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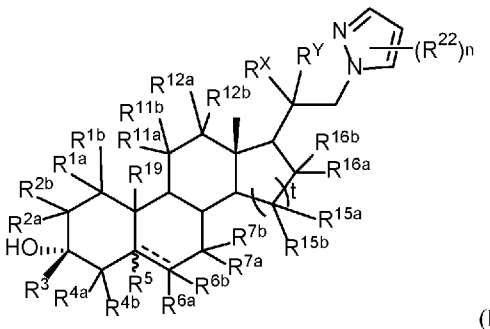
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(54) Title: COMPOSITIONS AND METHODS FOR TREATING CNS DISORDERS



(I)

(57) Abstract: Provided herein is a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or XI: or a pharmaceutically acceptable salt thereof, pharmaceutical compositions comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, and methods of using the compounds, *e.g.*, in the treatment of CNS-related disorders.

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COMPOSITIONS AND METHODS FOR TREATING CNS DISORDERS

Cross-Reference to Related Applications

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/867,618, filed on June 27, 2019, the entire content of which is incorporated by reference herein.

Background of the Invention

[0002] Brain excitability is defined as the level of arousal of an animal, a continuum that ranges from coma to convulsions, and is regulated by various neurotransmitters. In general, neurotransmitters are responsible for regulating the conductance of ions across neuronal membranes. At rest, the neuronal membrane possesses a potential (or membrane voltage) of approximately –70 mV, the cell interior being negative with respect to the cell exterior. The potential (voltage) is the result of ion (K^+, Na^+, Cl^-, organic anions) balance across the neuronal semipermeable membrane. Neurotransmitters are stored in presynaptic vesicles and are released under the influence of neuronal action potentials. When released into the synaptic cleft, an excitatory chemical transmitter such as acetylcholine will cause membrane depolarization (change of potential occurs from -70 mV to -50 mV). This effect is mediated by postsynaptic nicotinic receptors which are stimulated by acetylcholine to increase membrane permeability to Na^+ ions. The reduced membrane potential stimulates neuronal excitability in the form of a postsynaptic action potential.

[0003] In the case of the GABA receptor complex (GRC), the effect on brain excitability is mediated by γ-aminobutyric acid (GABA), a neurotransmitter. GABA has a profound influence on overall brain excitability because up to 40% of the neurons in the brain utilize GABA as a neurotransmitter. GABA regulates the excitability of individual neurons by regulating the conductance of chloride ions across the neuronal membrane. GABA interacts with its recognition site on the GRC to facilitate the flow of chloride ions down an electrochemical gradient of the GRC into the cell. An intracellular increase in the levels of this anion causes hyperpolarization of the transmembrane potential, rendering the neuron less susceptible to excitatory inputs, *i.e.*, reduced neuron excitability. In other words, the higher the chloride ion concentration in the neuron, the lower the brain excitability and level of arousal.

[0004] It is well–documented that the GRC is responsible for the mediation of anxiety, seizure activity, and sedation. Thus, GABA and drugs that act like GABA or facilitate the

effects of GABA (e.g., the therapeutically useful barbiturates and benzodiazepines (BZs), such as Valium®) produce their therapeutically useful effects by interacting with specific regulatory sites on the GRC. Accumulated evidence has now indicated that in addition to the benzodiazepine and barbiturate binding site, the GRC contains a distinct site for neuroactive steroids. See, e.g., Lan, N. C. et al., Neurochem. Res. (1991) 16:347–356.

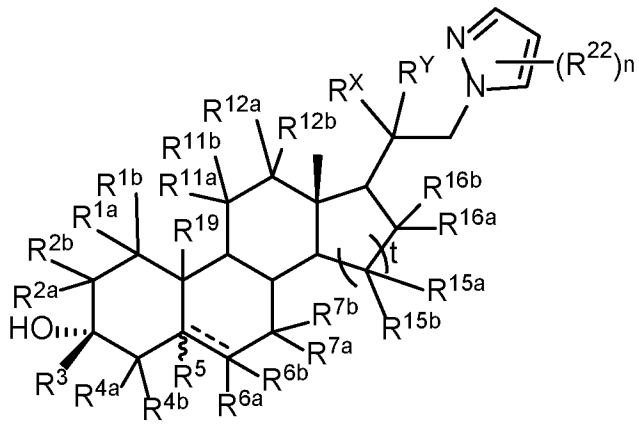
[0005] Neuroactive steroids can occur endogenously. The most potent endogenous neuroactive steroids are 3α–hydroxy-5-reduced pregnan-20-one and 3α-21-dihydroxy-5-reduced pregnan-20-one, metabolites of hormonal steroids progesterone and deoxycorticosterone, respectively. The ability of these steroid metabolites to alter brain excitability was recognized in 1986 (Majewska, M. D. *et al., Science* 232:1004-1007 (1986); Harrison, N. L. *et al., J Pharmacol. Exp. Ther.* 241:346-353 (1987)).

[0006] New and improved compounds are needed that act as modulating agents for brain excitability, as well as agents for the prevention and treatment of CNS-related diseases. The compounds, compositions, and methods described herein are directed toward this end.

Summary of the Invention

[0007] Provided herein are compounds designed, for example, to act as GABA modulators. In some embodiments, such compounds are envisioned to be useful as therapeutic agents for treating a CNS-related disorder.

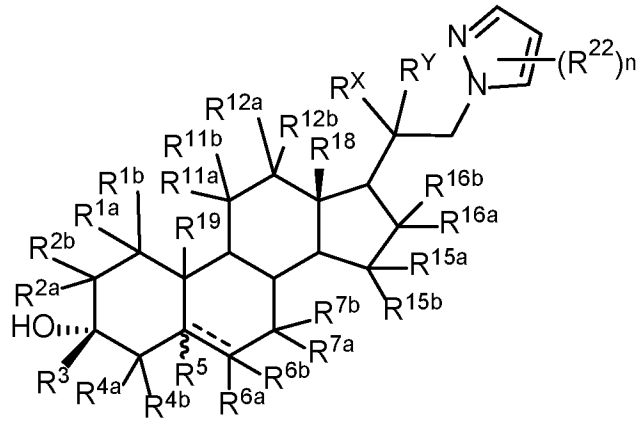
[0008] In an aspect, provided herein is a compound of Formula **I**:



(I)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

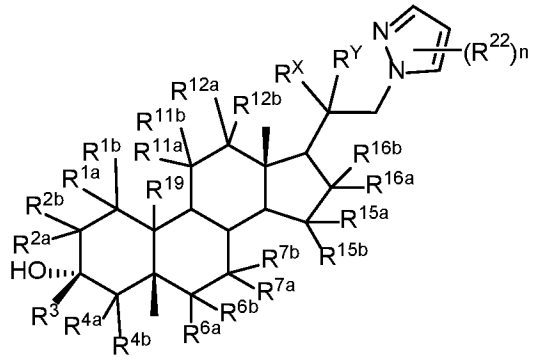
[0009] In an aspect, provided herein is a compound of Formula **II**:



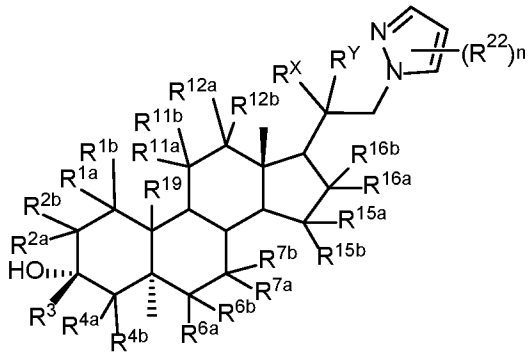
(II)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0010] In some embodiments, the compound of Formula **II** is a compound of Formula **IIIa** or **IIIb**:



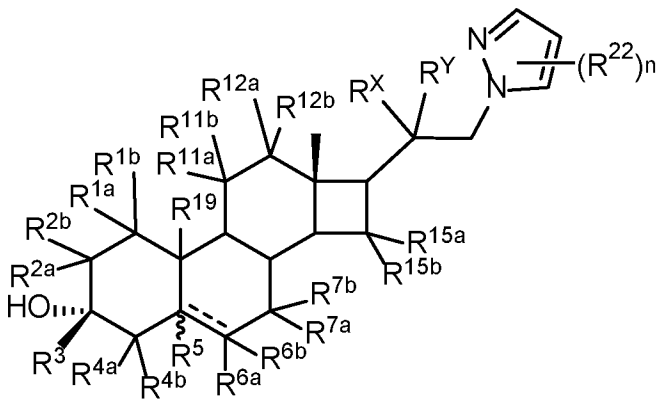
(IIIa)



(IIIb)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

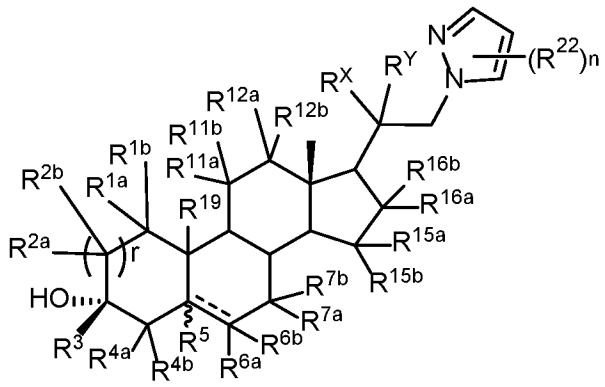
[0011] In an aspect, provided herein is a compound of Formula **V**:



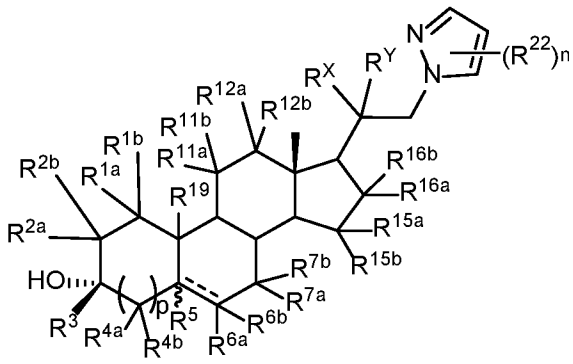
(V)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0012] In an aspect, provided herein is a compound of Formula **VIa** or **VIb**:



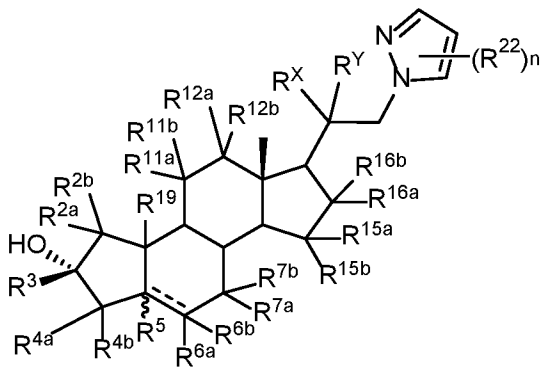
(VIa)



(VIb)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

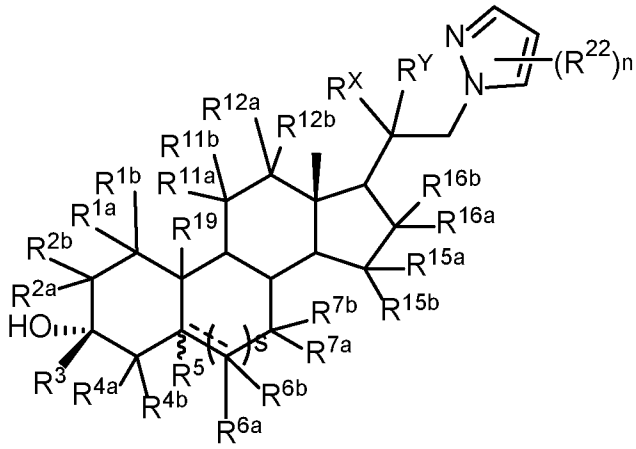
[0013] In an aspect, provided herein is a compound of Formula **VII**:



(VII)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

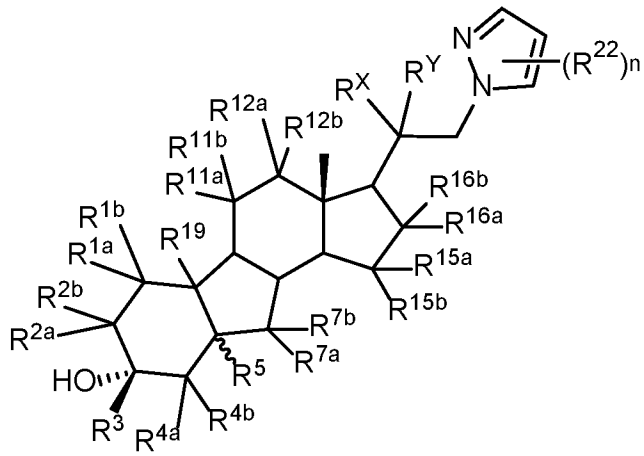
[0014] In another aspect, provided herein is a compound of Formula **VIII**:



(VIII)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

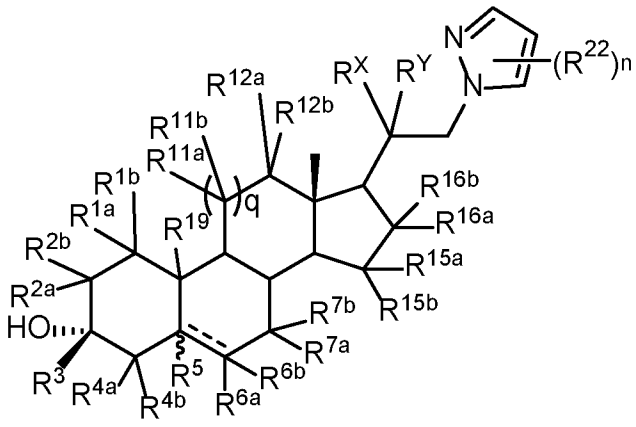
[0015] In an aspect, provided herein is a compound of Formula **IX**:



(IX)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0016] In an aspect, provided herein is a compound of Formula **X**:



(X)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0017] In one aspect, provided herein is a pharmaceutically acceptable salt of a compound described herein (*e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X).

[0018] In one aspect, provided herein is a pharmaceutical composition comprising a compound described herein (*e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In certain embodiments, the compound of the present invention is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the compound of the present invention is provided in a therapeutically effective amount.

[0019] In one aspect, provided herein is a method of treating a CNS-related disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound described herein or a pharmaceutically acceptable salt thereof. In some embodiments, the CNS–related disorder is a sleep disorder, a mood disorder, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, tinnitus, or status epilepticus. In some embodiments, the CNS-related disorder is depression. In some embodiments, the CNS-related disorder is postpartum depression. In some embodiments, the CNS-related disorder is major depressive disorder. In some embodiments, the major depressive disorder is moderate major depressive disorder. In some embodiments, the major depressive disorder is severe major depressive disorder.

[0020] In some embodiments, the compound is selected from the group consisting of the compounds identified in **Table 1** herein.

[0021] Compounds of the present invention as described herein, act, in certain embodiments, as GABA modulators, *e.g.*, effecting the $GABA_A$ receptor in either a positive or negative manner. As modulators of the excitability of the central nervous system (CNS), as mediated by their ability to modulate $GABA_A$ receptor, such compounds are expected to have CNS-activity.

[0022] Thus, in another aspect, provided are methods of treating a CNS–related disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present invention. In certain embodiments, CNS–related disorder is a sleep disorder, a mood disorder, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, tinnitus, or status epilepticus. In certain embodiments, the CNS-related disorder is depression. In certain embodiments, the CNS-related disorder is postpartum depression. In certain embodiments, the CNS-related disorder is major depressive disorder. In certain embodiments, the major depressive disorder is moderate major depressive disorder. In certain embodiments, the major depressive disorder is severe major depressive disorder. In certain embodiments, the compound is administered orally, subcutaneously, intravenously, or intramuscularly. In certain embodiments, the compound is administered orally. In certain embodiments, the compound is administered chronically. In certain embodiments, the compound is administered continuously, *e.g.,* by continuous intravenous infusion.

Detailed Description of Certain Embodiments of the Invention

[0023] As generally described herein, the present invention provides compounds designed, for example, to act as $GABA_A$ receptor modulators. In certain embodiments, such compounds are envisioned to be useful as therapeutic agents for treating a CNS-related disorder (e.g., a disorder as described herein, for example depression, such as post-partum depression or major depressive disorder).

Definitions

Chemical definitions

[0024] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0025] Isomers, *e.g.*, stereoisomers, can be isolated from mixtures by methods known to those skilled in the art, including chiral high performance liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0026] "Stereoisomers": It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non–superimposable mirror images of each other are termed "enantiomers." When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R– and S–sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as

dextrorotatory or levorotatory (*i.e.*, as (+) or (–)–isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[0027] As used herein a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (*i.e.*, in enantiomeric excess). In other words, an "S" form of the compound is substantially free from the "R" form of the compound and is, thus, in enantiomeric excess of the "R" form. The term "enantiomerically pure" or "pure enantiomer" denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

[0028] In the compositions provided herein, an enantiomerically pure compound can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising enantiomerically pure R–position/center/ carbon compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure R– compound. In certain embodiments, the enantiomerically pure R–compound in such compositions can, for example, comprise, at least about 95% by weight R–compound and at most about 5% by weight S–compound, by total weight of the compound. For example, a pharmaceutical composition comprising enantiomerically pure S–compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure S–compound. In certain embodiments, the enantiomerically pure S–compound in such compositions can, for example, comprise, at least about 95% by weight S–compound and at most about 5% by weight R–compound, by total weight of the compound. In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

[0029] The term "diastereomierically pure" denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight,

more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of a single diastereomer. Methods for determining diastereomeric and enantiomeric purity are well-known in the art. Diastereomeric purity can be determined by any analytical method capable of quantitatively distinguishing between a compound and its diastereomers, such as high performance liquid chromatography (HPLC).

[0030] The articles "a" and "an" may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example "an analogue" means one analogue or more than one analogue.

[0031] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0032] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0033] "Alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C_{1-20} alkyl"). In some embodiments, an alkyl group has 1 to 12 carbon atoms ("C_{1-12} alkyl"). In some embodiments, an alkyl group has 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl", also referred to herein as "lower alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–

pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8) and the like. Unless otherwise specified, each instance of an alkyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents; *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkyl group is unsubstituted $C_{1–10}$ alkyl (*e.g.,* $–CH_3$). In certain embodiments, the alkyl group is substituted $C_{1–10}$ alkyl. Common alkyl abbreviations include Me ($-CH_3$), Et ($-CH_2CH_3$), iPr ($-CH(CH_3)_2$), nPr ($-CH_2CH_2CH_3$), n-Bu ($-CH_2CH_2CH_2CH_3$), or i-Bu ($-CH_2CH(CH_3)_2$).

[0034] "Alkylene" refers to an alkyl group wherein two hydrogens are removed to provide a divalent radical, and which may be substituted or unsubstituted. Unsubstituted alkylene groups include, but are not limited to, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), butylene ($-CH_2CH_2CH_2CH_2-$), pentylene ($-CH_2CH_2CH_2CH_2CH_2-$), hexylene ($-CH_2CH_2CH_2CH_2CH_2CH_2-$), and the like. Exemplary substituted alkylene groups, *e.g.,* substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted methylene ($-CH(CH_3)-$, $-C(CH_3)_2-$), substituted ethylene ($-CH(CH_3)CH_2-$,$-CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2-$,$-CH_2C(CH_3)_2-$), substituted propylene ($-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-CH_2CH_2C(CH_3)_2-$), and the like. When a range or number of carbons is provided for a particular alkylene group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. Alkylene groups may be substituted or unsubstituted with one or more substituents as described herein.

[0035] "Alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon double bonds (*e.g.,* 1, 2, 3, or 4 carbon–carbon double bonds), and optionally one or more carbon–carbon triple bonds (*e.g.,* 1, 2, 3, or 4 carbon–carbon triple bonds) ("$C_{2–20}$ alkenyl"). In certain embodiments, alkenyl does not contain any triple bonds. In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("$C_{2–10}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("$C_{2–9}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("$C_{2–8}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("$C_{2–7}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("$C_{2–6}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("$C_{2–5}$ alkenyl"). In some

embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkenyl group is unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-10} alkenyl.

[0036] "Alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon triple bonds (*e.g.,* 1, 2, 3, or 4 carbon–carbon triple bonds), and optionally one or more carbon–carbon double bonds (*e.g.,* 1, 2, 3, or 4 carbon–carbon double bonds) ("C_{2-20} alkynyl"). In certain embodiments, alkynyl does not contain any double bonds. In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently

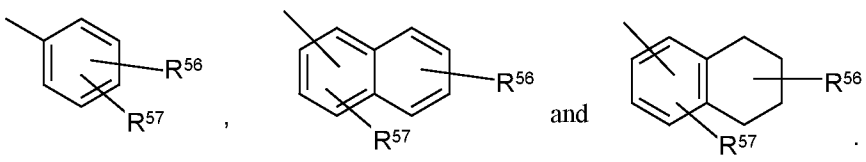
optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents; *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkynyl group is unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-10} alkynyl.

[0037] The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, which further comprises 1 or more (*e.g.*, 1, 2, 3, or 4) heteroatoms (*e.g.*, oxygen, sulfur, nitrogen, boron, silicon, phosphorus) within the parent chain, wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is inserted between a carbon atom and the parent molecule, *i.e.*, between the point of attachment. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon atoms and 1, 2, 3, or 4 heteroatoms ("heteroC_{1-10} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1, 2, 3, or 4 heteroatoms ("heteroC_{1-9} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1, 2, 3, or 4 heteroatoms ("heteroC_{1-8} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1, 2, 3, or 4 heteroatoms ("heteroC_{1-7} alkyl"). In some embodiments, a heteroalkyl group is a group having 1 to 6 carbon atoms and 1, 2, or 3 heteroatoms ("heteroC_{1-6} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms ("heteroC_{1-5} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1or 2 heteroatoms ("heteroC_{1-4} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom ("heteroC_{1-3} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom ("heteroC_{1-2} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms ("heteroC_{2-6} alkyl"). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-10} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-10} alkyl.

[0038] "Aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.*, anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, and trinaphthalene. Particularly aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl. Unless otherwise specified, each instance of an aryl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is substituted C_{6-14} aryl.

[0039] In certain embodiments, an aryl group substituted with one or more of groups selected from halo, C_{1-8} alkyl, C_{1-8} haloalkyl, cyano, hydroxy, C_{1-8} alkoxy, and amino.

[0040] Examples of representative substituted aryls include the following



and

wherein one of R^{56} and R^{57} may be hydrogen and at least one of R^{56} and R^{57} is each independently selected from C_{1-8} alkyl, C_{1-8} haloalkyl, 4-10 membered heterocyclyl, alkanoyl, C_{1-8} alkoxy, heteroaryloxy, alkylamino, arylamino, heteroarylamino, $NR^{58}COR^{59}$, $NR^{58}SOR^{59}$ $NR^{58}SO_2R^{59}$, COOalkyl, COOaryl, $CONR^{58}R^{59}$, $CONR^{58}OR^{59}$, $NR^{58}R^{59}$,

$SO_2NR^{58}R^{59}$, S-alkyl, SOalkyl, SO_2alkyl, Saryl, SOaryl, SO_2aryl; or R^{56} and R^{57} may be joined to form a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group N, O, or S. R^{60} and R^{61} are independently hydrogen, C_{1-8} alkyl, C_{1-4} haloalkyl, C_{3-10} cycloalkyl, 4-10 membered heterocyclyl, C_{6-10} aryl, substituted C_{6-10} aryl, 5-10 membered heteroaryl, or substituted 5-10 membered heteroaryl .

[0041] "Fused aryl" refers to an aryl having two of its ring carbon in common with a second aryl or heteroaryl ring or with a carbocyclyl or heterocyclyl ring.

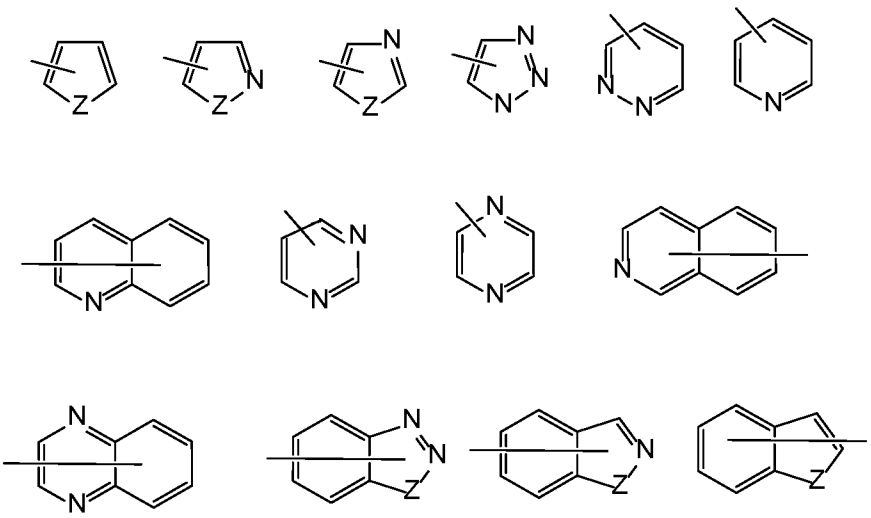
[0042] "Heteroaryl" refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system (*e.g.,* having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5–10 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.,* either the ring bearing a heteroatom (*e.g.,* 2–indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5–indolyl).

