 (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5
 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted
 heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or
 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl
 20 (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In
 embodiments, R²⁰ is independently hydrogen, R^{20A}-substituted or unsubstituted C₁-C₆ alkyl,
 R^{20A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{20A}-substituted or unsubstituted
 C₃-C₆ cycloalkyl, R^{20A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{20A}-
 substituted or unsubstituted phenyl, or R^{20A}-substituted or unsubstituted 5 to 6 membered
 25 heteroaryl. In embodiments, R²⁰ is independently hydrogen, unsubstituted C₁-C₆ alkyl,
 unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6
 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0185] R^{20A} is independently oxo, halogen, -CX^{20A}₃, -CHX^{20A}₂, -CH₂X^{20A}, -OCX^{20A}₃,
 -OCH₂X^{20A}, -OCHX^{20A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -
 30 SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -
 NHC(O)-OH, -NHOH, R^{20B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-
 C₂), R^{20B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6
 membered, 2 to 3 membered, or 4 to 5 membered), R^{20B}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{20B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to

- 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{20B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{20B} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{20A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{20A} is independently
- 5 oxo, halogen, $-CX^{20A}_3$, $-CHX^{20A}_2$, $-CH_2X^{20A}$, $-OCX^{20A}_3$, $-OCH_2X^{20A}$, $-OCHX^{20A}_2$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),
- 10 unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{20A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -
- 15 CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{20B} -substituted or unsubstituted C_1 - C_6 alkyl, R^{20B} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{20B} -substituted or unsubstituted
- 20 C_3 - C_6 cycloalkyl, R^{20B} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{20B} -substituted or unsubstituted phenyl, or R^{20B} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{20A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -
- 25 OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3 - C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.
- 30 **[0186]** In embodiments, R^{21} is independently hydrogen, R^{21A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{21A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{21A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{21A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5
- 35 membered, or 5 to 6 membered), R^{21A} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or

phenyl), or R^{21A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²¹ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²¹ is independently hydrogen, R^{21A}-substituted or unsubstituted C₁-C₆ alkyl, R^{21A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{21A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{21A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{21A}-substituted or unsubstituted phenyl, or R^{21A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R²¹ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0187] R^{21A} is independently oxo, halogen, -CX^{21A}₃, -CHX^{21A}₂, -CH₂X^{21A}, -OCX^{21A}₃, -OCH₂X^{21A}, -OCHX^{21A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, R^{21B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{21B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{21B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{21B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{21B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{21B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{21A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{21A} is independently oxo, halogen, -CX^{21A}₃, -CHX^{21A}₂, -CH₂X^{21A}, -OCX^{21A}₃, -OCH₂X^{21A}, -OCHX^{21A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments,

R^{21A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{21B} -substituted or unsubstituted C_1 - C_6 alkyl, R^{21B} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{21B} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{21B} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{21B} -substituted or unsubstituted phenyl, or R^{21B} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{21A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3 - C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0188] In embodiments, R^{22} is independently hydrogen, R^{22A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{22A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{22A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{22A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{22A} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{22A} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{22} is independently hydrogen, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{22} is independently hydrogen, R^{22A} -substituted or unsubstituted C_1 - C_6 alkyl, R^{22A} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{22A} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{22A} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{22A} -substituted or unsubstituted phenyl, or R^{22A} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{22} is independently hydrogen, unsubstituted C_1 - C_6 alkyl,

unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0189] R^{22A} is independently oxo, halogen, -CX^{22A}₃, -CHX^{22A}₂, -CH₂X^{22A}, -OCX^{22A}₃,

-OCH₂X^{22A}, -OCHX^{22A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -

5 SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, R^{22B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{22B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{22B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{22B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to

10 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{22B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{22B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{22A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{22A} is independently

oxo, halogen, -CX^{22A}₃, -CHX^{22A}₂, -CH₂X^{22A}, -OCX^{22A}₃, -OCH₂X^{22A}, -OCHX^{22A}₂, -CN,

15 -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl

20 (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments,

R^{22A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

25 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{22B}-substituted or unsubstituted C₁-C₆ alkyl, R^{22B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{22B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{22B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{22B}-

30 substituted or unsubstituted phenyl, or R^{22B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{22A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -

CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -

OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

- 5 **[0190]** In embodiments, R²³ is independently hydrogen, R^{23A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{23A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{23A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{23A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{23A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{23A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²³ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²³ is independently hydrogen, R^{23A}-substituted or unsubstituted C₁-C₆ alkyl, R^{23A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{23A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{23A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{23A}-substituted or unsubstituted phenyl, or R^{23A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R²³ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.
- 10 **[0191]** R^{23A} is independently oxo, halogen, -CX^{23A}₃, -CHX^{23A}₂, -CH₂X^{23A}, -OCX^{23A}₃, -OCH₂X^{23A}, -OCHX^{23A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, R^{23B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{23B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{23B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{23B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{23B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{23B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
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membered). X^{23A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{23A} is independently oxo, halogen, $-CX^{23A}_3$, $-CHX^{23A}_2$, $-CH_2X^{23A}$, $-OCX^{23A}_3$, $-OCH_2X^{23A}$, $-OCHX^{23A}_2$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NH₂SO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{23A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NH₂SO₂H, -NHC(=O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{23B} -substituted or unsubstituted C₁-C₆ alkyl, R^{23B} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{23B} -substituted or unsubstituted C₃-C₆ cycloalkyl, R^{23B} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{23B} -substituted or unsubstituted phenyl, or R^{23B} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{23A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NH₂SO₂H, -NHC(=O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0192] In embodiments, R^{24} is independently hydrogen, R^{24A} -substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{24A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{24A} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{24A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{24A} -substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{24A} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{24} is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl

(e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²⁴ is independently hydrogen, R^{24A}-substituted or unsubstituted C₁-C₆ alkyl, R^{24A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{24A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{24A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{24A}-substituted or unsubstituted phenyl, or R^{24A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R²⁴ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0193] R^{24A} is independently oxo, halogen, -CX^{24A}₃, -CHX^{24A}₂, -CH₂X^{24A}, -OCX^{24A}₃, -OCH₂X^{24A}, -OCHX^{24A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, R^{24B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{24B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{24B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{24B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{24B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{24B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{24A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{24A} is independently oxo, halogen, -CX^{24A}₃, -CHX^{24A}₂, -CH₂X^{24A}, -OCX^{24A}₃, -OCH₂X^{24A}, -OCHX^{24A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{24A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -

NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{24B}-substituted or unsubstituted C₁-C₆ alkyl, R^{24B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{24B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{24B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{24B}-substituted or unsubstituted phenyl, or R^{24B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{24A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0194] In embodiments, R²⁵ is independently hydrogen, R^{25A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{25A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{25A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{25A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{25A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{25A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²⁵ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²⁵ is independently hydrogen, R^{25A}-substituted or unsubstituted C₁-C₆ alkyl, R^{25A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{25A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{25A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{25A}-substituted or unsubstituted phenyl, or R^{25A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R²⁵ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0195] R^{25A} is independently oxo, halogen, $-CX^{25A}_3$, $-CHX^{25A}_2$, $-CH_2X^{25A}$, $-OCX^{25A}_3$, $-OCH_2X^{25A}$, $-OCHX^{25A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, R^{25B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{25B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{25B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{25B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{25B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{25B} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{25A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{25A} is independently oxo, halogen, $-CX^{25A}_3$, $-CHX^{25A}_2$, $-CH_2X^{25A}$, $-OCX^{25A}_3$, $-OCH_2X^{25A}$, $-OCHX^{25A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{25A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{25B} -substituted or unsubstituted C_1 - C_6 alkyl, R^{25B} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{25B} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{25B} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{25B} -substituted or unsubstituted phenyl, or R^{25B} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{25A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl,

unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0196] In embodiments, R²⁶ is independently hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{26A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{26A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), -OR²⁸, -OC(O)R²⁸, -OC(O)OR²⁸, or -OC(O)NR²⁸R²⁹ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R²⁶ is independently hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), -OR²⁸, -OC(O)R²⁸, -OC(O)OR²⁸, or -OC(O)NR²⁸R²⁹ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R²⁶ is independently hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{26A}-substituted or unsubstituted C₁-C₆ alkyl, R^{26A}-substituted or unsubstituted phenyl, -OR²⁸, -OC(O)R²⁸, -OC(O)OR²⁸, or -OC(O)NR²⁸R²⁹ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R²⁶ is independently hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), unsubstituted C₁-C₄ alkyl, unsubstituted phenyl, -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃.

[0197] R^{26A} is independently oxo, halogen, -CX^{26A}₃, -CHX^{26A}₂, -CH₂X^{26A}, -OCX^{26A}₃, -OCH₂X^{26A}, -OCHX^{26A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, R^{26B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{26B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{26B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{26B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{26B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{26B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{26A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{26A} is independently oxo, halogen, -CX^{26A}₃, -CHX^{26A}₂, -CH₂X^{26A}, -OCX^{26A}₃, -OCH₂X^{26A}, -OCHX^{26A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl

- (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{26A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{26B}-substituted or unsubstituted C₁-C₆ alkyl, R^{26B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{26B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{26B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{26B}-substituted or unsubstituted phenyl, or R^{26B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{26A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.
- [0198]** In embodiments, R²⁷ is independently hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{27A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{27A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), -OR³⁰, -OC(O)R³⁰, -OC(O)OR³⁰, or -OC(O)NR³⁰R³¹ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R²⁷ is independently hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), -OR³⁰, -OC(O)R³⁰, -OC(O)OR³⁰, or -OC(O)NR³⁰R³¹ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R²⁷ is independently hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), R^{27A}-substituted or unsubstituted C₁-C₆ alkyl, R^{27A}-substituted or unsubstituted phenyl, -OR³⁰, -OC(O)R³⁰, -OC(O)OR³⁰, or -OC(O)NR³⁰R³¹ (e.g. -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃). In embodiments, R²⁷ is independently hydrogen, halogen (e.g. -F, -Cl, -Br, or -I), unsubstituted C₁-C₄ alkyl, unsubstituted phenyl, -OH, -OCH₃, -OCH₂CH₃, -OC(O)H, -OC(O)CH₃, -OC(O)OH, -OC(O)OCH₃, -OC(O)NH₂ or -OC(O)NHCH₃.

[0199] R^{27A} is independently oxo, halogen, $-CX^{27A}_3$, $-CHX^{27A}_2$, $-CH_2X^{27A}$, $-OCX^{27A}_3$, $-OCH_2X^{27A}$, $-OCHX^{27A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, R^{27B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{27B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{27B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{27B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{27B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{27B} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{27A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{27A} is independently oxo, halogen, $-CX^{27A}_3$, $-CHX^{27A}_2$, $-CH_2X^{27A}$, $-OCX^{27A}_3$, $-OCH_2X^{27A}$, $-OCHX^{27A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{27A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{27B} -substituted or unsubstituted C_1 - C_6 alkyl, R^{27B} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{27B} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{27B} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{27B} -substituted or unsubstituted phenyl, or R^{27B} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{27A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl,

unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0200] In embodiments, R²⁸ is independently hydrogen, R^{28A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{28A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{28A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{28A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{28A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{28A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²⁸ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²⁸ is independently hydrogen, R^{28A}-substituted or unsubstituted C₁-C₆ alkyl, R^{28A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{28A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{28A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{28A}-substituted or unsubstituted phenyl, or R^{28A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R²⁸ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0201] R^{28A} is independently oxo, halogen, -CX^{28A}₃, -CHX^{28A}₂, -CH₂X^{28A}, -OCX^{28A}₃, -OCH₂X^{28A}, -OCHX^{28A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, R^{28B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{28B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{28B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{28B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{28B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{28B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{28A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{28A} is independently oxo, halogen, -CX^{28A}₃, -CHX^{28A}₂, -CH₂X^{28A}, -OCX^{28A}₃, -OCH₂X^{28A}, -OCHX^{28A}₂, -CN,

- OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),
- 5 unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{28A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -
- 10 CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{28B}-substituted or unsubstituted C₁-C₆ alkyl, R^{28B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{28B}-substituted or unsubstituted
- 15 C₃-C₆ cycloalkyl, R^{28B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{28B}-substituted or unsubstituted phenyl, or R^{28B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{28A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -
- 20 OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.
- 25 **[0202]** In embodiments, R²⁹ is independently hydrogen, R^{29A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{29A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{29A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{29A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5
- 30 membered, or 5 to 6 membered), R^{29A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{29A}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²⁹ is independently hydrogen, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5
- 35 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted

heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R²⁹ is independently hydrogen, R^{29A}-substituted or unsubstituted C₁-C₆ alkyl, R^{29A}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{29A}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{29A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{29A}-substituted or unsubstituted phenyl, or R^{29A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R²⁹ is independently hydrogen, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0203] R^{29A} is independently oxo, halogen, -CX^{29A}₃, -CHX^{29A}₂, -CH₂X^{29A}, -OCX^{29A}₃, -OCH₂X^{29A}, -OCHX^{29A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, R^{29B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{29B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{29B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{29B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{29B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{29B}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{29A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{29A} is independently oxo, halogen, -CX^{29A}₃, -CHX^{29A}₂, -CH₂X^{29A}, -OCX^{29A}₃, -OCH₂X^{29A}, -OCHX^{29A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{29A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{29B}-substituted or unsubstituted C₁-C₆ alkyl,

R^{29B} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{29B} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{29B} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{29B} -substituted or unsubstituted phenyl, or R^{29B} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{29A} is independently oxo, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-CI_3$, $-CHI_2$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3 - C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0204] In embodiments, R^{30} is independently hydrogen, R^{30A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{30A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{30A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{30A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{30A} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{30A} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{30} is independently hydrogen, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{30} is independently hydrogen, R^{30A} -substituted or unsubstituted C_1 - C_6 alkyl, R^{30A} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{30A} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{30A} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{30A} -substituted or unsubstituted phenyl, or R^{30A} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{30} is independently hydrogen, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3 - C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0205] R^{30A} is independently oxo, halogen, $-CX^{30A}_3$, $-CHX^{30A}_2$, $-CH_2X^{30A}$, $-OCX^{30A}_3$, $-OCH_2X^{30A}$, $-OCHX^{30A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, -

SO_2NH_2 , $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}=\text{(O)NHNH}_2$, $-\text{NHC}=\text{(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC}=\text{(O)H}$, $-\text{NHC(O)-OH}$, $-\text{NHOH}$, $\text{R}^{30\text{B}}$ -substituted or unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, $\text{C}_1\text{-C}_4$, or $\text{C}_1\text{-C}_2$), $\text{R}^{30\text{B}}$ -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), $\text{R}^{30\text{B}}$ -substituted or unsubstituted cycloalkyl (e.g., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, $\text{C}_4\text{-C}_6$, or $\text{C}_5\text{-C}_6$), $\text{R}^{30\text{B}}$ -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), $\text{R}^{30\text{B}}$ -substituted or unsubstituted aryl (e.g., $\text{C}_6\text{-C}_{12}$, $\text{C}_6\text{-C}_{10}$, or phenyl), or $\text{R}^{30\text{B}}$ -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $\text{X}^{30\text{A}}$ is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$. In embodiments, $\text{R}^{30\text{A}}$ is independently oxo, halogen, $-\text{CX}^{30\text{A}}_3$, $-\text{CHX}^{30\text{A}}_2$, $-\text{CH}_2\text{X}^{30\text{A}}$, $-\text{OCX}^{30\text{A}}_3$, $-\text{OCH}_2\text{X}^{30\text{A}}$, $-\text{OCHX}^{30\text{A}}_2$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}=\text{(O)NHNH}_2$, $-\text{NHC}=\text{(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC}=\text{(O)H}$, $-\text{NHC(O)-OH}$, $-\text{NHOH}$, unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, $\text{C}_1\text{-C}_4$, or $\text{C}_1\text{-C}_2$), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, $\text{C}_4\text{-C}_6$, or $\text{C}_5\text{-C}_6$), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., $\text{C}_6\text{-C}_{12}$, $\text{C}_6\text{-C}_{10}$, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $\text{R}^{30\text{A}}$ is independently oxo, halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC(O)NHNH}_2$, $-\text{NHC(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC(O)H}$, $-\text{NHC(O)OH}$, $-\text{NHOH}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $\text{R}^{30\text{B}}$ -substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, $\text{R}^{30\text{B}}$ -substituted or unsubstituted 2 to 6 membered heteroalkyl, $\text{R}^{30\text{B}}$ -substituted or unsubstituted $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{R}^{30\text{B}}$ -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, $\text{R}^{30\text{B}}$ -substituted or unsubstituted phenyl, or $\text{R}^{30\text{B}}$ -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, $\text{R}^{30\text{A}}$ is independently oxo, halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC(O)NHNH}_2$, $-\text{NHC(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC(O)H}$, $-\text{NHC(O)OH}$, $-\text{NHOH}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, unsubstituted $\text{C}_1\text{-C}_6$ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted $\text{C}_3\text{-C}_6$ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0206] In embodiments, R^{31} is independently hydrogen, R^{31A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{31A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{31A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{31A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{31A} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{31A} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{31} is independently hydrogen, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{31} is independently hydrogen, R^{31A} -substituted or unsubstituted C_1 - C_6 alkyl, R^{31A} -substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{31A} -substituted or unsubstituted C_3 - C_6 cycloalkyl, R^{31A} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{31A} -substituted or unsubstituted phenyl, or R^{31A} -substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{31} is independently hydrogen, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3 - C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

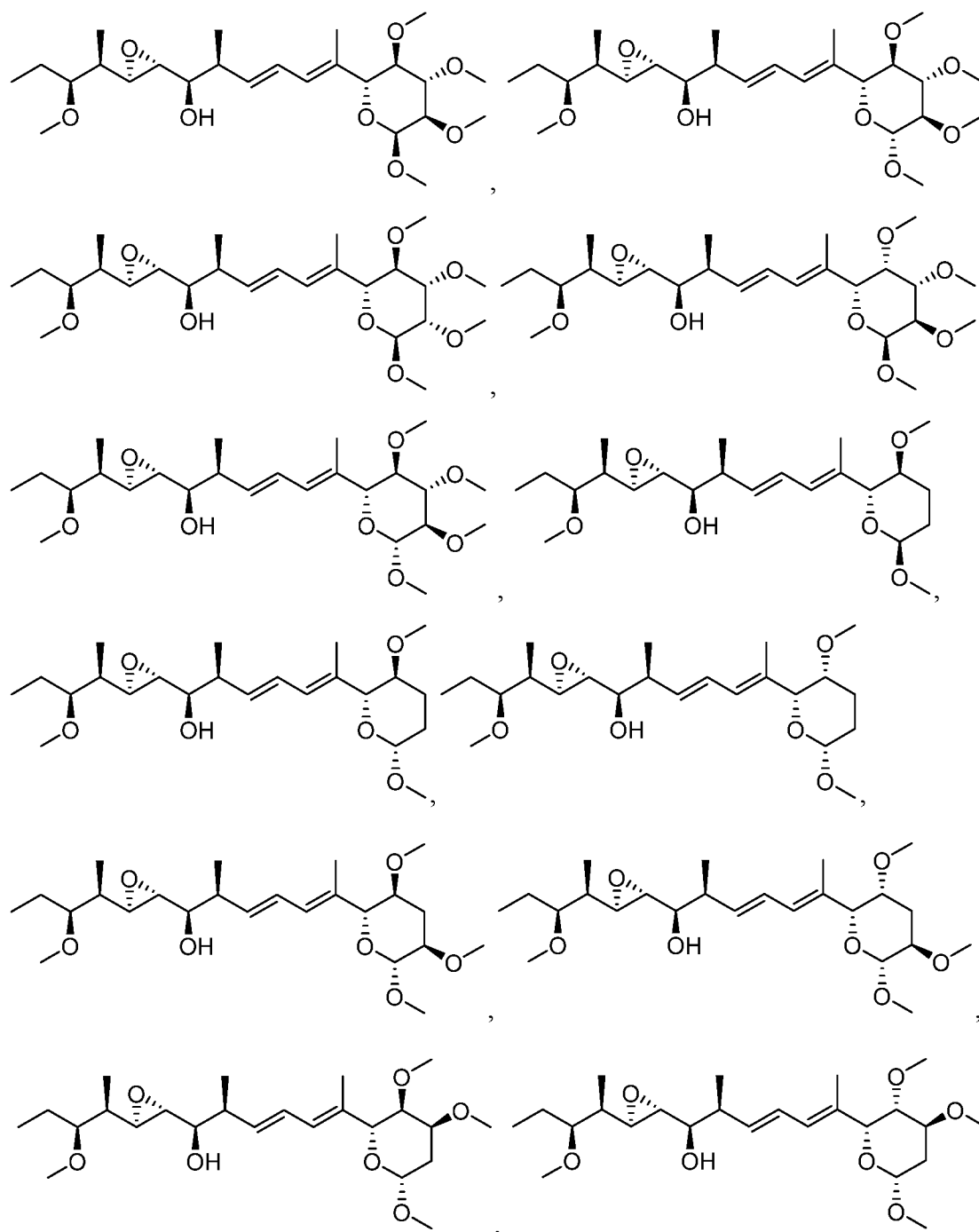
[0207] R^{31A} is independently oxo, halogen, $-CX^{31A}_3$, $-CHX^{31A}_2$, $-CH_2X^{31A}$, $-OCX^{31A}_3$, $-OCH_2X^{31A}$, $-OCHX^{31A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, R^{31B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{31B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{31B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{31B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{31B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{31B} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{31A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{31A} is independently oxo, halogen, $-CX^{31A}_3$, $-CHX^{31A}_2$, $-CH_2X^{31A}$, $-OCX^{31A}_3$, $-OCH_2X^{31A}$, $-OCHX^{31A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$,

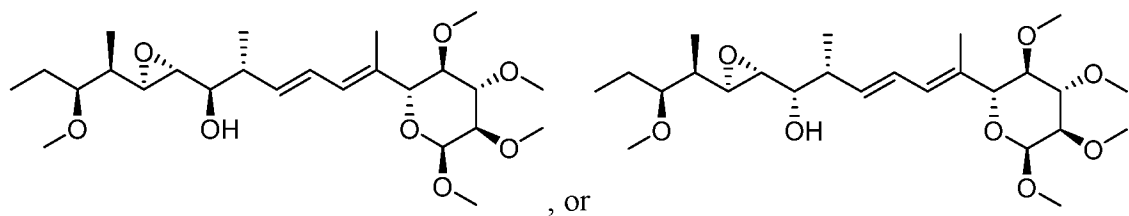
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{31A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{31B}-substituted or unsubstituted C₁-C₆ alkyl, R^{31B}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{31B}-substituted or unsubstituted C₃-C₆ cycloalkyl, R^{31B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{31B}-substituted or unsubstituted phenyl, or R^{31B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{31A} is independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0208] R^{1B}, R^{2B}, R^{3B}, R^{4B}, R^{5B}, R^{10B}, R^{11B}, R^{12B}, R^{13B}, R^{14B}, R^{15B}, R^{16B}, R^{17B}, R^{18B}, R^{19B}, R^{20B}, R^{21B}, R^{22B}, R^{23B}, R^{24B}, R^{25B}, R^{26B}, R^{27B}, R^{28B}, R^{29B}, R^{30B}, and R^{31B} are independently oxo, halogen, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1B}, R^{2B}, R^{3B}, R^{4B}, R^{5B}, R^{10B}, R^{11B}, R^{12B}, R^{13B}, R^{14B}, R^{15B}, R^{16B}, R^{17B}, R^{18B}, R^{19B},

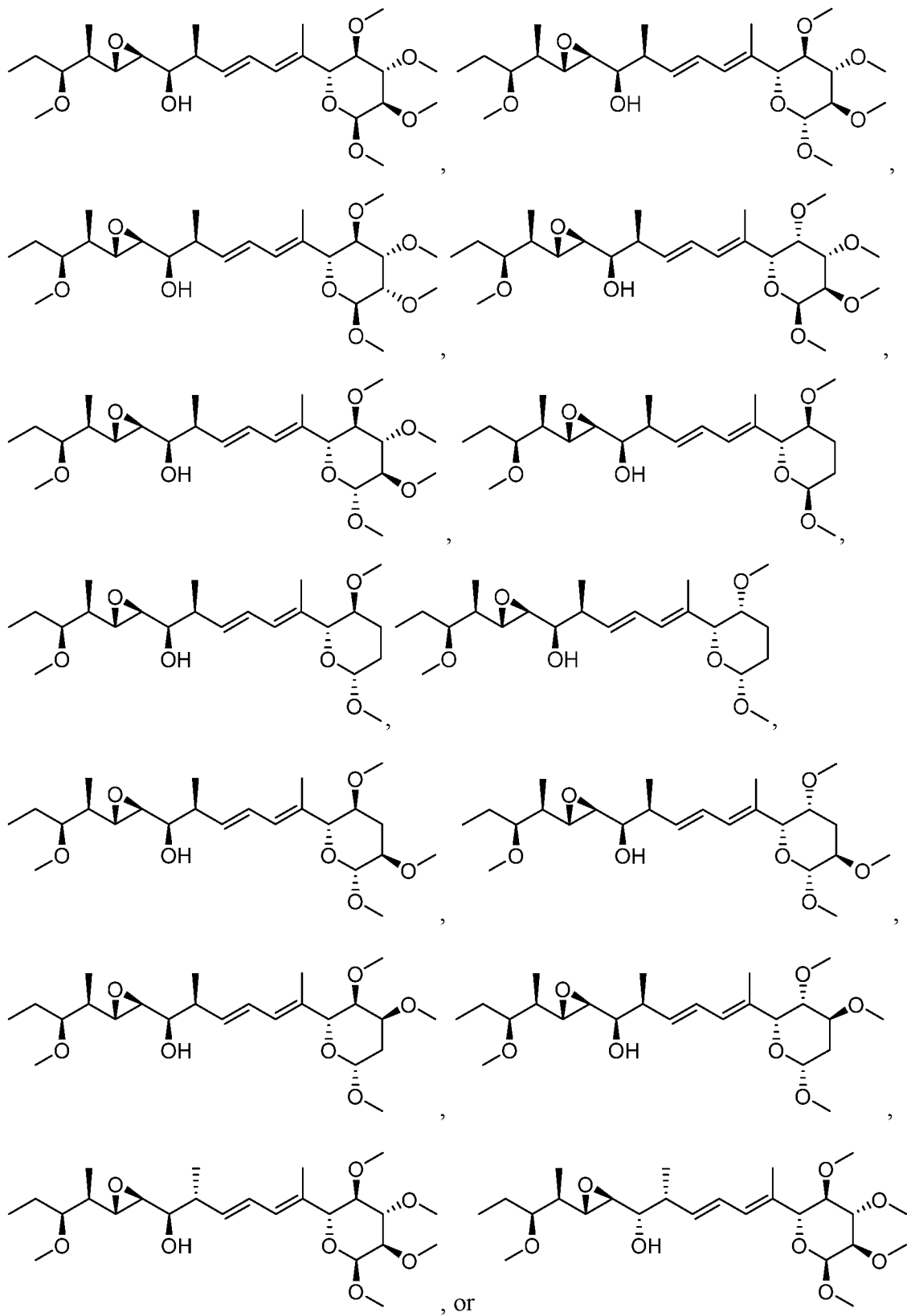
R^{20B} , R^{21B} , R^{22B} , R^{23B} , R^{24B} , R^{25B} , R^{26B} , R^{27B} , R^{28B} , R^{29B} , R^{30B} , and R^{31B} are independently oxo, halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}(\text{O})\text{NHNH}_2$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NH}\text{SO}_2\text{H}$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, unsubstituted C_1 - C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3 - C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0209] In embodiments, the compound is selected from:

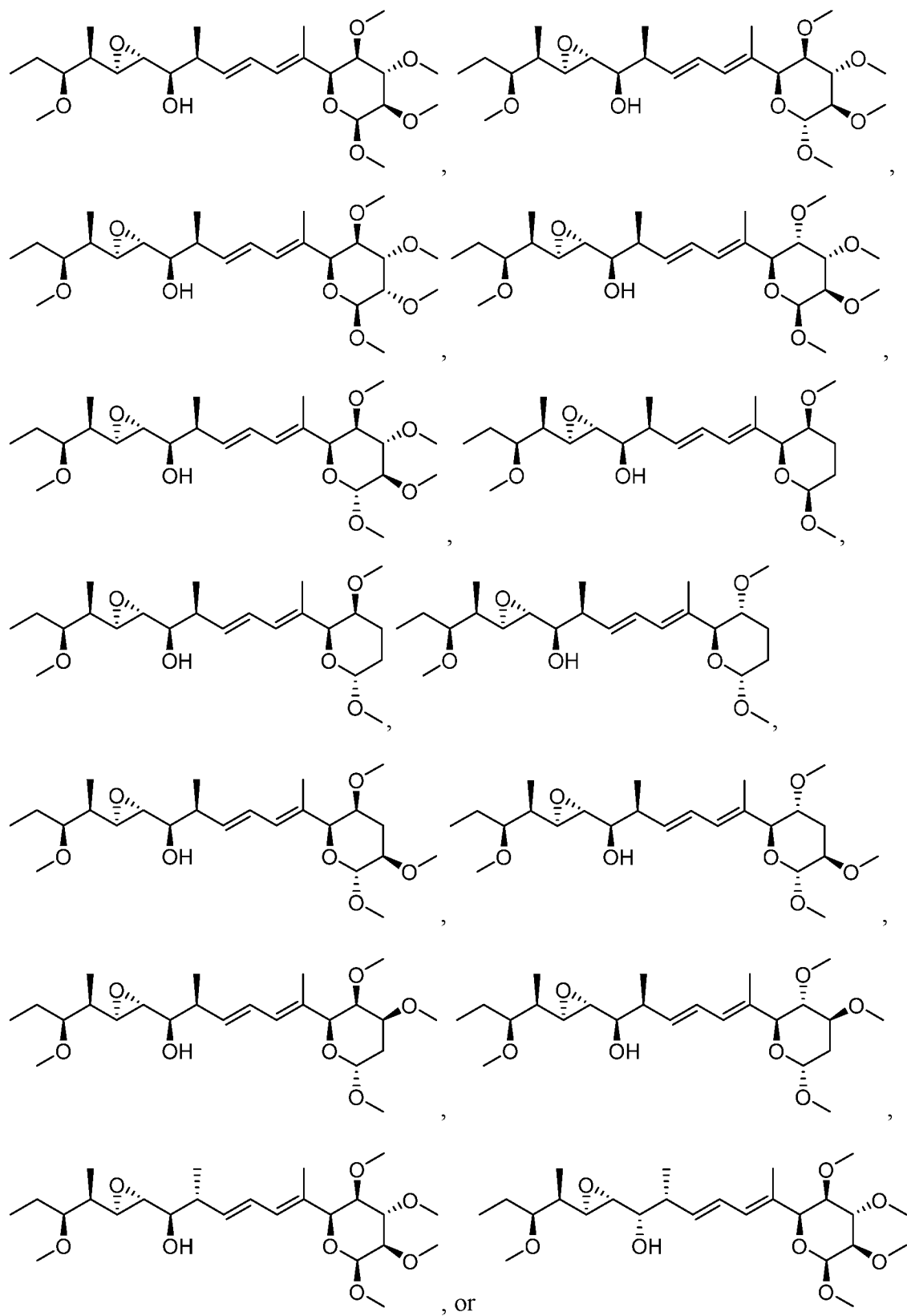




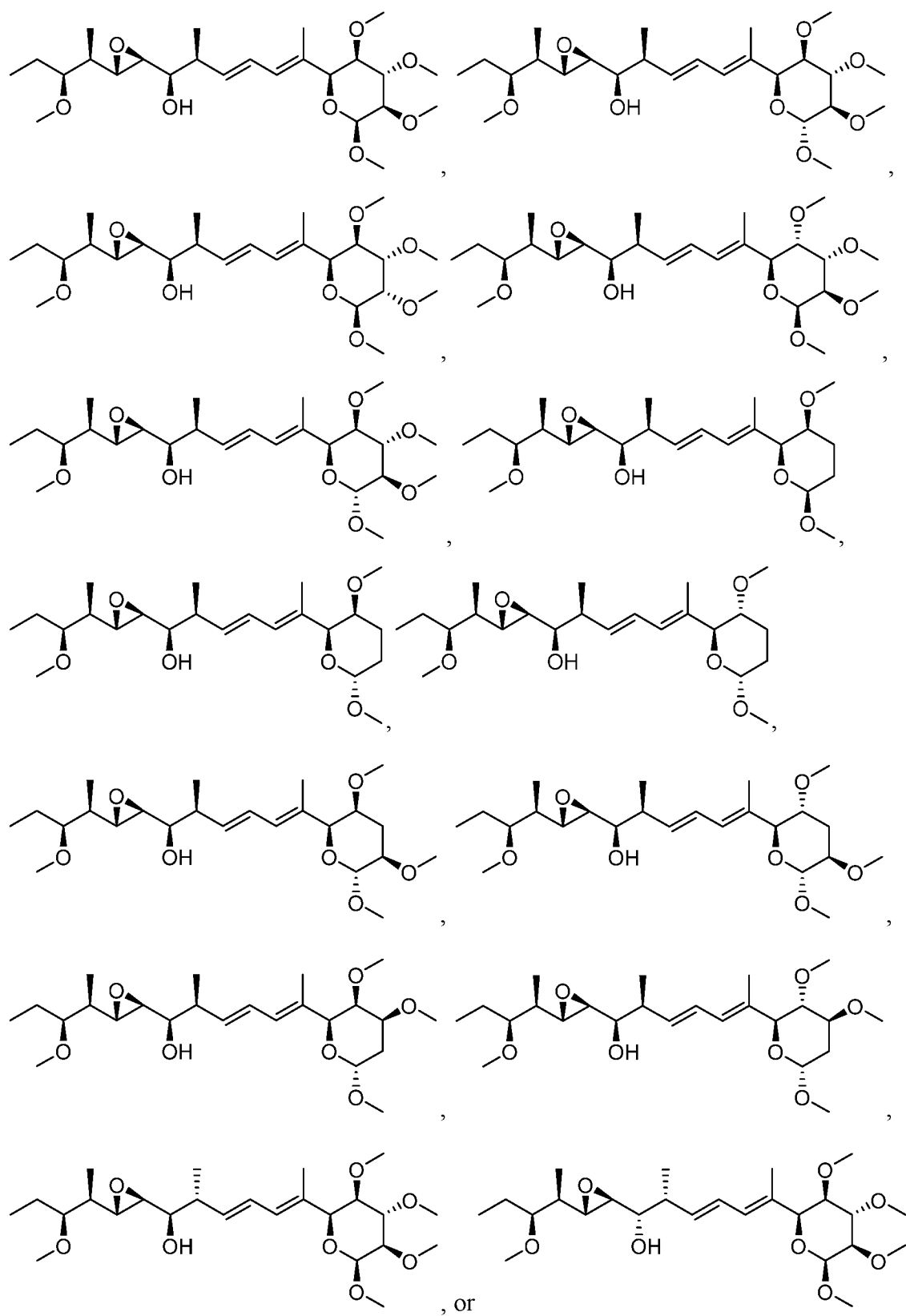
[0210] In embodiments, the compound is selected from:



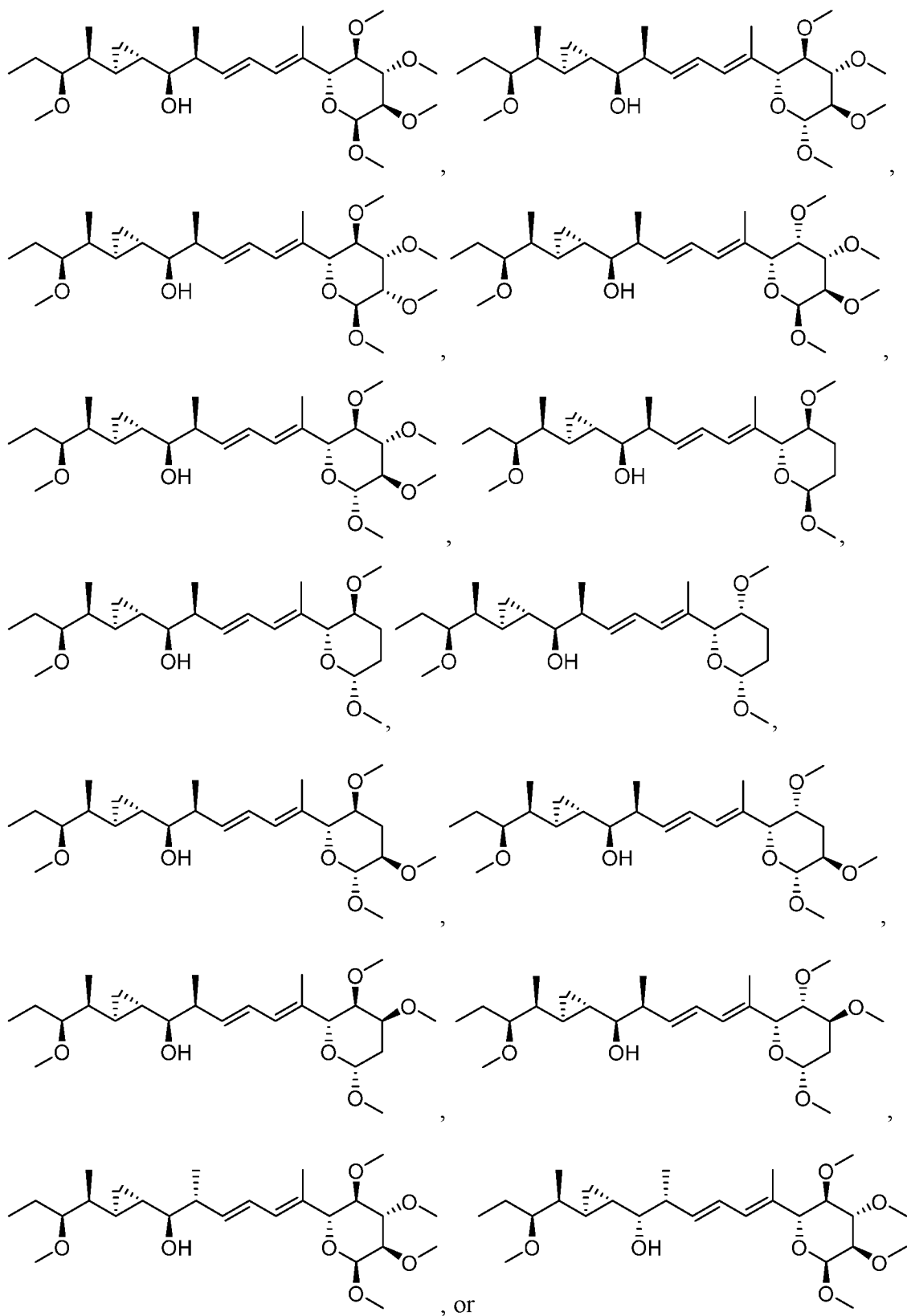
[0211] In embodiments, the compound is selected from:



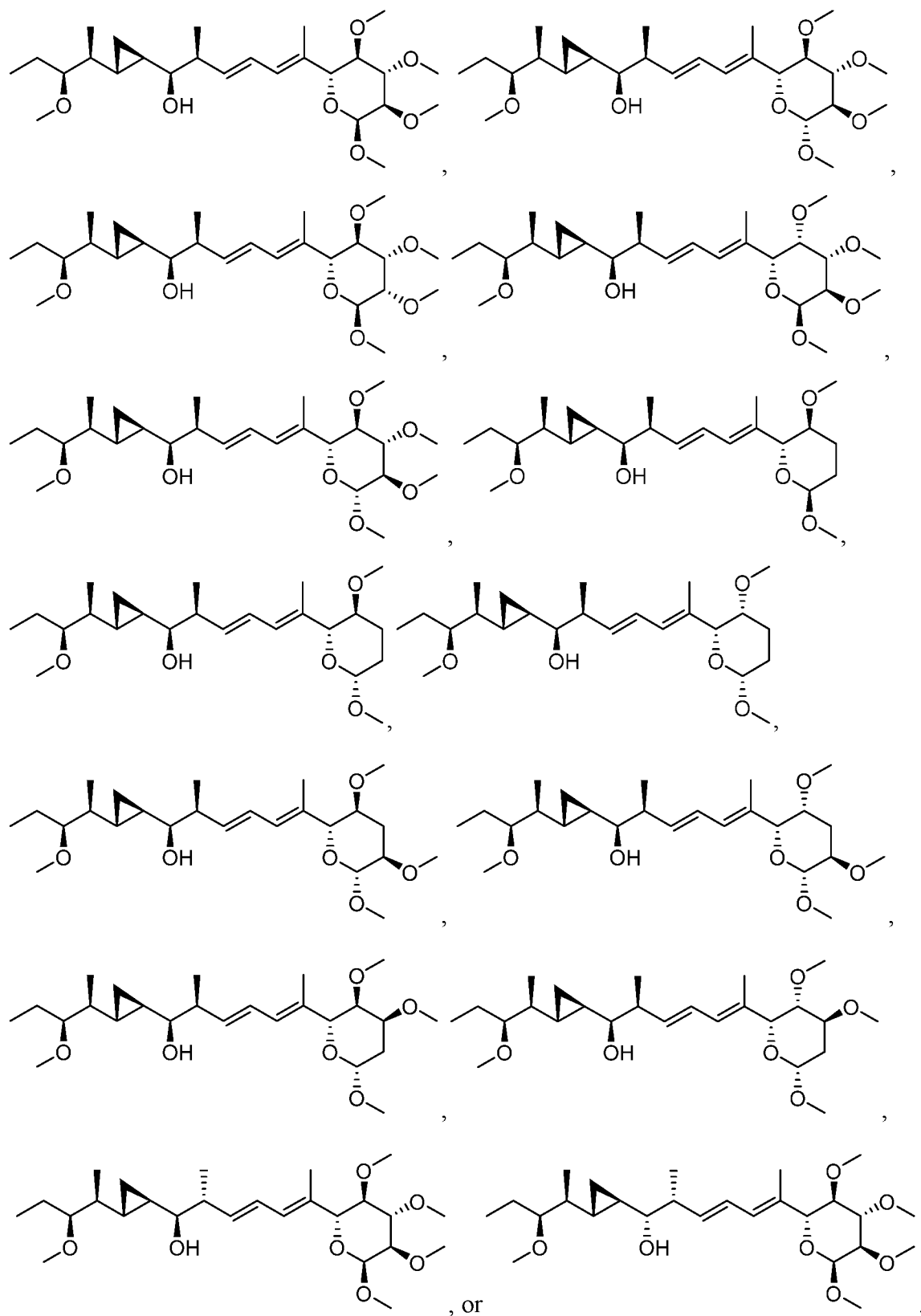
[0212] In embodiments, the compound is selected from:



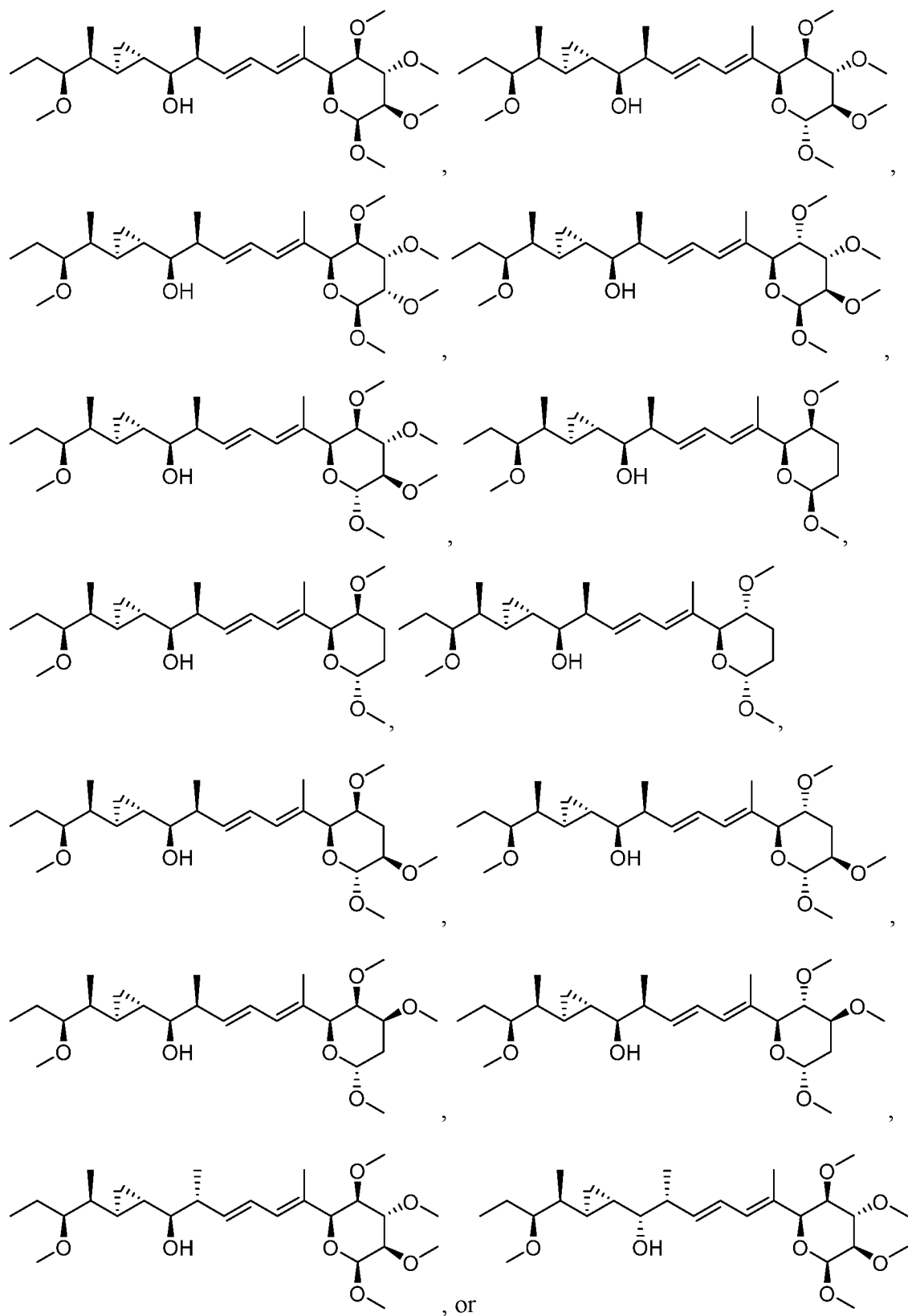
[0213] In embodiments, the compound is selected from:



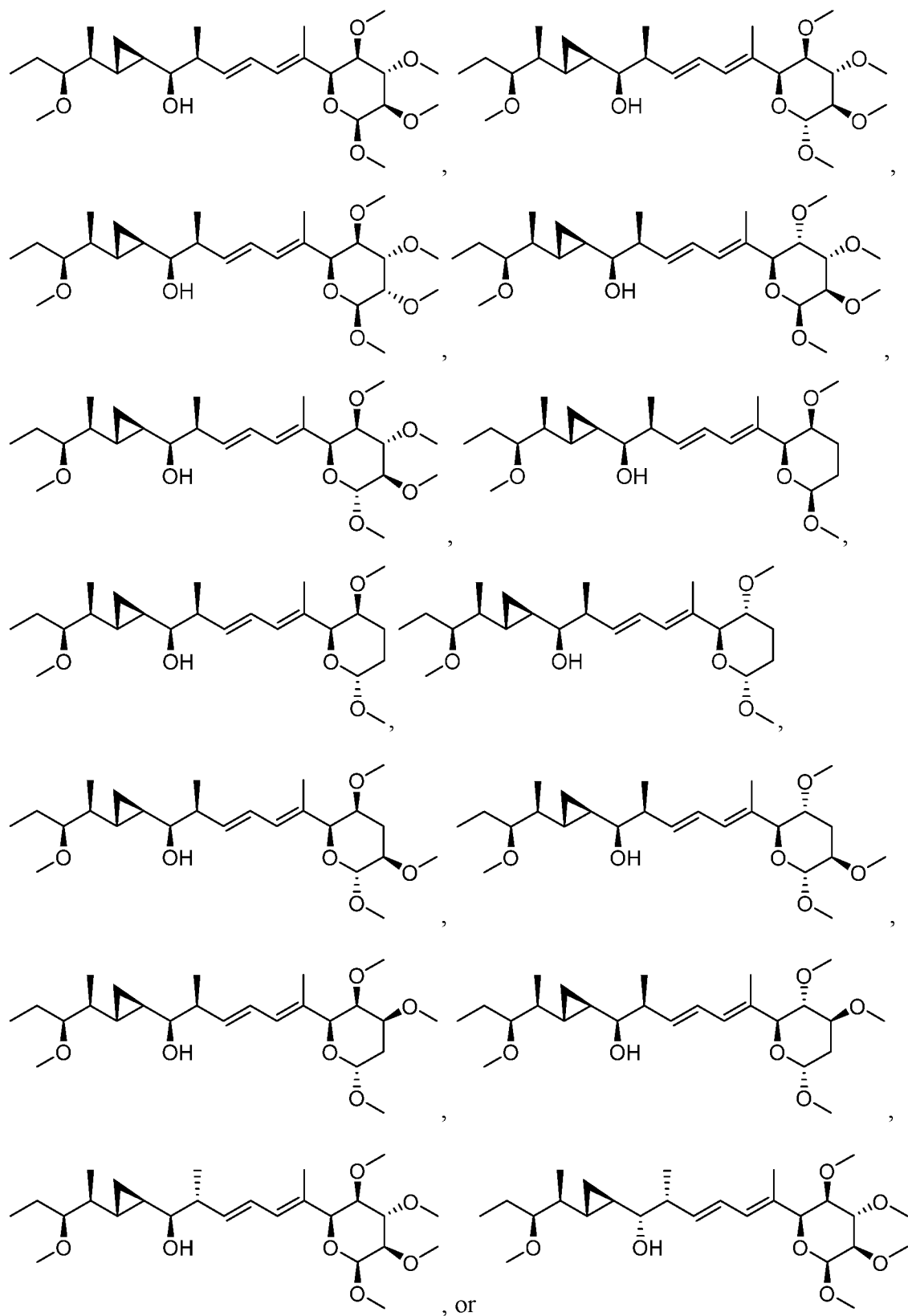
[0214] In embodiments, the compound is selected from:



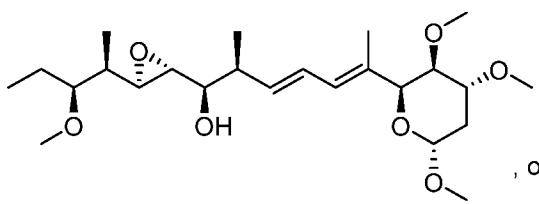
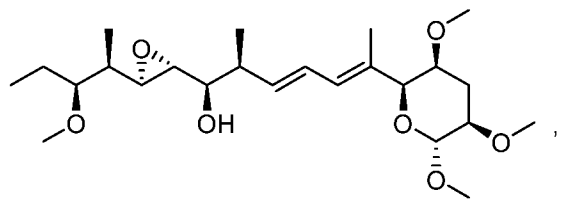
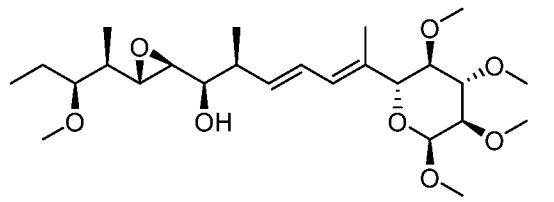
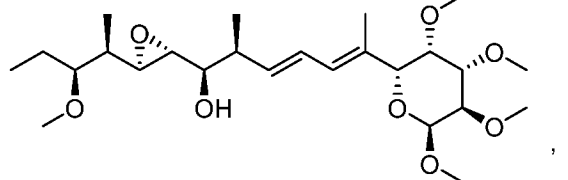
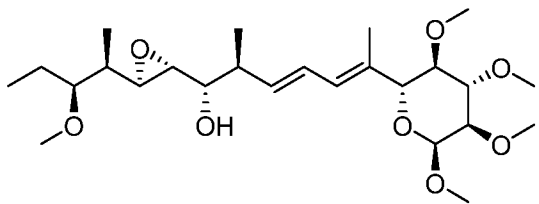
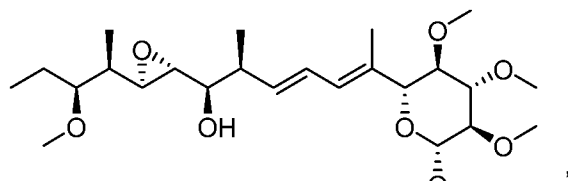
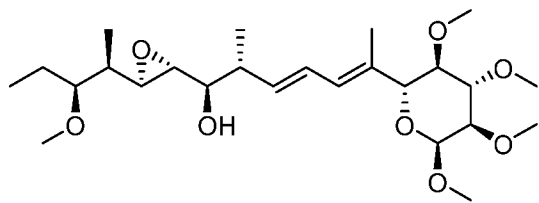
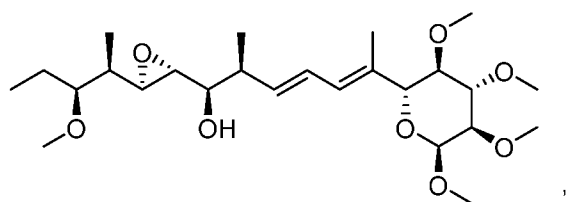
[0215] In embodiments, the compound is selected from:



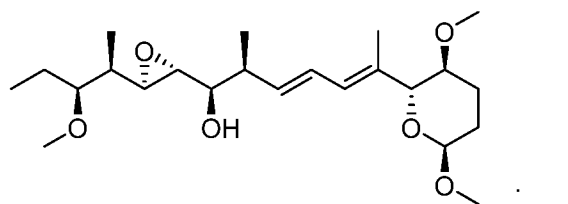
[0216] In embodiments, the compound is selected from:



[0217] In embodiments, the compound are selected from:



5



[0218] In embodiments, the compound is a compound described herein (e.g., in an aspect, embodiment, example, table, figure, scheme, appendix, or claim).

10 [0219] III. Pharmaceutical Compositions

[0220] Also provided herein are pharmaceutical formulations. In embodiments, the pharmaceutical formulation includes a compound (e.g. Formulae (I), (II), (IIA), (IIB), (IIA-1), (IIA-2), (IIB-1), (IIB-2), (III), (IIIA), (IIIB), (IIIA-1), (IIIA-2), (IIIB-1) and (IIIB-2)) described above (including all embodiments thereof) and a pharmaceutically acceptable excipient.

15 [0221] The pharmaceutical composition may contain a dosage of the compound in a therapeutically effective amount.

[0222] 1. Formulations

[0223] The pharmaceutical composition may be prepared and administered in a wide variety of dosage formulations. Compounds described herein (e.g., having a structure of Formula (I), (II), (IIA), (IIB), (IIA-1), (IIA-2), (IIB-1), (IIB-2), (III), (IIIA), (IIIB), (IIIA-1), (IIIA-2), (IIIB-1), or (IIIB-2)) may be administered orally, rectally, or by injection (e.g. intravenously,

intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally).

[0224] For preparing pharmaceutical compositions from compounds described herein (e.g., having a structure of Formula (I), (II), (IIA), (IIB), (IIA-1), (IIA-2), (IIB-1), (IIB-2), (III), (IIIA), (IIIB), (IIIA-1), (IIIA-2), (IIIB-1), or (IIIB-2)), pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substance that may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0225] In powders, the carrier may be a finely divided solid in a mixture with the finely divided active component. In tablets, the active component may be mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0226] The powders and tablets preferably contain from 5% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term “preparation” is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0227] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0228] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0229] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as

desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0230] Also included are solid form preparations that are intended to be converted, shortly

before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0231] The pharmaceutical preparation is preferably in unit dosage form. In such form the

preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0232] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

[0233] Some compounds may have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include:

Polysorbate 20, 60, and 80; Pluronic F-68, F-84, and P-103; cyclodextrin; and polyoxyl 35 castor oil. Such co-solvents are typically employed at a level between about 0.01 % and about 2% by weight. Viscosity greater than that of simple aqueous solutions may be desirable to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation, and/or otherwise to improve the formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and salts thereof, and combinations of the foregoing. Such agents are typically employed at a level between about 0.01% and about 2% by weight.

[0234] The pharmaceutical compositions may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides, and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841;

5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes.

[0235] The pharmaceutical composition may be intended for intravenous use. The pharmaceutically acceptable excipient can include buffers to adjust the pH to a desirable range for intravenous use. Many buffers including salts of inorganic acids such as phosphate, borate, and sulfate are known.

[0236] 2. Effective Dosages

[0237] The pharmaceutical composition may include compositions wherein the active ingredient is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, *inter alia*, on the condition being treated. For example, when administered in methods to treat leukemia (e.g., chronic lymphocytic leukemia), such compositions will contain amounts of active ingredients effective to achieve the desired result (e.g. increasing the extent of cancer cell death in the patient).

[0238] The dosage and frequency (single or multiple doses) of compounds administered can vary depending upon a variety of factors, including route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated; presence of other diseases or other health-related problems; kind of concurrent treatment; and complications from any disease or treatment regimen. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds disclosed herein.

[0239] Dosages may be varied depending upon the requirements of the subject and the compound being employed. The dose administered to a subject, in the context of the pharmaceutical compositions presented herein, should be sufficient to effect a beneficial therapeutic response in the subject over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side effects. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached.

[0240] Dosage amounts and intervals can be adjusted individually to provide levels of the administered compounds effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0241] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is entirely effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound
5 potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration, and the toxicity profile of the selected agent.

[0242] 3. Toxicity

[0243] The ratio between toxicity and therapeutic effect for a particular compound is its therapeutic index and can be expressed as the ratio between LD₅₀ (the amount of compound
10 lethal in 50% of the population) and ED₅₀ (the amount of compound effective in 50% of the population). Compounds that exhibit high therapeutic indices are preferred. Therapeutic index data obtained from cell culture assays and/or animal studies can be used in formulating a range of dosages for use in humans. The dosage of such compounds preferably lies within a range of plasma concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary
15 within this range depending upon the dosage form employed and the route of administration utilized. See, *e.g.* Fingl *et al.*, *In: THE PHARMACOLOGICAL BASIS OF THERAPEUTICS*, Ch.1, p.1, 1975. The exact formulation, route of administration, and dosage can be chosen by the individual physician in view of the patient's condition and the particular method in which the compound is used.

[0244] When parenteral application is needed or desired, particularly suitable admixtures for the compounds included in the pharmaceutical composition may be injectable, sterile solutions, oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. In particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-block
25 polymers, and the like. Ampoules are convenient unit dosages. Pharmaceutical admixtures suitable for use in the pharmaceutical compositions presented herein may include those described, for example, in *Pharmaceutical Sciences* (19th Ed., Mack Pub. Co., Easton, PA) and WO 96/05309, the teachings of both of which are hereby incorporated by reference.