[0043] In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen,

oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5–14 membered heteroaryl.

[0044] Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0045] Examples of representative heteroaryls include the following:



wherein each Z is selected from carbonyl, N, NR^{65}, O, and S; and R^{65} is independently hydrogen, C_{1-8} alkyl, C_{3-10} cycloalkyl, 4-10 membered heterocyclyl, C_{6-10} aryl, and 5-10 membered heteroaryl.

[0046] "Carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or

contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be saturated or can be partially unsaturated. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C_{3-10} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-10} carbocyclyl.

[0047] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C_{3-10} cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C_{3-10} cycloalkyl.

[0048] "Heterocyclyl" or "heterocyclic" refers to a radical of a 3– to 10–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("3–10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one

or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

[0049] In some embodiments, a heterocyclyl group is a 5–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0050] Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5–membered

heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0051] "Nitrogen-containing heterocyclyl" group means a 4- to 7- membered non-aromatic cyclic group containing at least one nitrogen atom, for example, but without limitation, morpholine, piperidine (*e.g.* 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (*e.g.* 2-pyrrolidinyl and 3-pyrrolidinyl), azetidine, pyrrolidone, imidazoline, imidazolidinone, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Particular examples include azetidine, piperidone and piperazone.

[0052] "Hetero" when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, *e.g.,* heteroalkyl, cycloalkyl, *e.g.,* heterocyclyl, aryl, *e.g,.* heteroaryl, cycloalkenyl, *e.g,.* cycloheteroalkenyl, and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[0053] "Acyl" refers to a radical $-C(O)R^{20}$, where R^{20} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, as defined herein. "Alkanoyl" is an acyl group wherein R^{20} is a group other than hydrogen. Representative acyl groups

include, but are not limited to, formyl (-CHO), acetyl (-C(=O)CH_3), cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl (-C(=O)Ph), benzylcarbonyl (-C(=O)CH_2Ph), —C(O)-C_{1-8} alkyl, –C(O)-$(CH_2)_t$(C_{6-10} aryl), –C(O)-$(CH_2)_t$(5-10 membered heteroaryl), –C(O)-$(CH_2)_t$(C_{3-10} cycloalkyl), and –C(O)-$(CH_2)_t$(4-10 membered heterocyclyl), wherein t is an integer from 0 to 4. In certain embodiments, R^{21} is C_{1-8} alkyl, substituted with halo or hydroxy; or C_{3-10} cycloalkyl, 4-10 membered heterocyclyl, C_{6-10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_{1-4} alkyl, halo, unsubstituted C_{1-4} alkoxy, unsubstituted C_{1-4} haloalkyl, unsubstituted C_{1-4} hydroxyalkyl, or unsubstituted C_{1-4} haloalkoxy or hydroxy.

[0054] "Alkoxy" refers to the group –OR^{29} where R^{29} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, *i.e.* with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

[0055] In certain embodiments, R^{29} is a group that has 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent, selected from the group consisting of amino, substituted amino, C_{6-10} aryl, aryloxy, carboxyl, cyano, C_{3-10} cycloalkyl, 4-10 membered heterocyclyl, halogen, 5-10 membered heteroaryl, hydroxyl, nitro, thioalkoxy, thioaryloxy, thiol, alkyl-S(O)-, aryl–S(O)-, alkyl–$S(O)_2$- and aryl-$S(O)_2$-. Exemplary 'substituted alkoxy' groups include, but are not limited to, –O-$(CH_2)_t$(C_{6-10} aryl), –O-$(CH_2)_t$(5-10 membered heteroaryl), –O-$(CH_2)_t$(C_{3-10} cycloalkyl), and –O-$(CH_2)_t$(4-10 membered heterocyclyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocyclyl groups present, may themselves be substituted by unsubstituted C_{1-4} alkyl, halo, unsubstituted C_{1-4} alkoxy, unsubstituted C_{1-4} haloalkyl, unsubstituted C_{1-4} hydroxyalkyl, or unsubstituted C_{1-4} haloalkoxy or hydroxy. Particular exemplary 'substituted alkoxy' groups are -OCF_3, -OCH_2CF_3, -OCH_2Ph, -OCH_2-cyclopropyl, -OCH_2CH_2OH, and -$OCH_2CH_2NMe_2$.

[0056] "Amino" refers to the radical -NH_2.

[0057] "Oxo group" refers to –C(=O)–.

[0058] "Substituted amino" refers to an amino group of the formula -N(R^{38})$_2$ wherein R^{38} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstitued heteroaryl, or an amino protecting group, wherein at least one of R^{38} is not a hydrogen. In certain embodiments, each R^{38} is independently selected from hydrogen, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocyclyl, or C_{3-10} cycloalkyl; or C_{1-8} alkyl, substituted with halo or hydroxy; C_{3-8} alkenyl, substituted with halo or hydroxy; C_{3-8} alkynyl, substituted with halo or hydroxy, or -$(CH_2)_t$(C_{6-10} aryl), -$(CH_2)_t$(5-10 membered heteroaryl), -$(CH_2)_t$(C_{3-10} cycloalkyl), or -$(CH_2)_t$(4-10 membered heterocyclyl), wherein t is an integer between 0 and 8, each of which is substituted by unsubstituted C_{1-4} alkyl, halo, unsubstituted C_{1-4} alkoxy, unsubstituted C_{1-4} haloalkyl, unsubstituted C_{1-4} hydroxyalkyl, or unsubstituted C_{1-4} haloalkoxy or hydroxy; or both R^{38} groups are joined to form an alkylene group.

[0059] Exemplary "substituted amino" groups include, but are not limited to, –NR^{39}-C_{1-8} alkyl, –NR^{39}-$(CH_2)_t$(C_{6-10} aryl), –NR^{39}-$(CH_2)_t$(5-10 membered heteroaryl), –NR^{39}-$(CH_2)_t$(C_{3-10} cycloalkyl), and –NR^{39}-$(CH_2)_t$(4-10 membered heterocyclyl), wherein t is an integer from 0 to 4, for instance 1 or 2, each R^{39} independently represents H or C_{1-8} alkyl; and any alkyl groups present, may themselves be substituted by halo, substituted or unsubstituted amino, or hydroxy; and any aryl, heteroaryl, cycloalkyl, or heterocyclyl groups present, may themselves be substituted by unsubstituted C_{1-4} alkyl, halo, unsubstituted C_{1-4} alkoxy, unsubstituted C_{1-4} haloalkyl, unsubstituted C_{1-4} hydroxyalkyl, or unsubstituted C_{1-4} haloalkoxy or hydroxy. For the avoidance of doubt the term 'substituted amino' includes the groups alkylamino, substituted alkylamino, alkylarylamino, substituted alkylarylamino, arylamino, substituted arylamino, dialkylamino, and substituted dialkylamino as defined below. Substituted amino encompasses both monosubstituted amino and disubstituted amino groups.

[0060] "Carboxy" refers to the radical -C(O)OH.

[0061] "Cyano" refers to the radical -CN.

[0062] "Halo" or "halogen" refers to fluoro (F), chloro (Cl), bromo (Br), and iodo (I). In certain embodiments, the halo group is either fluoro or chloro.

[0063] "Haloalkyl" refers to an alkyl radical in which the alkyl group is substituted with one or more halogens. Typical haloalkyl groups include, but are not limited to, trifluoromethyl, difluoromethyl, fluoromethyl, chloromethyl, dichloromethyl, dibromoethyl, tribromomethyl, tetrafluoroethyl, and the like.

[0064] "Hydroxy" refers to the radical -OH.

[0065] "Nitro" refers to the radical $–NO_2$.

[0066] "Thioketo" refers to the group =S.

[0067] Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (*e.g.,* "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (*e.g.,* a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.,* a substituent which upon substitution results in a stable compound, *e.g.,* a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0068] Exemplary carbon atom substituents include, but are not limited to, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{aa}$, $–ON(R^{bb})_2$, $–N(R^{bb})_2$, $–N(R^{bb})_3^+X^–$, $–N(OR^{cc})R^{bb}$, –SH, $–SR^{aa}$, $–SSR^{cc}$, $–C(=O)R^{aa}$, $–CO_2H$, –CHO, $–C(OR^{cc})_2$, $–CO_2R^{aa}$, $–OC(=O)R^{aa}$, $–OCO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–OC(=O)N(R^{bb})_2$, $–NR^{bb}C(=O)R^{aa}$, $–NR^{bb}CO_2R^{aa}$, $–NR^{bb}C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–OC(=NR^{bb})R^{aa}$, $–OC(=NR^{bb})OR^{aa}$, –

$C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)_2R^{aa}$, $-OP(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, $-OP(=O)_2N(R^{bb})_2$, $-P(=O)(NR^{bb})_2$, $-OP(=O)(NR^{bb})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(NR^{bb})_2$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

[0069] each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{aa} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

[0070] each instance of R^{bb} is, independently, selected from hydrogen, –OH, $-OR^{aa}$, $-N(R^{cc})_2$, –CN, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)_2N(R^{cc})_2$, $-P(=O)(NR^{cc})_2$, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

[0071] each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl,

carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

[0072] each instance of R^{dd} is, independently, selected from halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3^+X^–$, $–N(OR^{ee})R^{ff}$, –SH, $–SR^{ee}$, $–SSR^{ee}$, $–C(=O)R^{ee}$, $–CO_2H$, $–CO_2R^{ee}$, $–OC(=O)R^{ee}$, $–OCO_2R^{ee}$, $–C(=O)N(R^{ff})_2$, $–OC(=O)N(R^{ff})_2$, $–NR^{ff}C(=O)R^{ee}$, $–NR^{ff}CO_2R^{ee}$, $–NR^{ff}C(=O)N(R^{ff})_2$, $–C(=NR^{ff})OR^{ee}$, $–OC(=NR^{ff})R^{ee}$, $–OC(=NR^{ff})OR^{ee}$, $–C(=NR^{ff})N(R^{ff})_2$, $–OC(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}SO_2R^{ee}$, $–SO_2N(R^{ff})_2$, $–SO_2R^{ee}$, $–SO_2OR^{ee}$, $–OSO_2R^{ee}$, $–S(=O)R^{ee}$, $–Si(R^{ee})_3$, $–OSi(R^{ee})_3$, $–C(=S)N(R^{ff})_2$, $–C(=O)SR^{ee}$, $–C(=S)SR^{ee}$, $–SC(=S)SR^{ee}$, $–P(=O)_2R^{ee}$, $–P(=O)(R^{ee})_2$, $–OP(=O)(R^{ee})_2$, $–OP(=O)(OR^{ee})_2$, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

[0073] each instance of R^{ee} is, independently, selected from $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

[0074] each instance of R^{ff} is, independently, selected from hydrogen, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

[0075] each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1–6}$ alkyl, $–ON(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_3^+X^–$, $–NH(C_{1–6}$ alkyl$)_2^+X^–$, $–NH_2(C_{1–6}$ alkyl$)^+X^–$, $–NH_3^+X^–$, $–N(OC_{1–6}$ alkyl$)(C_{1–6}$ alkyl), $–N(OH)(C_{1–6}$ alkyl), –NH(OH), –SH, $–SC_{1–6}$ alkyl, $–SS(C_{1–6}$ alkyl), $–C(=O)(C_{1–6}$ alkyl), $–CO_2H$, $–CO_2(C_{1–6}$ alkyl), $–OC(=O)(C_{1–6}$ alkyl), $–OCO_2(C_{1–6}$ alkyl), $–C(=O)NH_2$, $–C(=O)N(C_{1–6}$ alkyl$)_2$, $–OC(=O)NH(C_{1–6}$ alkyl), $–NHC(=O)(C_{1–6}$ alkyl), $–N(C_{1–6}$ alkyl$)C(=O)(C_{1–6}$ alkyl), $–NHCO_2(C_{1–6}$ alkyl), $–NHC(=O)N(C_{1–6}$ alkyl$)_2$, $–NHC(=O)NH(C_{1–6}$ alkyl), $–NHC(=O)NH_2$,

–C(=NH)O(C_{1-6} alkyl),–OC(=NH)(C_{1-6} alkyl), –OC(=NH)OC_{1-6} alkyl, –C(=NH)N(C_{1-6} alkyl)$_2$, –C(=NH)NH(C_{1-6} alkyl), –C(=NH)NH_2, –OC(=NH)N(C_{1-6} alkyl)$_2$, –OC(NH)NH(C_{1-6} alkyl), –OC(NH)NH_2, –NHC(NH)N(C_{1-6} alkyl)$_2$, –NHC(=NH)NH_2, –$NHSO_2$(C_{1-6} alkyl), –SO_2N(C_{1-6} alkyl)$_2$, –SO_2NH(C_{1-6} alkyl), –SO_2NH_2,–SO_2C_{1-6} alkyl, –SO_2OC_{1-6} alkyl, –OSO_2C_{1-6} alkyl, –SOC_{1-6} alkyl, –Si(C_{1-6} alkyl)$_3$, –OSi(C_{1-6} alkyl)$_3$ –C(=S)N(C_{1-6} alkyl)$_2$, C(=S)NH(C_{1-6} alkyl), C(=S)NH_2, –C(=O)S(C_{1-6} alkyl), –C(=S)SC_{1-6} alkyl, –SC(=S)SC_{1-6} alkyl, –P(=O)$_2$(C_{1-6} alkyl), –P(=O)(C_{1-6} alkyl)$_2$, –OP(=O)(C_{1-6} alkyl)$_2$, –OP(=O)(OC_{1-6} alkyl)$_2$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein X^- is a counterion.

[0076] A "counterion" or "anionic counterion" is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.*, F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HSO_4^-, sulfonate ions (*e.g.*, methansulfonate, trifluoromethanesulfonate, p–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), and carboxylate ions (*e.g.*, acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

[0077] These and other exemplary substituents are described in more detail in the **Detailed Description**, and **Claims**. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other definitions

[0078] As used herein, the term "modulation" refers to the inhibition or potentiation of $GABA_A$ receptor function. A "modulator" (*e.g.*, a modulator compound) may be, for example, an agonist, partial agonist, antagonist, or partial antagonist of the $GABA_A$ receptor.

[0079] "Pharmaceutically acceptable" means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0080] "Pharmaceutically acceptable salt" refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non–toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3–(4–hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2–ethane–disulfonic acid, 2–hydroxyethanesulfonic acid, benzenesulfonic acid, 4–chlorobenzenesulfonic acid, 2–naphthalenesulfonic acid, 4–toluenesulfonic acid, camphorsulfonic acid, 4–methylbicyclo[2.2.2]–oct–2–ene–1–carboxylic acid, glucoheptonic acid, 3–phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N–methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term "pharmaceutically acceptable cation" refers to an acceptable cationic counter–ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like. See, *e.g.,* Berge, *et al., J. Pharm. Sci.* (1977) 66(1): 1–79.

[0081] The term "prodrug" is intended to encompass therapeutically inactive compounds that, under physiological conditions, are converted into the therapeutically active agents of the present invention. One method for making a prodrug is to design selected moieties that are hydrolyzed or cleaved at a targeted *in vivo* site of action under physiological conditions to reveal the desired molecule which then produces its therapeutic effect. In certain embodiments, the prodrug is converted by an enzymatic activity of the subject.

[0082] In an alternate embodiment, the present invention provides prodrugs of compound described herein, wherein the prodrug includes a cleavable moiety on the C3 hydroxy as depicted in Formulae depicted herein.

[0083] "Tautomers" refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci– and nitro– forms of phenylnitromethane, that are likewise formed by treatment with acid or base. Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0084] A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.,* a male or female of any age group, *e.g.,* a pediatric subject (*e.g,* infant, child, adolescent) or adult subject (*e.g.,* young adult, middle–aged adult or senior adult)) and/or a non-human animal, *e.g.*, a mammal such as primates (*e.g.,* cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human ("human subject"). In certain embodiments, the subject is a non-human animal.

[0085] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups include, but are not limited to, $–R^{aa}$, $–N(R^{bb})_2$, $–C(=O)SR^{aa}$, $–C(=O)R^{aa}$, $–CO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–C(=NR^{bb})N(R^{bb})_2$, $–S(=O)R^{aa}$, $–SO_2R^{aa}$, $–Si(R^{aa})_3$, $–P(R^{cc})_2$, $–P(R^{cc})_3$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)(OR^{cc})_2$, $–P(=O)_2N(R^{bb})_2$, and $–P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0086] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), 2–methoxyethoxymethyl (MEM), benzyl (Bn), triisopropylsilyl (TIPS), *t*–butyldimethylsilyl (TBDMS), *t*–butylmethoxyphenylsilyl (TBMPS), methanesulfonate (mesylate), and tosylate (Ts).

[0087] In certain embodiments, the substituent present on an sulfur atom is an sulfur protecting group (also referred to as a thiol protecting group). Sulfur protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0088] In certain embodiments, the substituent present on a nitrogen atom is an amino protecting group (also referred to herein as a nitrogen protecting group). Amino protecting groups include, but are not limited to, $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-C(=O)R^{aa}$, $-C(=O)OR^{aa}$, $-C(=O)N(R^{cc})_2$, $-S(=O)_2R^{aa}$, $-C(=NR^{cc})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14–membered heterocyclyl, C_{6-14} aryl, and 5–14–membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Amino protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0089] Exemplary amino protecting groups include, but are not limited to amide groups *(e.g.,* $-C(=O)R^{aa}$), which include, but are not limited to, formamide and acetamide; carbamate groups (*e.g.,* $-C(=O)OR^{aa}$), which include, but are not limited to, 9–fluorenylmethyl carbamate (Fmoc), *t*–butyl carbamate (BOC), and benzyl carbamate (Cbz); sulfonamide groups (*e.g.,* $-S(=O)_2R^{aa}$), which include, but are not limited to, *p*–toluenesulfonamide (Ts), methanesulfonamide (Ms), and *N*–[2–(trimethylsilyl)ethoxy]methylamine (SEM).

[0090] Disease, disorder, and condition are used interchangeably herein.

[0091] As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a subject is suffering from the specified

disease, disorder or condition, which reduces the severity of the disease, disorder or condition, or retards or slows the progression of the disease, disorder or condition ("therapeutic treatment"), and also contemplates an action that occurs before a subject begins to suffer from the specified disease, disorder or condition.

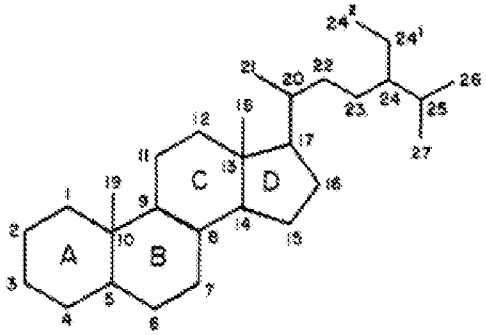
[0092] In general, the "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response, *e.g.*, to treat a CNS-related disorder, is sufficient to induce anesthesia or sedation. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of the invention may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the age, weight, health, and condition of the subject.

[0093] As used herein, and unless otherwise specified, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a disease, disorder or condition, or to delay or minimize one or more symptoms associated with the disease, disorder or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the disease, disorder or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

[0094] In an alternate embodiment, the present invention contemplates administration of the compounds of the present invention or a pharmaceutically acceptable salt or a pharmaceutically acceptable composition thereof, as a prophylactic before a subject begins to suffer from the specified disease, disorder or condition. As used herein, and unless otherwise specified, a "prophylactically effective amount" of a compound is an amount sufficient to prevent a disease, disorder or condition, or one or more symptoms associated with the disease, disorder or condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the disease, disorder or condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

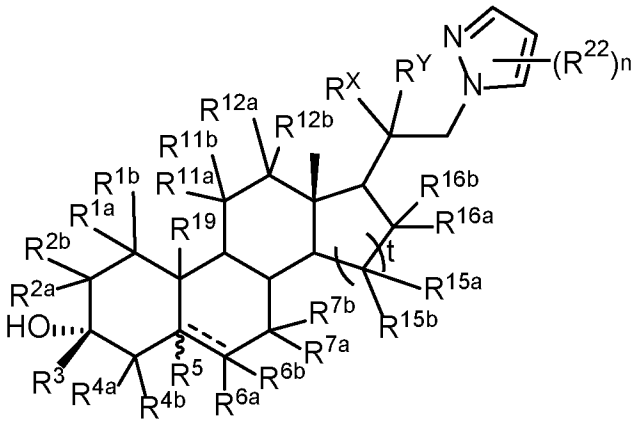
Compounds

[0095] It should be appreciated that formulas described herein may reference particular carbon atoms, such as C17, C3, C19, etc. These references are based on the position of carbon atoms according to steroid nomenclature known and used in the industry, as shown below:



For example, C17 refers to the carbon at position 17 and C3 refers to the carbon at position 3.

[0096] In one aspect, provided herein is a compound of Formula **I**:



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

------ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, -OR^{Q1}, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

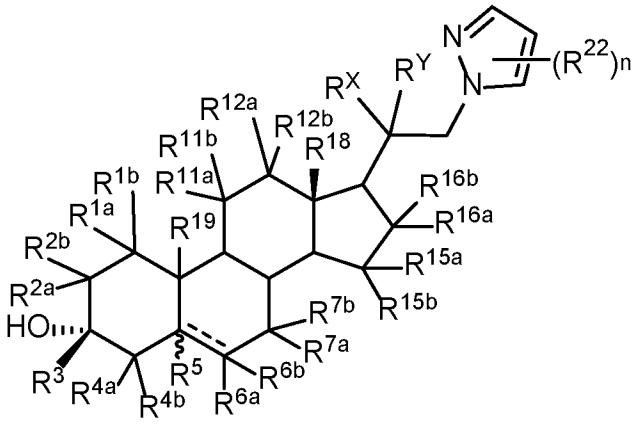
each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, $-OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})\ N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

R^{19} is hydrogen or substituted or unsubstituted alkyl;

n is 0, 1, 2, or 3; and

t is 2 or 3.

[0097] In an aspect, provided herein is a compound of Formula **II**:



(II)

or a pharmaceutically acceptable salt thereof;

wherein:

represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl,

substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})\ N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, -

$OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

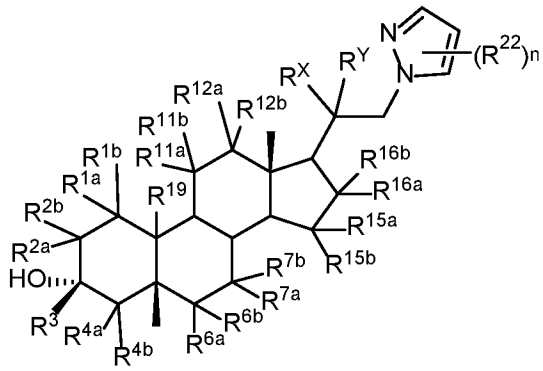
R^{19} is hydrogen or substituted or unsubstituted alkyl;

R^{18} is substituted or unsubstituted alkyl; and

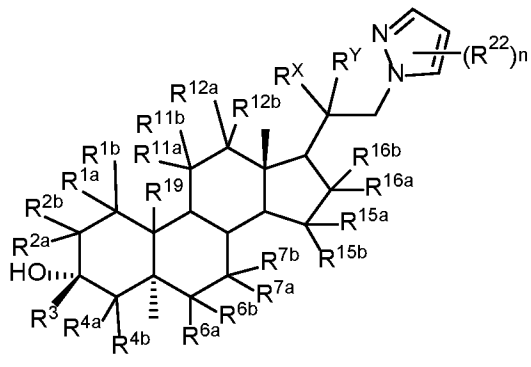
n is 0, 1, 2, or 3;

provided that when R^5 is hydrogen, R^{18} is not $-CH_3$.

[0098] In some embodiments, the compound of Formula **II** is a compound of Formula **IIIa** or **IIIb**:



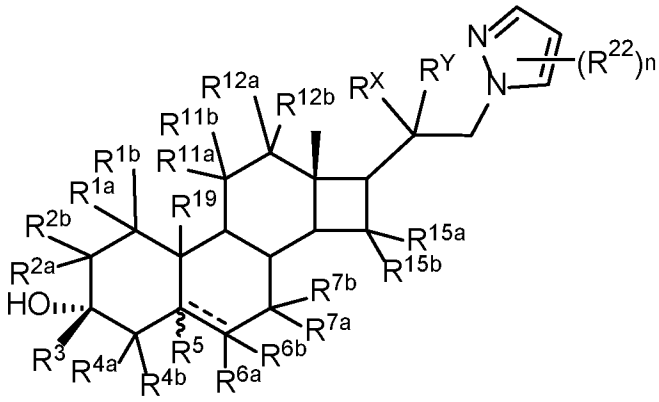
(IIIa)



(IIIb)

or a pharmaceutically acceptable salt thereof.

[0099] In an aspect, provided herein is a compound of Formula **V**:



(V)

or a pharmaceutically acceptable salt thereof;

wherein:

$\cdots\cdots$ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted

or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})\ N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

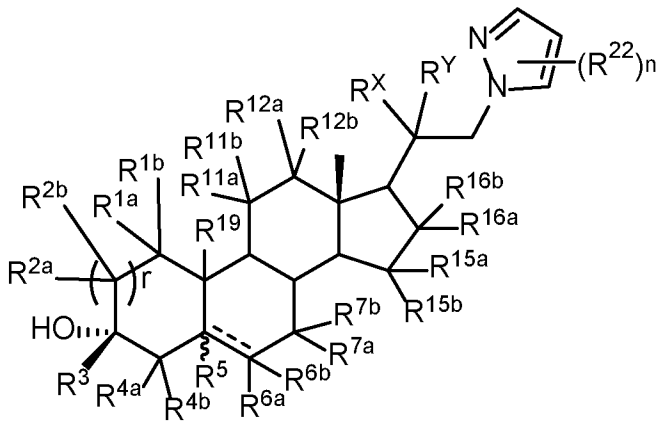
each of R^{15a} or R^{15b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, $-OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, -

$N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

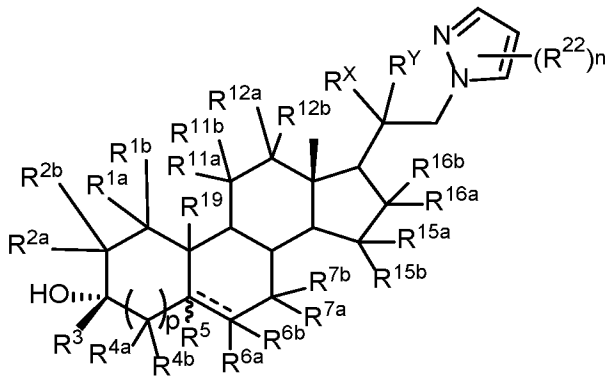
R^{19} is hydrogen or substituted or unsubstituted alkyl; and

n is 0, 1, 2, or 3.

[0100] In an aspect, provided herein is a compound of Formula **VIa** or **VIb**:



(VIa)



(VIb)

or a pharmaceutically acceptable salt thereof;

wherein:

------ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$,

$-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, $-OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})\ N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

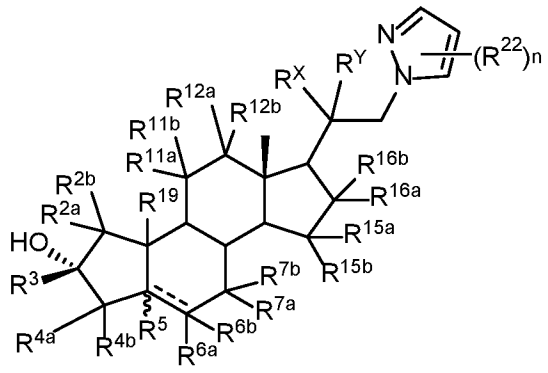
R^{19} is hydrogen or substituted or unsubstituted alkyl;

r is 2 or 3;

p is 2 or 3; and

n is 0, 1, 2, or 3.

[0101] In an aspect, provided herein is a compound of Formula **VII**:



(VII)

or a pharmaceutically acceptable salt thereof;

wherein:

------ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted

or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})\ N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

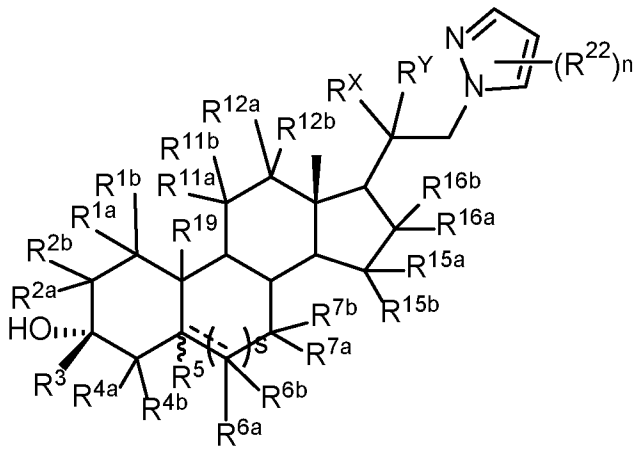
each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, $-OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, -

$N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

R^{19} is hydrogen or substituted or unsubstituted alkyl; and

n is 0, 1, 2, or 3.

[0102] In an aspect, provided herein is a compound of Formula **VIII**:



(VIII)

or a pharmaceutically acceptable salt thereof;

wherein:

------ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, -NO_2, -CN, -OR^{GA}, -$N(R^{GA})_2$, -$C(=O)R^{GA}$, -$C(=O)OR^{GA}$, -$OC(=O)R^{GA}$, -$OC(=O)OR^{GA}$, -$C(=O)N(R^{GA})_2$, -$N(R^{GA})C(=O)R^{GA}$, -$OC(=O)N(R^{GA})_2$, -$N(R^{GA})C(=O)OR^{GA}$, -$N(R^{GA})C(=O)N(R^{GA})_2$, -$SR^{GA}$, -$S(=O)R^{GA}$, -$S(=O)_2R^{GA}$, -$S(=O)_2OR^{GA}$, -$OS(=O)_2R^{GA}$, -$S(=O)_2N(R^{GA})_2$, -$N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, -NO_2, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR^{A1}, -$N(R^{A1})_2$, -SR^{A1}, -$C(=O)R^{A1}$, -$C(=O)OR^{A1}$, -$C(=O)SR^{A1}$, -$C(=O)N(R^{A1})_2$, -$OC(=O)R^{A1}$, -$OC(=O)OR^{A1}$, -$OC(=O)N(R^{A1})_2$, -$OC(=O)SR^{A1}$, -$OS(=O)_2R^{A1}$, -$OS(=O)_2OR^{A1}$, -$OS(=O)_2N(R^{A1})_2$, -$N(R^{A1})C(=O)R^{A1}$, -$N(R^{A1})C(=NR^{A1})R^{A1}$, -$N(R^{A1})C(=O)OR^{A1}$, -$N(R^{A1})C(=O)N(R^{A1})_2$, -$N(R^{A1})C(=NR^{A1})N(R^{A1})_2$, -$N(R^{A1})S(=O)_2R^{A1}$, -$N(R^{A1})S(=O)_2OR^{A1}$, -$N(R^{A1})S(=O)_2N(R^{A1})_2$, -$SC(=O)R^{A1}$, -$SC(=O)OR^{A1}$, -$SC(=O)SR^{A1}$, -$SC(=O)N(R^{A1})_2$, -$S(=O)_2R^{A1}$, -$S(=O)_2OR^{A1}$, or -$S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur

protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

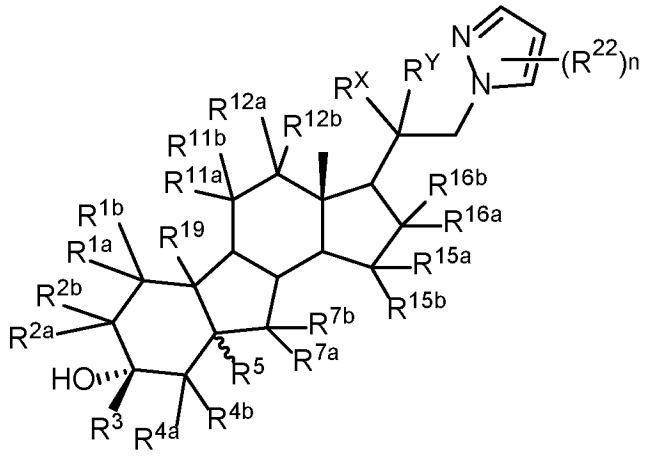
each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, $-OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})\ N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

R^{19} is hydrogen or substituted or unsubstituted alkyl;

s is 2; and

n is 0, 1, 2, or 3.

[0103] In an aspect, provided herein is a compound of Formula **IX**:



(IX)

or a pharmaceutically acceptable salt thereof;

wherein:

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})\ N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

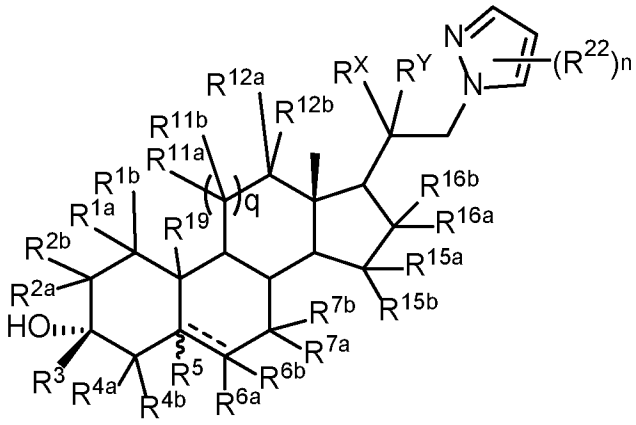
each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, $-OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})\ N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

R^{19} is hydrogen or substituted or unsubstituted alkyl; and

n is 0, 1, 2, or 3.

[0104] In another aspect, provided herein is a compound of Formula **X**:



(X)

or a pharmaceutically acceptable salt thereof;

wherein:

------ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, -

$C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted

alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR^{C3}, -$N(R^{C3})_2$, -SR^{C3}, -$C(=O)R^{C3}$, -$C(=O)OR^{C3}$, -$C(=O)SR^{C3}$, -$C(=O)N(R^{C3})_2$, -$OC(=O)R^{C3}$, -$OC(=O)OR^{C3}$, -$OC(=O)N(R^{C3})_2$, -$OC(=O)SR^{C3}$, -$OS(=O)_2R^{C3}$, -$OS(=O)_2OR^{C3}$, -$OS(=O)_2N(R^{C3})_2$, -$N(R^{C3})C(=O)R^{C3}$, -$N(R^{C3})C(=NR^{C3})R^{C3}$, -$N(R^{C3})C(=O)OR^{C3}$, -$N(R^{C3})C(=O)N(R^{C3})_2$, -$N(R^{C3})C(=NR^{C3})$ $N(R^{C3})_2$, -$N(R^{C3})S(=O)_2R^{C3}$, -$N(R^{C3})S(=O)_2OR^{C3}$, -$N(R^{C3})S(=O)_2N(R^{C3})_2$, -$SC(=O)R^{C3}$, -$SC(=O)OR^{C3}$, -$SC(=O)SR^{C3}$, -$SC(=O)N(R^{C3})_2$, -$S(=O)_2R^{C3}$, -$S(=O)_2OR^{C3}$, or -$S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

R^{19} is hydrogen or substituted or unsubstituted alkyl;

q is 2; and

n is 0, 1, 2, or 3.

Groups R^{1a} and R^{1b}

[0105] In some embodiments, each of R^{1a} and R^{1b} is independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR^{A1}, -$N(R^{A1})_2$, -$C(=O)R^{A1}$, -$C(=O)OR^{A1}$, or -$C(=O)N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0106] In some embodiments, each of R^{1a} and R^{1b} is independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, or $-OR^{A1}$, wherein each instance of R^{A1} is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0107] In some embodiments, each of R^{1a} and R^{1b} is independently hydrogen, unsubstituted C_{1-6} alkyl, C_{1-3} haloalkyl, or $-OR^{A1}$ wherein R^{A1} is hydrogen or unsubstituted alkyl.

[0108] In some embodiments, each of R^{1a} and R^{1b} is independently hydrogen or substituted or unsubstituted C_{1-6} alkyl.

[0109] In some embodiments, R^{1a} and R^{1b} is each independently hydrogen.

[0110] In some embodiments, R^{1a} and R^{1b} are both hydrogen.

Groups R^{2a} and R^{2b}

[0111] In some embodiments each of R^{2a} and R^{2b} is independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, or $-C(=O)N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0112] In some embodiments, each of R^{2a} and R^{2b} is independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, or $-OR^{A1}$, wherein each instance of R^{A1} is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0113] In some embodiments, each R^{2a} and R^{2b} is independently hydrogen, unsubstituted C_{1-6} alkyl, C_{1-3} haloalkyl, or $-OR^{A1}$ wherein R^{A1} is hydrogen or unsubstituted alkyl.

[0114] In some embodiments, R^{2a} and R^{2b} is each independently hydrogen.

[0115] In some embodiments, R^{2a} and R^{2b} are both hydrogen.

Groups R^{4a} and R^{4b}

[0116] In some embodiments, R^{4a} and R^{4b} is each independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, or $-C(=O)N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0117] In some embodiments, each of R^{4a} and R^{4b} is independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, or $-OR^{A1}$, wherein each instance of R^{A1} is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0118] In some embodiments, each R^{4a} and R^{4b} is independently hydrogen, unsubstituted C_{1-6} alkyl, C_{1-3} haloalkyl, or $-OR^{A1}$ wherein R^{A1} is hydrogen or unsubstituted alkyl.

[0119] In some embodiments, R^{4a} and R^{4b} is each independently hydrogen.

[0120] In some embodiments, R^{4a} and R^{4b} are both hydrogen.

Groups R^{7a} and R^{7b}

[0121] In some embodiments, each of R^{7a} and R^{7b} is independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, or $-C(=O)N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0122] In some embodiments, each R^{7a} and R^{7b} is independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, or $-OR^{A1}$, wherein each instance of R^{A1} is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0123] In some embodiments, each R^{7a} and R^{7b} is independently hydrogen, unsubstituted C_{1-6} alkyl, C_{1-3} haloalkyl, or $-OR^{A1}$ wherein $R^{A1}$is hydrogen or unsubstituted alkyl.

[0124] In some embodiments, R^{7a} and R^{7b} is each independently hydrogen.

[0125] In some embodiments, R^{7a} and R^{7b} are both hydrogen.

Groups R^{11a} and R^{11b}

[0126] In some embodiments, each R^{11a} and R^{11b} is independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, or $-C(=O)N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0127] In some embodiments, each R^{11a} and R^{11b} is independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, or $-OR^{A1}$, wherein each instance of R^{A1} is independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0128] In some embodiments, each R^{11a} and R^{11b} is independently hydrogen, unsubstituted C_{1-6} alkyl, C_{1-3} haloalkyl, or $-OR^{A1}$ wherein R^{A1} is unsubstituted alkyl.

[0129] In some embodiments, R^{11a} and R^{11b} is each independently hydrogen.

[0130] In some embodiments, R^{11a} and R^{11b} are both hydrogen.

Groups R^{12a} and R^{12b}

[0131] In some embodiments, each R^{12a}, and R^{12b} is independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, or $-C(=O)N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0132] In some embodiments, each R^{12a}, and R^{12b} is independently hydrogen, halogen, cyano, substituted or unsubstituted alkyl, or $-OR^{A1}$, wherein each instance of R^{A1} is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0133] In some embodiments, each R^{12a} and R^{12b} is independently hydrogen, unsubstituted C_{1-6} alkyl, C_{1-3} haloalkyl, or $-OR^{A1}$, wherein R^{A1} is hydrogen or unsubstituted alkyl.

[0134] In some embodiments, each R^{12a} and R^{12b} is each independently hydrogen.

[0135] In some embodiments, R^{12a} and R^{12b} are both hydrogen.

Groups R^{6a} and R^{6b}

[0136] In some embodiments, each R^{6a} and R^{6b} is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl.

[0137] In some embodiments, each R^{6a} and R^{6b} is independently hydrogen or substituted or unsubstituted alkyl.

[0138] In some embodiments, R^{6a} and R^{6b} is each independently hydrogen.

[0139] In some embodiments, R^{6a} and R^{6b} are both hydrogen.

Groups R^{15a} and R^{15b}

[0140] In some embodiments, each R^{15a} and R^{15b} is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heteroaryl.

[0141] In some embodiments, each R^{15a} and R^{15b} is independently hydrogen or substituted or unsubstituted alkyl.

[0142] In some embodiments, R^{15a} and R^{15b} is each independently hydrogen or unsubstituted alkyl.

[0143] In some embodiments, R^{15a} and R^{15b} is each independently hydrogen or unsubstituted $C_{1\text{-}6}$alkyl.

[0144] In some embodiments, R^{15a} and R^{15b} is each independently hydrogen or methyl.

[0145] In some embodiments, R^{15a} and R^{15b} is each independently hydrogen.

[0146] In some embodiments, R^{15a} and R^{15b} are both hydrogen.

Groups R^{16a} and R^{16b}

[0147] In some embodiments, each R^{16a} and R^{16b} is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heteroaryl.

[0148] In some embodiments, each R^{16a} and R^{16b} is independently hydrogen or substituted or unsubstituted alkyl.

[0149] In some embodiments, each R^{16a} and R^{16b} is independently hydrogen or unsubstituted alkyl.

[0150] In some embodiments, each R^{16a} and R^{16b} is each independently hydrogen.

[0151] In some embodiments, R^{16a} and R^{16b} are both hydrogen.

Group R^3

[0152] In some embodiments, R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl.

[0153] In some embodiments, R^3 is substituted or unsubstituted alkyl.

[0154] In some embodiments, R^3 is substituted or unsubstituted $C_{1\text{-}6}$alkyl.

[0155] In some embodiments, R^3 is $C_{1\text{-}3}$ alkyl optionally substituted with $C_{1\text{-}3}$ alkoxy.

[0156] In some embodiments, R^3 is methyl, ethyl, propyl, butyl, $-CH_2OCH_3$, or $-CH_2OCH_2CH_3$.

[0157] In some embodiments, R_3 is methyl, ethyl, or n-propyl.

[0158] In some embodiments, R^3 is methyl.

[0159] In some embodiments, R^3 is ethyl.

[0160] In some embodiments, R^3 is propyl.

Group R^{18}

[0161] In some embodiments, R^{18} is substituted or unsubstituted alkyl.

[0162] In some embodiments, R^{18} is substituted or unsubstituted $C_{1\text{-}6}$alkyl.

[0163] In some embodiments, R^{18} is substituted $C_{1\text{-}6}$alkyl.

[0164] In some embodiments, R^{18} is unsubstituted $C_{1\text{-}6}$alkyl.

[0165] In some embodiments, R^{18} is methyl.

Group R^{19}

[0166] In some embodiments, R^{19} is hydrogen or substituted or unsubstituted $C_{1\text{-}6}$alkyl.

[0167] In some embodiments, R^{19} is unsubstituted $C_{1\text{-}3}$alkyl.

[0168] In some embodiments, R^{19} is hydrogen.

[0169] In some embodiments R^{19} is $–CH_3$.

[0170] In some embodiments, R^{19} is hydrogen or methyl.

Group R^X and/or Group R^Y

[0171] In some embodiments, R^X is halo, -OH, $-OR^{Q1}$, or substituted or unsubstituted C_{1-3}alkyl.

[0172] In some embodiments, R^X is -OH.

[0173] In some embodiments, R^Y is halo or unsubstituted alkyl.

[0174] In some embodiments, R^Y is halo or unsubstituted C_{1-3}alkyl.

[0175] In some embodiments, R^Y is methyl, ethyl, or propyl.

[0176] In some embodiments, R^Y is methyl.

[0177] In some embodiments, R^X is -OH and R^Y is unsubstituted C_{1-3}alkyl.

[0178] In some embodiments, R^X is -OH and R^Y is methyl.

[0179] In some embodiments, R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclic ring, or a substituted or unsubstituted heterocyclic ring.

[0180] In some embodiments, R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted C_{3-7} carbocyclic ring, or a substituted or unsubstituted C_{3-7} heterocyclic ring.

[0181] In some embodiments, R^Y and R^X join together with the intervening atoms to form a substituted or unsubstituted 4-membered carbocyclic ring.

[0182] In some embodiments, R^Y and R^X join together with the intervening atoms to form a substituted or unsubstituted 4-membered heterocyclic ring.

[0183] In some embodiments, the 4-membered heterocyclic ring contains a heteroatom selected from N, O, and S.

Group R^{Q1}

[0184] In some embodiments, R^{Q1} is unsubstituted C_{1-6}alkyl.

[0185] In some embodiments, R^{Q1} is methyl.

Group R^{22}

[0186] In some embodiments, R^{22} is independently for each occurrence hydrogen, halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-N(R^{GA})C(=O)R^{GA}$, $-SR^{GA}$, $-S(=O)\ R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} carbocylyl, or substituted or unsubstituted C_{3-6} heterocylyl; wherein each instance of R^{GA} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted C_{3-6} heterocylyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0187] In some embodiments, R^{22} is independently for each occurrence halogen, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} carbocylyl; wherein each instance of R^{GA} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted C_{3-6} carbocylyl.

[0188] In some embodiments, R^{22} is independently for each occurrence hydrogen, halogen, -CN, unsubstituted C_{1-3} alkyl, substituted or unsubstituted C_{3-6} heterocylyl, C_{1-3} haloalkyl, or $-OR^{GA}$, wherein each instance of R^{GA} is independently hydrogen, substituted or unsubstituted C_{1-3} alkyl.

[0189] In some embodiments, R^{22} is located at the 4-position of the pyrazolyl.

[0190] In another embodiment, R^{22} is located at the 3-position of the pyrazolyl.

[0191] In another embodiment, R^{22} is located at the 5-position of the pyrazolyl.

[0192] In some embodiments, R^{22} is -CN.

[0193] In another embodiment, R^{22} is -CN located at the 4-position of the pyrazolyl.

Integer n

[0194] In some embodiments, n is 1 or 2.

[0195] In some embodiments, n is 1, 2, or 3.

[0196] In some embodiments, n is 0 or 1.

[0197] In some embodiments, n is 0.

[0198] In some embodiments, n is 1.

[0199] In some embodiments, n is 2.

[0200] In some embodiments, n is 3.

Integer t

[0201] In some embodiments, t is 2. In some embodiments t is 3.

Integer r

[0202] In some embodiments, r is 2. In some embodiments r is 3.

Integer p

[0203] In some embodiments, p is 2. In some embodiments p is 3.

Integer s

[0204] In some embodiments, s is 2.

Integer q

[0205] In some embodiments, q is 2.

Group R^5

[0206] In some embodiments, R^5 is methyl in the *alpha* or *beta* configuration.

[0207] In some embodiments, R^5 is methyl in the *alpha* configuration.

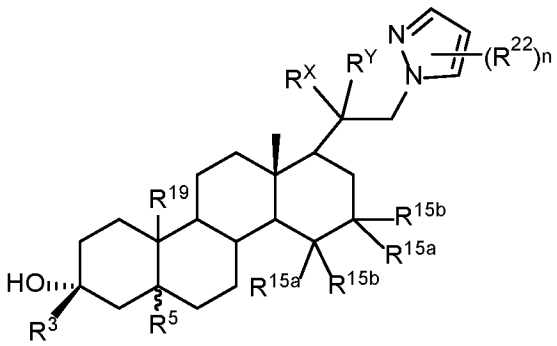
[0208] In some embodiments, R^5 is methyl in the *beta* configuration.

[0209] In some embodiments, R^5 is a hydrogen in the *alpha* or *beta* configuration.

[0210] In some embodiments, R^5 is a hydrogen in the *alpha* configuration.

[0211] In some embodiments, R^5 is a hydrogen in the *beta* configuration.