[0245] IV. Methods

[0246] 1. Methods of Treating Cancer

[0247] In another aspect a method of treating cancer is provided. In embodiments, the method includes administering to a subject in need thereof, a therapeutically effective amount of a compound (*e.g.* Formulae (I), (II), (IIA), (IIB), (IIA-1), (IIA-2), (IIB-1), (IIB-2), (III), (IIIA),

(IIIB), (IIIA-1), (IIIA-2), (IIIB-1) and (IIIB-2)) described above (including all embodiments thereof). The compound may be co-administered with a pharmaceutically acceptable excipient, as addressed in previous sections. The cancer may be leukemia, lymphoma, metastatic cancer or bone cancer. The cancer may be leukemia or lymphoma. The cancer may be chronic lymphocytic leukemia (CLL).

[0248] 2. Methods of Detecting Spliceosome Inhibition

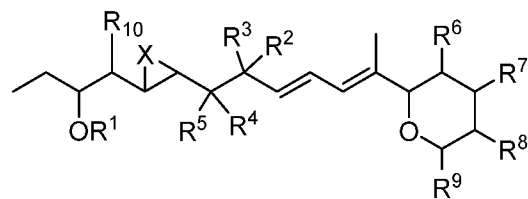
[0249] In another aspect, provided is a method of detecting spliceosome inhibition using a test compound (e.g. Formulae (I), (II), (IIA), (IIB), (IIA-1), (IIA-2), (IIB-1), (IIB-2), (III), (IIIA), (IIIB), (IIIA-1), (IIIA-2), (IIIB-1) and (IIIB-2)) described above (including all embodiments thereof). In embodiments, the method includes contacting a cell with the test compound, extracting an mRNA from the cell to produce an extracted mRNA, reverse transcribing the mRNA using intron-specific primers to form an intron cDNA, amplifying the intron cDNA to form a plurality of amplified intron cDNA's, and detecting the presence of the amplified intron cDNAs to detect spliceosome inhibition resulting from the test compound.

[0250] In another aspect, provided is a method of inhibiting a spliceosome. The method includes contacting a spliceosome with a compound provided herein (e.g. Formulae (I), (II), (IIA), (IIB), (IIA-1), (IIA-2), (IIB-1), (IIB-2), (III), (IIIA), (IIIB), (IIIA-1), (IIIA-2), (IIIB-1) and (IIIB-2)). In embodiments, the spliceosome is within a subject, such as a human subject or a cancer subject. In related embodiments, where the spliceosome is within a subject, the compound is provided in an amount effective to inhibit the spliceosome. In related embodiments, where the spliceosome is within a subject, the compound is provided in an amount effective to treat cancer. In other embodiments, the method is performed *in vitro*.

[0251] V. Embodiments

[0252] Embodiments contemplated herein include embodiments P1 to P4 following.

[0253] Embodiment P1. A compound with structure of Formula (I):



(I), wherein X is -O- or -C(R²⁶)(R²⁷)-; R²⁶ is hydrogen,

halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -OR²⁸, -

OC(O)R²⁸, -OC(O)OR²⁸, or -OC(O)NR²⁸R²⁹; R²⁷ is hydrogen, halogen, substituted or

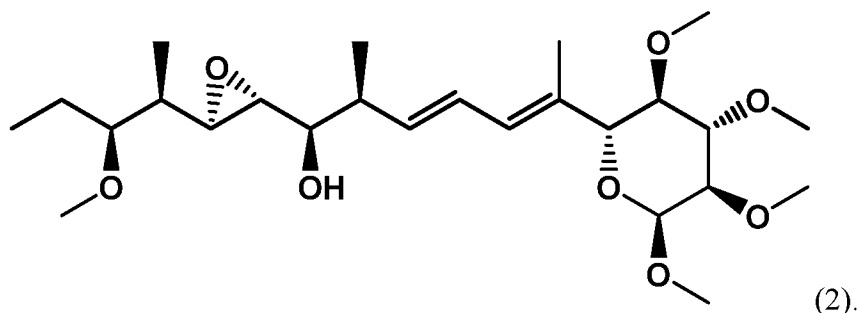
unsubstituted alkyl, substituted or unsubstituted aryl, -OR³⁰, -OC(O)R³⁰, -OC(O)OR³⁰,

or -OC(O)NR³⁰R³¹; R¹ is hydrogen, substituted or unsubstituted alkyl, -C(O)R¹¹, or -C(O)OR¹¹;

R^2 is hydrogen, halogen, substituted or unsubstituted alkyl, $-OR^{12}$, $-OC(O)R^{12}$, $-OC(O)OR^{12}$, or $-OC(O)NR^{12}R^{13}$; R^3 is hydrogen, halogen, substituted or unsubstituted alkyl, $-OR^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{14}$, or $-OC(O)NR^{14}R^{15}$; R^4 is hydrogen, halogen, substituted or unsubstituted alkyl, $-OR^{16}$, $-OC(O)R^{16}$, $-OC(O)OR^{16}$, or $-OC(O)NR^{16}R^{17}$; R^5 is hydrogen, halogen, substituted or unsubstituted alkyl, $-OR^{18}$, $-OC(O)R^{18}$, $-OC(O)OR^{18}$, or $-OC(O)NR^{18}R^{19}$; R^6 is hydrogen, $-OR^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, or $-OC(O)OR^{20}$; R^7 is hydrogen, $-OR^{21}$, $-C(O)R^{21}$, $-C(O)OR^{21}$, $-OC(O)R^{21}$, or $-OC(O)OR^{21}$; R^8 is hydrogen, $-OR^{22}$, $-C(O)R^{22}$, $-C(O)OR^{22}$, $-OC(O)R^{22}$, or $-OC(O)OR^{22}$; R^9 is hydrogen, $-OR^{23}$, $-C(O)R^{23}$, $-C(O)OR^{23}$, $-OC(O)R^{23}$, or $-OC(O)OR^{23}$; R^{10} is hydrogen, substituted or unsubstituted alkyl, $-OR^{24}$, $-OC(O)R^{24}$, $-OC(O)OR^{24}$, or $-OC(O)NR^{24}R^{25}$; and R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{28} , R^{29} , R^{30} , and R^{31} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

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[0254] Embodiment P2. The compound of embodiment P1 with structure of Compound (2):

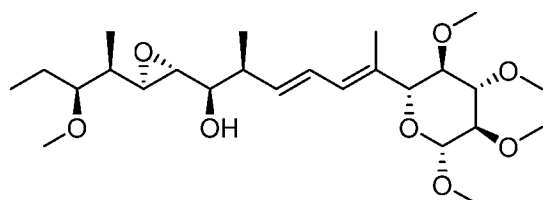


[0255] Embodiment P3. A pharmaceutical composition comprising a compound according to embodiment P1 and a pharmaceutically acceptable excipient.

20 [0256] Embodiment P4. A method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a compound of embodiment P1.

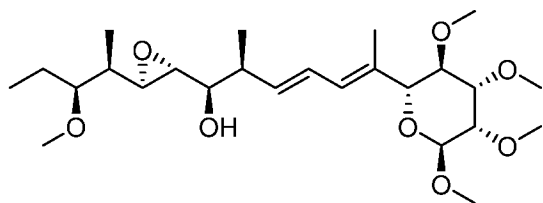
[0257] Embodiments contemplated herein include embodiments Q1 to Q12 following.

[0258] Embodiment Q1 The compound of embodiment Q1 with structure of the following compound:

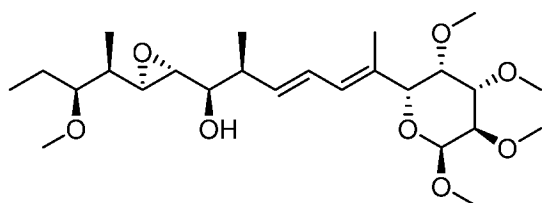


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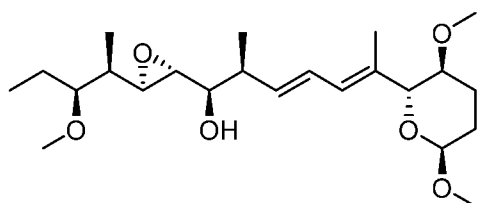
[0259] Embodiment Q2 The compound of embodiment Q2 with structure of the following compound:



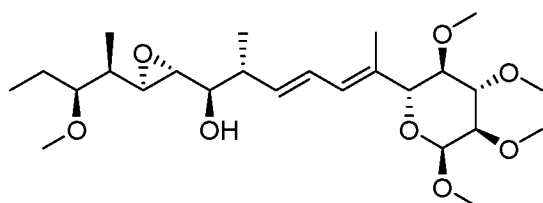
[0260] Embodiment Q3 The compound of embodiment Q3 with structure of the following compound:



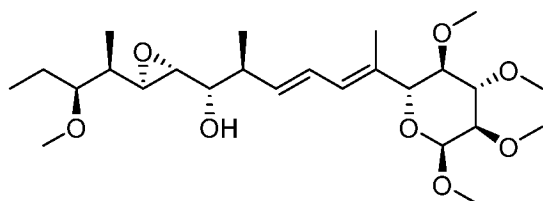
[0261] Embodiment Q4 The compound of embodiment Q4 with structure of the following compound:



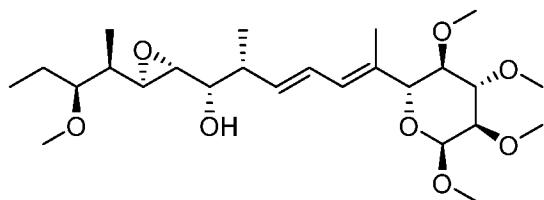
[0262] Embodiment Q5 The compound of embodiment Q5 with structure of the following compound:



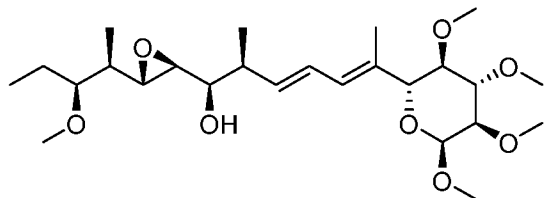
[0263] Embodiment Q6 The compound of embodiment Q6 with structure of the following compound:



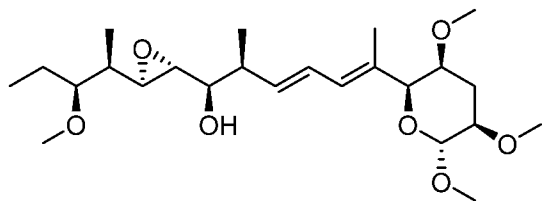
[0264] Embodiment Q7 The compound of embodiment Q7 with structure of the following compound:



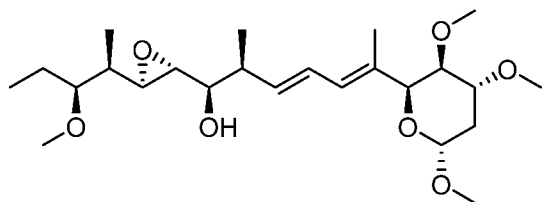
[0265] Embodiment Q8 The compound of embodiment Q8 with structure of the following compound:



5 [0266] Embodiment Q9 The compound of embodiment Q9 with structure of the following compound:



[0267] Embodiment Q10 The compound of embodiment Q10 with structure of the following compound:



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[0268] Embodiment Q11. A pharmaceutical composition comprising a compound according to embodiments Q1-Q10 and a pharmaceutically acceptable excipient.

[0269] Embodiment Q12. A method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a compound of embodiments of Q1-Q10.

15 [0270] VI. Examples

[0271] *Example 1 - A Carbohydrate-Derived Splice Modulator*

[0272] **Abstract** Small molecule splice modulators have recently been recognized for their clinical potential for diverse cancers. This combined with their use as tools to study the importance of splice-regulated events and their association with disease continues to fuel the discovery of new splice modulators. One of the key challenges found in the current class of

20

materials arises from their instability, where rapid metabolic degradation can lead to off-target responses. We now describe the preparation of bench-stable splice modulators by adapting carbohydrate motifs as a central scaffold to provide rapid access to potent splice modulators.

[0273] Introduction

5 [0274] In 2007, two Japanese teams revealed the importance of targeting the SF3b unit of the spliceosome for anti-tumor therapy [1,2]. These breakthroughs not only forwarded the spliceosome as an important target for cancer [2], but also identified two key families of polyketide spliceosome modulators (FIG. 1), including FD-895 (**1a**)[2], pladienolide B (**1b**)[3] and herboxidiene (**1c**) [4]. Since these discoveries, the development of splicing assays has been
10 instrumental in the advance of next generation splice modulators. The success of these discoveries was further marked by the translation of an analog of pladienolide D, E7101, into phase I clinical trials[5]. However, many of these natural products are subject to low stability and/or poor pharmacological properties[6]. To this end, our laboratory has been a part of a growing medicinal chemistry effort to identify next generation splice modulators with improved
15 pharmacological properties.

[0275] An attractive proposal suggested a method of analog development through the use of a consensus motif [7]. Pursuing this approach, their team has advanced the sudemycins [8] and a pladienolide-herboxidiene hybrid [9] as next generation leads. This, along with efforts at the Eisai Co. Ltd [10], H3 Biomedicine [11], Pfizer [12], Ghosh-Jurica laboratories [13], Koide
20 laboratory [14], and our laboratories [15], have provided a strong foundation for achieving analogs with improved pharmacological properties. We now report on an advanced new class of splice modulators that are more potent, stable and rapidly accessible analogs.

[0276] In addition to carbohydrates being ubiquitous biological scaffolds, they are also derived from the natural chiral pool, making them ideal scaffolds for medicinal chemical optimization
25 [16]. To expand on this hypothesis, we designed and prepared carbohydrate-derived compound, i.e. an analog of FD-895 whose core was derived from D-glucose.

[0277] Results

[0278] Our design began with FD-895 (**1a**) due to the fact that earlier medicinal chemistry efforts in our laboratory provided derivatives with improved pharmacological properties [6a].
30 From these studies, we determined that manipulation of the stereochemistry at the C16-C19 diad (FIG. 1) provided an effective means to improve activity. From these data, we targeted a side chain that contained the exact terminus (FIG. 1), epoxide (FIG. 1), and diene groups (FIG. 1) as

one of our more active analogs of FD-895 [6a]. Here, we incorporated already known SAR data to improve activity by selecting an improved C16-C19 stereodiad (shown in **2**, FIG. 1).

[0279] Clues obtained from the solution structure analysis of FD-895 (1a). While structural information on the eukaryotic spliceosome has recently been published [18],

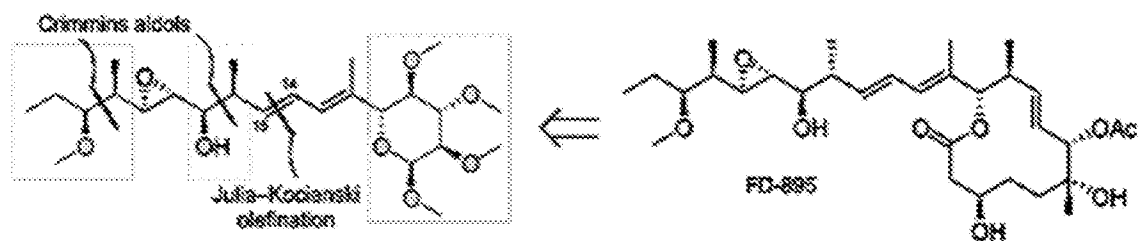
representation of the binding of a splice modulator with SF3b has yet to be established. We began by exploring the solution structure of the macrolide core of FD-895 (**1a**). Using multiple solvents (CDCl₃ and C₆D₆) for data acquisition, we identified a series of NOE interactions that, along with coupling constant data, allowed assignment of the solution structure of the macrolide core (FIG. 2A).

[0280] Design of a carbohydrate core motif. Using this structure and analyzing its space-filling model, we began to search for motifs that accurately represented the macrolide core. Our goal was to find a structural unit that offered an improved synthetic entry and diverse means of tailoring, while also addressing previous pharmacological issues (stability and solubility). We began by inspecting the overlap between the small herboxidiene (**1c**) and large FD-895 (**1a**) cores. While a clear overlay existed, it was evident that space occupied by the C4-C7 unit within **1a** may not be a requirement for activity. We realized that simple monosaccharides such as D-glucose or D-galactose could provide a strong overlap with these cores. After evaluating several structures, we turned our attention to explore α -methyl-2,3,4-trimethoxy-D-glucopyranoside (**3**) as a core mimetic [19].

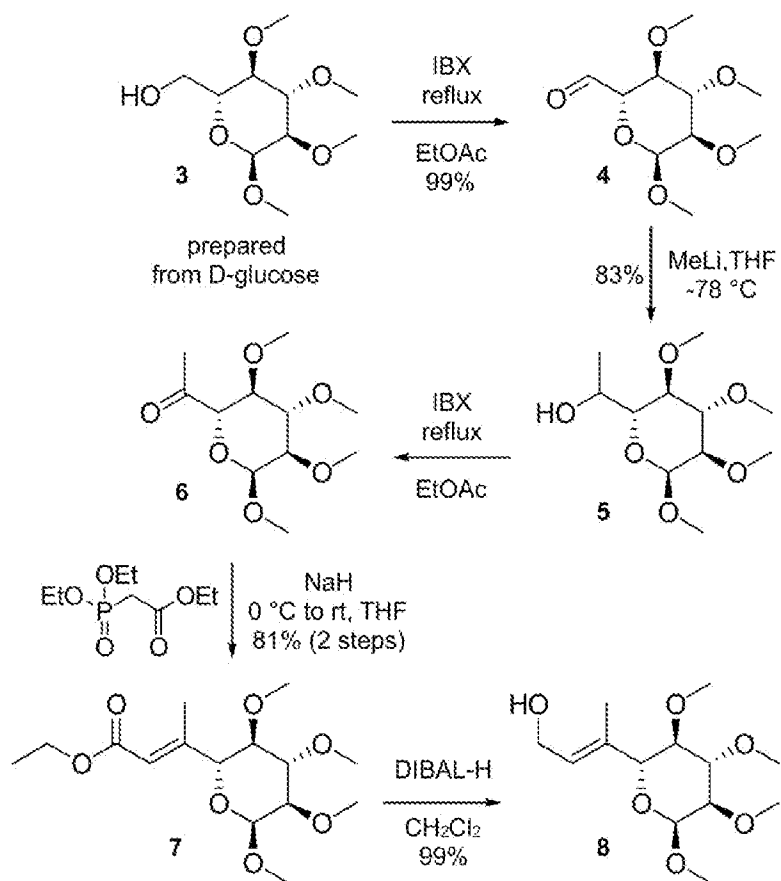
[0281] Structurally, glycoside **2** offered a functional map that lay between the core sizes of **1a** and **1c** (FIGS. 2A-2E). As illustrated in FIGS. 2D-2E, the C2, C3, and C4 methoxy groups in **2** provided an improved fit to **1a** relative to herboxadiene (FIGS. 2B-2C). Specifically, the C2 methoxy group of **2** filled the space taken by the C24 methyl group in **1a**. Likewise, the C3 methoxy of **2** was able to partially fill the space of the C29-C30 acetate, a region that was already shown to tolerate functional modifications [20]. With this support, we turned our attention to the synthesis and biological evaluation analog **2**.

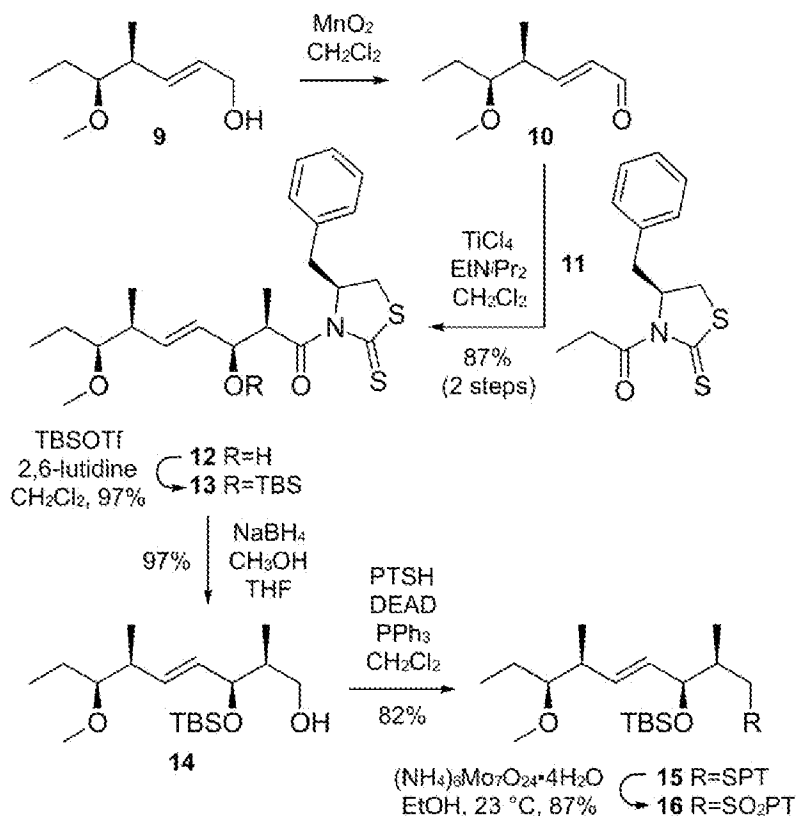
[0282] Synthetic plan. Our plan focused on using a late-stage Julia-Kocienski olefination to couple a side chain derived from FD-895 to the monosaccharide core (see Scheme A). Here, we envisioned that we could leverage the extensive efforts from our own laboratory for development of pladienolide/FD-895 side chain [6a,15b] as a means to probe the structure-activity relationships (SARs) of side chain incorporating analogs. We therefore set out towards preparation of core component **8** (Scheme 1) and side chain component **16** (Scheme 2).

Scheme A.



Scheme 1. Synthesis of core compound 8.



Scheme 2. Synthesis of side chain component 16

[0283] Synthesis of a carbohydrate core component 8. Synthesis of **8** was accomplished in 5 steps from **3**, a monosaccharide derivative that in turn was prepared in 3 steps (54% yield) from α -methyl-D-glucopyranoside [19]. We began by oxidizing to aldehyde **4**. Advantageously, we were able to reduce chromatographic purification efforts by using a combination of an IBX oxidation followed by solvent-dependent filtration through a pad of SiO_2 . The addition of MeLi to crude **4** occurred with minimal by-product formation providing alcohol **5** in 82% yield from **3**.

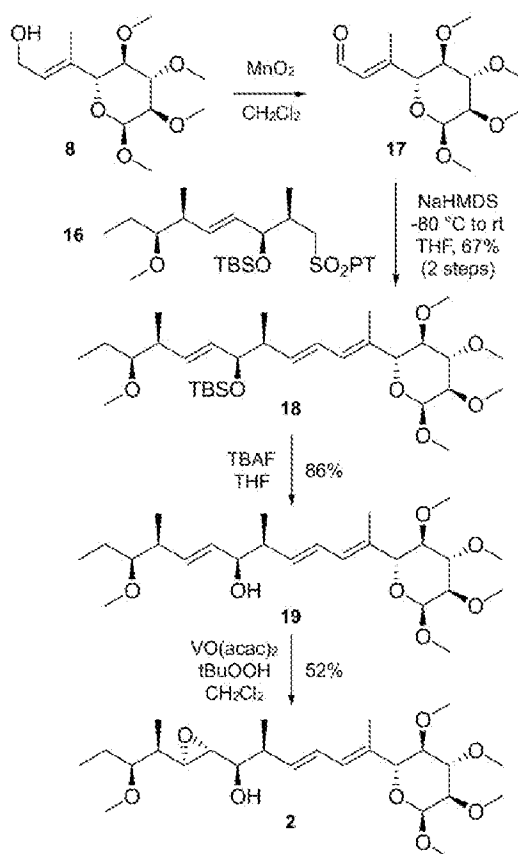
[0284] Repetition of the IBX oxidation procedure provided ketone **6**, which could be rapidly purified by passage through a SiO_2 plug. While small samples of **6** were purified for characterization, the crude product was readily subjected to a Horner–Wadsworth–Emmons olefination to afford ester **7**. We were able to convert **5** to **7** in two steps and 80% yield with a single purification. Finally, ester **7** was reduced with DIBAL-H to afford core unit **8**, which could be stored for months at -20°C without decomposition. Overall, this process provides access to **8** in 66% in 5 steps from **3** (36% in 8 steps from α -methyl-D-glucopyranoside).

[0285] Synthesis of the side chain component 16. The synthesis of the side chain component began with allylic alcohol **9**, an intermediate that was prepared at >10 g scale for the synthesis of FD-895 (**1a**) [6a]. Allylic oxidation with MnO_2 provided aldehyde **10**, which was purified through a SiO_2 plug and directly submitted to a Crimmins aldol condensation with auxiliary **11**,

to afford adduct **12** in 87% yield over two steps. NMR analyses on the crude product indicated that this reaction occurred without detectable formation of other isomeric products.

[0286] With **12** in hand, the carbinol was protected as TBS ether **13**, and the auxiliary was removed by NaBH₄ reduction. Optimization studies indicated that a 5:1 ratio of THF:CH₃OH provided a reproducibly high yield of **14**. Completion of this component was accomplished by a two-step installation of the 1-phenyl-1H-tetrazol-5-yl (PT) sulfone. While Mitsunobu conditions were effective at producing sulfone **15** in 82% yield at gram scales, oxidation often provided significant quantities of the corresponding sulfoxides (incomplete oxidation by-products). Typically, samples of these sulfoxides were collected after chromatographic purification and resubmitted to the oxidation conditions to afford a combined yield of 89% of component **16**. To date, we have completed the synthesis of gram quantities of **16** in 6 steps and 58% overall yield from **9** and 12 steps and 21% overall yield from auxiliary **11**.

Scheme 3. Component assembly



[0287] **Component assembly and completion of the synthesis of 2.** With components **8** and **16** in hand, the component coupling began by oxidizing allylic alcohol **8** to the corresponding aldehyde **19**. Purification *via* dry column vacuum chromatography using Geduran 60 silica gel was sufficient to afford pure **19** for coupling. After initial screening, we found the optimum yield (68%) of **18** was obtained when applying 1.05 eq. NaHMDS to 1.0 eq. of sulfone **8** and following

this by addition of 1.1 eq. of aldehyde **19**. The yield of this reaction also included recovery of 8% of sulfone **16** and 11% of the chromatographically separable *cis*-isomer of **18** (structure not shown). With samples of pure **18** at hand, deprotection with TBAF afforded alcohol **19**.

[0288] Next, we turned to the stereoselective VO(acac)₂ catalyzed epoxidation of allylic

alcohols²¹ to install the C12-C13 epoxide. As shown in FIG. 3A, treatment of **19** with 4.5 eq. of tBuOOH and 3 eq. of VO(acac)₂ at -20 °C for 6 h provided the desired stereoisomer with ~4:1 diastereoselectivity. While this was the major product, over warming or not starting the reaction at -78 °C resulted in epoxidation at C8-C9. This product was not stable as the C11 carbinol was capable of attacking the C8 center of the epoxide forming the corresponding furan analog (structure not shown). While additional optimization efforts will be required, the current conditions returned **2** in 52% yield with only traces of the undesired C8-C9 epoxidation (5-10% yield).

[0289] **Validation of the structural assignment of 2.** While the mechanism of the

VO(acac)₂/tBuOOH epoxidation suggests delivery of the correct stereochemical outcome, we wanted to gain further confirmation that the product was indeed **2**. We began by exploring other epoxidation conditions to prepare samples of the other isomer. Treatment of **19** with 1.2 eq. of *m*-CPBA at -78 °C in NaHCO₃ buffered CH₂Cl₂ followed by slow warming to room temperature afforded a ~1:1 mixture of both epoxides (FIG. 3B) in 62% yield. After chromatographic purification, we were able to obtain samples of both isomers.

[0290] Comparative NMR analyses on the epoxides from VO(acac)₂/tBuOOH and *m*-CPBA provided a solution (FIG. 3C). Using 2D NMR data set (see Supporting Information), we were able to fully assign the proton assignments in this product. First, we identified that the chemical shift and coupling patterns of the epoxide protons at C12-C13 provided the closest match to the configuration of the corresponding C16-C19 isomer **1e** (FIG. 4), with comparable chemical shifts and coupling constants.

[0291] **Stability and solubility of 2.** Early studies indicate that **2** was more soluble and stable in aqueous buffers than FD-895 (**1a**). Using capillary NMR and solvent ¹³C-satellites (QSCS) as a means of quantitation [22], we found that **2** was soluble up to 95±5 mM D₂O/DMSO-*d*₆ (10:1) at 23 °C, while FD-895 (**1a**) was limited to 15±5 mM under the same conditions. Additionally, we used NMR monitoring to show that while **1a** had a half-life of ~70 h in D₂O/DMSO-*d*₆ (10:1) at 37 °C [6a], carbohydrate-analog **2** showed no signs of decomposition even after 744 h (1 month) under the same conditions. While detailed partitioning, permeability, and metabolic stability analyses are ongoing, this initial evidence suggests that **2** offers the potential to improve pharmacological properties of this class of splice modulator.

[0292] Epoxide 2 displays potent activity in primary CLL-B cells in contrast to its

precursor alkene 19. We then screened the activity of **19** and **2** in primary CLL-B cells obtained from two CLL patients, that displayed potent in vitro cytotoxic activity (FIGS. 7A-7B) measured in form of specific induced apoptosis (% SIA) of **1a** (IC₅₀ value of 54.1±7.5 nM) and **1b** (IC₅₀ value of 84.4±1.2 nM). Interestingly, these studies indicated that alkene **19** did not display any activity (IC₅₀ value >50 µM in both sets of cells). Epoxide **2**, on the other hand, was active (IC₅₀ value of 153.0±11.8 nM) with ~3-fold loss of activity when compared to FD-895 (**1a**).