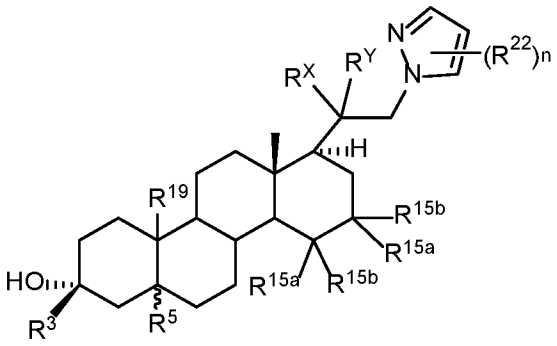
[0212] In some embodiments, the compound of Formula **I** is a compound of Formula **I-a**:



(I-a)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

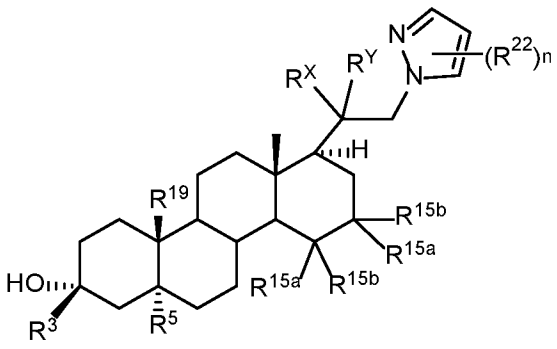
[0213] In some embodiments, the compound of Formula **I** is a compound of Formula **I-b**:



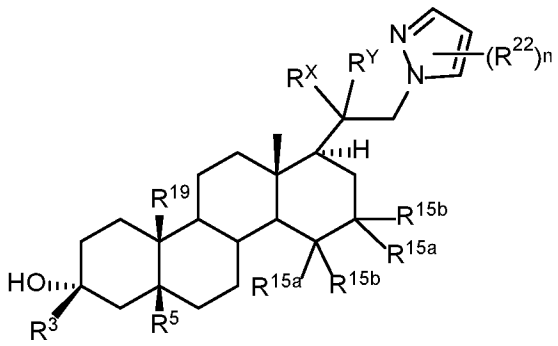
(I-b)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0214] In some embodiments, the compound of Formula **I** is a compound of Formula **I-c** or **I-d**:



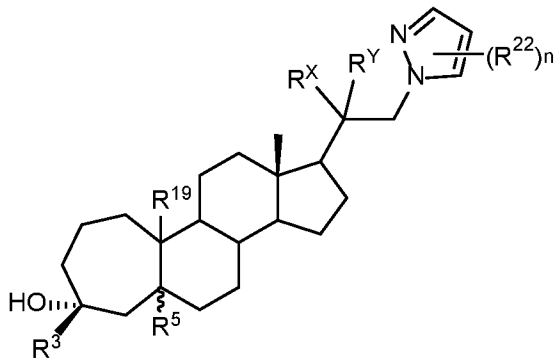
(I-c),



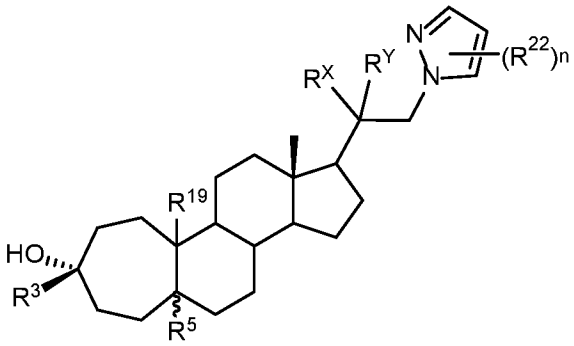
(I-d)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0215] In some embodiments, the compound of Formula **VIa** or **VIb** is a compound of Formula **VIa-a** or **VIb-a**:



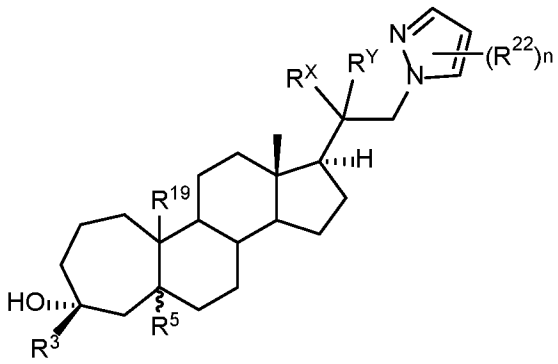
(VIa-a),



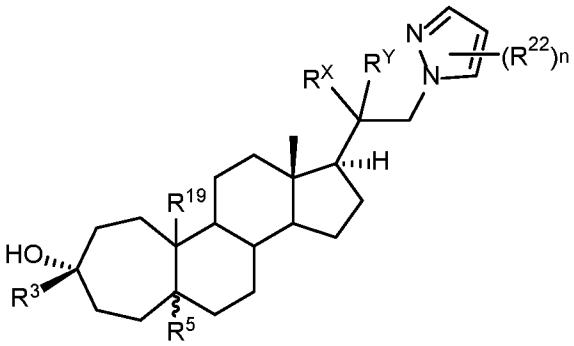
(VIb-a)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0216] In some embodiments, the compound of Formula **VIa** or **VIb** is a compound of Formula **VIa-b** or **VIb-b**:



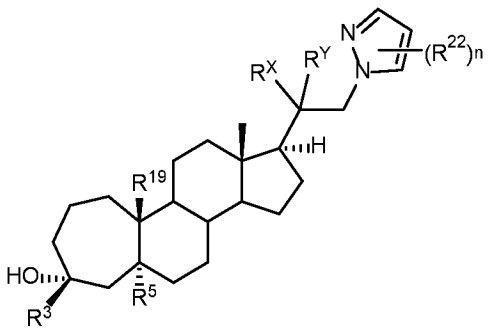
(VIa-b),



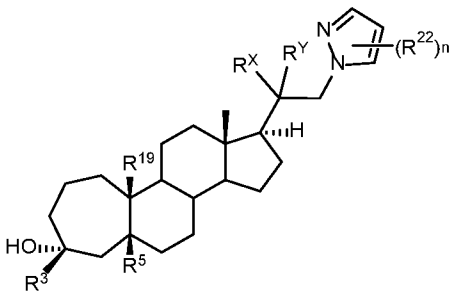
(VIb-b)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

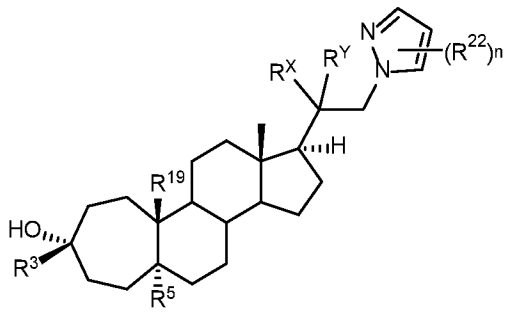
[0217] In some embodiments, the compound of Formula **VIa** or **VIb** is a compound of Formula **VIa-c, VIa-d, VIb-c** or **VIb-d**:

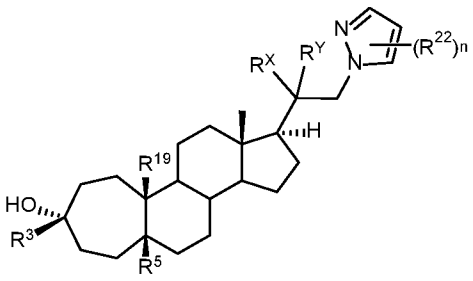


(VIa-c),



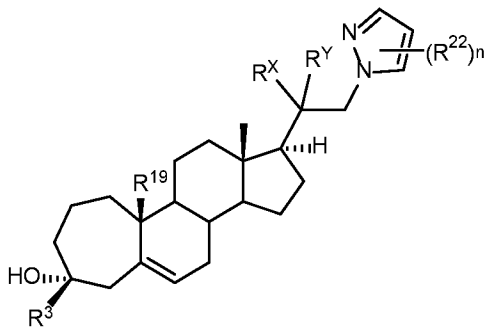
(VIa-d),



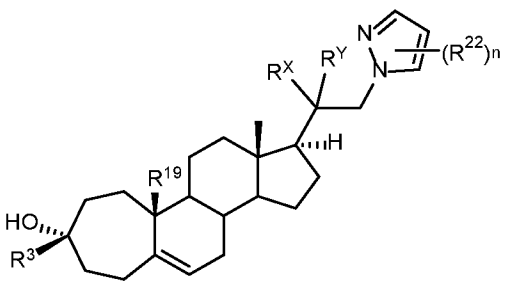
(VIb-c),  **(VIb-d)**,

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0218] In some embodiments, the compound of Formula **VIa** or **VIb** is a compound of Formula **VIa-e** or **VIb-e**:



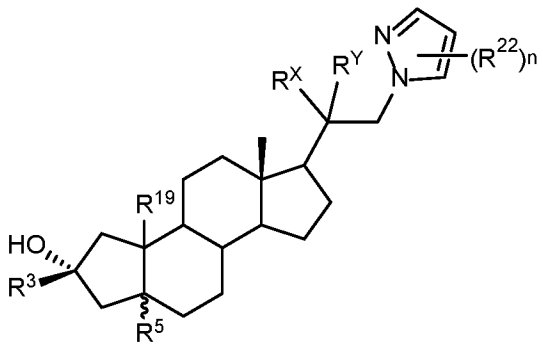
(VIa-e),



(VIb-e)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

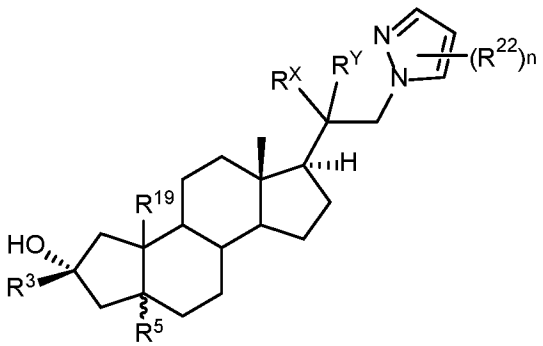
[0219] In some embodiments, the compound of Formula **VII** is a compound of Formula **VII-a:**



(VII-a)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

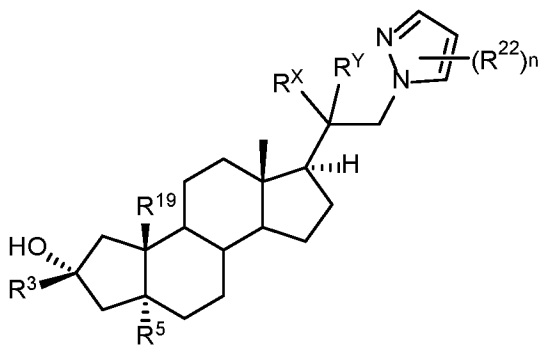
[0220] In some embodiments, the compound of Formula **VII** is a compound of Formula **VII-b:**



(VII-b)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0221] In some embodiments, the compound of Formula **VII** is a compound of Formula **VII-c**:

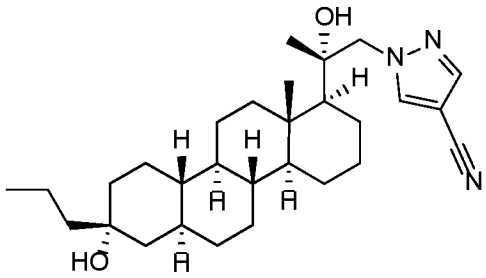
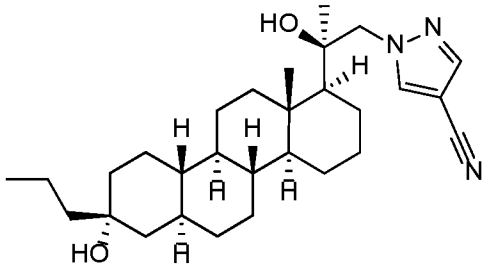
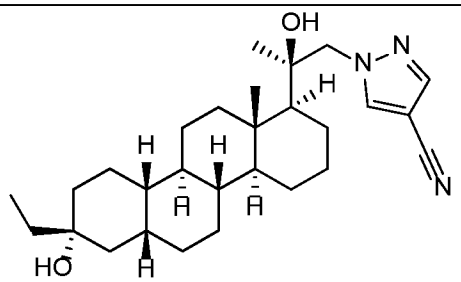
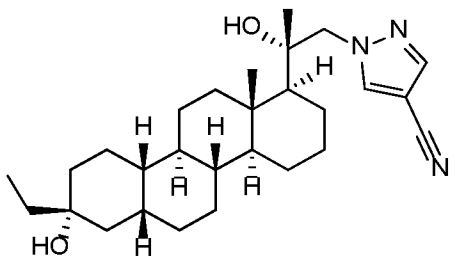
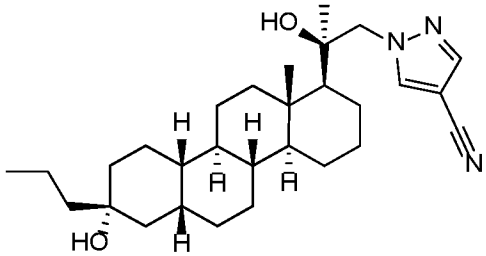


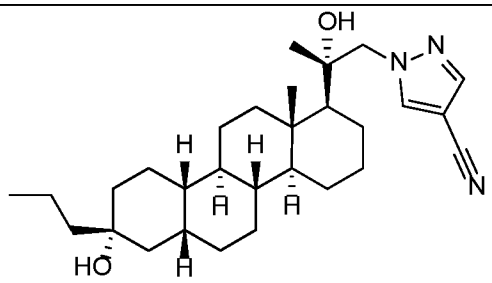
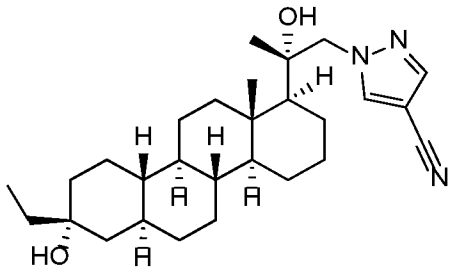
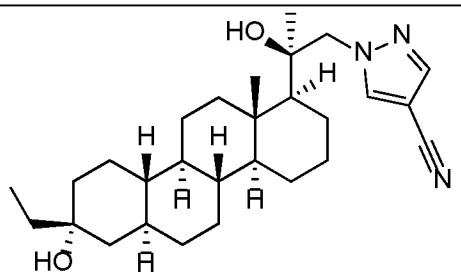
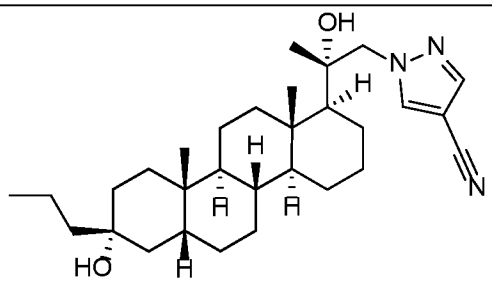
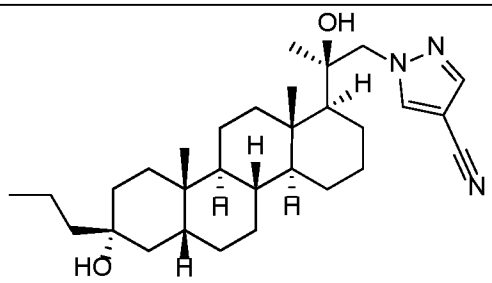
(VII-c)

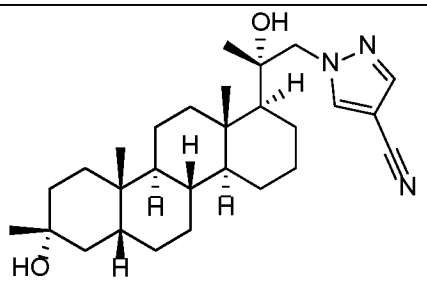
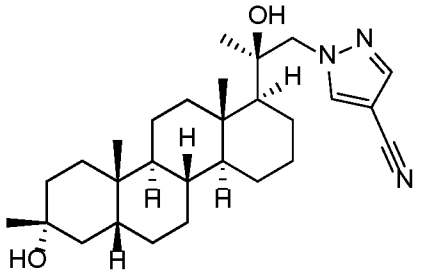
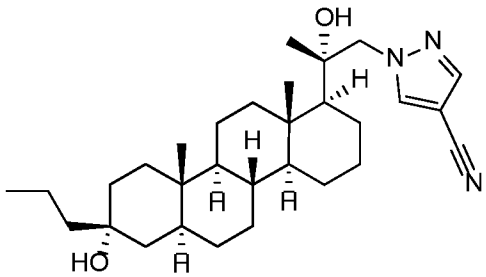
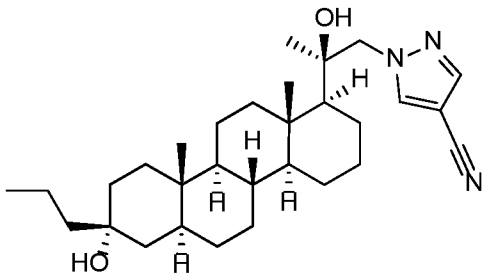
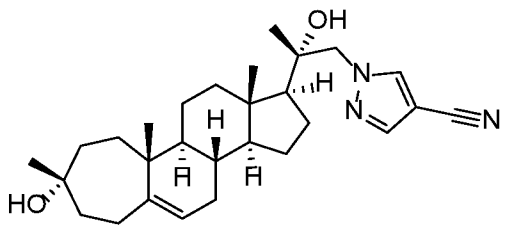
or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

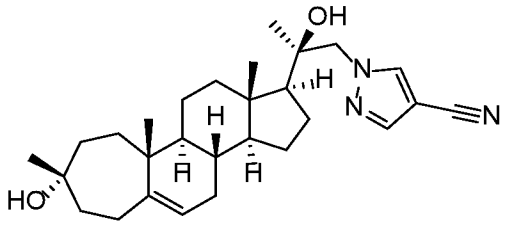
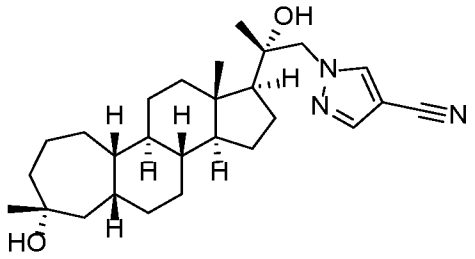
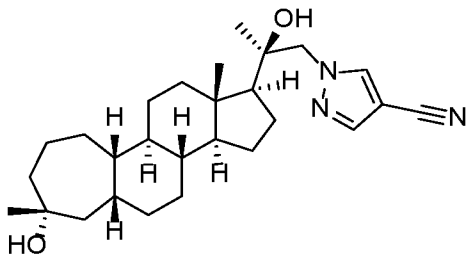
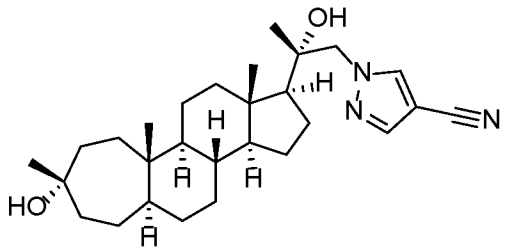
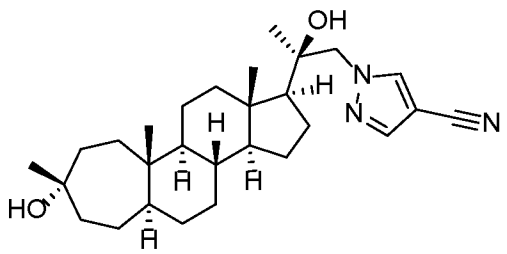
[0222] In some embodiments, the compound is selected from the group consisting of the compounds identified in **Table 1** below:

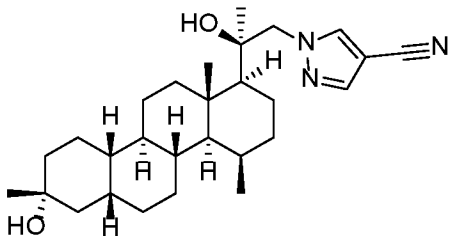
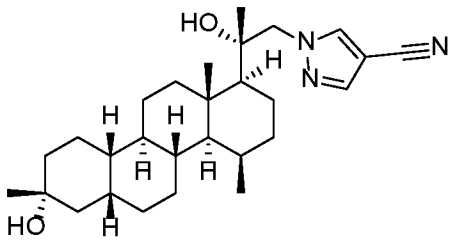
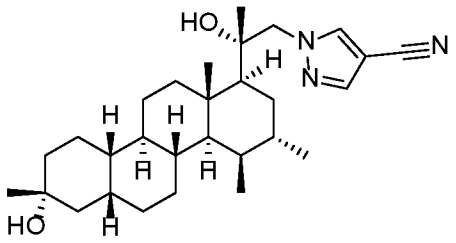
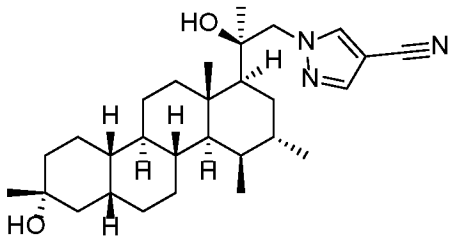
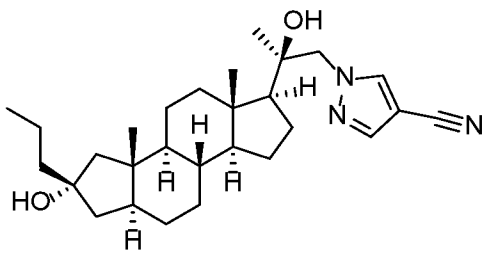
Table 1.

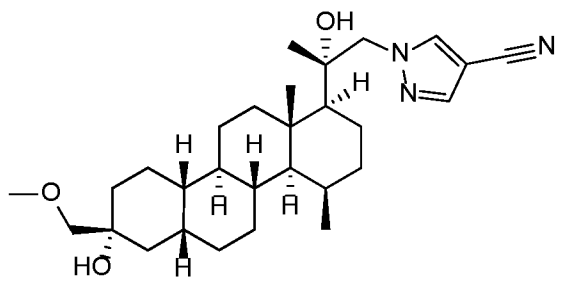
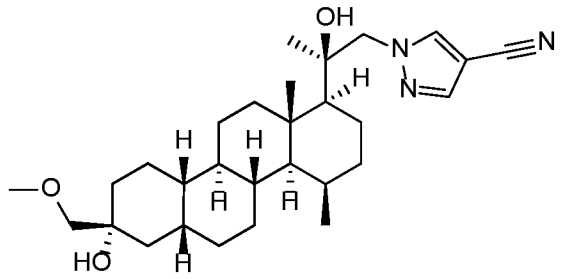
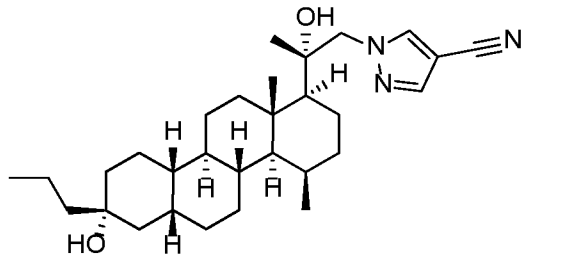
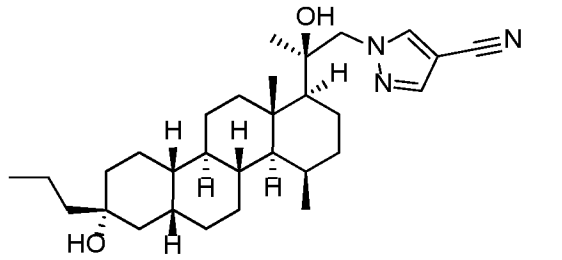
Compound No.	STRUCTURE
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[0223] In one aspect, provided herein is a pharmaceutically acceptable salt of a compound described herein (*e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X).

[0224] In one aspect, provided herein is a pharmaceutical composition comprising a compound described herein (*e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X) or a pharmaceutically acceptable salt thereof, and a pharmaceutically

acceptable excipient. In certain embodiments, the compound of the present invention is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the compound of the present invention is provided in a therapeutically effective amount.

[0225] Compounds of the present invention as described herein, act, in certain embodiments, as GAB_A modulators, *e.g.*, effecting the $GABA_A$ receptor in either a positive or negative manner. As modulators of the excitability of the central nervous system (CNS), as mediated by their ability to modulate $GABA_A$ receptor, such compounds are expected to have CNS-activity.

[0226] Thus, in an aspect, provided herein is amethod of modulating a GABAA receptor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims described herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein.

[0227] In another aspect, provided are methods of treating a CNS–related disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present invention. In certain embodiments, CNS–related disorder is a sleep disorder, a mood disorder, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, tinnitus, or status epilepticus. In certain embodiments, the CNS-related disorder is depression. In certain embodiments, the CNS-related disorder is postpartum depression. In certain embodiments, the CNS-related disorder is major depressive disorder. In certain embodiments, the major depressive disorder is moderate major depressive disorder. In certain embodiments, the major depressive disorder is severe major depressive disorder. In certain embodiments, the compound is administered orally, subcutaneously, intravenously, or intramuscularly. In certain embodiments, the compound is administered orally. In certain embodiments, the compound is administered chronically. In certain embodiments, the compound is administered continuously, *e.g.,* by continuous intravenous infusion.

[0228] Exemplary compounds of the invention may be synthesized from the following known starting materials using methods known to one skilled in the art or certain references,

In one aspect, provided herein is a pharmaceutically acceptable salt of a compound described herein (*e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X).

Alternative Embodiments

[0229] In an alternative embodiment, compounds described herein may also comprise one or more isotopic substitutions. For example, hydrogen may be ^{2}H (D or deuterium) or ^{3}H (T or tritium); carbon may be, for example, ^{13}C or ^{14}C; oxygen may be, for example, ^{18}O; nitrogen may be, for example, ^{15}N, and the like. In other embodiments, a particular isotope (e.g., ^{3}H, ^{13}C, ^{14}C, ^{18}O, or ^{15}N) can represent at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 99.9% of the total isotopic abundance of an element that occupies a specific site of the compound.

Pharmaceutical Compositions

[0230] In one aspect, provided herein is a pharmaceutical composition comprising a compound described herein (*e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In certain embodiments, the compound of the present invention is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the compound of the present invention is provided in a therapeutically effective amount.

[0231] In certain embodiments, the pharmaceutical composition comprises an effective amount of the active ingredient. In certain embodiments, the pharmaceutical composition comprises a therapeutically effective amount of the active ingredient.

[0232] The pharmaceutical compositions provided herein can be administered by a variety of routes including, but not limited to, oral (enteral) administration, parenteral (by injection) administration, rectal administration, transdermal administration, intradermal administration, intrathecal administration, subcutaneous (SC) administration, intravenous (IV) administration, intramuscular (IM) administration, and intranasal administration.

[0233] Generally, the compounds provided herein are administered in an effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated,

the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0234] When used to prevent the onset of a CNS-disorder, the compounds provided herein will be administered to a subject at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Subjects at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

[0235] The pharmaceutical compositions provided herein can also be administered chronically ("chronic administration"). Chronic administration refers to administration of a compound or pharmaceutical composition thereof over an extended period of time, e.g., for example, over 3 months, 6 months, 1 year, 2 years, 3 years, 5 years, etc, or may be continued indefinitely, for example, for the rest of the subject's life. In certain embodiments, the chronic administration is intended to provide a constant level of the compound in the blood, e.g., within the therapeutic window over the extended period of time.

[0236] The pharmaceutical compositions of the present invention may be further delivered using a variety of dosing methods. For example, in certain embodiments, the pharmaceutical composition may be given as a bolus, e.g., in order to raise the concentration of the compound in the blood to an effective level. The placement of the bolus dose depends on the systemic levels of the active ingredient desired throughout the body, e.g., an intramuscular or subcutaneous bolus dose allows a slow release of the active ingredient, while a bolus delivered directly to the veins (e.g., through an IV drip) allows a much faster delivery which quickly raises the concentration of the active ingredient in the blood to an effective level. In other embodiments, the pharmaceutical composition may be administered as a continuous infusion, e.g., by IV drip, to provide maintenance of a steady-state concentration of the active ingredient in the subject's body. Furthermore, in still yet other embodiments, the pharmaceutical composition may be administered as first as a bolus dose, followed by continuous infusion.

[0237] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms"

refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or excipients and processing aids helpful for forming the desired dosing form.

[0238] With oral dosing, one to five and especially two to four and typically three oral doses per day are representative regimens. Using these dosing patterns, each dose provides from about 0.01 to about 20 mg/kg of the compound provided herein, with preferred doses each providing from about 0.1 to about 10 mg/kg, and especially about 1 to about 5 mg/kg.

[0239] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses, generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight.

[0240] Injection dose levels range from about 0.1 mg/kg/hour to at least 20 mg/kg/hour, all for from about 1 to about 120 hours and especially 24 to 96 hours. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 5 g/day for a 40 to 80 kg human patient.

[0241] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0242] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable excipients known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable excipient and the like.

[0243] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s). When formulated as an ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or Formulation. All such known transdermal formulations and ingredients are included within the scope provided herein.

[0244] The compounds provided herein can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[0245] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

[0246] The compounds of the present invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington's Pharmaceutical Sciences.

[0247] The present invention also relates to the pharmaceutically acceptable acid addition salt of a compound of the present invention. The acid which may be used to prepare the pharmaceutically acceptable salt is that which forms a non-toxic acid addition salt, i.e., a salt containing pharmacologically acceptable anions such as the hydrochloride, hydroiodide, hydrobromide, nitrate, sulfate, bisulfate, phosphate, acetate, lactate, citrate, tartrate, succinate, maleate, fumarate, benzoate, para-toluenesulfonate, and the like.

[0248] In another aspect, the invention provides a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable excipient, e.g., a composition suitable for injection, such as for intravenous (IV) administration.

[0249] Pharmaceutically acceptable excipients include any and all diluents or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, preservatives, lubricants and the like, as suited to the particular dosage form desired, e.g., injection. General considerations in the formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and Remington: The Science and Practice of Pharmacy, 21st Edition (Lippincott Williams & Wilkins, 2005).

[0250] For example, injectable preparations, such as sterile injectable aqueous suspensions, can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. Exemplary excipients that can be employed include, but are not limited to, water, sterile saline or phosphate–buffered saline, or Ringer's solution.

[0251] In certain embodiments, the pharmaceutical composition further comprises a cyclodextrin derivative. The most common cyclodextrins are α–, β– and γ– cyclodextrins consisting of 6, 7 and 8 α–l ,4–linked glucose units, respectively, optionally comprising one or more substituents on the linked sugar moieties, which include, but are not limited to, substituted or unsubstituted methylated, hydroxyalkylated, acylated, and sulfoalkylether substitution. In certain embodiments, the cyclodextrin is a sulfoalkyl ether β–cyclodextrin, e.g., for example, sulfobutyl ether β–cyclodextrin, also known as CAPTISOL®. See, e.g., U.S. 5,376,645. In certain embodiments, the composition comprises hexapropyl–β–cyclodextrin. In a more particular embodiment, the composition comprises hexapropyl–β–cyclodextrin (10–50% in water).

[0252] The injectable composition can be sterilized, for example, by filtration through a bacterial–retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0253] Generally, the compounds provided herein are administered in an effective amount. The amount of the compound actually administered will typically be determined by

a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, response of the individual patient, the severity of the patient's symptoms, and the like.

[0254] The compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include pre–filled, pre–measured ampules or syringes of the liquid compositions. In such compositions, the compound is usually a minor component (from about 0.1% to about 50% by weight or preferably from about 1% to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[0255] The compounds provided herein can be administered as the sole active agent, or they can be administered in combination with other active agents. In one aspect, the present invention provides a combination of a compound of the present invention and another pharmacologically active agent. Administration in combination can proceed by any technique apparent to those of skill in the art including, for example, separate, sequential, concurrent, and alternating administration.

[0256] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation. General considerations in the formulation and/or manufacture of pharmaceutical compositions can be found, for example, in Remington: The Science and Practice of Pharmacy 21st ed., Lippincott Williams & Wilkins, 2005.

[0257] In one aspect, provided is a kit comprising a composition (e.g., a solid composition) comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X.

Combination Therapy

[0258] A compound or composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) may be administered in combination with an additional agent or therapy. A subject to be administered a compound disclosed herein may have a disease, disorder, or condition, or a symptom thereof, that would benefit from treatment with another agent or therapy. Combination therapy may be achieved by administering two or more agents, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. In some embodiments, the two or more agents in the combination therapy can be administered simultaneously. In other embodiments, the two or more agents in the combination therapy are administered separately. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

[0259] Combination therapy can also include two or more administrations of one or more of the agents used in the combination using different sequencing of the component agents. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc. Exemplary additional agents are described below.

Selective Serotonin Reuptake Inhibitor (SSRI)

[0260] In some embodiments, the compound or composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) is administered in combination with an SSRI(s). SSRIs include antidepressants that increase the level of serotonin in the brain. Exemplary SSRIs include, but are not limited to, Citalopram (Celexa),

Escitalopram (Lexapro), Fluoxetine (Prozac), Fluvoxamine (Luvox), Paroxetine (Paxil), and Sertraline (Zoloft).

Norepinephrine Reuptake Inhibitor (NERI)

[0261] In some embodiments, the compound or composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) is administered in combination with an NERI(s). Exemplary NERIs include, but are not limited to, Atomoxetine (Strattera), Reboxetine (Edronax, Vestra), Bupropion (Wellbutrin, Zyban), Duloxetine, Desipramine (Norpramin), Amedalin (UK-3540-1), Daledalin (UK-3557-15), Edivoxetine (LY-2216684), Esreboxetine, Lortalamine (LM-1404), Nisoxetine (LY-94,939), Talopram (tasulopram) (Lu 3-010), Talsupram (Lu 5-005), Tandamine (AY-23,946), and Viloxazine (Vivalan).

Antipsychotics

[0262] In some embodiments, the compound or composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) is administered in combination with an antipsychotic agent(s). Antipsychotics include D2 antagonists, lowering dopaminergic neurotransmission in the dopamine pathways. Exemplary antipsychotics include, but are not limited to, Asenapine (Saphris), Aripiprazole (Abilify), Cariprazine (Vrayar), Clozapine (Clozaril), Droperidol, Fluperlapine, Mesoridazine, Quetiapine Hemifumarate, Raclopride, Spiperone, Sulpiride, Trimethobenzamide hydrochloride, Trifluoperazine Dihydrochloride, lurasidone (Latuda), Olanzapine (Zyprexa), Quetiapine (Seroquel), Zotepine, Risperidone (Risperdal), Ziprasidone (Geodon), Mesotidazine, Chlorpromazine hydrochloride, and Haloperidol (Haldol).

Cannabinoids

[0263] In some embodiments, the compound or composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) is administered in

combination with a cannabinoid(s). Exemplary cannabinoids include, but are not limited to, Cannabidiol (Epidiolex), Tetrahydrocannabinolic Acid, Tetrahydrocannabinol, Cannabidolic Acid, Cannabinol, Cannabigerol, Cannabichromene, Tetrahydrocannabivarin, and Cannabidivarin.

NMDA Receptor Antagonists

[0264] In some embodiments, the compound or composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) is administered in combination with an NMDA receptor antagonist(s). NMDA receptor antagonists are a class of drugs that inhibit the action of the N-methyl-d-aspartate receptor. Exemplary NMDA antagonists include, but are not limited to, Ketamine, Esketamine, Ketobemidone, Ifendopril, 5,7-Dichlorokynurenic Acid, Licostinel, Memantine, Gavestinel, Phencyclidine, Dextromethorphan, Remacemide, Selfotel, Tiletamine, Dextropropoxyphene, Aptiganel, Dexanabinol, and Amantadine. NMDA receptor antagonists also include opioids such as Methadone, Dextropropoxyphene, Pethidine, Levorphanol, Tramadol, Neramexane, and Ketobemidone.

GABA Receptor Agonists

[0265] In some embodiments, the compound or composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) is administered in combination with GABA receptor agaonist(s). GABA receptor agonist are a class of drugs that are agonists for one or more of the GABA receptors. Exemplary GABA receptor agonists include, but are not limited to, Clobazam, Topiramate, Muscimol, Progabide, Riluzole, Baclofen, Gabapentin, Vigabatrin, Valproic Acid, Tiagabine, Lamotrigine, Pregabalin, Phenyloin, Carbamazepine, Thiopental, Thiamylal, Pentobarbital, Secobarbital, Hexobarbital, Butobarbital, Amobarbital, Barbital, Mephobarbital, Phenobarbital, Primidone, Midazolam, Triazolam, Lometazepam, Flutazolam, Nitrazepam, Fluritrazepam, Nimetazepam, Diazepam, Medazepam, Oxazolam, Prazeam, Tofisopam, Rilmazafonoe, Lorazepam, Temazepam, Oxazepam, Fluidazepam, Chlordizaepoxide, Cloxazolam, Flutoprazepam, Alprazolam, Estazolam, Bromazepam, Flurazepam, Clorazepate Potassium,

Haloxazolam, Ethyl Loflazepate, Qazepam, Clonazepam, Mexazolam, Etizolam, Brotizolam, Clotizaepam, Propofol, Fospropofol, Zolpidem, Zopiclone, Exzopiclone, Muscimol, TFQP/gaboxadol, Isoguvacine, Kojic amine, GABA, Homotaurine, Homohypotaurine, Trans-aminocyclopentane-3- carboxylic acid, Trans-amino-4-crotonic acid, b-guanidinopropionic acid, homo-b-proline, Isonipecotic acid, 3-((aminoiminomethyl)thio)-2-propenoic acid (ZAP A), Imidazoleacetic acid, and Piperidine-4-sulfonic acid (P4S).

Cholinesterase Inhibitors

[0266] In some embodiments, the compound or composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) is administered in combination with a cholinesterase inhibitor(s). In general, cholinergics are compounds which mimic the action of acetylcholine and/or butyrylcholine. Cholinesterase inhibitors are a class of drugs that prevent the breakdown of acetylcholine. Exemplary cholinesterase inhibitors include, but are not limited to, Donepizil (Aricept), Tacrine (Cognex), Rivastigmine (Exelon, Exelon Patch), Galantamine (Razadyne, Reminyl), Memantine/Donepezil (Namzaric), Ambenonium (Mytelase), Neostigmine (Bloxiverz), Pyridostigmine (Mestinon Timespan, Regonol), and Galantamine (Razadyne).

[0267] The present disclosure also contemplates, among other things administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) to a subject has been previously administered an agent selected from the group consisting of a bronchial muscle/airway relaxant, an antiviral, oxygen, an antibody, and an antibacterial. In some embodiments an additional agent is administered to a subject prior to administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) and an additional agent is selected from the group consisting of a bronchial muscle/airway relaxant, an antiviral, oxygen, an antibody, and an antibacterial. In some embodiments, a compound or pharmaceutical composition described herein (e.g., a

compound Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) is co-administered with to a subject with an agent selected from a bronchial muscle/airway relaxant, an antiviral, oxygen, and an antibacterial.

Methods of Use and Treatment

[0268] In an aspect, compounds described herein, *e.g.*, compounds of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X are envisioned to be useful as therapeutic agents for treating a CNS-related disorder (*e.g.*, sleep disorder, a mood disorder such as depression, a schizophrenia spectrum disorder, a convulsive disorder, epileptogenesis, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, or tinnitus) in a subject in need (*e.g.*, a subject with Rett syndrome, Fragile X syndrome, or Angelman syndrome). Exemplary CNS conditions related to GABA-modulation include, but are not limited to, sleep disorders [*e.g.*, insomnia], mood disorders [*e.g.*, depression depression (*e.g.*, major depressive disorder (MDD)), dysthymic disorder (*e.g.*, mild depression), bipolar disorder (*e.g.*, I and/or II), anxiety disorders (*e.g.*, generalized anxiety disorder (GAD), social anxiety disorder), stress, post-traumatic stress disorder (PTSD), compulsive disorders (*e.g.*, obsessive compulsive disorder (OCD))], schizophrenia spectrum disorders [*e.g.*, schizophrenia, schizoaffective disorder], convulsive disorders [*e.g.*, epilepsy (*e.g.*, status epilepticus (SE)), seizures], disorders of memory and/or cognition [*e.g.*, attention disorders (*e.g.*, attention deficit hyperactivity disorder (ADHD)), dementia (*e.g.*, Alzheimer's type dementia, Lewis body type dementia, vascular type dementia], movement disorders [*e.g.*, Huntington's disease, Parkinson's disease], personality disorders [*e.g.*, anti-social personality disorder, obsessive compulsive personality disorder], autism spectrum disorders (ASD) [*e.g.*, autism, monogenetic causes of autism such as synaptophathy's, *e.g.*, Rett syndrome, Fragile X syndrome, Angelman syndrome], pain [*e.g.*, neuropathic pain, injury related pain syndromes, acute pain, chronic pain], traumatic brain injury (TBI), vascular diseases [*e.g.*, stroke, ischemia, vascular malformations], substance abuse disorders and/or withdrawal syndromes [*e.g.*, addition to opiates, cocaine, and/or alcohol], and tinnitus.

[0269] In certain embodiments, CNS–related disorder is a sleep disorder, a mood disorder, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory

and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, tinnitus, or status epilepticus. In certain embodiments, the CNS-related disorder is depression. In certain embodiments, the CNS-related disorder is postpartum depression. In certain embodiments, the CNS-related disorder is major depressive disorder. In certain embodiments, the major depressive disorder is moderate major depressive disorder. In certain embodiments, the major depressive disorder is severe major depressive disorder.

[0270] In an aspect, provided is a method of alleviating or preventing seizure activity in a subject, comprising administering to the subject in need of such treatment an effective amount of a compound of the present invention. In some embodiments, the method alleviates or prevents epileptogenesis.

[0271] In yet another aspect, provided is a combination of a compound of the present invention and another pharmacologically active agent. The compounds provided herein can be administered as the sole active agent or they can be administered in combination with other agents. Administration in combination can proceed by any technique apparent to those of skill in the art including, for example, separate, sequential, concurrent and alternating administration.

[0272] In another aspect, provided is a method of treating or preventing brain excitability in a subject susceptible to or afflicted with a condition associated with brain excitability, comprising administering to the subject an effective amount of a compound of the present invention to the subject.

[0273] In yet another aspect, provided is a method of treating or preventing stress or anxiety in a subject, comprising administering to the subject in need of such treatment an effective amount of a compound of the present invention, or a composition thereof.

[0274] In yet another aspect, provided is a method of alleviating or preventing insomnia in a subject, comprising administering to the subject in need of such treatment an effective amount of a compound of the present invention, or a composition thereof.

[0275] In yet another aspect, provided is a method of inducing sleep and maintaining substantially the level of REM sleep that is found in normal sleep, wherein substantial

rebound insomnia is not induced, comprising administering an effective amount of a compound of the present invention.

[0276] In yet another aspect, provided is a method of alleviating or preventing premenstrual syndrome (PMS) or postnatal depression (PND) in a subject, comprising administering to the subject in need of such treatment an effective amount of a compound of the present invention.

[0277] In yet another aspect, provided is a method of treating or preventing mood disorders in a subject, comprising administering to the subject in need of such treatment an effective amount of a compound of the present invention. In certain embodiments the mood disorder is depression.

[0278] In yet another aspect, provided is a method of cognition enhancement or treating memory disorder by administering to the subject a therapeutically effective amount of a compound of the present invention. In certain embodiments, the disorder is Alzheimer's disease. In certain embodiments, the disorder is Rett syndrome.

[0279] In yet another aspect, provided is a method of treating attention disorders by administering to the subject a therapeutically effective amount of a compound of the present invention. In certain embodiments, the attention disorder is ADHD.

[0280] Inflammation of the central nervous system (CNS) (neuroinflammation) is recognized to be a feature of all neurological disorders. Major inflammatory neurological disorders include multiple sclerosis (characterized by an immune-mediated response against myelin proteins), and meningoencephalitis (where infectious agents triggered the inflammatory response). Additional scientific evidence suggests a potential role of inflammatory mechanisms in other neurological conditions such as Alzheimer's disease, Parkinson's disease, Huntington' disease, amyotrophic lateral sclerosis, stroke and traumatic brain injuries. In one embodiment, the compounds of the present invention are useful in treating neuroinflammation. In another embodiment, the compounds of the present invention are useful in treating inflammation in neurological conditions, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, stroke, and traumatic brain injuries.

[0281] In certain embodiments, the compound is administered to the subject chronically. In certain embodiments, the compound is administered to the subject orally, subcutaneously, intramuscularly, or intravenously.

Neuroendocrine Disorders and Dysfunction

[0282] Provided herein are methods that can be used for treating neuroendocrine disorders and dysfunction. As used herein, "neuroendocrine disorder" or "neuroendocrine dysfunction" refers to a variety of conditions caused by imbalances in the body's hormone production directly related to the brain. Neuroendocrine disorders involve interactions between the nervous system and the endocrine system. Because the hypothalamus and the pituitary gland are two areas of the brain that regulate the production of hormones, damage to the hypothalamus or pituitary gland, e.g., by traumatic brain injury, may impact the production of hormones and other neuroendocrine functions of the brain. In some embodiments, the neuroendocrine disorder or dysfunction is associated with a women's health disorder or condition (e.g., a women's health disorder or condition described herein). In some embodiments, the neuroendocrine disorder or dysfunction is associated with a women's health disorder or condition is polycystic ovary syndrome.

[0283] Symptoms of neuroendocrine disorder include, but are not limited to, behavioral, emotional, and sleep-related symptoms, symptoms related to reproductive function, and somatic symptoms; including but not limited to fatigue, poor memory, anxiety, depression, weight gain or loss, emotional lability, lack of concentration, attention difficulties, loss of lipido, infertility, amenorrhea, loss of muscle mass, increased belly body fat, low blood pressure, reduced heart rate, hair loss, anemia, constipation, cold intolerance, and dry skin.

Neurodegenerative Diseases and Disorders

[0284] The methods described herein can be used for treating neurodegenerative diseases and disorders. The term "neurodegenerative disease" includes diseases and disorders that are associated with the progressive loss of structure or function of neurons, or death of neurons. Neurodegenerative diseases and disorders include, but are not limited to, Alzheimer's disease (including the associated symptoms of mild, moderate, or severe cognitive impairment); amyotrophic lateral sclerosis (ALS); anoxic and ischemic injuries; ataxia and convulsion (including for the treatment and prevention and prevention of seizures that are caused by schizoaffective disorder or by drugs used to treat schizophrenia); benign forgetfulness; brain

edema; cerebellar ataxia including McLeod neuroacanthocytosis syndrome (MLS); closed head injury; coma; contusive injuries (*e.g.,* spinal cord injury and head injury); dementias including multi-infarct dementia and senile dementia; disturbances of consciousness; Down syndrome; drug-induced or medication-induced Parkinsonism (such as neuroleptic-induced acute akathisia, acute dystonia, Parkinsonism, or tardive dyskinesia, neuroleptic malignant syndrome, or medication-induced postural tremor); epilepsy; fragile X syndrome; Gilles de la Tourette's syndrome; head trauma; hearing impairment and loss; Huntington's disease; Lennox syndrome; levodopa-induced dyskinesia; mental retardation; movement disorders including akinesias and akinetic (rigid) syndromes (including basal ganglia calcification, corticobasal degeneration, multiple system atrophy, Parkinsonism-ALS dementia complex, Parkinson's disease, postencephalitic parkinsonism, and progressively supranuclear palsy); muscular spasms and disorders associated with muscular spasticity or weakness including chorea (such as benign hereditary chorea, drug-induced chorea, hemiballism, Huntington's disease, neuroacanthocytosis, Sydenham's chorea, and symptomatic chorea), dyskinesia (including tics such as complex tics, simple tics, and symptomatic tics), myoclonus (including generalized myoclonus and focal cyloclonus), tremor (such as rest tremor, postural tremor, and intention tremor) and dystonia (including axial dystonia, dystonic writer's cramp, hemiplegic dystonia, paroxysmal dystonia, and focal dystonia such as blepharospasm, oromandibular dystonia, and spasmodic dysphonia and torticollis); neuronal damage including ocular damage, retinopathy or macular degeneration of the eye; neurotoxic injury which follows cerebral stroke, thromboembolic stroke, hemorrhagic stroke, cerebral ischemia, cerebral vasospasm, hypoglycemia, amnesia, hypoxia, anoxia, perinatal asphyxia and cardiac arrest; Parkinson's disease; seizure; status epilecticus; stroke; tinnitus; tubular sclerosis, and viral infection induced neurodegeneration (*e.g.,* caused by acquired immunodeficiency syndrome (AIDS) and encephalopathies). Neurodegenerative diseases also include, but are not limited to, neurotoxic injury which follows cerebral stroke, thromboembolic stroke, hemorrhagic stroke, cerebral ischemia, cerebral vasospasm, hypoglycemia, amnesia, hypoxia, anoxia, perinatal asphyxia and cardiac arrest. Methods of treating or preventing a neurodegenerative disease also include treating or preventing loss of neuronal function characteristic of neurodegenerative disorder.

Mood disorders

[0285] Also provided herein are methods for treating a mood disorder, for example clinical depression, postnatal depression or postpartum depression, perinatal depression, atypical depression, melancholic depression, psychotic major depression, cataonic depression, seasonal affective disorder, dysthymia, double depression, depressive personality disorder, recurrent brief depression, minor depressive disorder, bipolar disorder or manic depressive disorder, depression caused by chronic medical conditions, treatment-resistant depression, refractory depression, suicidality, suicidal ideation, or suicidal behavior. In some embodiments, the method described herein provides therapeutic effect to a subject suffering from depression (e.g., moderate or severe depression). In some embodiments, the mood disorder is associated with a disease or disorder described herein (e.g., neuroendocrine diseases and disorders, neurodegenerative diseases and disorders (e.g., epilepsy), movement disorders, tremor (e.g., Parkinson's Disease), women's health disorders or conditions).

[0286] **Clinical depression** is also known as major depression, major depressive disorder (MDD), severe depression, unipolar depression, unipolar disorder, and recurrent depression, and refers to a mental disorder characterized by pervasive and persistent low mood that is accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities. Some people with clinical depression have trouble sleeping, lose weight, and generally feel agitated and irritable. Clinical depression affects how an individual feels, thinks, and behaves and may lead to a variety of emotional and physical problems. Individuals with clinical depression may have trouble doing day-to-day activities and make an individual feel as if life is not worth living.

[0287] **Peripartum depression** refers to depression in pregnancy. Symptoms include irritability, crying, feeling restless, trouble sleeping, extreme exhaustion (emotional and/or physical), changes in appetite, difficulty focusing, increased anxiety and/or worry, disconnected feeling from baby and/or fetus, and losing interest in formerly pleasurable activities.

[0288] **Postnatal depression (PND)** is also referred to as **postpartum depression (PPD)**, and refers to a type of clinical depression that affects women after childbirth. Symptoms can include sadness, fatigue, changes in sleeping and eating habits, reduced sexual desire, crying episodes, anxiety, and irritability. In some embodiments, the PND is a

treatment-resistant depression (e.g., a treatment-resistant depression as described herein). In some embodiments, the PND is refractory depression (e.g., a refractory depression as described herein).