[0293] Compound 2 modulates splicing. We then turned to RT-PCR analysis to determine if the activity of **2** also included a comparable splice response as **1a** and **1b** in CLL-B cells. Using unspliced *RNU6A* and unmodulated *GAPDH* (top, FIG. 5) as controls, we were able to obtain complementary splice modulation in all six genes selected from our prior studies to provide a diversity of intron retention (IR) response.^{15a} This included comparable modification of IR in *DNAJB1*, *ARF4*, *PRPF4*, *RIOK3*, *SF3A1*, and *U2AF2* (FIG. 4 and FIG. 8) from primary CLL-B cells. In contrast, alkene precursor **19** was inactive for all six genes (FIG. 5), indicating that the epoxide in **2** is essential for activity.

[0294] Additionally, we were able to confirm that compound **2** also induced alternate splicing (AS) events. As shown in FIG. 6, treatment of CLL-B cells with **1a**, **1b** and **2** resulted in a decrease in the long (anti-apoptotic) form and increased the expression of short (pro-apoptotic) form of *MCL1*. Similarly, *BCL-X* demonstrates comparable AS events (FIG. 6). This indicates that cell death induced by **1a**, **1b** and **2** is not exclusively derived through AS of *MCL1* but may also include other players. This fact is further supported by RNAseq analyses [15a], which implicates the involvement of other pathways. Efforts are now underway to explore the roles of IR and AS events as well as to identify structural motifs that enrich specific events.

[0295] Experimental Section**[0296] A. General experimental methods.**

[0297] Chemical reagents were purchased from Acros, Fluka, Sigma-Aldrich, or TCI. Deuterated NMR solvents were purchased from Cambridge Isotope Laboratories. All reactions were conducted with rigorously dried anhydrous solvents that were obtained by passing through a solvent column composed of activated A1 alumina. Anhydrous *N,N*-dimethylformamide was obtained by passage over activated molecular sieves and a subsequent NaOCN column to remove traces of dimethylamine. Triethylamine (Et₃N) was dried over Na and freshly distilled. Ethyl-*N,N*-diisopropylamine (EtN/Pr₂) was distilled from ninhydrin, then from potassium hydroxide. Anhydrous CH₃CN was obtained by distillation from CaH₂. All reactions were performed under positive pressure of Ar in oven-dried glassware sealed with septa, with stirring from a Teflon

coated stir bars using an IKAMAG RCT-basic mechanical stirrer (IKA GmbH). Solutions were heated using either a sand or silicon oil bath. Analytical Thin Layer Chromatography (TLC) was performed on Silica Gel 60 F254 precoated glass plates (EM Sciences). Preparative TLC (pTLC) was conducted on Silica Gel 60 plates (EM Sciences). Visualization was achieved with UV light and/or an appropriate stain (I_2 on SiO_2 , $KMnO_4$, bromocresol green, dinitrophenylhydrazine, ninhydrin, and ceric ammonium molybdate). Flash chromatography was carried out Geduran Silica Gel 60 (40-63 mesh) from EM Biosciences. Yields and characterization data correspond to isolated, chromatographically and spectroscopically homogeneous materials. ^1H NMR spectra were recorded on Varian Mercury 300, Varian Mercury 400 spectrometers, Varian Mercury Plus 400, a JEOL ECA500, or a Varian VX500 spectrometer. A majority of the ^{13}C NMR spectra were recorded at 125 MHz on a Varian VX500 spectrometer equipped with an Xsens Cold probe. The remaining spectra were either collected at 125 MHz on a JEOL ECA 500, 100 MHz on a Varian Mercury 400 or 100 MHz on a Varian Mercury Plus 400 spectrometer. Chemical shifts for ^1H NMR and ^{13}C NMR analyses were referenced to the reported values of Gottlieb,¹ using the signal from the residual solvent for ^1H spectra, or to the ^{13}C signal from the deuterated solvent. Chemical shift δ values for ^1H and ^{13}C spectra are reported in parts per million (ppm) relative to these referenced values, and multiplicities are abbreviated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All ^{13}C NMR spectra were recorded with complete proton decoupling. FID files were processed using MestraNova 6.0.2. (MestreLab Research).

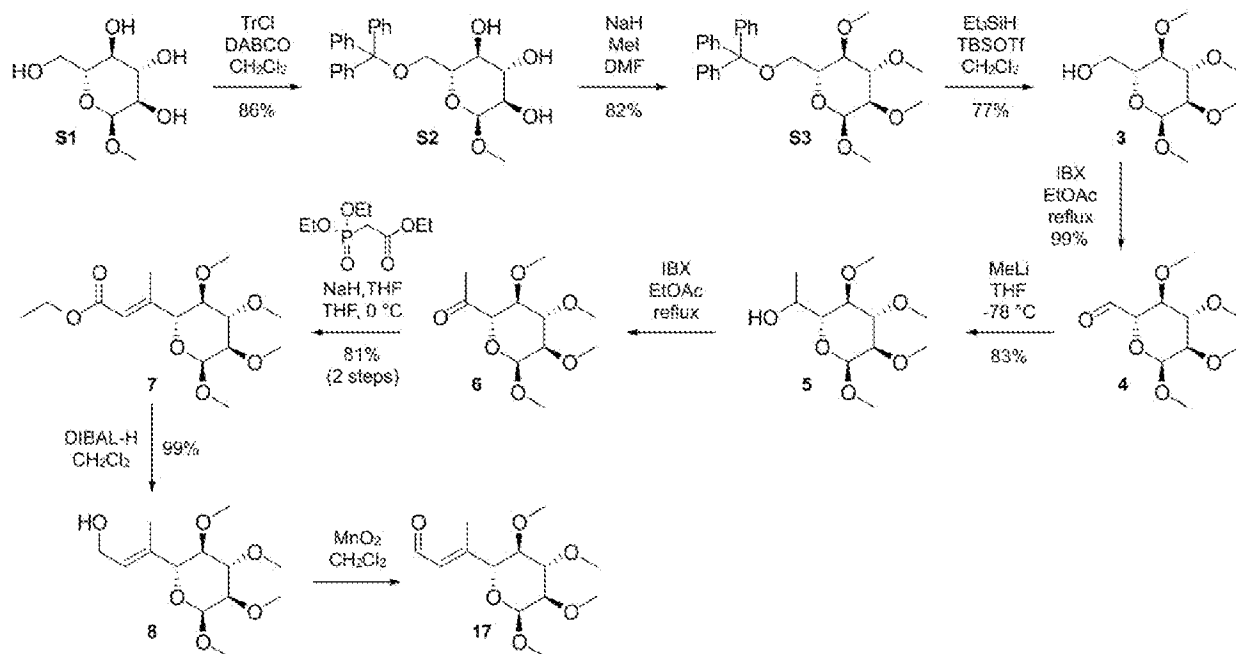
Electrospray (ESI) mass spectrometric analyses were performed using a ThermoFinnigan LCQ Deca spectrometer, and high-resolution analyses were conducted using a ThermoFinnigan MAT900XL mass spectrometer with electron impact (EI) ionization. A Thermo Scientific LTQ Orbitrap XL mass spectrometer was used for high-resolution electrospray ionization mass spectrometry analysis (HR-ESI-MS). FTIR spectra were obtained on a Nicolet magna 550 series II spectrometer as thin films on either KBr or NaCl discs, and peaks are reported in wavenumbers (cm^{-1}). Optical rotations $[\alpha]_D$ were measured using a Perkin-Elmer Model 241 polarimeter with the specified solvent and concentration and are quoted in units of $deg\ cm^2\ g^{-1}$. Spectral data were collected for all new compounds.

[0298] B. Synthesis of core chain component 8.

[0299] Component **8** was prepared in 8 steps in 36% overall yield from α -methyl-D-glucopyranoside (**S1**) as shown in Scheme 1 (above) and Scheme S1 (below). Preparation of 6-trityl- α -methyl- α -D-glucopyranoside **S2** was achieved by modification of methods developed by Crich,^{S1} as described below. The following section provides a complete description of the synthetic procedures and spectroscopic properties of intermediated **S2-S3**, **3-8** and **19**.

[0300] Scheme S1 depicts the synthesis of core component 8. Preparation of 8 required three chromatographic purifications as the crude products of S2, 3, 4, and 6 could be used without additional purification. Flash chromatography was required to purify intermediates S3, 5, and 7. The final materials were stored. Aldehyde 19 was prepared immediately before the component

Scheme S1.



[0301] (2*S*,3*R*,4*S*,5*R*,6*R*)-2,3,4,5-tetramethoxy-6-((trityloxy)methyl)tetrahydro-2*H*-pyran (S3). Trityl ether S2 (10.1 g, 23.2 mmol), prepared from α -methyl-D-glucopyranoside (S1)

according to the DABCO method of Gadakh, S1 was suspended in DMF (110 mL), placed under a strict Ar atmosphere and cooled to 0 °C. NaH (4.82 g, 120.4 mmol) was added in four portions over the period of 15 min. After stirring at 0 °C for 1.5 h, MeI (11.53 mL, 185.2 mmol) was added in a drop wise fashion. The reaction was then slowly warmed to rt and stirred at rt for 12 h. In order to optimize yield, the mixture was retreated prior to work up by cooling the flask to 0 °C and adding an additional aliquot of NaH (2.41, 60.2 mmol). After 30 min, a second aliquot of MeI (5.7 mL, 92.6 mmol) was added and the mixture was warmed to rt. After 7 h at rt, satd. NH₄Cl (200 mL) was added in a drop wise fashion. The mixture was extracted with EtOAc (3 × 200 mL), washed with H₂O (200 mL) and satd. NH₄Cl (200 mL), dried over Na₂SO₄ and concentrated on a rotary evaporator. Pure S3 (9.13 g, 82%) was obtained by flash chromatography eluting with a gradient of hexanes to EtOAc.

[0302] Intermediate S3: TLC (1:1 hexanes/EtOAc): R_f = 0.67; ¹H NMR (CDCl₃, 500 MHz) δ 7.49 (m, 6H), 7.29 (m, 6H), 7.24 (m, 3H), 4.92 (d, J = 3.6 Hz, 1H), 3.62 (s, 3H), 3.60 (m, 1H), 3.56 (s, 3H), 3.48 (t, J = 9.2 Hz, 1H), 3.44 (s, 3H), 3.39 (dd, J = 2.0, 10.0 Hz, 1H), 3.30 (m, 2H),

3.27 (s, 3H), 3.11 (dd, $J = 4.3, 10.0$ Hz, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 144.1, 128.9, 127.9, 127.1, 97.4, 86.3, 83.8, 82.0, 80.0, 70.2, 62.5, 61.1, 60.6, 59.2, 55.1; HR-ESI-MS m/z calcd. for $\text{C}_{29}\text{H}_{34}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 501.2248, found 501.2249.

[0303] (2R,3R,4S,5R,6S)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)methanol (3).

5 Intermediate S3 (8.78 g, 18.4 mmol) was dissolved in CH_2Cl_2 (180 mL). Et_3SiH (5.86 mL, 36.7 mmol) was added neat followed by the addition of TBSOTf (0.04 mL, 0.2 mmol). An immediate yellow color appeared. If the CH_2Cl_2 is not sufficiently dry additional amounts of TBSOTf will be required. After 2 h, the yellow color disappeared and TLC analysis indicated that the reaction was complete. Satd. NaHCO_3 solution (0.1 mL) was added and the mixture was dried with
10 Na_2SO_4 and concentrated on a rotary evaporator. Pure S3 (9.13 g, 83%) was obtained by extraction between hexanes and CH_3CN . Briefly, the crude product was dissolved in CH_3CN (100 mL) and washed with hexanes (3×200 mL). The CH_3CN was collected and dried via rotary evaporation to afford pure 3 (4.34 g, 77%) as a white solid.

[0304] Alcohol 3: TLC (1:1 hexanes/EtOAc): $R_f = 0.13$; ^1H NMR (CD_3OD , 500 MHz) δ 4.83
15 (d, $J = 3.6$ Hz, 1H), 3.74 (dd, $J = 2.2, 11.9$ Hz, 1H), 3.65 (dd, $J = 4.6, 11.9$ Hz, 1H), 3.58 (s, 3H), 3.53 (s, 3H), 3.47 (s, 3H), 3.45 (m, 2H), 3.38 (s, 3H), 3.18 (dd, $J = 3.6, 9.6$ Hz, 1H), 3.12 (dd, $J = 8.9, 10.0$ Hz, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 98.4, 84.7, 83.0, 80.6, 72.5, 61.9, 61.0, 60.8, 58.8, 55.4; HR-ESI-MS m/z calcd. for $\text{C}_{10}\text{H}_{20}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 259.1152, found 259.1155.

[0305] 1-((2S,3S,4S,5R,6S)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)ethan-1-one (5). Alcohol 5 was prepared through a back-to-back two-step procedure without purification of intermediate aldehyde 4. Alcohol 3 (2.21 g, 9.4 mmol) was dissolved in EtOAc (120 mL). IBX (5.57 g, 20.6 mmol) was added as a solid and the mixture was brought to reflux with vigorous stirring. After 4 h, the mixture was cooled to 0 °C and flushed through a pad SiO_2 (200 g) washing with EtOAc (400 mL). The combined fractions were dried and submitted immediately
25 for the next step. Aldehyde 4 (2.19 g, 9.4 mmol) was dried by azeotropic removal of toluene (3×200 mL). The resulting wax was dissolved in THF (100 mL) and cooled to -80 °C. A 1.6 M solution of MeLi in ether (23.4 mL, 37.4 mmol) was added slowly to this solution. After 15 min at -80 °C, the mixture was warmed to rt over 2 h and stirred at rt for an additional 1 h. Satd. NH_4Cl (100 mL) was added slowly. The mixture was extracted with EtOAc (3×50 mL), washed
30 with brine (200 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure 5 (1.95 g, 83%) was obtained as a ~2:1 mixtures of isomers by flash chromatography eluting with a gradient of hexanes to EtOAc.

[0306] Alcohol 5: TLC (1:1 hexanes/EtOAc): $R_f = 0.16$; ^1H NMR (CDCl_3 , 500 MHz) δ 4.82 (d, $J = 3.6$ Hz, 1H, minor), 4.78 (d, $J = 3.6$ Hz, 1H, major), 3.98 (m, 1H, both), 3.62 (s, 3H,

minor), 3.61 (s, 3H, major), 3.58 (s, 3H, both), 3.55 (m, 1H, both), 3.51 (s, 3H, minor), 3.51 (s, 3H, major), 3.46 (m, 2H, both), 3.40 (s, 3H, major), 3.38 (s, 3H, minor), 3.30 (dd, $J = 1.6, 9.9$ Hz, 1H, minor), 3.24 (dd, $J = 8.6, 9.2$ Hz 1H, minor), 3.16 (dd, $J = 3.6, 9.6$ Hz, 1H, both), 3.09 (dd, $J = 8.8, 9.9$ Hz, 1H, major), 2.75 (d, $J = 4.7$ Hz, OH, 1H, major), 1.77 (d, $J = 9.7$ Hz, OH, 1H, minor), 1.29 (d, $J = 6.6$ Hz, 3H, minor), 1.23 (d, $J = 6.5$ Hz, 3H, major); ^{13}C NMR (CDCl_3 , 125 MHz) δ 97.6, 97.3, 83.9, 83.9, 82.5, 82.2, 82.0, 79.9, 72.9, 72.1, 68.8, 65.5, 61.0, 60.9, 60.8, 60.4, 59.2, 59.1, 55.2, 55.2, 20.4, 18.3; HR-ESI-MS m/z calcd. for $\text{C}_{11}\text{H}_{22}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 273.1309, found 273.1308.

[0307] 1-((2S,3S,4S,5R,6S)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)ethan-1-one

(6). Alcohol 5 (1.0 g, 4.0 mmol) was dissolved in EtOAc (50 mL). IBX (3.36 g, 12.0 mmol) was added as a solid and the mixture was brought to reflux with vigorous stirring. After 4 h, a second aliquot of IBX (3.36 g, 12.0 mmol) was added and the mixture was continued to stir at reflux for an additional 4 h. The mixture was cooled to 0 °C and flushed through a pad SiO_2 (200 g) washing with EtOAc (400 mL). The combined fractions were dried and used immediately as a crude product 6 (992.3 mg, 99%). Samples of pure ketone were obtained by flash chromatography eluting with a gradient of hexanes to EtOAc.

[0308] Ketone 6: TLC (1:1 hexanes/EtOAc): $R_f = 0.40$; ^1H NMR (CDCl_3 , 500 MHz) δ 4.85 (d, $J = 3.5$ Hz, 1H), 4.00 (d, $J = 10$ Hz, 1H), 3.61 (s, 3H), 3.53 (t, $J = 9.2$ Hz, 1H), 3.51 (s, 3H), 3.49 (s, 3H), 3.43 (s, 3H), 3.22 (t, $J = 9.8$ Hz, 1H), 3.20 (dd, $J = 3.6, 9.7$ Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 205.0, 98.0, 83.5, 81.4, 80.8, 74.1, 61.2, 60.6, 59.3, 55.8, 28.3; HR-ESI-MS m/z calcd. for $\text{C}_{11}\text{H}_{20}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 271.1152, found 271.1149.

[0309] Ethyl (E)-3-((2R,3R,4S,5R,6S)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)but-2-enoate (7).

NaH (400 mg, 60% w/w in oil, 10.0 mmol) was suspended in THF (30 mL) and cooled to 0 °C. Triethyl phosphonoacetate (2.51 g, 11.2 mmol) was added in a drop wise fashion to the suspension of NaH. After stirring for 1.5 h, crude ketone 5 (992.0 mg, 4.0 mmol) dissolved in THF (10 mL) was added. The mixture was warmed to rt. TLC analysis indicated that the reaction was complete after 3 h. Satd. NH_4Cl (50 mL) was added slowly. The mixture was extracted with EtOAc (3×100 mL), washed with brine (200 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure 7 (0.982 g, 81%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc.

[0310] Ester 7: TLC (1:1 hexanes/EtOAc): $R_f = 0.59$; ^1H NMR (CDCl_3 , 500 MHz) δ 5.94 (dd, $J = 0.7, 1.5$ Hz, 1H), 4.80 (d, $J = 3.6$ Hz, 1H), 4.16 (dq, $J = 1.2, 7.2$ Hz, 1H), 3.89 (d, $J = 9.8$ Hz, 1H), 3.61 (s, 3H), 3.52 (s, 3H), 3.50 (dd, $J = 8.8, 9.6$ Hz, 1H), 3.42 (s, 3H), 3.38 (s, 3H), 3.20 (dd, $J = 3.6, 9.6$ Hz, 1H), 3.04 (dd, $J = 8.7, 9.8$ Hz, 1H), 2.20 (d, $J = 2.2$ Hz, 1H), 1.28 (t, $J = 7.1$ Hz,

1H); ¹³C NMR (CDCl₃, 125 MHz) δ 166.3, 153.9, 119.7, 97.6, 83.2, 82.5, 81.5, 75.1, 61.1, 60.5, 59.9, 59.1, 55.3, 15.0, 14.3; HR-ESI-MS *m/z* calcd. for C₁₅H₂₆O₇ [M+Na]⁺: 341.1574, found 341.1571.

[0311] Ethyl (E)-3-((2R,3R,4S,5R,6S)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)but-

2-enoate (8). Ester 7 (981.0 mg, 3.1 mmol) was dissolved in CH₂Cl₂ (40 mL) and cooled to -78 °C. A 1.0 M solution of DIBAL-H in toluene (9.3 mL, 9.3 mmol) was added drop wise. After 20 min, the reaction mixture was slowly warmed to rt over 2 h and then stirred at rt for 1 h. The mixture was recooled to -78 °C and EtOAc (5 mL) was added, followed by a satd. Solution of Rochelle's salt (100 mL). The mixture was warmed to rt and stirred at rt for 5 h until the mixture provided two clear phases. The crude product was recovered by extraction EtOAc (3 × 100 mL), washed with brine (100 mL), drying over Na₂SO₄ and concentration on a rotary evaporator. Pure 8 (0.845 g, 99%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:2 hexanes/EtOAc.

[0312] Allylic alcohol 8: TLC (1:1 hexanes/EtOAc): R_f = 0.09; ¹H NMR (CDCl₃, 500 MHz) δ 5.76 (dt, *J* = 2.1, 6.8 Hz, 1H), 4.79 (d *J* = 3.6 Hz, 1H), 4.25 (dq, *J* = 6.3, 13.1 Hz, 1H), 3.86 (d, *J* = 9.8 Hz, 1H), 3.62 (s, 3H), 3.52 (s, 3H), 3.50 (m, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 3.19 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.05 (dd, *J* = 8.8, 9.8 Hz, 1H), 1.73 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 134.9, 130.0, 97.6, 83.3, 81.8, 81.6, 75.6, 61.2, 60.3, 59.4, 59.2, 55.4, 12.5; HR-ESI-MS *m/z* calcd. for C₁₃H₂₄O₆ [M+Na]⁺: 299.1465, found 299.1463.

[0313] C. Synthesis of side chain component 16.

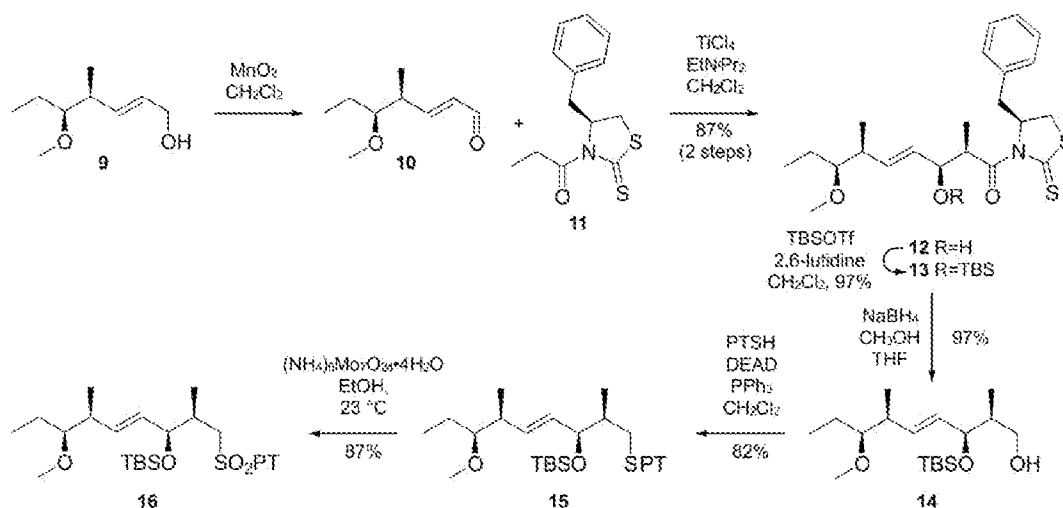
[0314] Sulfone **16** was prepared in 6 steps in 58% overall yield from allylic alcohol **9**, as shown in Scheme 2 (in the manuscript) and Scheme S2 (below). Gram scaled preparation of allylic alcohol **9** was accomplished in 11 steps and 27% overall yield from L-Phe.^{S1} The bulk of the effort in preparing **9** arose from the preparation of auxiliary **11**, which was readily recycled.^{S1} The following section provides a complete description of the synthetic procedures and spectroscopic properties of intermediated **10**, **12**, **13**, and **14-16**.

[0315] (2R,3S,6S,7S,E)-1-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-7-methoxy-2,6-dimethylnon-4-en-1-one (12). Allylic alcohol **9** [2] (1.12 g, 7.1 mmol) was dissolved in CH₂Cl₂ (50 mL) and MnO₂ (9.31 g, 107.2 mmol) was added as a powder. The slurry was vigorously stirred at rt until TLC indicated complete conversion, typically 24-36 h. The mixture was applied to a DCVC column containing 150 g SiO₂. The column was washed with EtOAc (3 × 100 mL) and dried via rotary evaporation. The resulting product, aldehyde **10** (1.12 g, 99% yield) was further dried via toluene azeotrope (3 × 10 mL) and used immediately without further purification. Crimmins auxiliary **11** (2.28 g, 8.6 mmol) was dissolved in CH₂Cl₂ (70 mL) and

cooled 0 °C. TiCl_4 (0.99 mL, 9.0 mmol) was added in a drop wise fashion. After 5 min at 0 °C, EtN^iPr_2 (1.64 mL, 9.4 mmol) was added in a drop wise fashion. The mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. Aldehyde **10** (1.12, 7.2 mmol) was dissolved in CH_2Cl_2 (25 mL) and added in a drop wise fashion. The mixture was stirred at -78 °C for 2.5 h then slowly warmed over 1.5 h to 0 °C. After 15 min at 0 °C, satd. NH_4Cl (50 mL) was added. The mixture was extracted with EtOAc (3×100 mL), washed with brine (50 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure adduct **12** (2.65 g, 87%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/ EtOAc .

[0316] Adduct **12**: TLC (3:1 hexanes/ EtOAc): $R_f = 0.39$; ^1H NMR (CDCl_3 , 500 MHz) δ 7.34 (m, 2H), 7.28 (m, 3H), 5.73 (ddd, $J = 1.3, 7.8, 15.6$ Hz, 1H), 5.51 (ddd, $J = 1.1, 5.8, 15.6$ Hz, 1H), 5.38 (ddd, $J = 4.0, 7.3, 11.3$ Hz, 1H), 4.79 (dq, $J = 3.2, 7.0$ Hz, 1H), 4.60 (m, 1H), 3.38 (dd, $J = 4.6, 11.8$ Hz, 1H), 3.35 (s, 3H), 3.24 (dd, $J = 4.0, 13.2$ Hz, 1H), 3.04 (dd, $J = 10.4, 13.2$ Hz, 1H), 2.92 (m, 1H), 2.89 (d, $J = 11.6$ Hz, 1H), 2.42 (td, $J = 6.8, 12.1$ Hz, 1H), 1.59 (s, OH, 1H), 1.53 (dq, $J = 4.3, 7.5, 14.9$ Hz, 1H), 1.41 (td, $J = 7.1, 14.1$ Hz, 1H), 1.18 (d, $J = 7.0$ Hz, 1H), 1.03 (d, $J = 6.8$ Hz, 1H), 0.89 (t, $J = 7.4$ Hz, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 201.8, 197.7, 136.5, 135.4, 129.6, 129.1, 128.7, 127.4, 86.3, 72.2, 69.1, 57.8, 43.4, 39.5, 37.1, 31.9, 23.8, 16.2, 11.4, 9.8; HR-ESI-MS m/z calcd. for $\text{C}_{22}\text{H}_{31}\text{NO}_3\text{S}_2$ $[\text{M}+\text{Na}]^+$: 444.1638, found 444.1639.

Scheme S2. Synthesis of side chain component **16**. Preparation of **16** required four chromatographic purifications as the crude products of **10** and **13** could be used without additional purification. Flash chromatography was required to purify intermediates **12**, **14**, **15** and **16**. The materials was stored at **16**, and used as described in Scheme 3 and Scheme S3.



[0317] (2*R*,3*S*,6*S*,7*S*,*E*)-1-((*S*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-((tert-butylidimethylsilyl)oxy)-7-methoxy-2,6-dimethylnon-4-en-1-one (**13**). Adduct **12** (3.22 g, 7.64

mmol) and 2,6-lutidine (2.65 mL, 22.9 mmol) were dissolved in CH₂Cl₂ (125 mL) and cooled 0 °C. TBSOTf (3.50 mL, 15.3 mmol) was added in a drop wise fashion. After 15 min at 0 °C, the mixture was warmed to 10 °C over 2 h. After 15 min at 10 °C, satd. NaHCO₃ (0.5 mL) was added and the mixture was stirred at rt for 30 min. The mixture was applied to a DCVC column containing 200 g SiO₂. The column was washed with EtOAc (3 × 200 mL) and dried via rotary evaporation. The resulting product 10 (3.98 g, 97% yield) was further dried via toluene azeotrope (3 × 50 mL) and used as is. Pure samples of 13 were obtained for spectroscopic analyses via flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc.

[0318] Adduct **13**: TLC (3:1 hexanes/EtOAc): R_f = 0.75; ¹H NMR (CDCl₃, 500 MHz) δ 7.34 (m, 2H), 7.28 (m, 3H), 5.59 (d, *J* = 6.9 Hz, 1H), 5.57 (d, *J* = 6.1 Hz, 1H), 5.33 (dddd, *J* = 1.2, 3.5, 7.4, 10.8 Hz, 1H), 4.80 (t, *J* = 6.6 Hz, 1H), 4.51 (t, *J* = 6.5 Hz, 1H), 3.35 (m, 1H), 3.31 (m, 1H), 3.30 (s, 3H), 3.19 (dd, *J* = 3.4, 13.1 Hz, 1H), 2.99 (dd, *J* = 11.0, 13.2 Hz, 1H), 2.87 (dd, *J* = 4.3, 6.7 Hz, 1H), 2.84 (d, *J* = 11.6 Hz, 1H), 2.33 (h, *J* = 6.7, 1H), 1.67 (m, 1H), 1.50 (ttd, *J* = 3.6, 7.5, 14.8 Hz, 1H), 1.38 (pq, 7.1, 14.1 Hz, 1H), 1.26 (dd, *J* = 6.5, 4.27 Hz, 1H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.84 (t, *J* = 7.5 Hz, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 201.2, 196.3, 136.8, 135.1, 131.1, 129.5, 129.1, 127.3, 86.2, 75.2, 69.3, 57.6, 45.2, 39.4, 37.2, 31.6, 26.1, 25.9, 23.8, 18.4, 16.0, 14.2, 9.7, -3.7, -4.2; HR-ESI-MS *m/z* calcd. for C₂₈H₄₅NO₃S₂Si [M+Na]⁺: 558.2502, found 558.2503.