[0289] In some embodiments, a subject having PND also experienced depression, or a symptom of depression during pregnancy. This depression is referred to herein as) **perinatal depression**. In an embodiment, a subject experiencing perinatal depression is at increased risk of experiencing PND.

[0290] **Atypical depression (AD)** is characterized by mood reactivity (*e.g.,* paradoxical anhedonia) and positivity, significant weight gain or increased appetite. Patients suffering from AD also may have excessive sleep or somnolence (hypersomnia), a sensation of limb heaviness, and significant social impairment as a consequence of hypersensitivity to perceived interpersonal rejection.

[0291] **Melancholic depression** is characterized by loss of pleasure (anhedonia) in most or all activities, failures to react to pleasurable stimuli, depressed mood more pronounced than that of grief or loss, excessive weight loss, or excessive guilt.

[0292] **Psychotic major depression (PMD)** or psychotic depression refers to a major depressive episode, in particular of melancholic nature, where the individual experiences psychotic symptoms such as delusions and hallucinations.

[0293] **Catatonic depression** refers to major depression involving disturbances of motor behavior and other symptoms. An individual may become mute and stuporose, and either is immobile or exhibits purposeless or bizarre movements.

[0294] **Seasonal affective disorder (SAD)** refers to a type of seasonal depression wherein an individual has seasonal patterns of depressive episodes coming on in the fall or winter.

[0295] **Dysthymia** refers to a condition related to unipolar depression, where the same physical and cognitive problems are evident. They are not as severe and tend to last longer (*e.g.,* at least 2 years).

[0296] **Double depression** refers to fairly depressed mood (dysthymia) that lasts for at least 2 years and is punctuated by periods of major depression.

[0297] **Depressive Personality Disorder (DPD)** refers to a personality disorder with depressive features.

[0298] **Recurrent Brief Depression (RBD)** refers to a condition in which individuals have depressive episodes about once per month, each episode lasting 2 weeks or less and typically less than 2-3 days.

[0299] **Minor depressive disorder** or minor depression refers to a depression in which at least 2 symptoms are present for 2 weeks.

[0300] **Bipolar disorder or manic depressive disorder** causes extreme mood swings that include emotional highs (mania or hypomania) and lows (depression). During periods of mania the individual may feel or act abnormally happy, energetic, or irritable. They often make poorly thought out decisions with little regard to the consequences. The need for sleep is usually reduced. During periods of depression there may be crying, poor eye contact with others, and a negative outlook on life. The risk of suicide among those with the disorder is high at greater than 6% over 20 years, while self-harm occurs in 30-40%. Other mental health issues such as anxiety disorder and substance use disorder are commonly associated with bipolar disorder.

[0301] **Depression caused by chronic medical conditions** refers to depression caused by chronic medical conditions such as cancer or chronic pain, chemotherapy, chronic stress.

[0302] **Treatment-resistant depression** refers to a condition where the individuals have been treated for depression, but the symptoms do not improve. For example, antidepressants or physchological counseling (psychotherapy) do not ease depression symptoms for individuals with treatment-resistant depression. In some cases, individuals with treatment-resistant depression improve symptoms, but come back. **Refractory depression** occurs in patients suffering from depression who are resistant to standard pharmacological treatments, including tricyclic antidepressants, MAOIs, SSRIs, and double and triple uptake inhibitors and/or anxiolytic drugs, as well as non-pharmacological treatments (e.g., psychotherapy, electroconvulsive therapy, vagus nerve stimulation and/or transcranial magnetic stimulation).

[0303] **Post-surgical depression** refers to feelings of depression that follow a surgical procedure (e.g., as a result of having to confront one's mortality). For example, individuals

may feel sadness or empty mood persistently, a loss of pleasure or interest in hobbies and activities normally enjoyed, or a persistent felling of worthlessness or hopelessness.

[0304] Mood disorder associated with conditions or disorders of women's health refers to mood disorders (e.g., depression) associated with (e.g., resulting from) a condition or disorder of women's health (e.g., as described herein).

[0305] Suicidality, suicidal ideation, suicidal behavior refers to the tendency of an individual to commit suicide. Suicidal ideation concerns thoughts about or an unusual preoccupation with suicide. The range of suicidal ideation varies greatly, from e.g., fleeting thoughts to extensive thoughts, detailed planning, role playing, incomplete attempts. Symptoms include talking about suicide, getting the means to commit suicide, withdrawing from social contact, being preoccupied with death, feeling trapped or hopeless about a situation, increasing use of alcohol or drugs, doing risky or self-destructive things, saying goodbye to people as if they won't be seen again.

[0306] Symptoms of depression include persistent anxious or sad feelings, feelings of helplessness, hopelessness, pessimism, worthlessness, low energy, restlessness, difficulty sleeping, sleeplessness, irritability, fatigue, motor challenges, loss of interest in pleasurable activities or hobbies, loss of concentration, loss of energy, poor self-esteem, absence of positive thoughts or plans, excessive sleeping, overeating, appetite loss, insomnia,self-harm, thoughts of suicide, and suicide attempts. The presence, severity, frequency, and duration of symptoms may vary on a case to case basis. Symptoms of depression, and relief of the same, may be ascertained by a physician or psychologist (e.g., by a mental state examination).

[0307] In some embodiments, the method comprises monitoring a subject with a known depression scale, *e.g.*, the Hamilton Depression (HAM-D) scale, the Clinical Global Impression-Improvement Scale (CGI), and the Montgomery–Åsberg Depression Rating Scale (MADRS). In some embodiments, a therapeutic effect can be determined by reduction in Hamilton Depression (HAM-D) total score exhibited by the subject. Reduction in the HAM-D total score can happen within 4, 3, 2, or 1 days; or 96, 84, 72, 60, 48, 24, 20, 16, 12, 10, 8 hours or less. The therapeutic effect can be assessed across a specified treatment period. For example, the therapeutic effect can be determined by a decrease from baseline in HAM-D total score after administering a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X (e.g., 12, 24, or 48 hours after

administration; or 24, 48, 72, or 96 hours or more; or 1 day, 2 days, 14 days, 21 days, or 28 days; or 1 week, 2 weeks, 3 weeks, or 4 weeks; or 1 month, 2 months, 6 months, or 10 months; or 1 year, 2 years, or for life).

[0308] In some embodiments, the subject has a mild depressive disorder, *e.g.*, mild major depressive disorder. In some embodiments, the subject has a moderate depressive disorder, *e.g.*, moderate major depressive disorder. In some embodiments, the subject has a severe depressive disorder, *e.g.*, severe major depressive disorder. In some embodiments, the subject has a very severe depressive disorder, *e.g.*, very severe major depressive disorder. In some embodiments, the baseline HAM-D total score of the subject (i.e., prior to treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X) is at least 24. In some embodiments, the baseline HAM-D total score of the subject is at least 18. In some embodiments, the baseline HAM-D total score of the subject is between and including 14 and 18. In some embodiments, the baseline HAM-D total score of the subject is between and including 19 and 22. In some embodiments, the HAM-D total score of the subject before treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, is greater than or equal to 23. In some embodiments, the baseline score is at least 10, 15, or 20. In some embodiments, the HAM-D total score of the subject after treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, is about 0 to 10 (e.g., less than 10; 0 to 10, 0 to 6, 0 to 4, 0 to 3, 0 to 2, or 1.8). In some embodiments, the HAM-D total score after treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, is less than 10, 7, 5, or 3. In some embodiments, the decrease in HAM-D total score is from a baseline score of about 20 to 30 (e.g., 22 to 28, 23 to 27, 24 to 27, 25 to 27, 26 to 27) to a HAM-D total score at about 0 to 10 (e.g., less than 10; 0 to 10, 0 to 6, 0 to 4, 0 to 3, 0 to 2, or 1.8) after treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X. In some embodiments, the decrease in the baseline HAM-D total score to HAM-D total score after treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, is at least 1, 2, 3, 4, 5, 7, 10, 25, 40, 50, or 100 fold). In some embodiments, the percentage decrease in the baseline HAM-D total score to HAM-D total score after treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, is at least 50% (e.g., 60%, 70%, 80%, or 90%). In some embodiments, the therapeutic effect is measured as a

decrease in the HAM-D total score after treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, relative to the baseline HAM-D total score (e.g., 12, 24, 48 hours after administration; or 24, 48, 72, 96 hours or more; or 1 day, 2 days, 14 days, or more) is at least 10, 15, or 20 points.

[0309] In some embodiments, the method of treating a depressive disorder, e.g., major depressive disorder provides a therapeutic effect (e.g., as measured by reduction in Hamilton Depression Score (HAM-D)) within 14, 10, 4, 3, 2, or 1 days, or 24, 20, 16, 12, 10, or 8 hours or less. In some embodiments, the method of treating the depressive disorder, e.g., major depressive disorder, provides a therapeutic effect (*e.g.*, as determined by a statistically significant reduction in HAM-D total score) within the first or second day of the treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X. In some embodiments, the method of treating the depressive disorder, e.g., major depressive disorder, provides a therapeutic effect (*e.g.*, as determined by a statistically significant reduction in HAM-D total score) within less than or equal to 14 days since the beginning of the treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X. In some embodiments, the method of treating the depressive disorder, e.g., major depressive disorder, provides a therapeutic effect (*e.g.*, as determined by a statistically significant reduction in HAM-D total score) within less than or equal to 21 days since the beginning of the treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X. In some embodiments, the method of treating the depressive disorder, e.g., major depressive disorder, provides a therapeutic effect (*e.g.*, as determined by a statistically significant reduction in HAM-D total score) within less than or equal to 28 days since the beginning of the treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X. In some embodiments, the therapeutic effect is a decrease from baseline in HAM-D total score after treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X (e.g., treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, once a day for 14 days). In some embodiments, the HAM-D total score of the subject before treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, is at least 24. In some embodiments, the HAM-D total score of the subject before treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or

X, is at least 18. In some embodiments, the HAM-D total score of the subject before treatment with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, is between and including 14 and 18. In some embodiments, the decrease in HAM-D total score after treating the subject with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, relative to the baseline HAM-D total score is at least 10. In some embodiments, the decrease in HAM-D total score after treating the subject with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, relative to the baseline HAM-D total score is at least 15 (*e.g.*, at least 17). In some embodiments, the HAM-D total score associated with treating the subject with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, is no more than a number ranging from 6 to 8. In some embodiments, the HAM-D total score associated with treating the subject with a compound described herein, *e.g.*, a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, is no more than 7.

[0310] In some embodiments, the method provides therapeutic effect (e.g., as measured by reduction in Clinical Global Impression-Improvement Scale (CGI)) within 14, 10, 4, 3, 2, or 1 days, or 24, 20, 16, 12, 10, or 8 hours or less. In some embodiments, the CNS-disorder is a depressive disorder, *e.g.*, major depressive disorder. In some embodiments, the method of treating the depressive disorder, *e.g.*, major depressive disorder provides a therapeutic effect within the second day of the treatment period. In some embodiments, the therapeutic effect is a decrease from baseline in CGI score at the end of a treatment period (e.g., 14 days after administration).

[0311] In some embodiments, the method provides therapeutic effect (e.g., as measured by reduction in Montgomery–Åsberg Depression Rating Scale (MADRS)) within 14, 10, 4, 3, 2, or 1 days, or 24, 20, 16, 12, 10, or 8 hours or less. In some embodiments, the CNS-disorder is a depressive disorder, *e.g.*, major depressive disorder. In some embodiments, the method of treating the depressive disorder, *e.g.*, major depressive disorder provides a therapeutic effect within the second day of the treatment period. In some embodiments, the therapeutic effect is a decrease from baseline in MADRS score at the end of a treatment period (e.g., 14 days after administration).

[0312] A therapeutic effect for major depressive disorder can be determined by a reduction in Montgomery–Åsberg Depression Rating Scale (MADRS) score exhibited by the

subject. For example, the MADRS score can be reduced within 4, 3, 2, or 1 days; or 96, 84, 72, 60, 48, 24, 20, 16, 12, 10, 8 hours or less. The Montgomery–Åsberg Depression Rating Scale (MADRS) is a ten-item diagnostic questionnaire (regarding apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts) which psychiatrists use to measure the severity of depressive episodes in patients with mood disorders.

[0313] In some embodiments, the method provides therapeutic effect (e.g., as measured by reduction in Edinburgh Postnatal Depression Scale (EPDS)) within 4, 3, 2, 1 days; 24, 20, 16, 12, 10, 8 hours or less. In some embodiments, the therapeutic effect is an improvement measured by the EPDS.

[0314] In some embodiments, the method provides therapeutic effect (e.g., as measured by reduction in Generalized Anxiety Disorder 7-Item Scale (GAD-7)) within 4, 3, 2, 1 days; 24, 20, 16, 12, 10, 8 hours or less.

Anxiety Disorders

[0315] Provided herein are methods for treating anxiety disorders (e.g., generalized anxiety disorder, panic disorder, obsessive compulsive disorder, phobia, post-traumatic stress disorder). **Anxiety disorder** is a blanket term covering several different forms of abnormal and pathological fear and anxiety. Current psychiatric diagnostic criteria recognize a wide variety of anxiety disorders.

[0316] **Generalized anxiety disorder** is a common chronic disorder characterized by long-lasting anxiety that is not focused on any one object or situation. Those suffering from generalized anxiety experience non-specific persistent fear and worry and become overly concerned with everyday matters. Generalized anxiety disorder is the most common anxiety disorder to affect older adults.

[0317] In **panic disorder**, a person suffers from brief attacks of intense terror and apprehension, often marked by trembling, shaking, confusion, dizziness, nausea, difficulty breathing. These panic attacks, defined by the APA as fear or discomfort that abruptly arises and peaks in less than ten minutes, can last for several hours and can be triggered by stress, fear, or even exercise; although the specific cause is not always apparent. In addition to recurrent unexpected panic attacks, a diagnosis of panic disorder also requires that said

attacks have chronic consequences: either worry over the attacks' potential implications, persistent fear of future attacks, or significant changes in behavior related to the attacks. Accordingly, those suffering from panic disorder experience symptoms even outside of specific panic episodes. Often, normal changes in heartbeat are noticed by a panic sufferer, leading them to think something is wrong with their heart or they are about to have another panic attack. In some cases, a heightened awareness (hypervigilance) of body functioning occurs during panic attacks, wherein any perceived physiological change is interpreted as a possible life threatening illness (i.e. extreme hypochondriasis).

[0318] **Obsessive compulsive disorder** is a type of anxiety disorder primarily characterized by repetitive obsessions (distressing, persistent, and intrusive thoughts or images) and compulsions (urges to perform specific acts or rituals). The OCD thought pattern may be likened to superstitions insofar as it involves a belief in a causative relationship where, in reality, one does not exist. Often the process is entirely illogical; for example, the compulsion of walking in a certain pattern may be employed to alleviate the obsession of impending harm. And in many cases, the compulsion is entirely inexplicable, simply an urge to complete a ritual triggered by nervousness. In a minority of cases, sufferers of OCD may only experience obsessions, with no overt compulsions; a much smaller number of sufferers experience only compulsions.

[0319] The single largest category of anxiety disorders is that of **phobia**, which includes all cases in which fear and anxiety is triggered by a specific stimulus or situation. Sufferers typically anticipate terrifying consequences from encountering the object of their fear, which can be anything from an animal to a location to a bodily fluid.

[0320] **Post-traumatic stress disorder** or **PTSD** is an anxiety disorder which results from a traumatic experience. Post-traumatic stress can result from an extreme situation, such as combat, rape, hostage situations, or even serious accident. It can also result from long term (chronic) exposure to a severe stressor, for example soldiers who endure individual battles but cannot cope with continuous combat. Common symptoms include flashbacks, avoidant behaviors, and depression.

Women's Health Disorders

[0321] Provided herein are methods for treating conditions or disorders related to women's health. Conditions or disorders related to women's health include, but are not

limited to, gynecological health and disorders (e.g., premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD)), **pregnancy issues** (e.g., miscarriage, abortion), infertility and related disorders (e.g., polycystic ovary syndrome (PCOS)), other disorders and conditions**,** and issues related to women's overall health and wellness (e.g., menopause).

[0322] **Gynecological health and disorders** affecting women include menstruation and menstrual irregularities; urinary tract health, including urinary incontinence and pelvic floor disorders; and such disorders as bacterial vaginosis, vaginitis, uterine fibroids, and vulvodynia.

[0323] **Premenstrual syndrome (PMS)** refers to physical and emotional symptoms that occur in the one to two weeks before a women's period. Symptoms vary but can include bleeding, mood swings, tender breasts, food cravings, fatigue, irritability, acne, and depression.

[0324] **Premenstrual dysphoric disorder (PMDD)** is a severe form of PMS. The symptoms of PMDD are similar to PMS but more severe and may interfere with work, social activity, and relationships. PMDD symptoms include mood swings, depressed mood or feelings of hopelessness, marked anger, increased interpersonal conflicts, tension and anxiety, irritability, decreased interest in usual activities, difficulty concentrating, fatigue, change in appetite, feeling out of control or overwhelmed, sleep problems, physical problems (e.g., bloating, breast tenderness, swelling, headaches, joint or muscle pain).

[0325] **Pregnancy issues** include preconception care and prenatal care, pregnancy loss (miscarriage and stillbirth), preterm labor and premature birth, sudden infant death syndrome (SIDS), breastfeeding, and birth defects.

[0326] **Miscarriage** refers to a pregnancy that ends on its own, within the first 20 weeks of gestation.

[0327] **Abortion** refers to the deliberate termination of a pregnancy, which can be performed during the first 28 weeks of pregnancy.

[0328] **Infertility and related disorders** include uterine fibroids, polycystic ovary syndrome, endometriosis, and primary ovarian insufficiency.

[0329] **Polycystic ovary syndrome (PCOS)** refers to an endocrine system disorder among women of reproductive age. PCOS is a set of symptoms resulting from an elevated male hormone in women. Most women with PCOS grow many small cysts on their ovaries. Symptoms of PCOS include irregular or no menstrual periods, heavy periods, excess body and facial hair, acne, pelvic pain, difficulty getting pregnant, and patches of thick, darker, velvety skin. PCOS may be associated with conditions including type 2 diabetes, obesity, obstructive sleep apnea, heart disease, mood disorders, and endometrial cancer.

[0330] **Other disorders and conditions** that affect only women include Turner syndrome, Rett syndrome, and ovarian and cervical cancers.

[0331] **Issues related to women's overall health and wellness** include violence against women, women with disabilities and their unique challenges, osteoporosis and bone health, and menopause.

[0332] **Menopause** refers to the 12 months after a woman's last menstrual period and marks the end of menstrual cycles. Menopause typically occurs in a woman's 40s or 50s. Physical symptoms such as hot flashes and emotional symptoms of menopause may disrupt sleep, lower energy, or trigger anxiety or feelings of sadness or loss. Menopause includes natural menopause and surgical menopause, which is a type of induced menopause due to an event such as surgery (e.g., hysterectomy, oophorectomy; cancer). It is induced when the ovaries are gravely damaged by, e.g., radiation, chemotherapy, or other medications.

Epilepsy

[0333] The compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or pharmaceutically acceptable salt, or a pharmaceutically acceptable composition thereof, can be used in a method described herein, for example in the treatment of a disorder described herein such as epilepsy, status epilepticus, or seizure.

[0334] Epilepsy is a brain disorder characterized by repeated seizures over time. Types of epilepsy can include, but are not limited to generalized epilepsy, *e.g.,* childhood absence epilepsy, juvenile nyoclonic epilepsy, epilepsy with grand-mal seizures on awakening, West syndrome, Lennox-Gastaut syndrome, partial epilepsy, *e.g.,* temporal lobe epilepsy, frontal lobe epilepsy, benign focal epilepsy of childhood.

Epileptogenesis

[0335] The compounds and methods described herein can be used to treat or prevent epileptogenesis. Epileptogenesis is a gradual process by which a normal brain develops epilepsy (a chronic condition in which seizures occur). Epileptogenesis results from neuronal damage precipitated by the initial insult (e.g., status epilepticus).

Status epilepticus (SE)

[0336] Status epilepticus (SE) can include, *e.g.,* convulsive status epilepticus, *e.g.,* early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus; non-convulsive status epilepticus, *e.g.,* generalized status epilepticus, complex partial status epilepticus; generalized periodic epileptiform discharges; and periodic lateralized epileptiform discharges. Convulsive status epilepticus is characterized by the presence of convulsive status epileptic seizures, and can include early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus. Early status epilepticus is treated with a first line therapy. Established status epilepticus is characterized by status epileptic seizures which persist despite treatment with a first line therapy, and a second line therapy is administered. Refractory status epilepticus is characterized by status epileptic seizures which persist despite treatment with a first line and a second line therapy, and a general anesthetic is generally administered. Super refractory status epilepticus is characterized by status epileptic seizures which persist despite treatment with a first line therapy, a second line therapy, and a general anesthetic for 24 hours or more.

[0337] Non-convulsive status epilepticus can include, *e.g.,* focal non-convulsive status epilepticus, *e.g.,* complex partial non-convulsive status epilepticus, simple partial non-convulsive status epilepticus, subtle non-convulsive status epilepticus; generalized non-convulsive status epilepticus, *e.g.,* late onset absence non-convulsive status epilepticus, atypical absence non-convulsive status epilepticus, or typical absence non-convulsive status epilepticus.

[0338] The compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X or pharmaceutically acceptable salt, or a pharmaceutically acceptable composition thereof, can also be administered as a prophylactic to a subject having a CNS disorder *e.g.,* a traumatic brain injury, status epilepticus, *e.g.,* convulsive status epilepticus, *e.g.,* early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status

epilepticus; non-convulsive status epilepticus, *e.g.*, generalized status epilepticus, complex partial status epilepticus; generalized periodic epileptiform discharges; and periodic lateralized epileptiform discharges; prior to the onset of a seizure.

Seizure

[0339] A seizure is the physical findings or changes in behavior that occur after an episode of abnormal electrical activity in the brain. The term "seizure" is often used interchangeably with "convulsion." Convulsions are when a person's body shakes rapidly and uncontrollably. During convulsions, the person's muscles contract and relax repeatedly.

[0340] Based on the type of behavior and brain activity, seizures are divided into two broad categories: generalized and partial (also called local or focal). Classifying the type of seizure helps doctors diagnose whether or not a patient has epilepsy.

[0341] Generalized seizures are produced by electrical impulses from throughout the entire brain, whereas partial seizures are produced (at least initially) by electrical impulses in a relatively small part of the brain. The part of the brain generating the seizures is sometimes called the focus.

[0342] There are six types of generalized seizures. The most common and dramatic, and therefore the most well-known, is the generalized convulsion, also called the grand-mal seizure. In this type of seizure, the patient loses consciousness and usually collapses. The loss of consciousness is followed by generalized body stiffening (called the "tonic" phase of the seizure) for 30 to 60 seconds, then by violent jerking (the "clonic" phase) for 30 to 60 seconds, after which the patient goes into a deep sleep (the "postictal" or after-seizure phase). During grand-mal seizures, injuries and accidents may occur, such as tongue biting and urinary incontinence.

[0343] Absence seizures cause a short loss of consciousness (just a few seconds) with few or no symptoms. The patient, most often a child, typically interrupts an activity and stares blankly. These seizures begin and end abruptly and may occur several times a day. Patients are usually not aware that they are having a seizure, except that they may be aware of "losing time."

[0344] Myoclonic seizures consist of sporadic jerks, usually on both sides of the body. Patients sometimes describe the jerks as brief electrical shocks. When violent, these seizures may result in dropping or involuntarily throwing objects.

[0345] Clonic seizures are repetitive, rhythmic jerks that involve both sides of the body at the same time.

[0346] Tonic seizures are characterized by stiffening of the muscles.

[0347] Atonic seizures consist of a sudden and general loss of muscle tone, particularly in the arms and legs, which often results in a fall.

[0348] Seizures described herein can include epileptic seizures; acute repetitive seizures; cluster seizures; continuous seizures; unremitting seizures; prolonged seizures; recurrent seizures; status epilepticus seizures, e.g., refractory convulsive status epilepticus, non-convulsive status epilepticus seizures; refractory seizures; myoclonic seizures; tonic seizures; tonic-clonic seizures; simple partial seizures; complex partial seizures; secondarily generalized seizures; atypical absence seizures; absence seizures; atonic seizures; benign Rolandic seizures; febrile seizures; emotional seizures; focal seizures; gelastic seizures; generalized onset seizures; infantile spasms; Jacksonian seizures; massive bilateral myoclonus seizures; multifocal seizures; neonatal onset seizures; nocturnal seizures; occipital lobe seizures; post traumatic seizures; subtle seizures; Sylvan seizures; visual reflex seizures; or withdrawal seizures. In some embodiments, the seizure is a generalized seizure associated with Dravet Syndrome, Lennox-Gastaut Syndrome, Tuberous Sclerosis Complex, Rett Syndrome or PCDH19 Female Pediatric Epilepsy.

Movement Disorders

[0349] Also described herein are methods for treating a movement disorder. As used herein, "movement disorders" refers to a variety of diseases and disorders that are associated with hyperkinetic movement disorders and related abnormalities in muscle control. Exemplary movement disorders include, but are not limited to, Parkinson's disease and parkinsonism (defined particularly by bradykinesia), dystonia, chorea and Huntington's disease, ataxia, tremor (e.g., essential tremor), myoclonus and startle, tics and Tourette syndrome, Restless legs syndrome, stiff person syndrome, and gait disorders.

Tremor

[0350] The methods described herein can be used to treat tremor, for example the compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X can be used to treat cerebellar tremor or intention tremor, dystonic tremor, essential tremor, orthostatic tremor, parkinsonian tremor, physiological tremor, psychogenic tremor, or rubral tremor. Tremor includes hereditary, degenerative, and idiopathic disorders such as Wilson's disease, Parkinson's disease, and essential tremor, respectively; metabolic diseases (e.g., thyroid-parathyroid-, liver disease and hypoglycemia); peripheral neuropathies (associated with Charcot-Marie-Tooth, Roussy-Levy, diabetes mellitus, complex regional pain syndrome); toxins (nicotine, mercury, lead, CO, Manganese, arsenic, toluene); drug-induced (narcoleptics, tricyclics, lithium, cocaine, alcohol, adrenaline, bronchodilators, theophylline, caffeine, steroids, valproate, amiodarone, thyroid hormones, vincristine); and psychogenic disorders. Clinical tremor can be classified into physiologic tremor, enhanced physiologic tremor, essential tremor syndromes (including classical essential tremor, primary orthostatic tremor, and task- and position-specific tremor), dystonic tremor, parkinsonian tremor, cerebellar tremor, Holmes' tremor (i.e., rubral tremor), palatal tremor, neuropathic tremor, toxic or drug-induced tremor, and psychogenic tremor.

[0351] **Tremor** is an involuntary, at times rhythmic, muscle contraction and relaxation that can involve oscillations or twitching of one or more body parts (*e.g.,* hands, arms, eyes, face, head, vocal folds, trunk, legs).

[0352] **Cerebellar tremor** or **intention tremor** is a slow, broad tremor of the extremities that occurs after a purposeful movement. Cerebellar tremor is caused by lesions in or damage to the cerebellum resulting from, *e.g.,* tumor, stroke, disease (*e.g.,* multiple sclerosis, an inherited degenerative disorder).

[0353] **Dystonic tremor** occurs in individuals affected by dystonia, a movement disorder in which sustained involuntary muscle contractions cause twisting and repetitive motions and/or painful and abnormal postures or positions. Dystonic tremor may affect any muscle in the body. Dystonic tremors occurs irregularly and often can be relieved by complete rest.

[0354] **Essential tremor** or benign essential tremor is the most common type of tremor. Essential tremor may be mild and nonprogressive in some, and may be slowly progressive, starting on one side of the body but affect both sides within 3 years. The hands are most

often affected, but the head, voice, tongue, legs, and trunk may also be involved. Tremor frequency may decrease as the person ages, but severity may increase. Heightened emotion, stress, fever, physical exhaustion, or low blood sugar may trigger tremors and/or increase their severity. Symptoms generally evolve over time and can be both visible and persistent following onset.

[0355] **Orthostatic tremor** is characterized by fast (*e.g.,* greater than 12 Hz) rhythmic muscle contractions that occurs in the legs and trunk immediately after standing. Cramps are felt in the thighs and legs and the patient may shake uncontrollably when asked to stand in one spot. Orthostatic tremor may occurs in patients with essential tremor.

[0356] **Parkinsonian tremor** is caused by damage to structures within the brain that control movement. Parkinsonian tremor is often a precursor to Parkinson's disease and is typically seen as a "pill-rolling" action of the hands that may also affect the chin, lips, legs, and trunk. Onset of parkinsonian tremor typically begins after age 60. Movement starts in one limb or on one side of the body and can progress to include the other side.

[0357] **Physiological tremor** can occur in normal individuals and have no clinical significance. It can be seen in all voluntary muscle groups. Physiological tremor can be caused by certain drugs, alcohol withdrawal, or medical conditions including an overactive thyroid and hypoglycemia. The tremor classically has a frequency of about 10 Hz.

[0358] **Psychogenic tremor** or hysterical tremor can occur at rest or during postural or kinetic movement. Patient with psychogenic tremor may have a conversion disorder or another psychiatric disease.

[0359] **Rubral tremor** is characterized by coarse slow tremor which can be present at rest, at posture, and with intention. The tremor is associated with conditions that affect the red nucleus in the midbrain, classical unusual strokes.

[0360] **Parkinson's Disease** affects nerve cells in the brain that produce dopamine. Symptoms include muscle rigidity, tremors, and changes in speech and gait. **Parkinsonism** is characterized by tremor, bradykinesia, rigidity, and postural instability. Parkinsonism shares symptoms found in Parkinson's Disease, but is a symptom complex rather than a progressive neurodegenerative disease.

[0361] **Dystonia** is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements or postures. Dystonic movements can be patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

[0362] **Chorea** is a neurological disorder characterized by jerky involuntary movements typically affecting the shoulders, hips, and face. **Huntington's Disease** is an inherited disease that causes nerve cells in the brain to waste away. Symptoms include uncontrolled movements, clumsiness, and balance problems. Huntington's disease can hinder walk, talk, and swallowing.

[0363] **Ataxia** refers to the loss of full control of bodily movements, and may affect the fingers, hands, arms, legs, body, speech, and eye movements.

[0364] **Myloclonus and Startle** is a response to a sudden and unexpected stimulus, which can be acoustic, tactile, visual, or vestibular.

[0365] **Tics** are an involuntary movement usually onset suddenly, brief, repetitive, but non-rhythmical, typically imitating normal behavior and often occurring out of a background of normal activity. Tics can be classified as motor or vocal, motor tics associated with movements while vocal tics associated with sound. Tics can be characterized as simple or complex. For example simple motor tics involve only a few muscles restricted to a specific body part. **Tourette Syndrome** is an inherited neuropsychiatric disorder with onset in childhood, characterized by multiple motor tics and at least one vocal tic.

[0366] **Restless Legs Syndrome** is a neurologic sensorimotor disorder characterized by an overwhelming urge to move the legs when at rest.

[0367] **Stiff Person Syndrome** is a progressive movement disorder characterized by involuntary painful spasms and rigidity of muscles, usually involving the lower back and legs. Stiff-legged gait with exaggerated lumbar hyperlordosis typically results. Characteristic abnormality on EMG recordings with continuous motor unit activity of the paraspinal axial muscles is typically observed. Variants include "stiff-limb syndrome" producing focal stiffness typically affecting distal legs and feet.

[0368] **Gait disorders** refer to an abnormality in the manner or style of walking, which results from neuromuscular, arthritic, or other body changes. Gait is classified according to the system responsible for abnormal locomotion, and include hemiplegic gait, diplegic gait, neuropathic gait, myopathic gait, parkinsonian gait, choreiform gait, ataxic gait, and sensory gait.

Anesthesia / Sedation

[0369] Anesthesia is a pharmacologically induced and reversible state of amnesia, analgesia, loss of responsiveness, loss of skeletal muscle reflexes, decreased stress response, or all of these simultaneously. These effects can be obtained from a single drug which alone provides the correct combination of effects, or occasionally with a combination of drugs (*e.g.*, hypnotics, sedatives, paralytics, analgesics) to achieve very specific combinations of results. Anesthesia allows patients to undergo surgery and other procedures without the distress and pain they would otherwise experience.

[0370] Sedation is the reduction of irritability or agitation by administration of a pharmacological agent, generally to facilitate a medical procedure or diagnostic procedure.

[0371] Sedation and analgesia include a continuum of states of consciousness ranging from minimal sedation (anxiolysis) to general anesthesia.

[0372] **Minimal sedation is a**lso known as anxiolysis. Minimal sedation is a drug-induced state during which the patient responds normally to verbal commands. Cognitive function and coordination may be impaired. Ventilatory and cardiovascular functions are typically unaffected.

[0373] **Moderate sedation/analgesia (conscious sedation) is a** drug-induced depression of consciousness during which the patient responds purposefully to verbal command, either alone or accompanied by light tactile stimulation. No interventions are usually necessary to maintain a patent airway. Spontaneous ventilation is typically adequate. Cardiovascular function is usually maintained.

[0374] **Deep sedation/analgesia is a** drug-induced depression of consciousness during which the patient cannot be easily aroused, but responds purposefully (not a reflex withdrawal from a painful stimulus) following repeated or painful stimulation. Independent ventilatory function may be impaired and the patient may require assistance to maintain a

patent airway. Spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

[0375] **General anesthesia is a** drug-induced loss of consciousness during which the patient is not arousable, even to painful stimuli. The ability to maintain independent ventilatory function is often impaired and assistance is often required to maintain a patent airway. Positive pressure ventilation may be required due to depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

[0376] Sedation in the intensive care unit (ICU) allows the depression of patients' awareness of the environment and reduction of their response to external stimulation. It can play a role in the care of the critically ill patient, and encompasses a wide spectrum of symptom control that will vary between patients, and among individuals throughout the course of their illnesses. Heavy sedation in critical care has been used to facilitate endotracheal tube tolerance and ventilator synchronization, often with neuromuscular blocking agents.

[0377] In some embodiments, sedation (*e.g.*, long-term sedation, continuous sedation) is induced and maintained in the ICU for a prolonged period of time (*e.g.*, 1 day, 2 days, 3 days, 5 days, 1 week, 2 week, 3 weeks, 1 month, 2 months). Long-term sedation agents may have long duration of action. Sedation agents in the ICU may have short elimination half-life.

[0378] Procedural sedation and analgesia, also referred to as conscious sedation, is a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows a subject to tolerate unpleasant procedures while maintaining cardiorespiratory function.

[0379] Also described herein are methods of ameliorating one or more symptoms of a respiratory condition in a subject, comprising administering to the subject an effective amount of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof).

[0380] In one aspect, provided herein is a method of treating a subject wherein the subject exhibits one or more symptoms of a respiratory condition and/or has been diagnosed with a respiratory condition, comprising administering to said subject an effective amount of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof).

[0381] In some embodiments, the present disclosure contemplates a method of treating a subject comprising administering to said subject a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof), wherein the subject has a respiratory condition.

[0382] In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) to a subject exhibiting symptoms of a respiratory condition, may result in the reduction of the severity of one or more symptoms of a respiratory condition or retard or slow the progression of one or more symptoms of a respiratory condition.

[0383] In some embodiments, a subject with a respiratory condition has been or is being treated with mechanical ventilation or oxygen. In some embodiments, a subject with a respiratory condition has been or is being treated with mechanical ventilation.

[0384] In some embodiments, a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) is administered to a subject that is being or has been treated with mechanical ventilation. In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) continues

throughout a subject's treatment with mechanical ventilation. In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) continues after a subject has ended treatment with mechanical ventilation.

[0385] In some embodiments, a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) is administered to a subject who is receiving or has received treatment with a sedative. In some embodiments, a sedative is propofol or a benzodiazepine.

[0386] In some embodiments, the present disclosure includes administering to a subject in need thereof a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) in an amount sufficient to increase oxygen saturation in blood. In some embodiments, oxygen saturation in blood is measured using pulse oximetry.

[0387] In some embodiments, the present disclosure contemplates a method of treating a cytokine storm in a patient. In some embodiments a method of treating a cytokine storm comprising the step of administering to the patient a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof). In some embodiments, a symptom of a cytokine storm is lung inflammation. In some embodiments, a patient undergoing a cytokine storm has acute respiratory distress syndrome (ARDS).

Respiratory condition

[0388] In some embodiments, a subject with a respiratory condition suffers from respiratory distress. In some embodiments, respiratory distress includes acute respiratory distress.

[0389] In some embodiments, a subject with a respiratory condition may exhibit one or more symptoms selected from the group consisting of airway hyper-responsiveness, inflammation of lung tissue, lung hypersensitivity, and inflammation-related pulmonary pain.

[0390] In some embodiments a subject with a respiratory condition may exhibit inflammation of lung tissue. In some embodiments, inflammation of lung tissue is bronchitis or bronchiectasis. In some embodiments, inflammation of lung tissue is pneumonia. In some embodiments, pneumonia is ventilator-associated pneumonia or hospital-acquired pneumonia. In some embodiments, pneumonia is ventilator-associated pneumonia.

[0391] In some embodiments, administration of the compound or pharmaceutical composition described herein to a subject exhibiting symptoms of a respiratory condition, results in reduction of the severity of respiratory distress in a subject with a respiratory condition or retard or slow the progression of respiratory distress in a subject with a respiratory condition.

[0392] In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) to a subject exhibiting symptoms of a respiratory condition, results in reduction of the severity of airway hyper-responsiveness in a subject with a disease associated with a coronavirus or retard or slow the progression of airway hyper-responsiveness in a subject with a respiratory condition.

[0393] In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) to a subject exhibiting symptoms of a respiratory condition, results in reduction of the severity of inflammation of lung tissue in a subject with a respiratory condition or retard

or slow the progression of inflammation of lung tissue in a subject with a respiratory condition. In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) to a subject exhibiting symptoms of a respiratory condition, results in reduction of the severity of pneumonia in a subject with a respiratory condition or retard or slow the progression of pneumonia in a subject with a respiratory condition.

[0394] In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) to a subject exhibiting symptoms of a respiratory condition, results in reduction of the severity of lung hypersensitivity in a subject with a respiratory condition or retard or slow the progression of lung hypersensitivity in a subject with a respiratory condition.

[0395] In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutical salt thereof, or a composition comprising a compound of Formula I, II, IIIa, IIIb, V, VIa, VIb, VII, VIII, IX, or X, or a pharmaceutically acceptable salt thereof) to a subject exhibiting symptoms of a respiratory condition, results in reduction of the severity of inflammation-related pulmonary pain in a subject with a respiratory condition or retard or slow the progression of inflammation-related pulmonary pain in a subject with a respiratory condition.

[0396] In some embodiments, a subject with a respiratory condition is undergoing or has undergone treatment for an infection, fibrosis, a fibrotic episode, chronic obstructive pulmonary disease, Sarcoidosis (or pulmonary sarcoidosis) or asthma/asthma-related inflammation.

[0397] In some embodiments, a subject exhibits symptoms of and/or has been diagnosed with asthma. In some embodiments, a subject is or has undergone an asthmatic attack.

[0398] In some embodiments, a subject is undergoing or has undergone treatment for fibrosis or a fibrotic episode. In some embodiments, the fibrosis is cystic fibrosis.

[0399] In some embodiments, a respiratory condition is the result of and/or related to a disease or condition selected from the group consisting of cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, pulmonary sarcoidosis, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus- Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders such as Huntington, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, or Sjogren's disease.

Infections

[0400] The present disclosure contemplates, among other things, treatment of a subject who has an infection. The present disclosure contemplates, among other things, treatment of a subject who has a disease associated with an infection. In some embodiments, an infection is a viral infection or a bacterial infection. In some embodiments, an infection is a viral infection. In some embodiments, an infection is a bacterial infection.

[0401] In some embodiments, a viral infection is an infection of a virus selected from the group consisting of a coronavirus, an influenza virus, human rhinovirus, a human parainfluenza virus, human metapneumovirus and a hantavirus. In some embodiments, a virus is a coronavirus. In some embodiments, a coronavirus is selected from the group consisting of SARS-CoV, SARS-CoV-2, and MERS-CoV.

[0402] The present disclosure contemplates, among other things, treatment of a subject who has a disease associated with coronavirus. In some embodiments, a disease associated with a coronavirus is selected from the group consisting of coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). In some embodiments, a disease associated with a coronavirus is selected from the group consisting of COVID-19. In some embodiments, a coronavirus is selected from a group consisting of SARS-CoV-1, SARS-CoV-2, and 2012-nCoV. In some embodiments, a coronavirus is SARS-CoV-2.

[0403] In some embodiments, a bacterial infection is an infection of a bacteria selected from the group consisting of *Streptococcus pneumoniae*, *Chlamydia pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Haemophilus influenzae*. In some embodiments, *Staphylococcus aureus* is methicillin-resistant *Staphylococcus aureus.*

Examples

[0404] In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

Materials and Methods

[0405] The compounds provided herein can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, *etc.*) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization.

[0406] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described

in T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

[0407] The compounds provided herein may be isolated and purified by known standard procedures. Such procedures include (but are not limited to) trituration, column chromatography, HPLC, or supercritical fluid chromatography (SFC). The following schemes are presented with details as to the preparation of representative oxysterols that have been listed herein. The compounds provided herein may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis. Exemplary chiral columns available for use in the separation/purification of the enantiomers/diastereomers provided herein include, but are not limited to, CHIRALPAK® AD-10, CHIRALCEL® OB, CHIRALCEL® OB-H, CHIRALCEL® OD, CHIRALCEL® OD-H, CHIRALCEL® OF, CHIRALCEL® OG, CHIRALCEL® OJ and CHIRALCEL® OK.

[0408] **^{1}H-NMR** reported herein (e.g., for the region between δ (ppm) of about 0.5 to about 4 ppm) will be understood to be an exemplary interpretation of the NMR spectrum (e.g., exemplary peak integratations) of a compound.

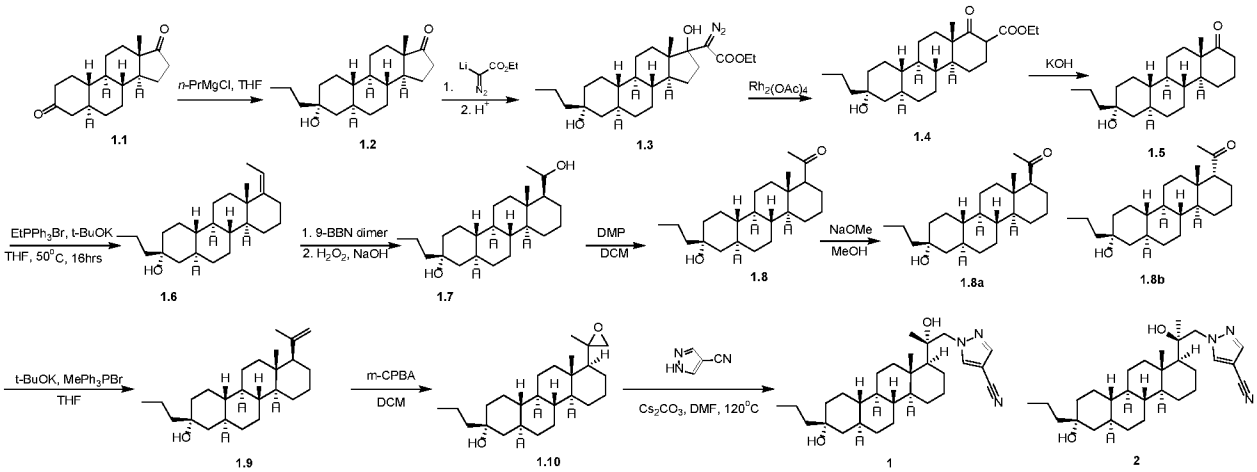
[0409] **LC-ELSD/MS:** (Mobile Phase: 1.5ML/4L TFA in water (solvent A) and 0.75ML/4L TFA in acetonitrile (solvent B), using the elution gradient 30%-90% (solvent B) over 0.9 minutes and holding at 90% for 0.6 minutes at a flow rate of 1.2 ml/min; Column: Xtimate C18 2.1*30mm, 3um; Wavelength: UV 220 nm; Column temperature: 50°C; MS ionization: ESI; Detector: PDA & ELSD.

Abbreviations:

[0410] PE: petroleum ether; EtOAc: ethyl acetate; THF: tetrahydrofuran; PCC: pyridinium chlorochromate; TLC: thin layer chromatography; PCC: pyridinium chlorochromate; t-BuOK: potassium tert-butoxide; 9-BBN: 9-borabicyclo[3.3.1]nonane; Pd(*t*-$Bu_3P)_2$: bis(tri-tert-butylphosphine)palladium(0); AcCl: acetyl chloride; *i*-PrMgCl: Isopropylmagnesium chloride; TBSCl: tert-Butyl(chloro)dimethylsilane; $(i\text{-PrO})_4$Ti: titanium tetraisopropoxide; BHT: 2,6-di-t-butyl-4-methylphenoxide; Me: methyl; *i*-Pr: iso-propyl; *t*-Bu: tert-butyl; Ph: phenyl; Et: ethyl; Bz: benzoyl; BzCl: benzoyl chloride; CsF: cesium fluoride; DCC: dicyclohexylcarbodiimide; DCM: dichloromethane; DMAP: 4-dimethylaminopyridine; DMP: Dess-Martin periodinane; EtMgBr: ethylmagnesium bromide;

EtOAc: ethyl acetate; TEA: triethylamine; AlaOH: alanine; Boc: t-butoxycarbonyl. Py: pyridine; TBAF: tetra-n-butylammonium fluoride; THF: tetrahydrofuran; TBS: t-butyldimethylsilyl; TMS: trimethylsilyl; $TMSCF_3$: (Trifluoromethyl)trimethylsilane; Ts: p-toluenesulfonyl; Bu: butyl; $Ti(OiPr)_4$: tetraisopropoxytitanium; LAH: Lithium Aluminium Hydride; LDA: lithium diisopropylamide; $LiOH.H_2O$: lithium hydroxide hydrates; MAD: methyl aluminum bis(2,6-di-t-butyl-4-methylphenoxide); MeCN: acetonitrile; NBS: N-bromosuccinimide; Na_2SO_4: sodium sulfate; $Na_2S_2O_3$: sodium thiosulfate; MeCN: acetonitrile; MeOH: methanol; Boc: t-butoxycarbonyl; MTBE: methyl tert-butyl ether; K-selectride: Potassium tri(s-butyl)borohydride; 9-BBNdimer: 9-borabicyclo(3.3.1)nonane(dimer); DIPEA: diisopropylethylamine; DMF: dimethylformamide; FA: formic acid; SM: starting material.

Example 1 & 2: Synthesis of 1-((S)-2-hydroxy-2-((1S,4aS,4bR,6aS,8R,10aS,10bR,12aS)-8-hydroxy-12a-methyl-8-propyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile & 1-((R)-2-hydroxy-2-((1S,4aS,4bR,6aS,8R,10aS,10bR,12aS)-8-hydroxy-12a-methyl-8-propyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile



Synthesis of 1.2

[0411] To the solution of (5α)-Estrane-3,17-dione, **1.1** (20 g, 72.8 mmol) in THF (200 mL) was added n-PrMgCl (109 mL, 218 mmol, 2M in THF) dropwise at -60°C. After stirring at -60°C for 2 h, the reaction mixture was poured into saturated aqueous NH_4Cl (400 mL) at 0°C and extracted with EtOAc (2 x 200 mL). The combined organic layer was dried over Na_2SO_4, filtered, concentrated and purified by silica gel column (PE/EtOAc = 0-20%) to give **1.2** (18.4 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.43 (dd, J = 8.8, 19.3 Hz, 1H),

2.16-2.00 (m, 1H), 1.97-1.85 (m, 2H), 1.83-1.72 (m, 3H), 1.68-1.43 (m, 5H), 1.40-0.89 (m, 17H), 0.87 (s, 3H), 0.79-0.61 (m, 2H).

Synthesis of 1.3

[0412] To a solution of di-isopropylamine (19.4 mL, 0.718 g/mL, 139 mmol) in THF (64 mL) was added n-butyl-lithium (55.6 mL 2.5 M in hexane, 139 mmol) at -78°C. After stirring at -78°C for 10 min, the LDA solution was added to a solution of **1.2** (11.7 g, 36.7 mmol) and ethyl diazoacetate (20.8 g, 183 mmol) in THF (400 mL) at -78°C. After stirring at -78°C for 2 h, the reaction was quenched with acetic acid (10.9 g, 183 mmol) in THF (50 mL), stirred at 15°C for 16 h, poured into water (1000 mL) and extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (1500 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give **1.3** (20 g) as an oil, which was used as is.

Synthesis of 1.4

[0413] To a solution of **1.3** (20 g) and DME (200 mL) was added $Rh_2(OAc)_4$ (204 mg, 0.462 mmol) in one portion at 15°C. After stirring at 15°C for 2 h, the reaction mixture was concentrated to give **1.4** (20 g) as an oil, which was used as is.

Synthesis of 1.5

[0414] To a solution of **1.4** (20 g) in MeOH (200 mL) was added KOH (27.7 g, 494 mmol) at 15°C. After heating at 70°C for 1 h, the reaction mixture was poured into H_2O (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with HCl (1M, 100 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash-combi (0~15% of EtOAc in PE) to give **1.5** (4.0 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.62 (dt, J = 6.8, 14.1 Hz, 1H), 2.19 (br d, J = 10.3 Hz, 1H), 2.05 (dt, J = 2.6, 6.6 Hz, 1H), 1.93-1.57 (m, 8H), 1.54-1.12 (m, 12H), 1.12-1.05 (m, 4H), 1.05-0.84 (m, 7H), 0.65 (br dd, J = 2.8, 10.8 Hz, 2H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{22}H_{35}O$ $[M-H_2O+H]^+$ 315.2 found 315.2.