[0319] (2*S*,3*S*,6*S*,7*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,6-dimethylnon-4-en-1-ol (**14**). Adduct 13 (1.33 g, 2.5 mmol) was dissolved in a mixture of THF (53 mL) and CH₃OH (13 mL) and cooled to 0 °C. NaBH₄ (159.0 mg, 19.9 mmol) was added in 3 portions over 5 min. The mixture was stirred at 0 °C for 1.5 h. If not complete via TLC analysis additional NaBH₄ could be added to complete the reaction. If complete, satd. NH₄Cl (25 mL) was added. The resulting mixture was extracted with EtOAc (3 × 100 mL), washed with brine (50 mL), dried over Na₂SO₄ and concentrated on a rotary evaporator. Pure alcohol 14 (802.0 mg, 97%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc.

[0320] Alcohol **14**: TLC (3:1 hexanes/EtOAc): R_f = 0.55; ¹H NMR (CDCl₃, 500 MHz) δ 5.51 (m, 2H), 4.13 (m, 2H), 3.62 (ddd, *J* = 2.8, 8.6, 11.2 Hz, 1H), 3.46 (ddd, 4.2, 7.4, 11.2 Hz, 1H), 3.34 (s, 3H), 3.03 (bs, 1H), 2.89 (ddd, *J* = 4.1, 6.1, 7.4 Hz, 1H), 2.41 (m, 1H), 1.95 (m, 1H), 1.76 (bs, 1H), 1.53 (dtd, *J* = 4.3, 7.5, 14.8 Hz, 1H), 1.38 (ddt, *J* = 6.7, 7.7, 13.5 Hz, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.78 (dd, *J* = 7.1 Hz, 3H), 0.06 (s, 3H), 0.02 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 134.9, 129.9, 86.4, 78.2, 65.9, 57.6, 41.5, 39.4, 25.9, 23.5, 18.2, 16.2, 13.0, 9.8, -4.0, -4.9; HR-ESI-MS *m/z* calcd. for C₁₈H₃₈NO₃Si [M+Na]⁺: 353.2482, found 353.2485.

[0321] **5-(((2*R*,3*S*,6*S*,7*S*,*E*)-3-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-2,6-dimethylnon-4-en-1-yl)thio)-1-phenyl-1*H*-tetrazole (15).** Alcohol 14 (1.01 g, 3.1 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (819.5 mg, 4.6 mmol) and PPh₃ (1.20 g, 4.6 mmol) were dissolved in THF (50 mL). The solution was cooled to 0 °C. DEAD (720.0 μL, 4.6 mmol) was added in a drop wise fashion until a yellow color persists. Additional DEAD up to 1.2 mmol could be added if needed if the color does not persist. After 30 min, the solution was allowed to warm to rt over 30 min. After 4 h at rt, H₂O (20 mL) was added. The resulting mixture was extracted with EtOAc (3 × 50 mL), washed with brine (25 mL), dried over Na₂SO₄ and concentrated on a rotary evaporator. Pure sulfide 15 (1.24 g, 82%) was obtained by flash chromatography eluting with a gradient of hexanes to 2:1 hexanes/EtOAc.

[0322] Sulfide **15**: TLC (3:1 hexanes/EtOAc): *R*_f = 0.70; ¹H NMR (CDCl₃, 500 MHz) δ 7.56 (m, 5H), 5.55 (ddd, *J* = 0.8, 7.7, 15.5 Hz, 1H), 5.43 (ddd, *J* = 1.0, 7.7, 15.5 Hz, 1H), 4.13 (dd, *J* = 0.9, 4.1, 6.9 Hz, 1H), 3.51 (dd, *J* = 6.5, 12.7 Hz, 1H), 3.33 (s, 3H), 3.25 (dd, *J* = 7.3, 12.7 Hz, 1H), 2.89 (ddd, *J* = 4.3, 6.1, 7.0 Hz, 1H), 2.38 (h, *J* = 6.9 Hz, 1H), 2.03 (dh, *J* = 4.1, 6.8 Hz, 1H), 1.51 (dq, *J* = 4.3, 7.5, 14.9 Hz, 1H), 1.38 (pd, *J* = 7.3, 14.4 Hz, 1H), 1.01 (d, *J* = 6.9 Hz, 1H), 1.00 (d, *J* = 6.8 Hz, 1H), 0.88 (s, 9H), 0.88 (t, *J* = 7.4 Hz, 1H), 0.03 (s, 3H), 0.00 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 155.0, 135.0, 133.9, 130.4, 130.1, 129.9, 124.0, 86.3, 76.1, 57.7, 40.1, 39.3, 36.8, 26.0, 23.7, 18.3, 15.9, 14.6, 9.7, -3.8, -4.7; HR-ESI-MS *m/z* calcd. for C₂₅H₄₂N₄O₂SSi [M+Na]⁺: 513.2690, found 513.2693.

[0323] **5-(((2*R*,3*S*,6*S*,7*S*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2,6-dimethylnon-4-en-1-yl)sulfonyl)-1-phenyl-1*H*-tetrazole (16).** Sulfide 15 (1.95 g, 4.0 mmol) was dissolved in EtOH (40 mL) and cooled to 0 °C. In a vial, a 30% v/v solution of H₂O₂ (3.6 mL) was added to solid (NH₄)₆Mo₇O₂₄•4H₂O (2.45 g, 20.0 mmol) and shaken until the bubbling ceased (~ 5 min). This solution was then added to the cooled solution of 15 in EtOH via glass pipette. After 20 min, the mixture was warmed to rt and stirred overnight. The resulting mixture was diluted with H₂O (50 mL), extracted with EtOAc (3 × 50 mL), washed with brine (25 mL), dried over Na₂SO₄ and concentrated on a rotary evaporator. Pure sulfone 16 (1.82 g, 87%) was obtained by flash chromatography eluting with a gradient of hexanes to 2:1 hexanes/EtOAc. The remainder of the material was either the sulfide 15 (*R*_f higher than 16), the corresponding sulfoxide (*R*_f higher than 16) or a mixture of both. These materials were readily resubmitted to the oxidation procedure to provide additional samples of 16.

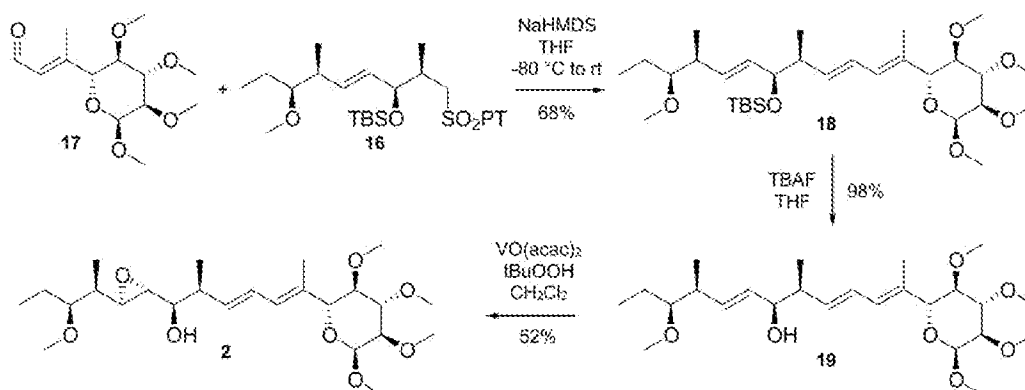
[0324] Sulfone **16**: TLC (3:1 hexanes/EtOAc): *R*_f = 0.66; ¹H NMR (CDCl₃, 500 MHz) δ 7.68 (m, 2H), 7.61 (m, 3H), 5.61 (ddd, *J* = 1.1, 7.9, 15.6 Hz, 1H), 5.36 (ddd, *J* = 1.1, 7.0, 15.6 Hz, 1H), 4.18 (dd, *J* = 4.3, 6.7 Hz, 1H), 4.07 (dd, *J* = 3.4, 14.4 Hz, 1H), 3.46 (dd, *J* = 9.1, 14.4 Hz,

1H), 3.34 (s, 3H), 2.90 (ddd, $J = 4.4, 6.0, 7.0$ Hz, 1H), 2.43 (m, 1H), 2.40 (tt, $J = 6.5, 13.6$ Hz, 1H), 1.51 (m, 1H), 1.39 (pq, $J = 7.3, 14.4$ Hz, 1H), 1.11 (d, $J = 6.9$ Hz, 3H), 1.02 (d, $J = 6.8$ Hz, 3H), 0.90 (t, $J = 7.4$ Hz, 3H), 0.89 (t, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 154.2, 136.2, 133.3, 131.6, 129.8, 128.9, 125.3, 86.2, 75.8, 58.5, 57.7, 39.3, 35.3, 26.0, 23.7, 18.3, 15.9, 15.3, 9.8, -4.0, -4.8; HR-ESI-MS m/z calcd. for $\text{C}_{25}\text{H}_{42}\text{N}_4\text{O}_4\text{SSi}$ $[\text{M}+\text{Na}]^+$: 545.2588, found 545.2587.

[0325] D. Procedures for the component coupling to alkene 19.

[0326] A two-step procedure was used to prepare alkene 18 from side chain component 16 and core component 9, as shown in Scheme 3 (in the manuscript) and Scheme S3 (below). The following section provides a complete description of the synthetic procedures and spectroscopic properties of intermediates 19-18.

Scheme S3. Synthesis of epoxide 2. Preparation of 16 required 3 chromatographic purifications as the crude product 19 as shown in Scheme S1 could be used without additional purification.



[0327] (*E*)-3-((2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5,6-Tetramethoxytetrahydro-2*H*-pyran-2-yl)but-2-enal (19). Allylic alcohol 8 (468.2 mg, 1.7 mmol) was dissolved in CH_2Cl_2 (20 mL) and MnO_2 (2.21 g, 25.4 mmol) was added as a powder. The slurry was vigorously stirred at rt until TLC indicated complete conversion, typically 20-24 h. The mixture was applied to a DCVC column containing 80 g SiO_2 . The column was washed with EtOAc (3×50 mL) and dried via rotary evaporation. The resulting product, aldehyde 19 (459.2 mg, 99% yield) was further dried via toluene azeotrope (3×10 mL) and used as is.

[0328] Aldehyde 19: TLC (1:1 hexanes/EtOAc): $R_f = 0.38$; ^1H NMR (CDCl_3 , 500 MHz) δ 10.11 (d, $J = 7.8$ Hz, 1H), 6.12 (d, $J = 7.1$ Hz, 1H), 4.83 (d, $J = 3.6$ Hz, 1H), 4.00 (d, $J = 9.8$ Hz, 1H), 3.64 (s, 3H), 3.54 (s, 3H), 3.53 (m, 1H), 3.45 (s, 3H), 3.41 (s, 3H), 3.22 (dd, $J = 3.6, 9.7$ Hz, 1H), 3.06 (dd, $J = 8.8, 9.8$ Hz, 1H); 2.23 (d, $J = 1.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ

191.2, 157.9, 129.5, 97.9, 83.5, 82.8, 81.8, 74.5, 61.2, 60.7, 59.3, 55.6, 14.3; HR-ESI-MS m/z calcd. for $C_{13}H_{22}O_6$ $[M+Ma]^+$: 297.1309, found 297.1306.

[0329] tert-Butyl(((2E,4E,6S,7S,8E,10S,11S)-11-methoxy-6,10-dimethyl-2-((2R,3R,4S,5R,6S)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)trideca-2,4,8-trien-7-

5 **yl)oxy)dimethylsilane (18).** Highly dry THF for this procedure was required and was distilled fresh from Na benzophenone ketyl prior to use. Sulfone 16 (568.4 mg, 1.09 mmol) was dissolved in freshly distilled THF (30 mL) and cooled to -78 °C. A 2 M solution of NaHMDS in THF (572.0 mL, 1.14 mmol) was added in a drop wise fashion. After 1 h at -78°C, freshly prepared and dried aldehyde 19 (328.2 mg, 1.19 mmol) was added in THF (15 mL). The solution was
10 warmed to rt over 1.5 h and stirred overnight. The resulting mixture was diluted with satd. NH_4Cl (50 mL), extracted with EtOAc (3×200 mL), washed with brine (25 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure alkene 18 (423.1 mg, 68%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc. This was accompanied by ~11% of the chromatographically isolable *cis*-C8,C9 isomer of 18 indicating that the reaction
15 occurred with ~6:1 ratio of *trans* : *cis*.

[0330] Alkene 18: TLC (1:1 hexanes/EtOAc): R_f = 0.62; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.22 (ddd, J = 1.2, 10.8, 15.8 Hz, 1H), 6.08 (dd, J = 1.5, 10.7 Hz, 1H), 5.69 (dd, J = 7.6, 15.2 Hz, 1H), 5.38 (m, 2H), 4.79 (d, J = 3.6 Hz, 1H), 3.90 (dd, J = 5.5, 6.4 Hz, 1H), 3.85 (d, J = 9.8 Hz, 1H), 3.62 (s, 3H), 3.52 (s, 3H), 3.49 (m, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 3.33 (s, 3H), 3.19 (dd, J = 3.6,
20 9.6 Hz, 1H), 3.07 (dd, J = 8.8, 9.8 Hz, 1H), 2.86 (dt, J = 4.3, 6.7 Hz, 1H), 2.31 (m, 2H), 1.79 (d, J = 1.3 Hz, 3H), 1.52 (m, 1H), 1.38 (pd, J = 7.4, 14.2 Hz, 1H), 1.00 (d, J = 6.8 Hz, 6H), 0.88 (s, 9H), 0.87 (t, J = 7.4 Hz, 3H), 0.02 (s, 3H), -0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.7, 134.1, 131.8, 131.3, 130.5, 125.4, 97.6, 86.3, 83.4, 82.0, 81.9, 77.8, 76.2, 61.2, 60.2, 59.2, 57.7, 55.2, 44.2, 39.7, 26.0, 23.7, 18.4, 16.4, 15.5, 12.7, 9.4, -3.9, -4.6; HR-ESI-MS m/z calcd. for
25 $C_{31}H_{58}O_7Si$ $[M+Na]^+$: 593.3844, found 593.3846.

[0331] E. Procedures for synthesis of epoxides 2 and 20.

[0332] A two-step procedure was used to convert alkene 19 to the targeted epoxide 2 or 20. The following section provides a complete description of the synthetic procedures and spectroscopic properties of intermediates 19 and epoxide 2, and the corresponding epoxide
30 isomer 20.

[0333] (2E,4E,6S,7S,8E,10S,11S)-11-methoxy-6,10-dimethyl-2-((2R,3R,4S,5R,6S)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)trideca-2,4,8-trien-7-ol (19). Alkene 18 (79.2 mg, 0.14 mmol) was dissolved in wet THF (8 mL) in an Oakridge 15 mL Teflon tube (Nalgene). Solid TBAF (108.8 mg, 0.41 mmol) was added and the mixture was stirred at rt until TLC

analysis showed complete conversion (typically 5-6 h). NH_4Cl (5 mL) was added and the resulting mixture was extracted with EtOAc (3×25 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. Pure alkene 19 (54.2 mg, 86%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc.

[0334] Alcohol **19**: TLC (1:1 hexanes/EtOAc): $R_f = 0.41$; ^1H NMR (CDCl_3 , 500 MHz) δ 6.33 (ddd, $J = 1.1, 10.9, 15.2$ Hz, 1H), 6.10 (dd, $J = 1.6, 10.7$ Hz, 1H), 5.64 (dd, $J = 8.2, 15.2$ Hz, 1H), 5.58 (dd, $J = 7.9, 15.5$ Hz, 1H), 5.45 (dd, $J = 6.9, 15.5$ Hz, 1H), 4.79 (d, $J = 3.6$ Hz, 1H), 3.97 (m, 2H), 3.85 (d, $J = 9.8$ Hz, 1H), 3.62 (s, 3H), 3.52 (s, 3H), 3.49 (m, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 3.34 (s, 3H), 3.19 (dd, $J = 3.6, 9.6$ Hz, 1H), 3.08 (dd, $J = 8.8, 9.8$ Hz, 1H), 2.89 (dt, $J = 4.1, 6.6$ Hz, 1H), 2.43 (m, 1H), 2.37 (m, 1H), 1.80 (d, $J = 1.3$ Hz, 1H), 1.52 (dq, $J = 4.1, 7.4, 14.8$ Hz, 1H), 1.38 (pd, $J = 7.3, 14.4$ Hz, 1H), 1.03 (d, $J = 6.8$ Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 136.9, 135.4, 132.5, 130.2, 130.0, 127.0, 97.6, 86.3, 83.4, 82.0, 81.9, 76.4, 76.1, 61.1, 60.3, 59.2, 57.7, 55.3, 43.5, 39.5, 23.7, 16.3, 15.8, 12.8, 9.6; HR-ESI-MS m/z calcd. for $\text{C}_{25}\text{H}_{44}\text{O}_7$ $[\text{M}+\text{Na}]^+$: 479.2979, found 479.2981.

[0335] **(1R,2S,3E,5E)-1-((2R,3R)-3-((2R,3S)-3-methoxypentan-2-yl)oxiran-2-yl)-2-methyl-6-((2R,3R,4S,5R,6S)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)hepta-3,5-dien-1-ol (2).**

Alkene 18 (42.1 mg, 73.8 μmol) was dissolved in CH_2Cl_2 (2 mL) in a 2 dram vial equipped with a Teflon cap. Solid $\text{VO}(\text{acac})_2$ (58.7 mg, 221.4 μmol) was added and the mixture was cooled to -78 °C. A solution of 5.5 M solution t-BuOOH in hexanes (58.7 μL , 332.0 μmol) was added and the mixture was warmed for 2 h over -20 °C. The flask was then stored at -20 °C for 6 h at which point dimethylsulfide (100 μL) was added. After 15 min at -20 °C, the mixture was warmed to rt and stirred for an additional 30 min. The resulting contents were flushed through a pad of SiO_2 (10 g) flushing with EtOAc (20 mL), and concentrated on a rotary evaporator. Epoxide 2 (22.8 mg, 52%) was obtained by flash chromatography eluting with a gradient of hexanes to 1:1 hexanes/EtOAc, followed by pTLC in a tank containing 2:1 hexanes/EtOAc.

[0336] Epoxide **2**: TLC (1:1 hexanes/EtOAc): $R_f = 0.39$; ^1H NMR (C_6D_6 , 500 MHz) δ 6.45 (ddd, $J = 1.1, 10.9, 15.1$ Hz, 1H), 6.30 (dd, $J = 1.1, 11.0$ Hz, 1H), 5.66 (dd, $J = 8.5, 15.1$ Hz, 1H), 4.68 (d, $J = 3.6$ Hz, 1H), 4.16 (d, $J = 9.7$ Hz, 1H), 3.84 (dd, $J = 8.7, 9.6$ Hz, 1H), 3.62 (s, 3H), 3.36 (s, 3H), 3.26 (s, 3H), 3.21 (m, 3H), 3.15 (s, 3H), 3.11 (s, 3H), 2.89 (dd, $J = 2.3, 6.8$ Hz, 1H), 2.85 (dd, $J = 2.3, 4.6$ Hz, 1H), 2.82 (td, $J = 4.8, 7.4$ Hz, 1H), 2.42 (h, $J = 7.6$ Hz, 1H), 1.85 (d, $J = 1.3$ Hz, 3H), 1.74 (bs, 1H), 1.55 (dt, $J = 4.3, 6.9$ Hz, 1H), 1.48 (qd, $J = 7.3, 14.6$ Hz, 1H), 1.36 (m, 1H), 1.14 (d, $J = 6.9$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.84 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (C_6D_6 , 125 MHz) δ 136.3, 133.2, 129.4, 126.6, 97.7, 83.5, 83.4, 82.2, 82.2, 76.2, 71.7, 60.6, 59.7,

58.8, 57.7, 57.2, 56.7, 54.6, 41.7, 38.7, 23.5, 16.2, 12.4, 10.4, 9.6; HR-ESI-MS m/z calcd. for $C_{25}H_{44}O_8$ $[M+Na]^+$: 495.2928, found 495.2926.

[0337] F. Biological Assays and Screens.

[0338] Primary chronic lymphocytic leukemia (CLL) cells sampling and cell culture.

5 Peripheral blood mononuclear cells (PBMC) from CLL patients were obtained from the CLL Research Consortium (CRC) tissue bank. This protocol was approved by the institutional review board (IRB) of the University of California, San Diego. Blood samples were taken from two CLL patients after written informed consent for blood sample collection and confirmation of diagnosis for CLL diseases, The PBMCs were separated from heparinized venous blood by density
10 gradient centrifugation using Ficoll-Hypaque media (GE Healthcare). The samples with >95% positivity for leukemic B cells was confirmed by staining for CD5 and CD19 followed by assessment using flow cytometry. CLL-B cells were maintained in RPMI 1640 medium supplemented with 10% FBS, 2 mM L-glutamine, and 100 U/mL of penicillin and 100 μ g/mL of streptomycin at 37 °C in an atmosphere containing 5% CO₂.

15 **[0339] *In vitro* cytotoxicity analyses.** The CLL-B cells (3×10^5 cells) were treated for 48 h with 10, 100, 300, and 1000 nM of **1a**, **1b**, **2** or **19** at 37 °C in an atmosphere containing 5% CO₂. Fludarabine (F-ara-A) dosed at 10 μ M was used as a control. The cells were centrifuged and labeled with CD19/CD5/DiOC6 and subjected to flow cytometry. The data was analyzed using FlowJo software. In order to discriminate the compound specific-induced apoptosis *versus*
20 background spontaneous cell death from in vitro culture conditions, we calculated the percentage of specific induced apoptosis (% SIA) using the following formula: % SIA = [(compound induced apoptosis – media only spontaneous apoptosis) / (100 – media only spontaneous apoptosis)] $\times$ 100. The dose-response curves were plotted to determine IC₅₀ values using the GraphPad Prism version 6.0c software.

25 **[0340] Reverse transcriptase PCR (RT-PCR) analyses:** CLL-B (5×10^6 cells/well) were treated with a given dose of compound from a DMSO stock solution over 4 h. RNA isolation and cDNA preparation, PCR reaction was performed in 20 μ L of reaction volume as described previously.^{S3} PCR conditions give by incubation at 94 °C for 3 min; 35 cycles of 94 °C for 30 s, 55-60 °C (annealing temperature: 55 °C for *GAPDH*, 53.6 °C for *RNU6A*, 58 °C for *DNAJB1*, 54
30 °C for *SF3A1*, 55 °C for *PRPF4*, 55 °C for *ARF4*, and 55 °C for *U2AF2*) for 30 s, and 72 °C for 1 min; followed by 72 °C for 5 min. PCR products were separated on a 2% agarose gel and stained with ethidium bromide. Details of the primers used for RT-PCR are provided in Table 1.

[0341] Quantitative reverse transcription-PCR (qRT-PCR): cDNA was prepared using identical methods as used for RT-PCR analysis. The amount of unspliced RNA for different

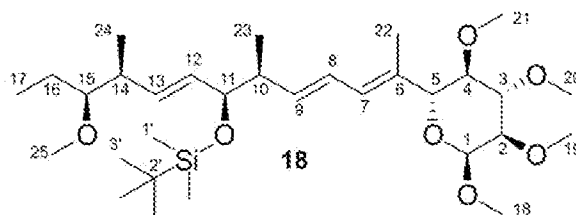
genes was determined using Power SYBR Green PCR master mix (Applied Biosystems) by qRT-PCR using specific primers designed for detection of the intron of each gene (Table 2). The qPCR was performed using 5 pM of each primer on 20 ng of the obtained cDNA. PCR conditions were as follows: one cycle of 50 °C for 2 min (UDG Incubation), one cycle of 95 °C for 10 min (UDG Inactivation), followed by 95 °C for 15 sec; 60 °C for 30 s for 40 cycles and adding a step for dissociation using a 7900 HT Fast Real Time PCR System (Applied Biosystems). Unspliced RNA levels were calculated using 2- $\Delta\Delta$ CT method.^{S4} GAPDH was used as a control for normalization.

Table 1. RT-PCR forward (FP) and reverse (RP) primers as defined by the exon, sequence and annealing temperature (Ta).

Primer	Direction	Exon	5' Sequence 3'	SEQ ID NO:	Ta
<i>DNAJB1</i>	FP	Exon 2	GAACCAAATCACTTTCCCCAA GGAAGG	1	58
	RP	Exon 3	AATGAGGTCCCCACGTTTCTCG GGTGT	2	
<i>SF3A1</i>	FP	Exon 6	GGCCTATGCTCAGATCGACT	3	54
	RP	Exon 7	ATCAGACTCGACCTCCATC	4	
<i>PRPF4</i>	FP	Exon 8	GAGTGGGCTTTGCAAGCTCT	5	55
	RP	Exon 9	CTGTCGAGACTCCAAAGCTT	6	
<i>ARF4</i>	FP	Exon 2	GATTGGATGCTGCTGGCAA	7	55
	RP	Exon 3	CACCAACATCCCATACTGTG	8	
<i>U2AF2</i>	FP	Exon 4	AGGTCCGTAAATACTGGGAC	9	55
	RP	Exon 5	CTCAGTGATGCCAAAGGGGA	10	
<i>GAPDH</i>	FP	Exon 2	TGGATATTGTTGCCATCATGA	11	55
	RP	Exon 3	TGGAATCATATTGGAACATGT	12	
<i>RNU6A</i>	FP	Intronless	CGCTTCGGCAGCACATATAC	13	53.6
	RP	Intronless	GAATTTGCGTGTCATCCTT	14	
<i>H2A</i>	FP	Intronless	ATGGCTGCGGTCCTCGAGTAT	15	61.0
	RP	Intronless	TCAGTTCCTCGTTGCGGA	16	

Table 2. Sequences of the qRT-PCR primers used in this study.

qRT-PCR primers			
Primer	Location	5' Sequence 3'	SEQ ID NO:
<i>DNAJB1</i> -FP	Intron 2	GGCCTGATGGGTCTTATCTATGG	19
<i>DNAJB1</i> -RP	Intron 2	TTAGATGGAAGCTGGCTCAAGAG	18
<i>RIOK3</i> -FP	Intron 3	CCTTATTGTGACAACCTTCATTGAG	19
<i>RIOK3</i> -RP	Intron 3	TGAAGATTTACTTAGGAGCACA	20
<i>SF3A1</i> -FP	Intron 6	GGTGTTCCCAGAGAGCAGTAG	21
<i>SF3A1</i> -RP	Intron 6	GCTGGGGCCATGTCTGTTTT	22
<i>PRPF4</i> -FP	Intron 8	TGCTTGACACTCAGACCCCA	23
<i>PRPF4</i> -RP	Intron 8	AAAATGCCAGAGTGTGACTGC	24
<i>ARF4</i> -FP	Intron 2	GTAAGAAAGTTTACAGATGACTT	25
<i>ARF4</i> -RP	Intron 2	AGATAATCAACATGCTTAACAAA	26
<i>U2AF2</i> -FP	Intron 4	TCTCCGTCAGTCATTCCCCT	27
<i>U2AF2</i> -RP	Intron 4	TCATTCCCCTGTCAACCACG	28
<i>GAPDH</i> -FP	Exon 3	TGGTCACCAGGGCTGCTT	29
<i>GAPDH</i> -RP	Exon 4	AGCTTCCCGTTCTCAGCCTT	30
FP: forward primer; RP reverse primer			

[0342] Tables of NMR results.5 **Table 3.** NMR data (¹H 500 MHz, ¹³C 100 MHz, CDCl₃) for alkene 18

No.	δ_H (J in Hz)	δ_C , type	gCOSY	HMBC
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1	4.79 d (3.6)	97.6, CH	2	2,5,18
2	3.19 dd (3.6, 9.6)	81.9, CH	1,3	3,19
3	3.49 m	83.4, CH	2,4	2,4,20
4	3.07 dd (8.8, 9.8)	82.0, CH	3,5	3,5,6,21
5	3.85 d (9.8)	76.2, CH	4	4,6,22
6		131.3, C		
7	6.08 dd (1.5, 10.7)	130.5, CH	8,22	5,8,9,22
8	6.22 ddd (1.2, 10.8, 15.2)	125.4, CH	7,9	7,10
9	5.69 dd (7.6, 15.2)	138.7, CH	8,10	7,10,11,23
10	2.31 m	44.2, CH	9,11,23	8,9,11,23
11	3.90 (5.5, 6.4)	77.8, CH	10,12	9,10,12,13,23
12	5.38 m	131.8, CH	11,13	11,14
13	5.38 m	134.1, CH	12,14	11,14,24
14	2.31 m	39.7, CH	13,15,24	12,13,15,16,24
15	2.86 dt (4.3, 6.7)	86.3, CH	14,16	13,19,24,25
16a	1.52 m	23.7, CH ₂	15,16b,19	14,19
16b	1.38 pd (7.4, 14.2)		15,16a,19	14,15,19
19	0.87 t (7.4)	9.4, CH ₃	16a,16b	15,16
18 ^a	3.39 s	55.2, CH ₃		1
19 ^a	3.41 s	60.2, CH ₃		2
20 ^a	3.62 s	61.2, CH ₃		3
21 ^b	3.52 s	59.2, CH ₃		4
22	1.79 d (1.3)	12.7, CH ₃	7	5,6,7,8
23	1.00 d (6.8)	15.5, CH ₃	10	9,10,11
24	1.00 d (6.8)	16.4, CH ₃	14	13,14,15
25 ^c	3.33 s	57.7, CH ₃		15
1a'	0.02 s	-4.6, CH ₃		
1b'	-0.01 s	-3.9, CH ₃		

2'		18.4, C		
3'	0.88 s	26.0, CH ₃		

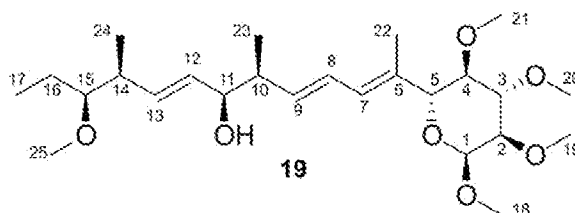
^a Protons and carbons at 18 and 20 were assigned by ¹H, ¹³C HMBC data.

^b Protons and carbons at 19 and 21 were assigned by ¹H, ¹³C HMBC data. However, they could not be unambiguously established due to the close proximity of C2 and C4.

^b The assignment of the protons and carbons at 25 was further confirmed by the fact that the chemical shifts of protons and carbons at 18, 19, 20 and 21 were comparable to that in precursors such as allylic alcohol **8**.

5

Table 4. NMR data (1H 500 MHz, 13C 100 MHz, CDCl₃) for alcohol **19**



No.	δ_H (J in Hz)	δ_C , type	gCOSY	HMBC
1	4.79 d (3.6)	97.6, CH	2	2,5,18
2	3.19 dd (3.6, 9.6)	81.9, CH	1,3	3,19
3	3.49 m	83.4, CH	2,4	2,4,20
4	3.08 dd (8.6, 9.8)	82.0, CH	3,5	3,5,6,21
5	3.85 d (9.8)	76.1, CH	4	4,6,7,22
6		130.2, C		
7	6.10 dd (1.6, 10.7)	130.0, CH	8,22	5,8,9,22
8	6.33 ddd (1.1, 10.9, 15.2)	127.0, CH	7,9	7,10
9	5.64 dd (8.2, 15.2)	136.9, CH	8,10	7,10,11,23
10	2.43 m	43.5, CH	9,11,23	8,9,11,23
11	3.97 m	76.4, CH	10,12	9
11-OH	3.97 m			11
12	5.45 dd (6.9, 15.5)	132.5, CH	11,13	11,13,14
13	5.58 dt (7.9, 15.5)	135.4, CH	12,14	11,12,14,24

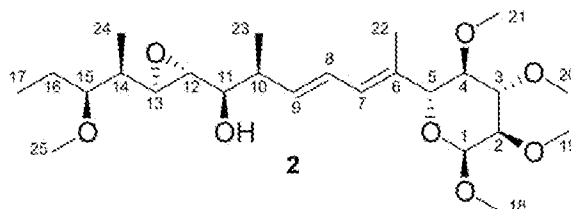
14	2.37 m	39.5, CH	13,15,24	12,13,15,16,24
15	2.89 dt (4.1, 6.6)	86.3, CH	14,16	13,19,24,25
16a	1.52 dqd (4.2, 7.4, 14.8)	23.7, CH ₂	15,16b,19	19
16b	1.39 pd (7.3, 14.4)		15,16a,19	14,15,19
19	0.88 t (7.4)	9.6, CH ₃	16a,16b	15,16
18 ^a	3.38 s	57.7, CH ₃		1
19 ^a	3.41 s	60.3, CH ₃		2
20 ^a	3.62 s	61.1, CH ₃		3
21 ^a	3.52 s	59.2, CH ₃		4
22	1.80 d (1.3)	12.8, CH ₃	7	5,6,7,8
23	1.03 d (6.8)	16.3, CH ₃	10	9,10,11
24	1.01 d (6.8)	15.8, CH ₃	14	13,14,15
25 ^b	3.34 s	55.3, CH ₃		15

^a Protons at carbons at 18, 19, 20 and 21 were assigned by ¹H, ¹³C HMBC data.

^b The assignment of the protons and carbons at 25 was further confirmed by the fact that the chemical shifts of protons and carbons at 18, 19, 20 and 21 were comparable to that in precursors such as allylic alcohol **8**.

5

Table 5. NMR data (1H 500 MHz, 13C 100 MHz, C6D6) for epoxide **2**



No.	δ_H (J in Hz)	δ_C , type	gCOSY	HMBC
1	4.68 d (3.6)	97.7, CH	2	2,5,18
2	3.21 m	82.2, CH ^b	1,3	3,19
3	3.84 dd (8.7, 9.6)	83.4, CH	2,4	2,4,20
4	3.21 m	82.2, CH ^b	3,5	3,5,6,21

5	4.16 d (9.7)	76.2, CH	4	4,6,7,22
6		133.2, C		
7	6.30 dd (1.1, 11.0)	129.4, CH	8,22	5,8,9,22
8	6.45 ddd (1.1, 10.9, 15.1)	126.6, CH	7,9	6,7,10
9	5.66 dd (8.5, 15.1)	136.3, CH	8,10	7,10,11,23
10	2.42 h (7.6)	41.7, CH	9,11,23	8,9,11,12,23
11	3.21 m	71.7, CH	10,12	9
11-OH	1.74 m			9,11
12	2.85 dd (2.3, 4.6)	58.8, CH	11 ^c	11
13	2.89 dd (2.3, 6.8)	57.7, CH	14 ^c	12,24
14	1.55 dt (4.3, 6.9)	38.7, CH	13,15,24	13, 24
15	2.82 td (4.8, 7.4)	83.5, CH	14,16	13,19,24,25
16a	1.48 qd (7.3, 14.6)	23.5, CH ₂	15,16b,19	14,15,19
16b	1.36 m		15,16a,19	15,19
19	0.84 t (7.4)	9.6, CH ₃	16a,16b	15,16
18 ^a	3.15 s	54.6, CH ₃		1
19 ^a	3.26 s	57.2, CH ₃		2
20 ^a	3.62 s	60.6, CH ₃		3
21 ^a	3.36 s	59.7, CH ₃		4
22	1.85 d (1.3)	12.4, CH ₃	7	5,6,7
23	1.14 d (6.9)	16.2, CH ₃	10	9,10,11
24	1.00 d (6.8)	10.4, CH ₃	14	13,14,15
25 ^b	3.11 s	56.7, CH ₃		15

^a Protons at carbons at 18, 19, 20 and 21 were assigned by ¹H, ¹³C HMBC data.

^b Protons at carbons 2 and 4 were assigned by ¹H, ¹³C HMBC data.

^c The gCOSY peak for 12,13 was not identified due to the proximity of protons at C12 and C13.

5 [0343] Conclusion

[0344] We describe herein the preparation of a carbohydrate-derived spliceosome inhibitor **2** in a total of 22 steps, including 12 longest linear steps from common building blocks (auxiliary **11**, D-glucose and propionaldehyde). Complete *in vitro* and *in vivo* pharmacological analyses can be conducted, and this improved stability along with its improved solubility in aqueous buffers suggests an important advance in optimization of splice modulators.

[0345] Overall, this development offers several medicinal chemical benefits. First, it demonstrates that the pyran or macrolide core commonly associated with the known spliceosome inhibitors can be replaced with materials directly available from monosaccharides in the chiral pool. Second, it provides a means to prepare highly stable materials that lack rapid degradation and/or metabolic instability. Third, the use of a carbohydrate motif offers ready access to explore the SAR contained within the core unit (macrolide of **1a-1b** or pyran in **1c**, FIG. 1). Here, one can envision application of the described route to provide derivatives with expanded functionality at the anomeric C1 center, stereoisomers at C1-C4 positions, as well as explore the use of deoxygenated materials and alternative ethers at C1-C4. While to date there has been no structural information on the complex of any established splice modulator with the Sf3b component of the spliceosome, the subsequent integration of a rational design could deliver a carbohydrate-derived splice modulator with enhanced binding and reduced pharmacological risk.

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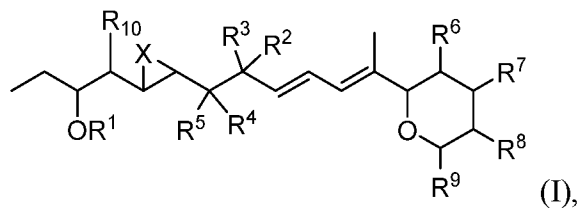
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[0348] *Example 2 – Synthesis of Carbohydrate-Derived Splice Modulators Q1-Q10*

[0349] Compounds in Embodiments Q1-Q10 were synthesized in similar manner as described above (e.g., Schemes 1-3) and confirmed by proton and carbon NMR and high-resolution mass spectrometry.

WHAT IS CLAIMED IS:

1. A compound with structure of Formula (I):



wherein,

X is -O- or -C(R²⁶)(R²⁷)-;

R²⁶ is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -OR²⁸, -OC(O)R²⁸, -OC(O)OR²⁸, or -OC(O)NR²⁸R²⁹;

R²⁷ is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -OR³⁰, -OC(O)R³⁰, -OC(O)OR³⁰, or -OC(O)NR³⁰R³¹;

R¹ is hydrogen, substituted or unsubstituted alkyl, -C(O)R¹¹, or -C(O)OR¹¹;

R² is hydrogen, halogen, substituted or unsubstituted alkyl, -OR¹², -OC(O)R¹², -OC(O)OR¹², or -OC(O)NR¹²R¹³;

R³ is hydrogen, halogen, substituted or unsubstituted alkyl, -OR¹⁴, -OC(O)R¹⁴, -OC(O)OR¹⁴, or -OC(O)NR¹⁴R¹⁵;

R⁴ is hydrogen, halogen, substituted or unsubstituted alkyl, -OR¹⁶, -OC(O)R¹⁶, -OC(O)OR¹⁶, or -OC(O)NR¹⁶R¹⁷;

R⁵ is hydrogen, halogen, substituted or unsubstituted alkyl, -OR¹⁸, -OC(O)R¹⁸, -OC(O)OR¹⁸, or -OC(O)NR¹⁸R¹⁹;

R^6 is hydrogen, $-OR^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, or $-OC(O)OR^{20}$.

R^7 is hydrogen, $-OR^{21}$, $-C(O)R^{21}$, $-C(O)OR^{21}$, $-OC(O)R^{21}$, or $-OC(O)OR^{21}$.

R^8 is hydrogen, $-OR^{22}$, $-C(O)R^{22}$, $-C(O)OR^{22}$, $-OC(O)R^{22}$, or $-OC(O)OR^{22}$.

R^9 is hydrogen, $-OR^{23}$, $-C(O)R^{23}$, $-C(O)OR^{23}$, $-OC(O)R^{23}$, or $-OC(O)OR^{23}$.

R¹⁰ is hydrogen, substituted or unsubstituted alkyl, -OR²⁴, -OC(O)R²⁴, -OC(O)OR²⁴, or -OC(O)NR²⁴R²⁵; and

$R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{28}, R^{29}, R^{30}$,
and R^{31} are independently hydrogen, substituted or unsubstituted alkyl, substituted or
unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

2. The compound of claim 1, wherein:

X is -O-;

R^1 is hydrogen or unsubstituted C_1 - C_4 alkyl; and

R^{10} is hydrogen or unsubstituted C_1 - C_4 alkyl.

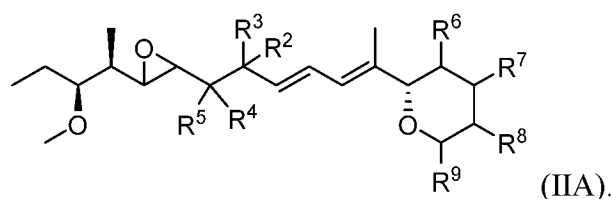
3. The compound of claim 2, wherein:

R^1 is hydrogen or $-CH_3$; and

R^{10} is hydrogen or $-CH_3$.

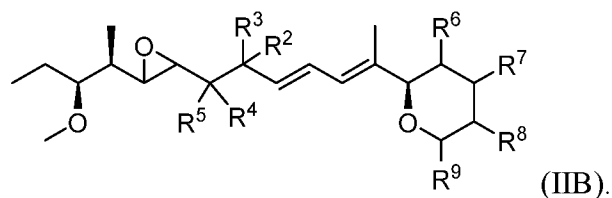
4. The compound of claim 3, the compound having a structure of Formula

(IIA):



5. The compound of claim 3, the compound having a structure of Formula

(IIB):



6. The compound of claim 1, wherein:

X is $-C(R^{26})(R^{27})-$;

R^1 is hydrogen or unsubstituted C_1 - C_4 alkyl; and

R^{10} is hydrogen or unsubstituted C_1 - C_4 alkyl.

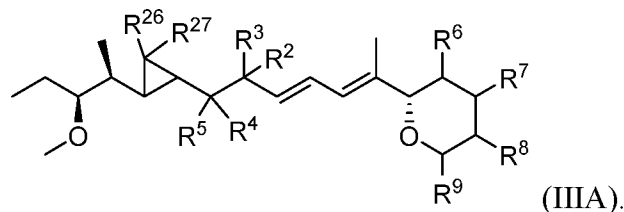
7. The compound of claim 6, wherein:

R^1 is hydrogen or $-CH_3$; and

R^{10} is hydrogen or $-CH_3$.

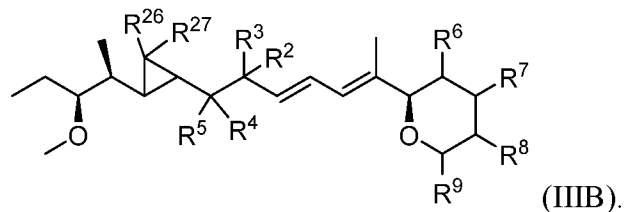
8. The compound of claim 7, the compound having a structure of Formula

(IIIA):



9. The compound of claim 7, the compound having a structure of Formula

(IIIB):



10. The compound of any one of claims 1-9, wherein:

one of R^4 and R^5 is hydrogen and the other one of R^4 and R^5 is $-OH$.

11. The compound of claim 10, wherein a chiral carbon where R^4 and R^5 are attached has (S) stereochemistry.

12. The compound of claim 10, wherein a chiral carbon where R^4 and R^5 are attached has (R) stereochemistry.

13. The compound of claim 10, wherein one of R^2 and R^3 is hydrogen and the other one of R^2 and R^3 is $-CH_3$.

14. The compound of claim 13, wherein a chiral carbon where R^2 and R^3 are attached has (S) stereochemistry.

15. The compound of claim 13, wherein a chiral carbon where R^2 and R^3 are attached has (R) stereochemistry.

16. The compound of claim 13, wherein:
 R^6 is hydrogen, $-OR^{20}$ or $-C(O)OR^{20}$;
 R^7 is hydrogen, $-OR^{21}$ or $-C(O)OR^{21}$;
 R^8 is hydrogen, $-OR^{22}$ or $-C(O)OR^{22}$;
 R^9 is hydrogen, $-OR^{23}$ or $-C(O)OR^{23}$; and
 R^{20} , R^{21} , R^{22} , and R^{23} are each independently hydrogen or unsubstituted C_1 - C_4 alkyl.

17. The compound of claim 16, wherein R^{20} , R^{21} , R^{22} , and R^{23} are each independently hydrogen or $-CH_3$.

18. The compound of claim 16, wherein at least one of R^6 , R^7 , R^8 , and R^9 is $-OCH_3$.

19. The compound of claim 18, wherein at least two of R^6 , R^7 , R^8 , and R^9 are $-OCH_3$.

20. The compound of claim 18, wherein R^6 , R^7 , R^8 and R^9 are $-OCH_3$.

21. The compound of claim 18, wherein:

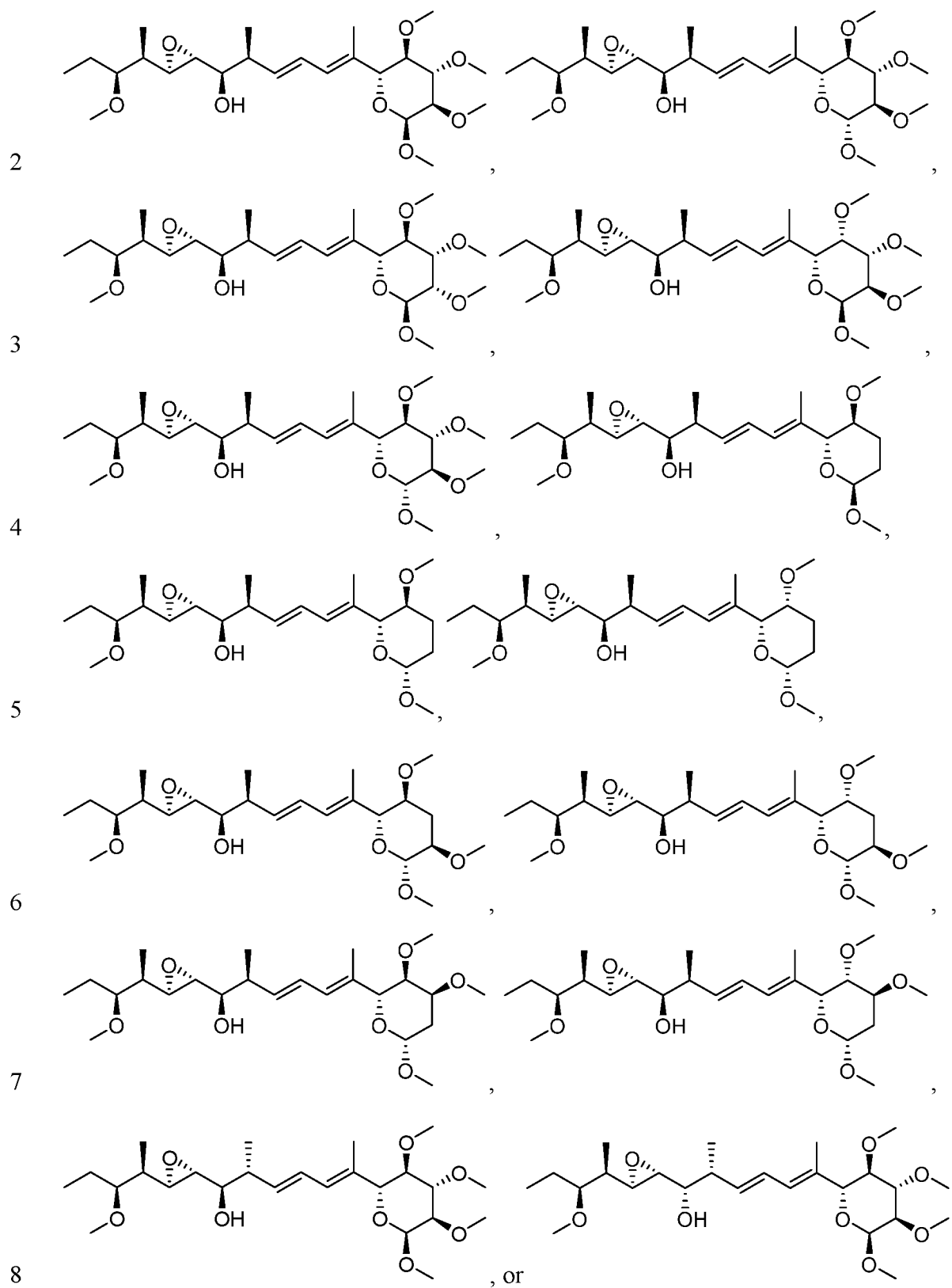
R^6 is $-OCH_3$;

R^7 is hydrogen;

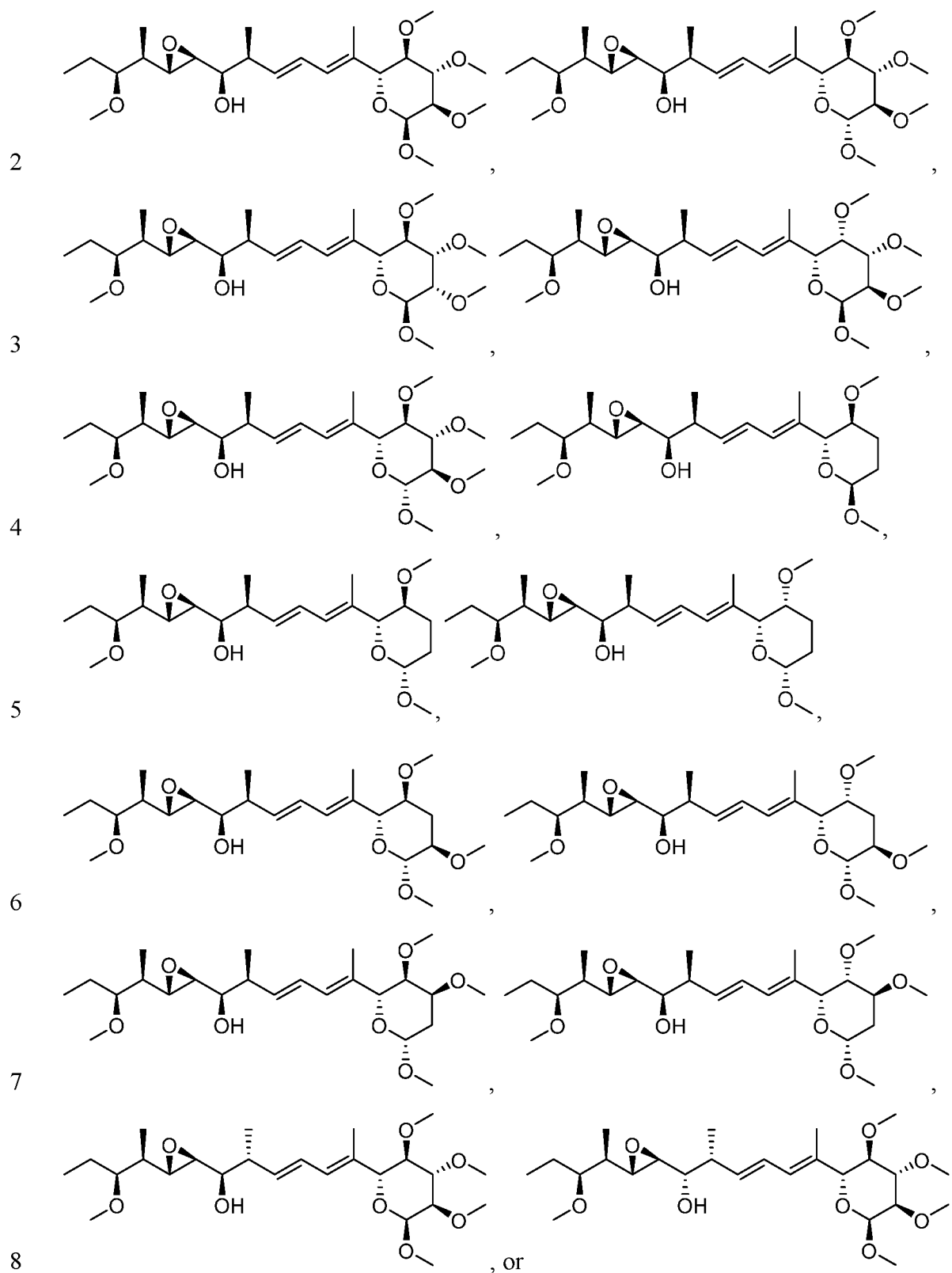
R^8 is hydrogen; and

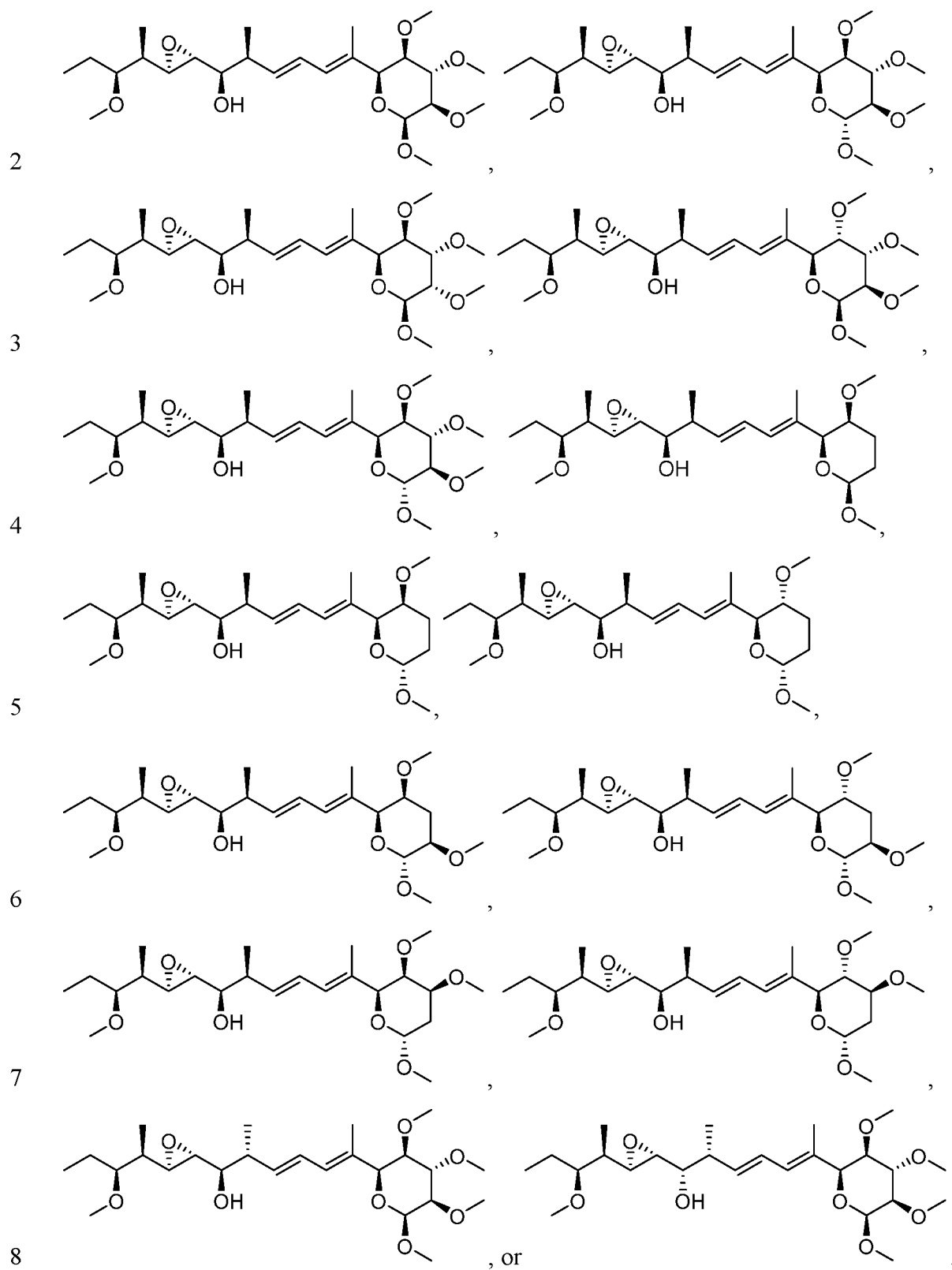
R^9 is $-OCH_3$.

22. The compound of claim 4, wherein the compound is selected from:

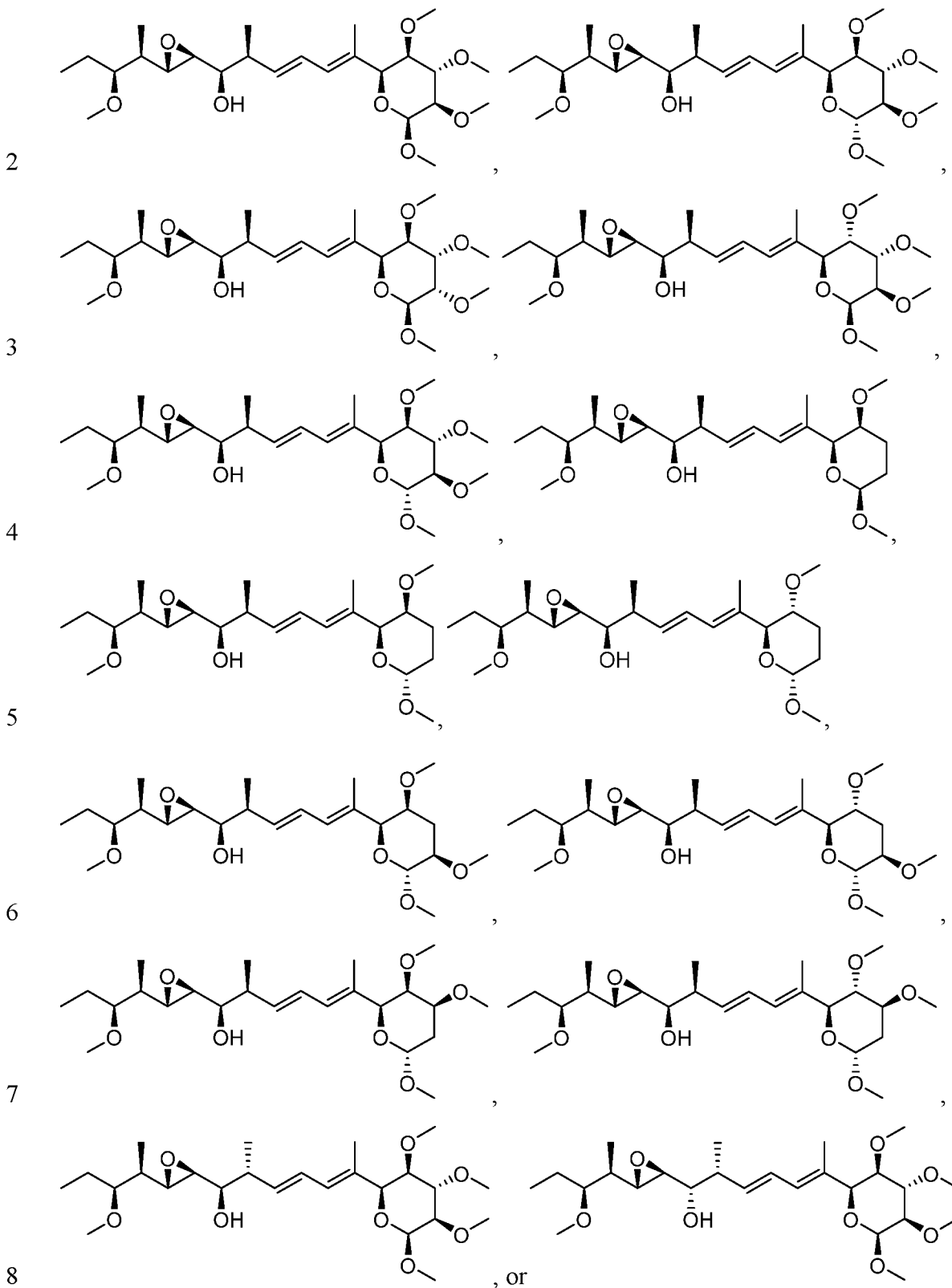


23. The compound of claim 4, wherein the compound is selected from:

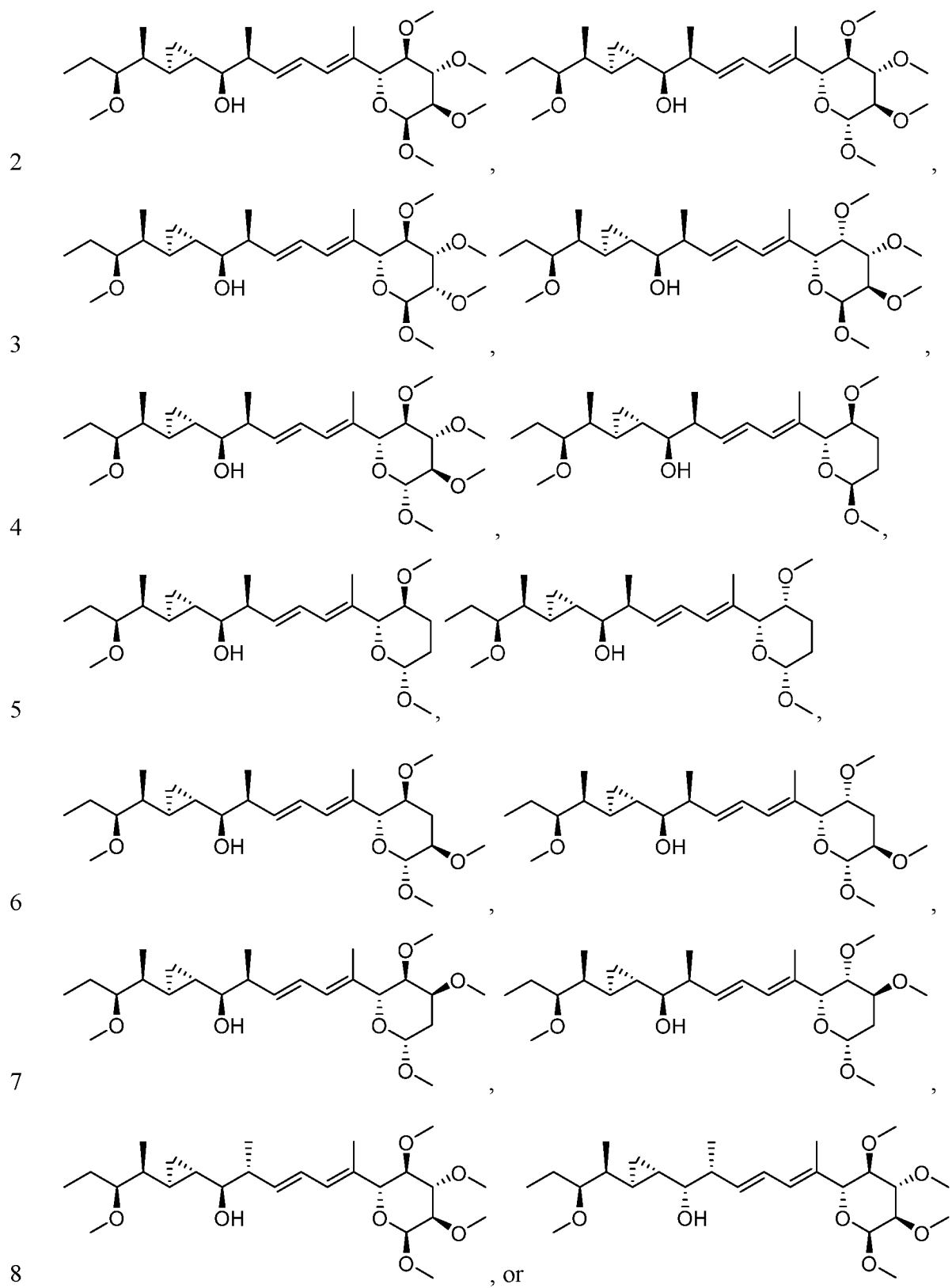




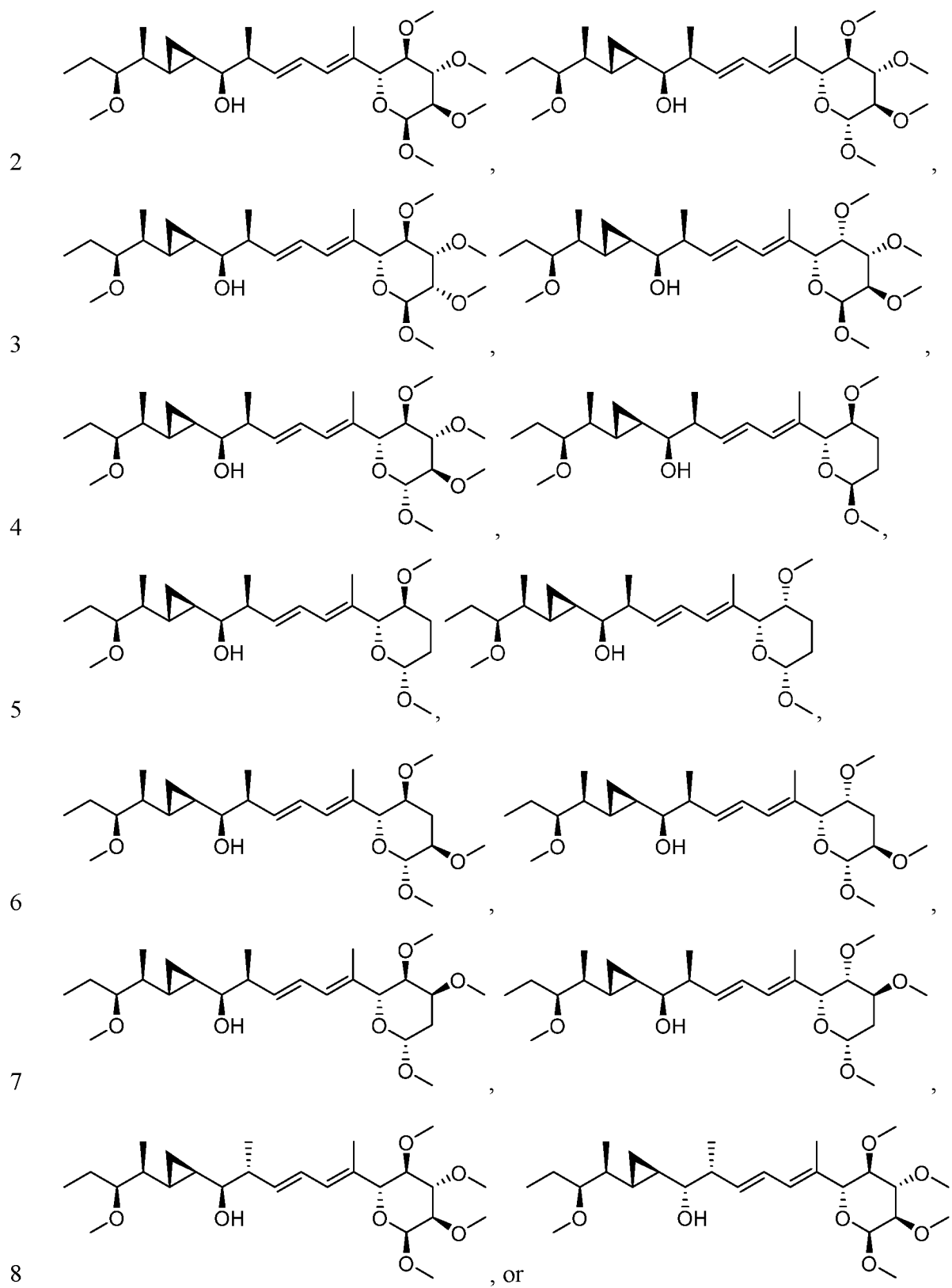
1 25. The compound of claim 5, wherein the compound is selected from:



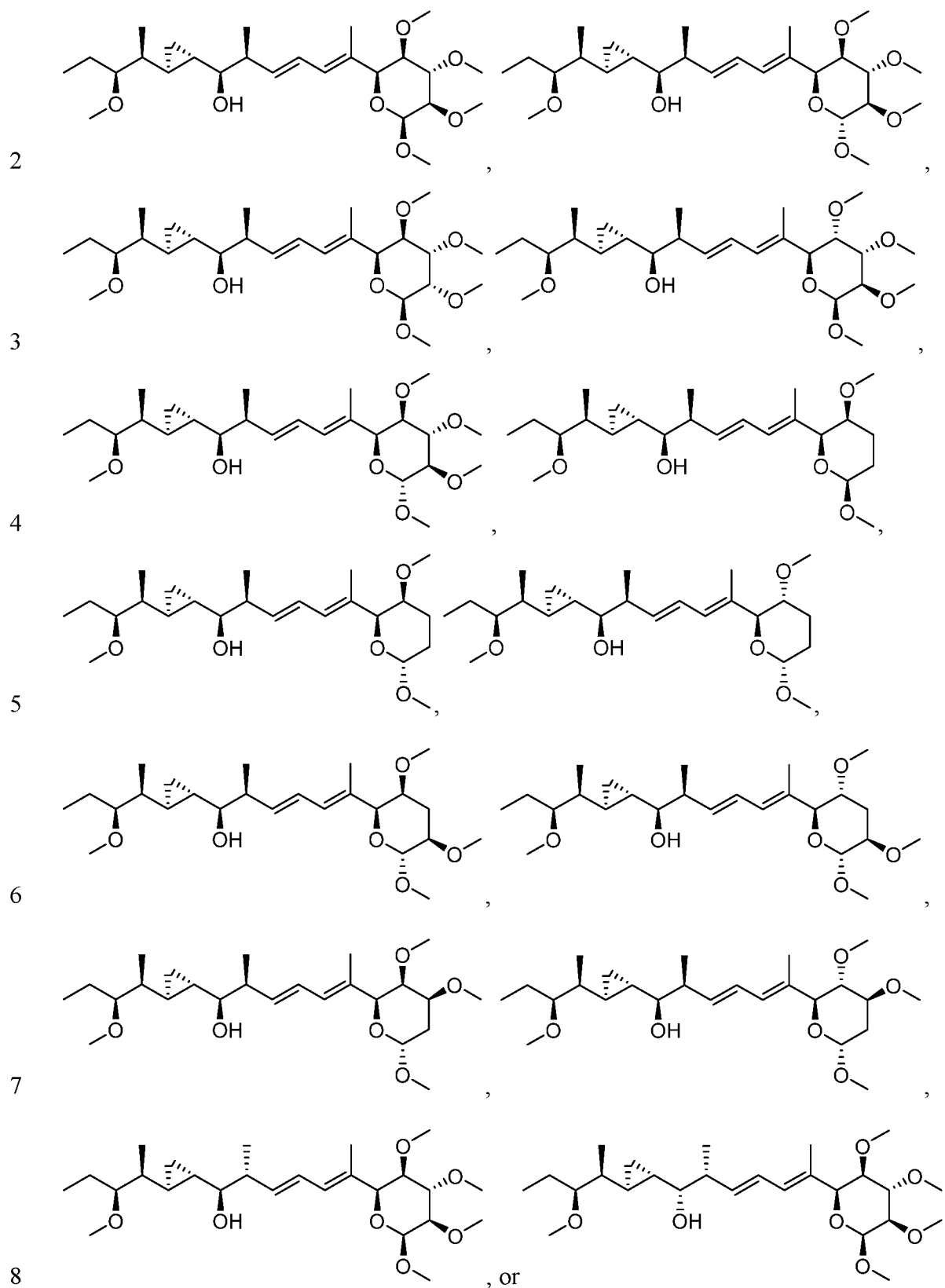
1 26. The compound of claim 8, wherein the compound is selected from:

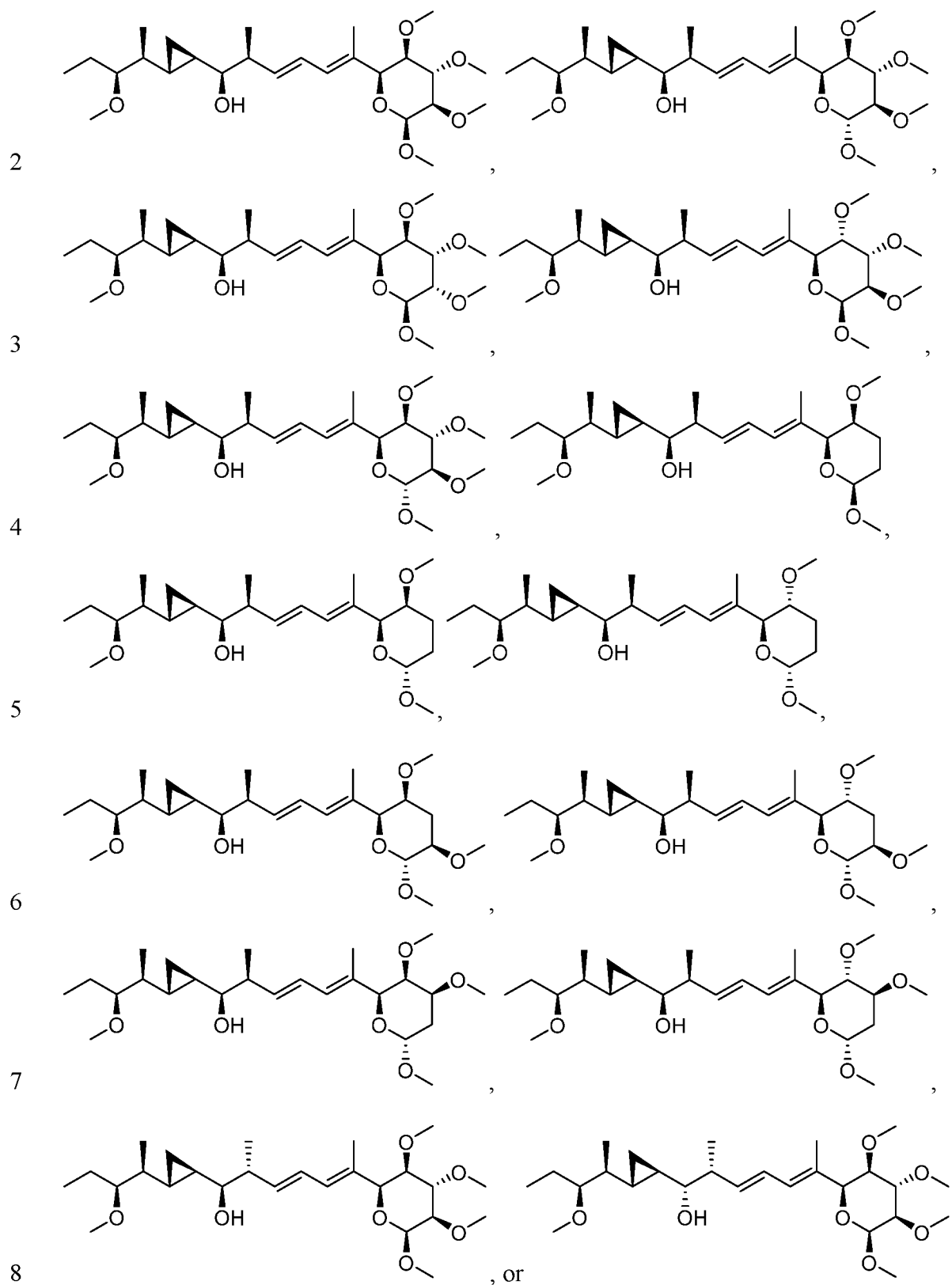


27. The compound of claim 8, wherein the compound is selected from:

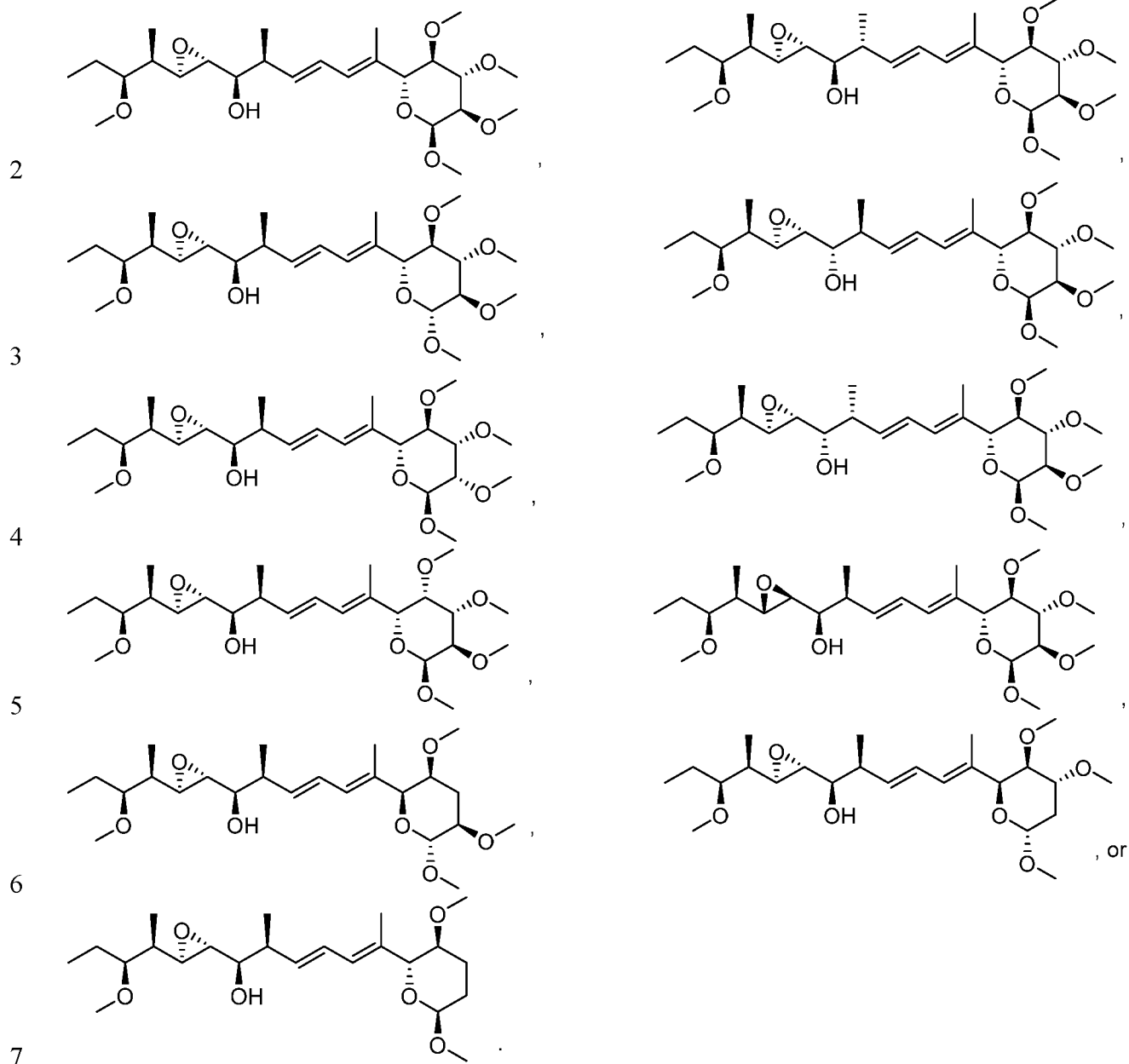


28. The compound of claim 9, wherein the compound is selected from:





30. The compound of claim 1, wherein the compound is selected from:



1 31. A pharmaceutical composition comprising a compound of any one of
2 claims 1-30 and a pharmaceutically acceptable excipient.

1 32. A method of treating cancer, the method comprising administering to a
2 subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-
3 30.

1 33. The method of claim 32, wherein the cancer is leukemia, lymphoma,
2 metastatic cancer, or bone cancer.

1 34. The method of any one of claims 32-33, wherein the cancer is chronic
2 lymphocytic leukemia (CLL).

1 35. A method of detecting spliceosome inhibition with a test compound, the
2 method comprising:

3 (i) contacting a cell with a test compound;

4 (ii) extracting an mRNA from said cell thereby producing an extracted mRNA;

5 (iii) reverse transcribing said extracted mRNA using intron-specific primers
6 thereby forming an intron cDNA;

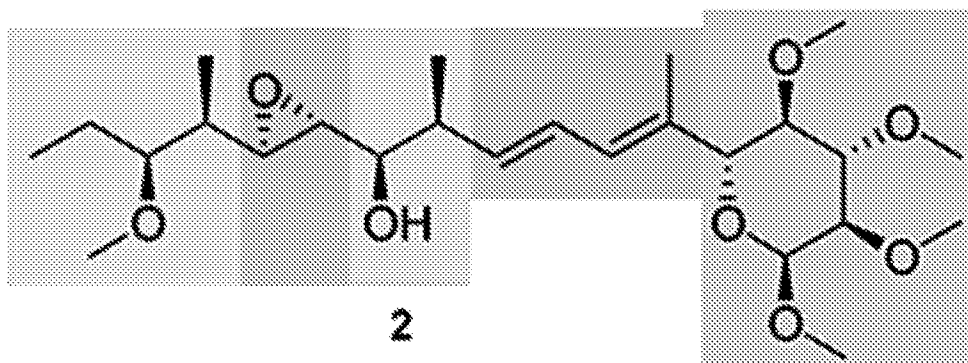
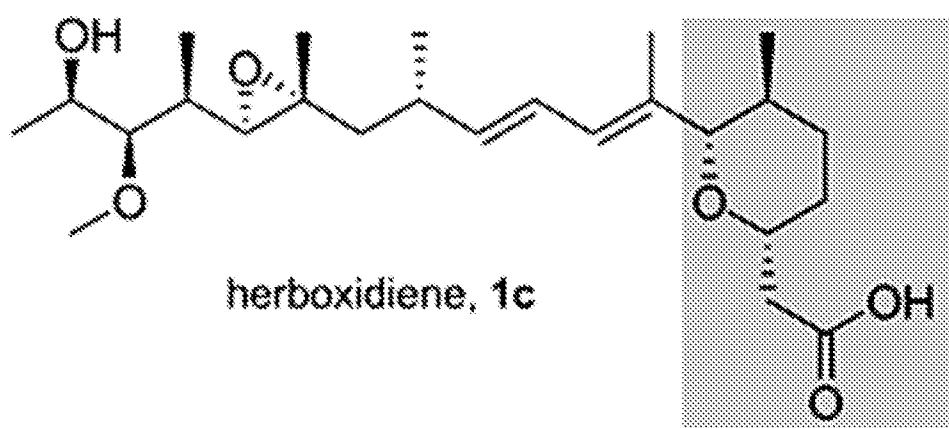
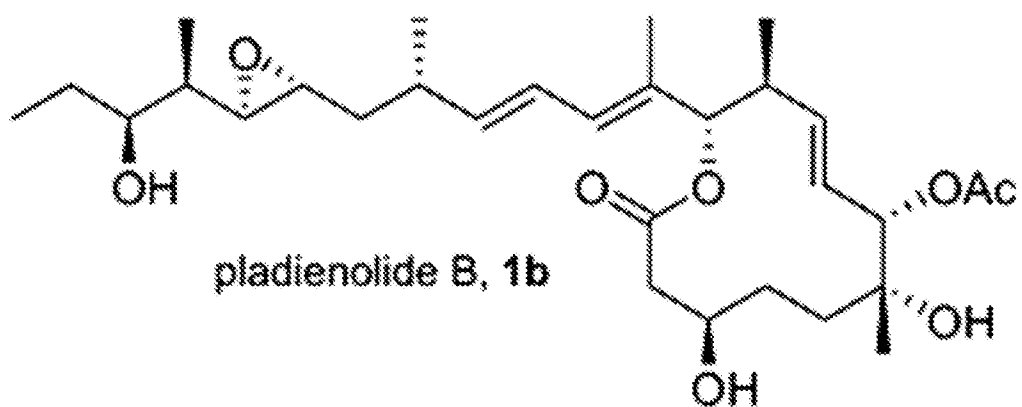
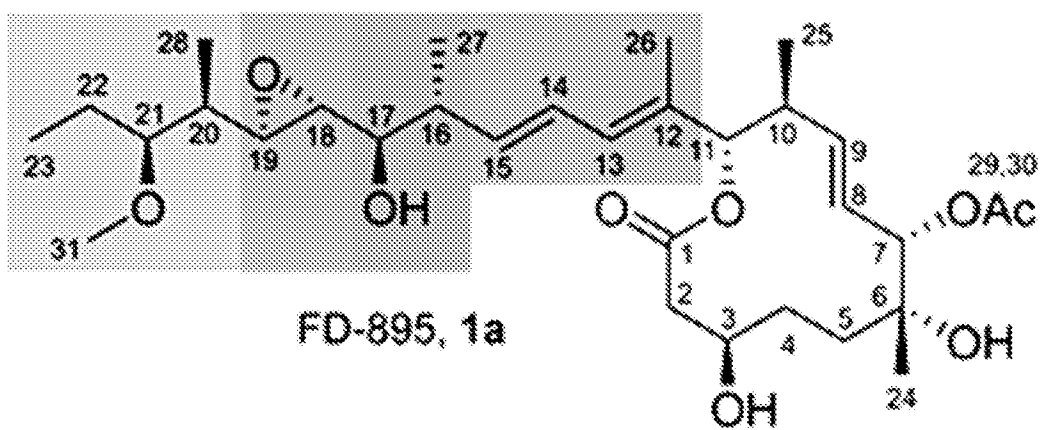
7 (iv) amplifying said intron cDNA thereby forming a plurality of amplified intron
8 cDNAs; and

9 (v) detecting the presence of said amplified intron cDNAs thereby detecting
10 spliceosome inhibition with said test compound.

1 36. The method of claim 35, wherein said cell is derived from a patient.

1 37. The method of any one of claims 35-36, wherein said cell is a cancer cell.

1 38. The method of any one of claims 35-37, wherein said extracting comprises
2 lysing said cell.



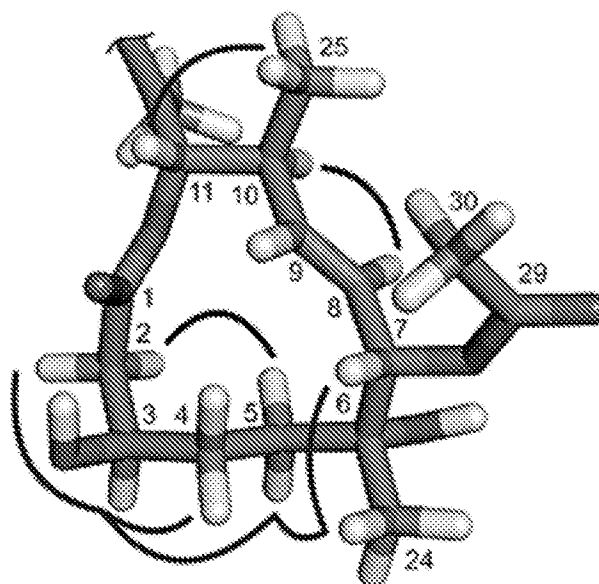
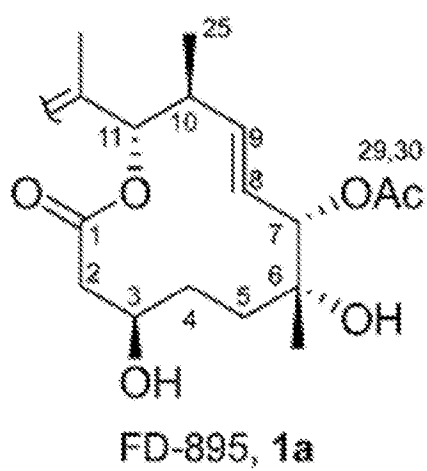


FIG. 2B

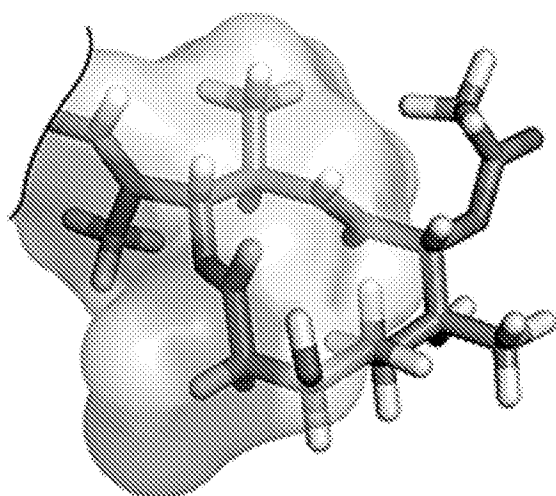


FIG. 2C

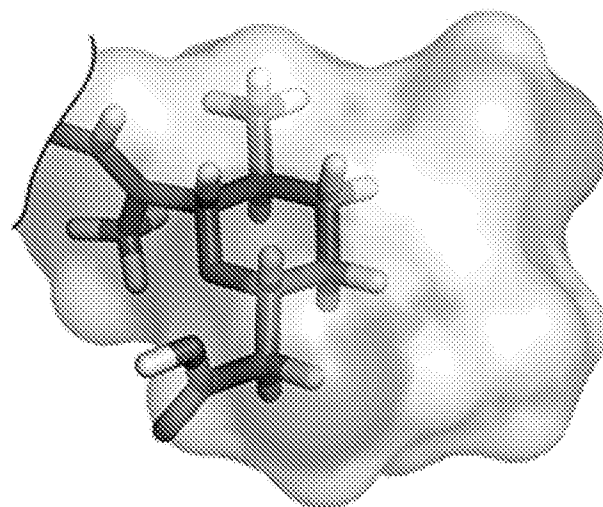


FIG. 2D

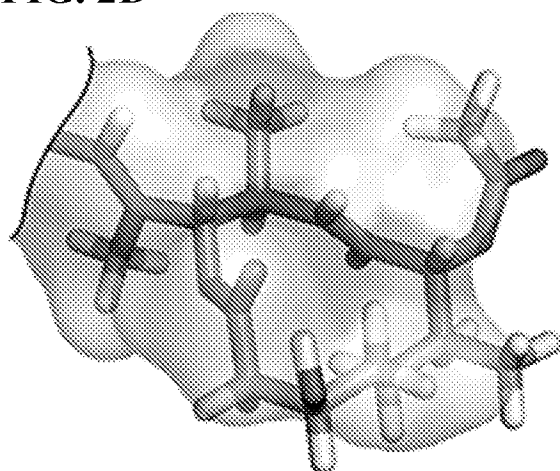
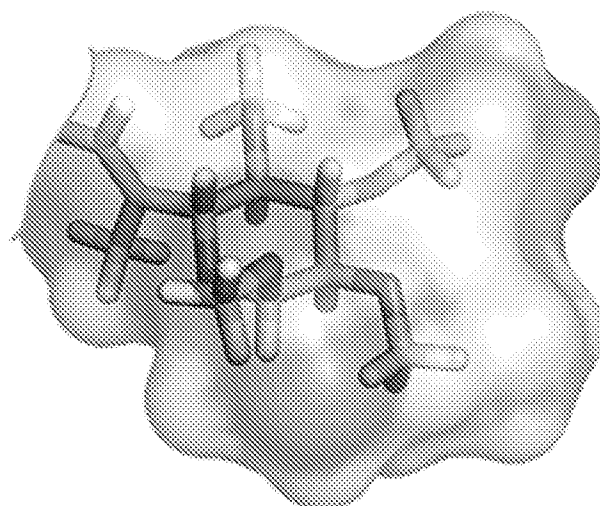


FIG. 2E



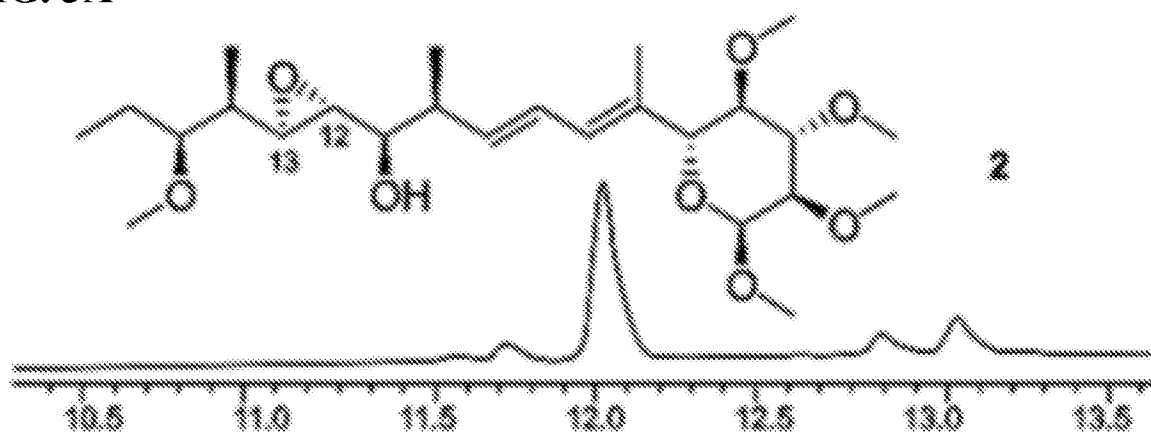


FIG. 3B

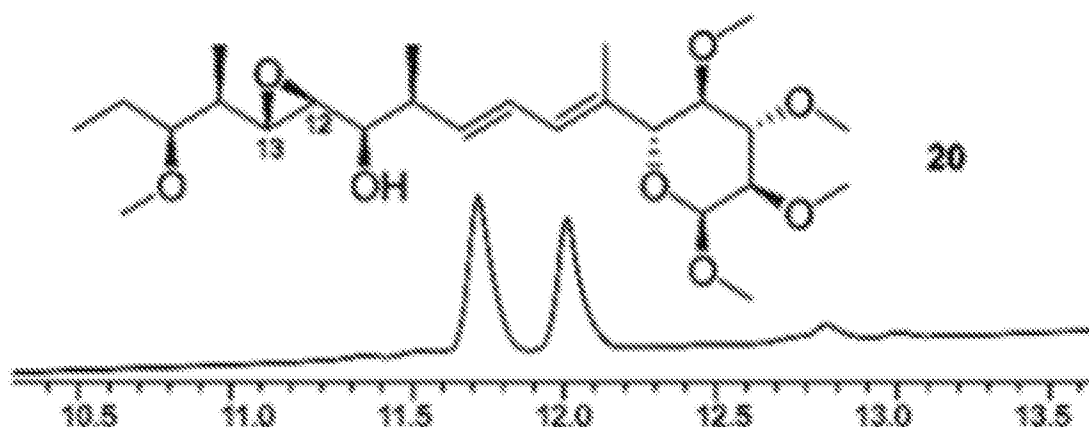


FIG. 3C

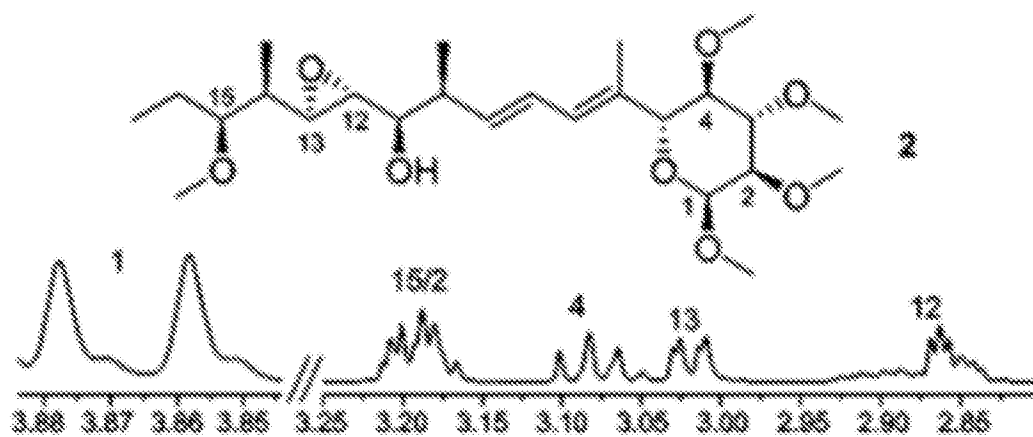
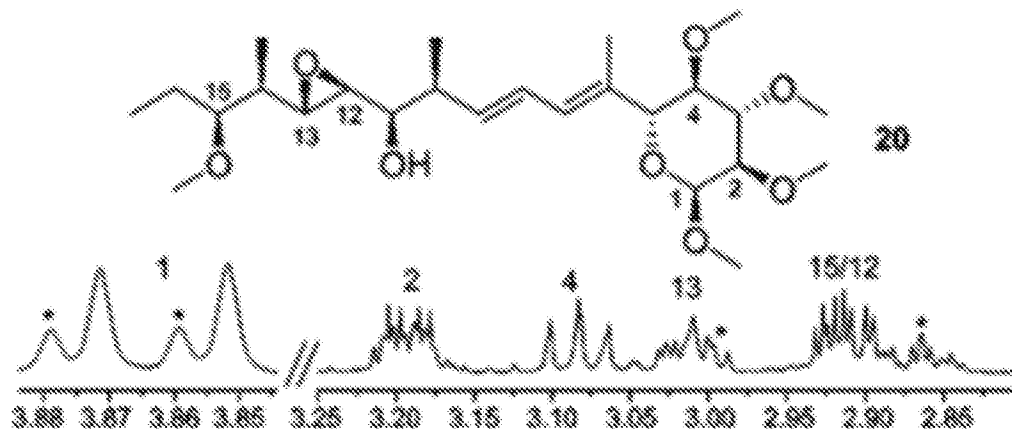


FIG. 3D



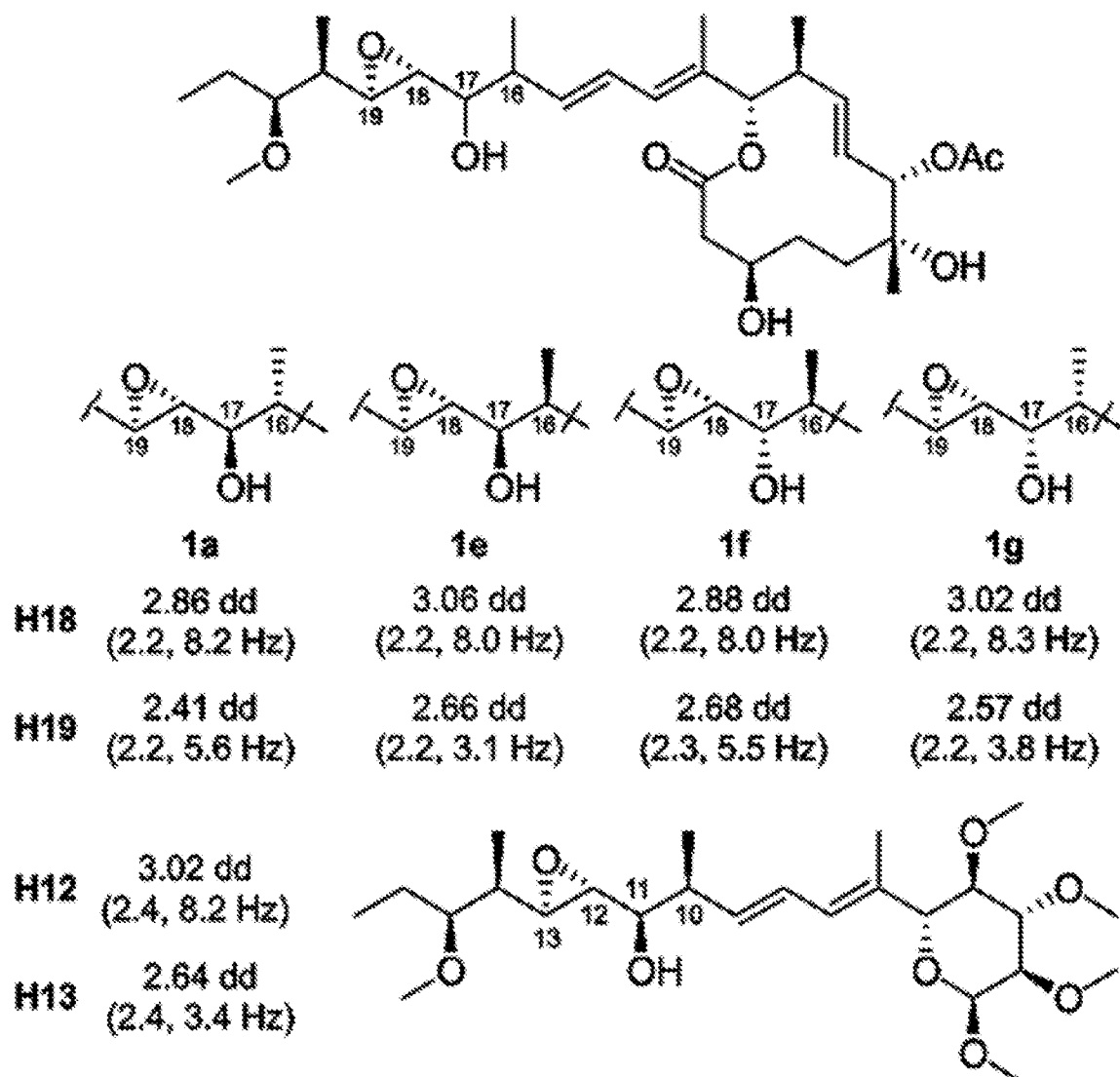
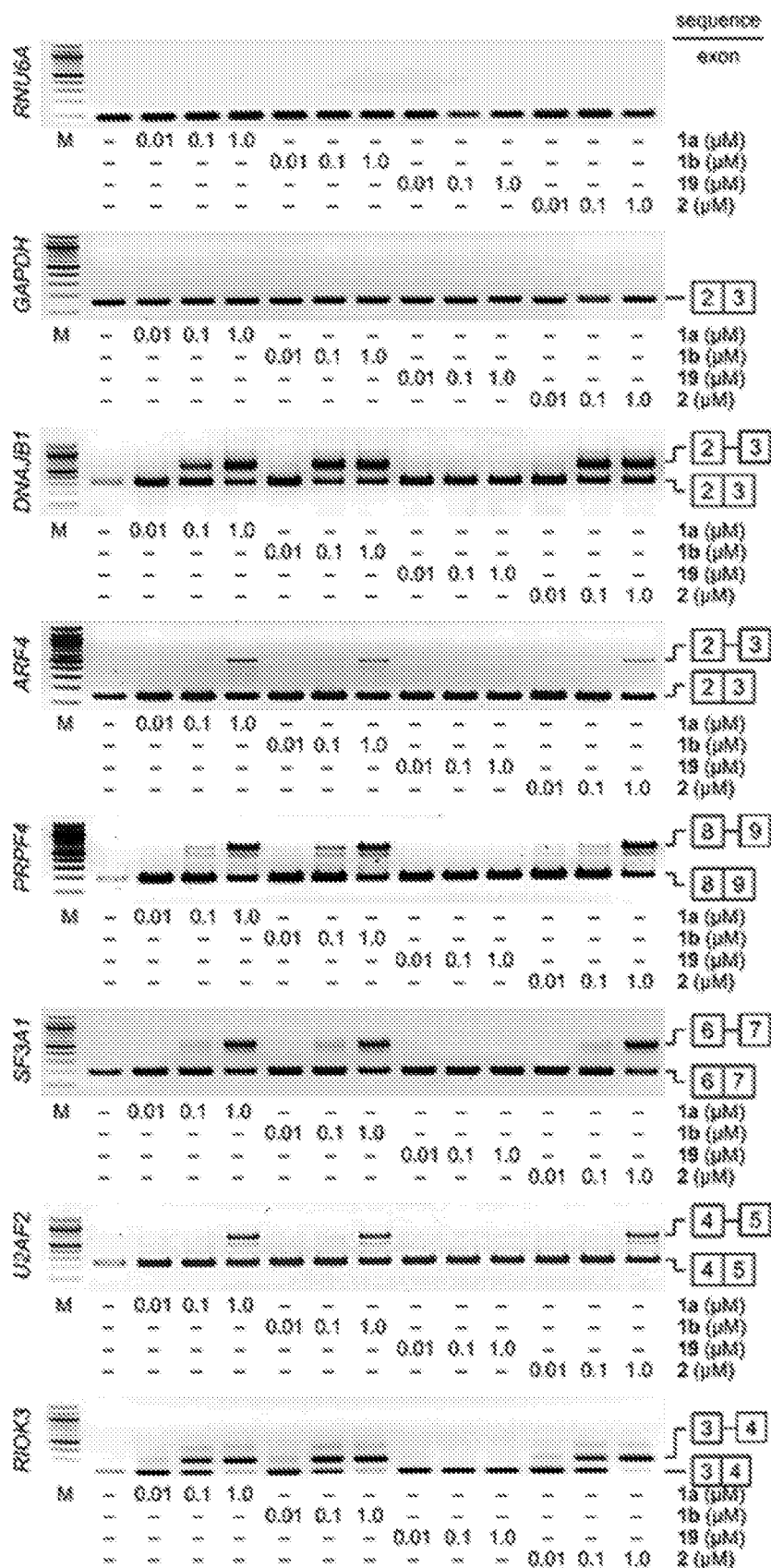
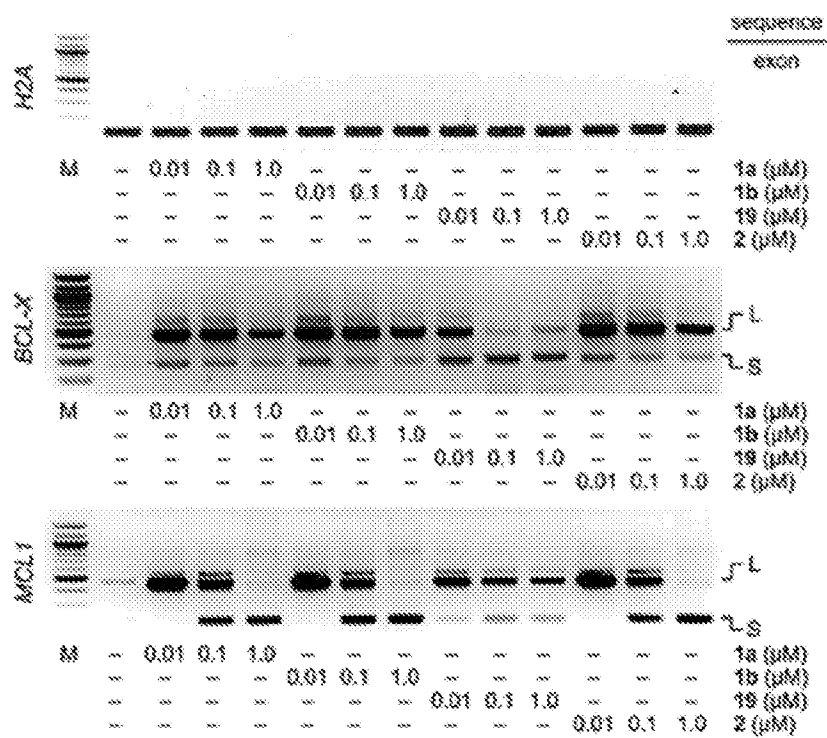


FIG. 5





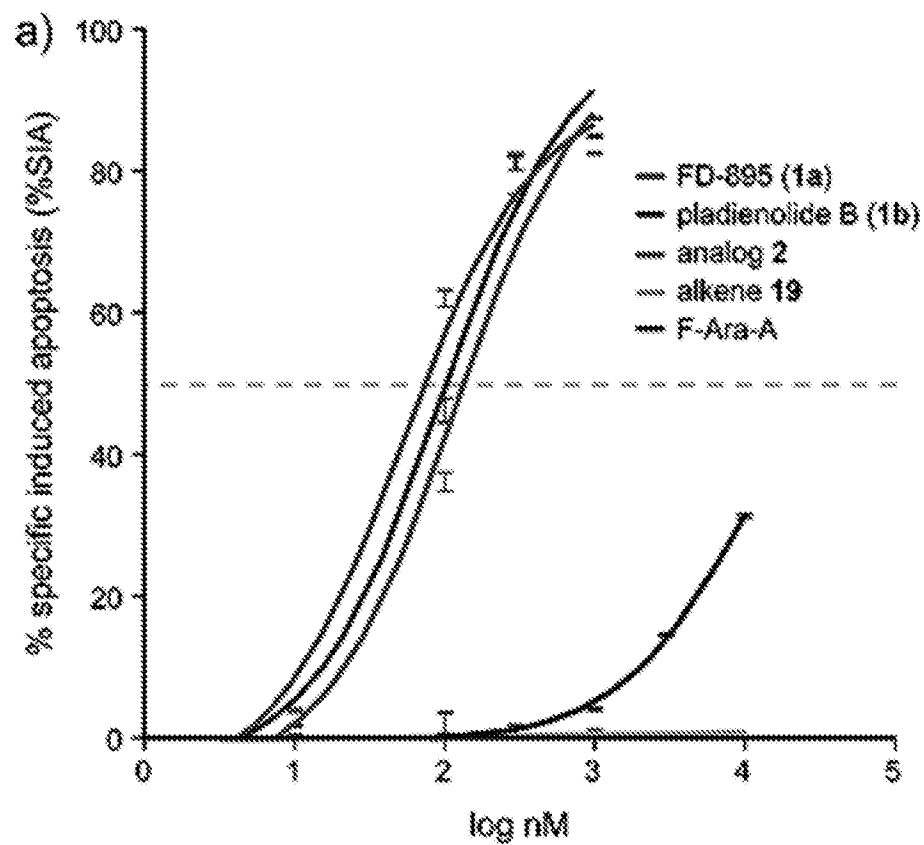
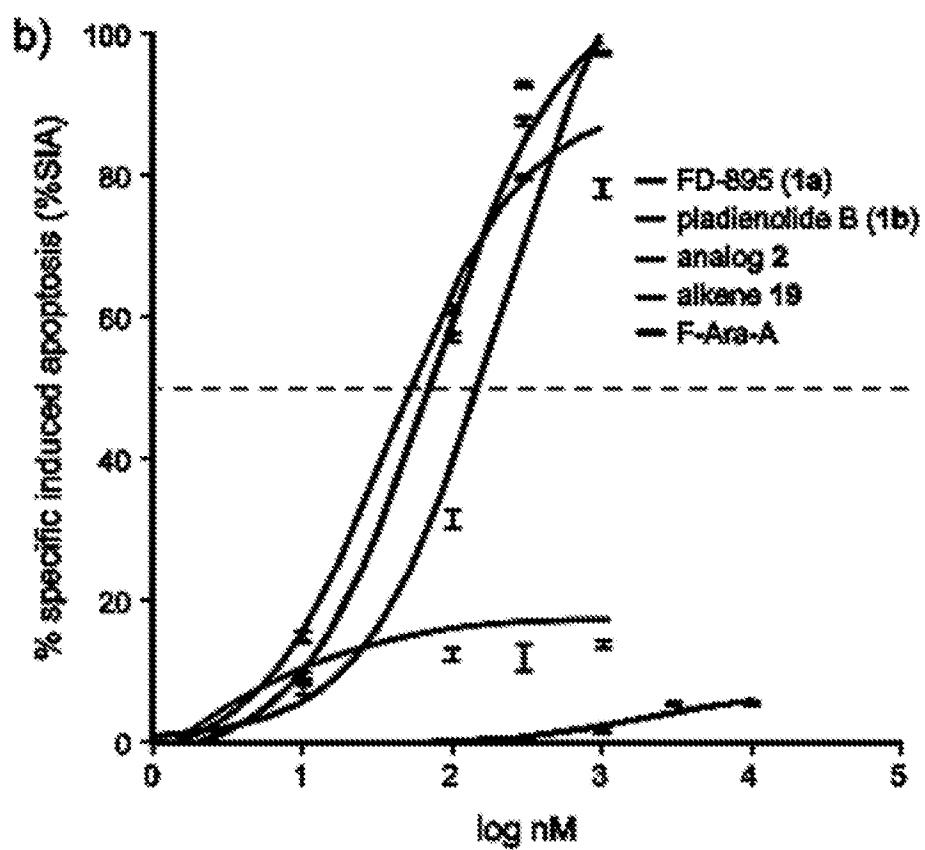
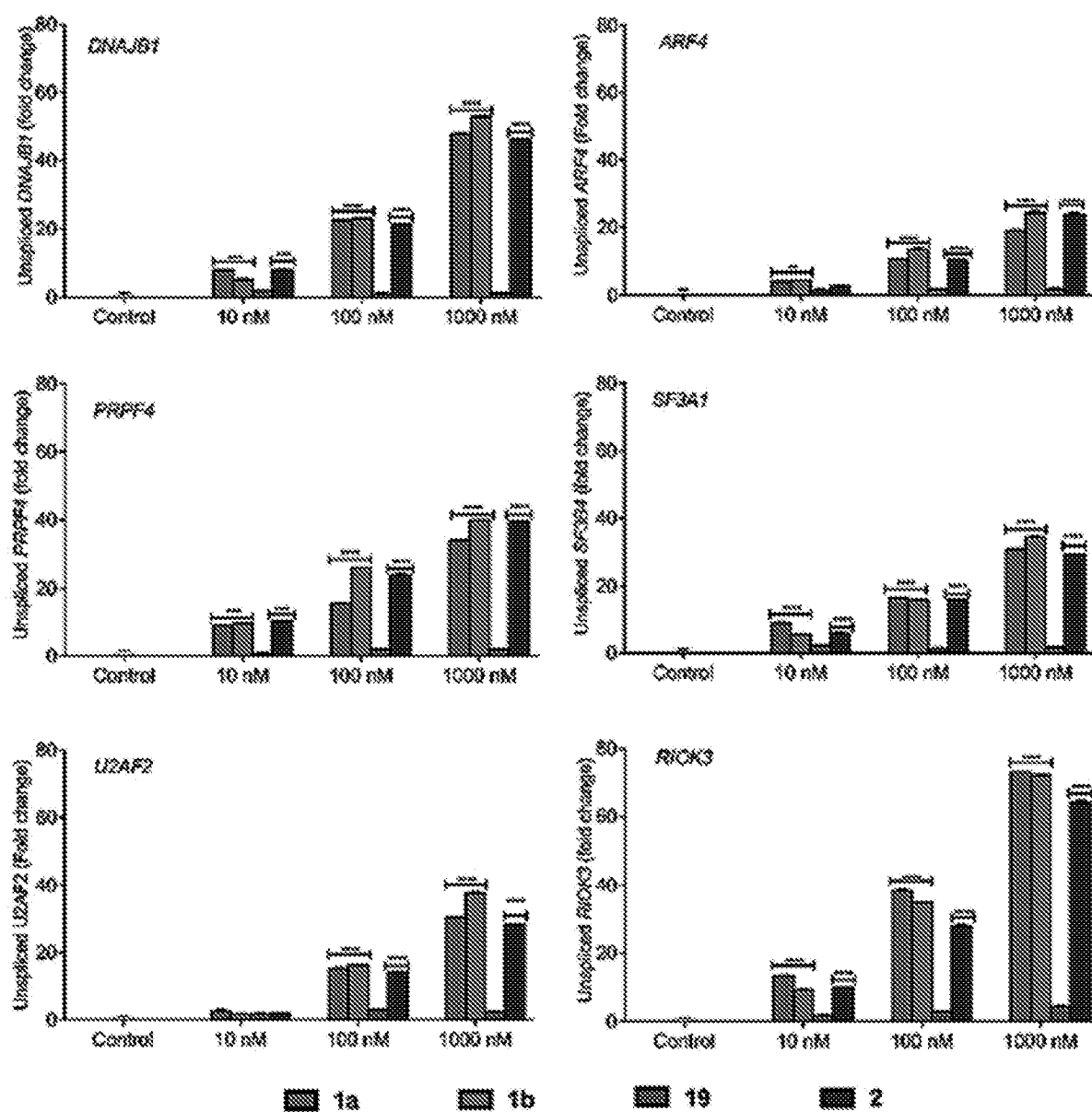


FIG. 7B





INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/21897

A. CLASSIFICATION OF SUBJECT MATTER
 IPC - A61K 47/50; C07D 405/14, 407/06 (2017.01)
 CPC - A61K 47/48384; C07D 405/14, 407/06

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 2015/133535 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 14 May 2015; paragraphs [0009]-[0010], [0044], [0079], [0115]	1-9, 10/1-9, 11/10/1-9, 12/10/1-9, 13/10/1-9, 14/13/10/1-9, 15/13/10/1-9, 16/13/10/1-9, 17/16/13/10/1-9, 18/16/13/10/1-9, 19/18/16/13/10/1-9, 21/18/16/13/10/1-9, 22-30
Y	US 2014/0134193 A1 (PFIZER INC.) 15 May 2014; paragraphs [0008], [0076]	1-9, 10/1-9, 11/10/1-9, 12/10/1-9, 13/10/1-9, 14/13/10/1-9, 15/13/10/1-9, 16/13/10/1-9, 17/16/13/10/1-9, 18/16/13/10/1-9, 19/18/16/13/10/1-9, 21/18/16/13/10/1-9, 22-30
A	US 2011/0086909 A1 (KOIDE, K et al.) 14 April 2011; paragraphs [0006]-[0012]	20/18/16/13/10/1-9

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

18 July 2017 (18.07.2017)

Date of mailing of the international search report

14 AUG 2017

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/21897

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.: 31-34, 38
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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, Claims 1-30 are directed toward a compound with structure of Formula (I).

Group II, Claims 35-37 are directed toward a method of detecting spliceosome inhibition with a test compound.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include Formula (I), not present in Group II; the special technical features of Group II include a spliceosome, not present in Group I.

Groups I and II share the technical features including: a compound. However, these shared technical features are previously disclosed by US 2015/0133535 A1 to The Regents of the University of California (hereinafter 'California').

California discloses a compound (a compound; paragraph [0009]).

Since none of the special technical features of the Groups I and II inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the California reference, unity of invention is lacking.

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.:
1-30

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/21897

-***-Continued from Box No. III Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

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