Synthesis of 1.6

[0415] To a suspension of Ph_3PEtBr (10.6 g, 28.8 mmol) in anhydrous THF (50 mL) was added t-BuOK (4.84 g, 43.2 mmol) at 15°C under N_2. After stirring at 45°C for 30 min, a solution of **1.5** (4.8 g, 14.4 mmol) in anhydrous THF (50 mL) was dropwise. After stirring for

16 h at 45°C, the reaction mixture was cooled, poured into ice-water (100 mL), stirred for 10 min, and extracted with EtOAc (2 x 100 mL). The combine organic phase was washed with saturated brine (2 x 200 mL), filtered and concentrated. The residue was purified by flash column (0~10% of EtOAc in PE) to give **1.6** (1.8 g, 36.2%) as a solid and recovered starting material **1.5** (1.2 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.15 (br t, J = 6.5 Hz, 1H), 2.50 (br d, J = 13.8 Hz, 1H), 2.25-2.06 (m, 1H), 2.02-1.59 (m, 9H), 1.41-1.02 (m, 14H), 0.95-0.61 (m, 4H).

Synthesis of 1.7

[0416] To a solution of **1.6** (1.8 g, 5.22 mmol) in THF (50 ml) was added 9-BBN dimer (3.80 g, 15.6 mmol) at 15°C. After stirring at 50°C for 16 h, the reaction mixture was cooled and diluted sequentially with EtOH (6.05 ml, 104 mmol, 0.789 g/ml) at 0°C, NaOH (20.8 mL, 5M, 104 mmol) dropwise and H_2O_2 (11.7 g, 104 mmol, 30% in water) dropwise maintaining inner temperature below 30°C. After stirring at 50°C for 1 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (130 mL). After stirring at 0°C for another 1 h, the reaction was checked by potassium iodide-starch test paper to confirm excess H_2O_2 was destroyed. The aqueous phase was extracted with DCM (3 x 50 mL). The combine organic phase was washed with saturated $Na_2S_2O_3$ (2 x 100 mL), brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **1.7** (800 mg) as a solid.

Synthesis of 1.8

[0417] To a solution of **1.7** (800 mg, 2.20 mmol) in DCM (30 mL) was added DMP (1.86 g, 4.40 mmol) at 25°C. After stirring at 25°C for 1 h, the mixture was diluted with $NaHCO_3$ (50 mL) and $Na_2S_2O_3$ (50 mL, sat.) and extracted with DCM (2 x 50 mL). The combined organic phase was washed with $NaHCO_3$ (100 mL), $Na_2S_2O_3$ (100 mL, sat.) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrate, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~15% of EtOAc in PE) to give **1.8** (740 mg) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.32 (dd, J = 3.3, 12.5 Hz, 1H), 2.18-2.13 (m, 4H), 1.92-1.66 (m, 9H), 1.46-1.20 (m, 12H), 1.11-0.67 (m, 14H).

Synthesis of 1.8a & 1.8b

[0418] To a solution of **1.8** (5.8 g, 16.0 mmol) in MeOH (100 mL) at 0°C was added MeONa (12.9 g, 240 mmol). After stirring at 70°C for 16 h, the reaction mixture was added

to saturated NH_4Cl (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with saturated brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue (200 mg) was purified by column (0~3% of acetone in DCM) to give **1.8a** (69.3 mg, 34.8%) and **1.8b** (16.0 mg, 8.04%) both as solids.

1.8a:^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.30 (dd, J = 3.3, 12.8 Hz, 1H), 2.14 (s, 3H), 1.86-1.59 (m, 8H), 1.51-1.21 (m, 9H), 1.15-0.89 (m, 14H), 0.87-0.50 (m, 5H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{24}H_{39}O$ $[M-H_2O+H]^+$ 343.3 found 343.3.

1.8b: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.47 (d, J = 5.9 Hz, 1H), 2.12 (s, 3H), 1.74 (br d, J = 12.5 Hz, 7H), 1.51-1.19 (m, 12H), 1.16-0.74 (m, 16H), 0.68-0.51 (m, 1H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{24}H_{39}O$ $[M-H_2O+H]^+$ 343.3 found 343.3.

Synthesis of 1.9

[0419] To a suspension of $MePh_3PBr$ (4.31 g, 12.2 mmol) in anhydrous THF (20 mL) was added t-BuOK (1.36 g, 12.2 mmol) at 15°C under N_2. After stirring at 40°C for 30 min, a solution of **1.8a** (2.2 g, 6.10 mmol) in anhydrous THF (20 mL) was dropwise. After stirring for 16 h at 40°C, the mixture was cooled, poured into ice-water (150 mL), stirred for 10 min, and extracted with EtOAc (2 x 100 mL). The combine organic phase was washed with saturated brine (2 x 100 mL), filtered and concentrated. The residue was purified by flash column (0~10% of EtOAc in PE) to give **1.9** (1.9 g, 87.1%) as a solid. **^{1}H NMR** (400 MHz, CDCl3) δH 4.80 (s, 1H), 4.61 (d, J = 2.0 Hz, 1H), 1.76 (br s, 4H), 1.73-1.47 (m, 11H), 1.37-1.18 (m, 7H), 1.13-0.84 (m, 12H), 0.83 (s, 3H), 0.81-0.53 (m, 3H).

Synthesis of 1.10

[0420] To a solution of **1.9** (700 mg, 1.95 mmol) in DCM (10 mL) was added m-CPBA (790 Mg, 85%, 3.90 mmol) at 0°C. After stirring at 25°C for 1 h, the mixture was quenched with $NaHCO_3$ (50 mL, sat. aq.) and $Na_2S_2O_3$ (20 mL, sat. aq.). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~10% of EtOAc in PE) to give **1.10** (340 mg, 46.5%) as a solid. **^{1}H NMR** (400 MHz, CDCl3) δH 2.77-2.55 (m, 2H), 1.82-1.65 (m, 8H), 1.54-1.47 (m, 2H), 1.47-1.25 (m, 8H), 1.06-0.88 (m, 16H), 0.84-0.56 (m, 5H), 0.55-0.54 (m, 1H).

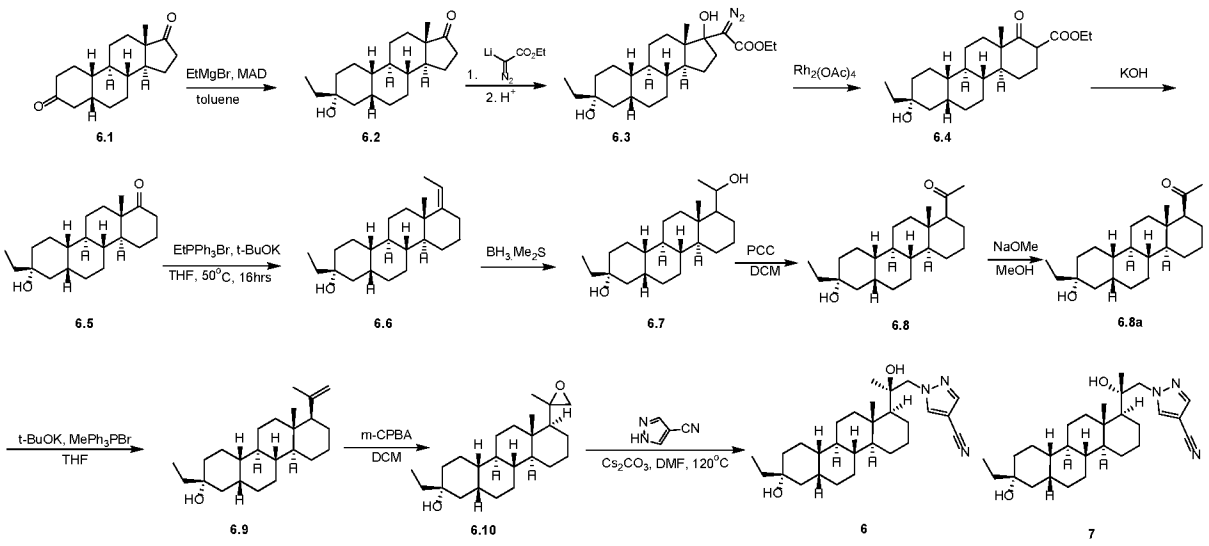
Synthesis of 1 & 2

[0421] To a solution of **1.10** (340 mg, 0.908 mmol) in DMF (10 mL) were added 1H-pyrazole-4-carbonitrile (168 mg, 1.81 mmol) and Cs_2CO_3 (593 mg, 1.81 mmol) at 20°C. After stirring at 120°C for 2 h, the mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was concentrated and purified by flash column (30~50% EtOAc in PE) to give mixture of diastereomers of **1 & 2** (350 mg) as a solid. The diastereomers were separated by SFC (Column DAICEL CHIRALCEL OD-H(250mm*30mm,5um) Condition 0.1%NH_3H_2O EtOH Begin B 30% End B 30% Gradient Time(min) 100%B Hold Time(min) FlowRate(ml/min) 50) to afford **2** (208.9 mg) and **1** (50.2 mg) both as solids.

[0422] **1: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.88 (s, 1H), 7.83 (s, 1H), 4.27 (d, J = 14.0 Hz, 1H), 4.00 (d, J = 13.9 Hz, 1H), 3.00 (s, 1H), 2.36 (br d, J = 12.8 Hz, 1H), 1.95-1.56 (m, 5H), 1.42-1.35 (m, 6H), 1.28-1.22 (m, 3H), 1.18 (s, 3H), 1.15-1.05 (m, 5H), 1.01 (s, 3H), 0.95-0.88 (m, 8H), 0.88-0.56 (m, 6H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{29}H_{42}N_3$ $[M-2H_2O+H]^+$ 432.4 found 432.4.

[0423] **2: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.92 (s, 1H), 7.79 (s, 1H), 4.52-4.13 (m, 2H), 2.47 (br s, 1H), 2.30 (br d, J = 13.0 Hz, 1H), 1.91-1.68 (m, 7H), 1.45-1.20 (m, 12H), 1.15-1.03 (m, 2H), 1.00-0.70 (m, 17H), 0.66-0.53 (m, 1H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{29}H_{42}N_3$ $[M-2H_2O+H]^+$ 432.3 found 432.3.

Example 6 & 7: Synthesis of 1-((R)-2-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-ethyl-8-hydroxy-12a-methyloctadecahydrochrysen-1-yl)-2-hydroxypropyl)-1H-pyrazole-4-carbonitrile & 1-((S)-2-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-ethyl-8-hydroxy-12a-methyloctadecahydrochrysen-1-yl)-2-hydroxypropyl)-1H-pyrazole-4-carbonitrile



Synthesis of 6.2

[0424] To a solution of BHT (144 g, 654 mmol) in toluene (165 mL) under nitrogen at 0°C was added $AlMe_3$ (2 M in toluene, 163 mL, 327 mmol) dropwise. After stirring at 25°C for 1 h, the MAD solution was used without further purification. To the MAD (327 mmol) solution was added a solution of (5β)-estrane-3,17-dione, **6.1** (30 g, 109 mmol) in DCM (100 mL) dropwise at -70°C. After stirring at -70°C for 1 h under N_2, EtMgBr (130 mL, 327 mmol, 2.5 M in ethyl ether) was added dropwise at -70°C. After stirring at -70°C for another 2 h, the reaction mixture was poured into saturated aqueous citric acid (100 mL) at 10°C and extracted with DCM (2 x 40 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 0-20%) to afford **6.2** (25g, 76%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.50-2.36 (m, 1H), 2.14-2.01 (m, 1H), 1.97-1.88 (m, 1H), 1.84-1.74 (m, 4H), 1.68-1.45 (m, 7H), 1.43-0.97 (m, 12H), 0.92-0.82 (m, 6H).

Synthesis of 6.3

[0425] To a solution of DIPA (34.7 g, 343 mmol) in THF (190 mL) was added BuLi (124 mL, 2.5 M in hexane, 312 mmol) at -70°C. After warming to 0°C and stirring for 1 h. The cold (-70°C) LDA solution (312 mL, 1.0 M, 312 mmol) was added to a stirred solution of **6.2** (19 g, 62.4 mmol) and ethyl diazoacetate (35.5 g, 312 mmmol) in THF (100 mL) at -78°C. After stirring at -70°C for 1h, the reaction mixture was quenched with acetic acid (18.7 g, 312 mmol) in THF (50 mL), warmed to 20°C, diluted with water (300 mL) and extracted with EtOAc (3 x 400 mL). The combined organic layers were washed with brine, dried by

Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash column (0-5% of EtOAc in PE) to give **6.3** (6 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.80 (m, 1H), 4.33-4.19 (m, 2H), 2.20-2.08 (m, 1H), 1.93-1.54 (m, 9H), 1.50-1.28 (m, 12H), 1.19-0.98 (m, 5H), 0.95-0.81 (m, 6H).

Synthesis of 6.4

[0426] To a solution of **6.3** (6.0 g, 14.3 mmol) in DME (30 mL) was added $Rh_2(OAc)_4$ (94.7 mg, 0.2 mmol) at 25°C. After stirring at 25°C for 12 h, the reaction mixture was concentrated to afford **6.4** (6 g) as a solid, which was used as is.

Synthesis of 6.5

[0427] To a mixture of **6.4** (6.00 g, 15.3 mmol) in MeOH/THF (30 mL/30 mL) was added KOH (8.58 g, 153 mmol). After stirring at 70°C for 12 h, the reaction mixture was extracted with ethyl acetate (4 x 80 mL). The combined organic phase was washed with water (80 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column (15~30% EtOAc in PE) to give **6.5** (3.9 g, 80%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.69-2.53 (m, 1H), 2.23-2.14 (m, 1H), 2.08-1.99 (m, 1H), 1.87-1.58 (m, 10H), 1.54-1.21 (m, 12H), 1.19-0.93 (s, 6H), 0.90-0.79 (m, 3H).

Synthesis of 6.6

[0428] To a suspension of Ph_3PEtBr (13.5 g, 36.5 mmol) in anhydrous THF (100 mL) was added t-BuOK (5.47 g, 48.8 mmol) at 15°C under N_2. After stirring at 40°C for 30 min, a solution of **6.5** (3.9 g, 12.2 mmol) in anhydrous THF (50 mL) was added dropwise. After stirring for 16 h, the mixture was cooled, poured into ice-water (150 mL), stirred for 10 min and extracted with EtOAc (2 x 100 mL). The combine organic phase was washed with saturated brine (2 x 200 mL), filtered and concentrated. The residue was purified by flash column (10%-30% Ethyl ether in PE) to give **6.6** (3.1 g,77%) a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.52-5.09 (m, 1H), 2.30-2.09 (m, 1H), 1.89-1.57 (m, 14H), 1.51-1.19 (m, 10H), 1.12-1.02 (m, 3H), 1.00-0.83 (m, 8H).

Synthesis of 6.7

[0429] To a solution of **6.6** (3.1 g, 9.4 mmol) in THF (10 ml) was added $BH_3{\cdot}Me_2S$ (2.81 mL, 28.1 mmol) at 0°C. After stirring at 15°C for 12 h, the reaction mixture was cooled and quenched sequentially with EtOH (5.46 ml,93.7 mmol, 0.789 g/ml) at 0 °C and NaOH (18.7

mL, 5M, 93.7 mmol). H_2O_2 (9.38 mL,93.7 mmol, 1.13 g/mL, 30% in water) was then added slowly until the inner temperature no longer rises and the inner temperature was maintained below 30°C. After stirring at 50°C for another 1 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (50 mL), stirred at 0°C for 1 h, and extracted with DCM (3 x 50 mL). The combine organic phase was washed with saturated $Na_2S_2O_3$ (2 x 50 mL), brine (2 x 50 mL), dried over anhydrous Na_2SO_4 filtered and concentrated to give **6.7** (3.26 g) as a solid, which was used as is.

Synthesis of 6.8

[0430] To a mixture of **6.7** (3.26 g, 9.35 mmol) and silica gel (5 g) in DCM (15 mL) was added PCC (3.01 g, 14.0 mmol) in portions. After stirring at 15°C for 1 h, the reaction mixture was filtered, and the filtrate was concentrated to give **6.8** (3.24 g) as an oil.

Synthesis of 6.8a

[0431] To a solution of **6.8** (2 g, 5.8 mmol) in MeOH (20 mL) at 0°C was added MeONa (4.67 g, 86.5 mmol). After stirring at 70°C for 16 h, the reaction mixture was added saturated NH_4Cl (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0-20% of EtOAc in PE) to give **6.8a** (1.5 g) as a solid.

Synthesis of 6.9

[0432] To a mixture of $MePPh_3Br$ (3.07 g, 8.63 mmol) in THF (12 mL) was added t-BuOK (966 mg, 8.63 mmol) at 15°C under N_2. After stirring at 50°C for 30 min, **6.8a** (1 g, 2.88 mmol) in THF (8 mL) was added in portions below 50°C. After stirring at 50°C for 1 h, the reaction mixture was quenched with 10% NH_4Cl aqueous (30 mL) at 15°C and extracted with EtOAc (2 x 30 mL). The combined organic phase was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/PE = 0 to 15%) to give **6.9** (720 mg, 72.5 %) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.80 (s, 1H), 4.62-4.58 (m, 1H), 1.86-1.58 (m, 5H), 1.57-1.50 (m, 6H), 1.49-1.39(m, 3H), 1.38-1.23 (m, 6H), 1.22-1.15(m, 2H), 1.14-0.85(m, 10H), 0.84-0.83(m, 3H), 0.82 (s, 3H).

Synthesis of 6.10

[0433] To a solution of **6.9** (720 mg, 2.08 mmol) in DCM (5 mL) was added m-CPBA (893 mg, 4.16 mmol, 80%) at 15°C. After stirring at 15°C for 1 h, the mixture was quenched with sat. $NaHCO_3$ and $Na_2S_2O_3$ (10 mL, v:v = 1:1) and extracted with DCM (2 x 10 mL). The combined organic phase was washed with sat. $NaHCO_3$ and $Na_2S_2O_3$ (10 mL, v: v = 1:1), dried over Na_2SO_4, filtered and concentrated to give **6.10** (900 mg) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.07-8.04 (m, 1H), 8.03-7.95 (m, 1H), 7.66-7.52 (m, 1H), 7.50-7.35 (m, 1H), 7.98 (s, 1H), 7.93 (s, 1H), 7.79 (s, 1H), 2.70-2.60 (m, 2H), 1.85-1.65 (m, 6H), 1.64-1.50 (m, 6H), 1.49-1.26 (m, 4H), 1.25-2.60 (m, 5H), 1.20-0.85(m, 10H).

Synthesis of 6 &7

[0434] To a solution of **6.10** (900 mg, 2.49 mmol) in DMF (5 mL) were added Cs_2CO_3 (2.43 g, 7.47 mmol) and 1H-pyrazole-4-carbonitrile (579 mg, 6.22 mmol). After stirring at 130°C for 12 h, the mixture was added into saturated NH_4Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with LiCl (10 mL, 5% in water), saturated brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford a mixture of diastereomers **6 & 7** (670 mg) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.98 (s, 1H), 7.93 (s, 1H), 7.79 (s, 1H), 4.25-4.211 (m, 2H), 2.50 (m, 2H), 2.38-2.30 (m, 1H), 2.05 (s, 3H), 1.73-1.60 (m, 6H), 1.59-1.52 (m, 5H), 1.51-1.47 (m, 5H), 1.46-1.24 (m, 3H), 1.23 (s, 1H), 1.00-0.88(m, 6H), 0.87-0.85(m, 6H).

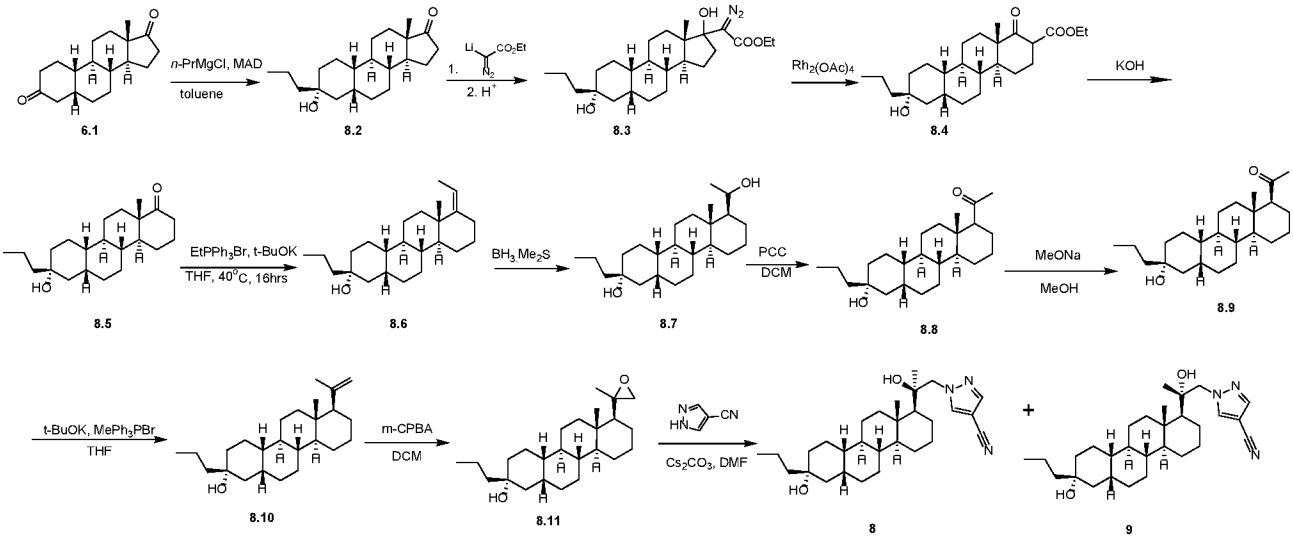
[0435] The diastereomers (670 mg) was were separated by SFC (DAICEL CHIRALCEL OJ-H (250mm*30mm,5um),Condition: 0.1% NH_3H_2O EtOH, Begin B: 25%, End B: 25%,FlowRate (ml/min):60) to afford **6** (212.6 mg, 31.8%) and **7** (55 mg) as solids. **7** was further purified by SFC (Column: DAICEL CHIRALCEL OJ-H (250mm*30mm, 5um), Condition: 0.1% NH_3H_2O EtOH, Begin B: 25%, End B: 25%, FlowRate (ml/min):60) to afford **7** (33.5 mg) as a solid.

[0436] **6: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.92 (s, 1H), 7.80 (s, 1H), 4.39-4.20 (m, 2H), 2.45-2.25 (m, 2H), 1.74-1.62 (m, 7H), 1.61-1.55 (m, 6H), 1.54-1.48 (m, 7H), 1.47-1.35 (m, 6H), 1.35-1.25 (m, 4H), 1.05-0.95 (m, 4H), 0.90-0.85(m, 3H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{28}H_{40}N_3$ $[M- 2H_2O+H]^+$ 418 found 418. **SFC** 99% de.

[0437] **7: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.88 (s, 1H), 7.86 (s, 1H), 4.30-4.24 (m, 1H), 4.01-3.95 (m, 1H), 3.05 (s, 1H), 2.42-2.38 (m, 1H), 1.84-1.74 (m, 2H), 1.73-1.45 (m, 9H),

1.44-1.19 (m, 11H), 1.18-1.00 (m, 6H), 0.99-0.86 (m, 9H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{28}H_{40}N_3$ $[M- 2H_2O+H]^+$ 418 found 418. **SFC** 100% de.

Example 8 & 9: Synthesis of 1-((R)-2-hydroxy-2-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-12a-methyl-8-propyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile & 1-((S)-2-hydroxy-2-((1S,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-12a-methyl-8-propyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile



Synthesis of 8.2

[0438] To a solution of BHT (96 g, 436 mmol) in toluene (300 mL) under nitrogen at 0°C was added $AlMe_3$ (2 M in toluene, 109 mL, 218 mmol) dropwise. After stirring at 25°C for 1 h, the MAD solution was used directly without further purification. To the fresh prepared MAD (218 mmol) solution was added a solution of **6.1** (20 g, 72.8 mmol) in DCM (80 mL) dropwise at -70°C. After stirring at -70°C for 1 h under N_2, n-PrMgCl (72.5 mL, 145 mmol, 2 M in ethyl ether) was added dropwise at -70°C. After stirring at -70°C for 2 h, the reaction mixture was poured into saturated aqueous citric acid (1000 mL) at 10°C and extracted with EtOAc (2 x 400 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~20% of EtOAc in PE) to afford **8.2** (12 g, 52%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.44 (dd, J = 8.5, 19.3 Hz, 1H), 2.15-2.07 (m, 1H), 2.13-2.00 (m, 1H), 1.98-1.88 (m, 1H), 1.86-1.59 (m, 6H), 1.54-1.00 (m, 18H), 0.93 (t, J = 7.2 Hz, 3H), 0.87 (s, 3H).

Synthesis of 8.3

[0439] To a solution of **8.2** (12.0 g, 37.6 mmol) and ethyl diazoacetate (19.7 mL, 188 mmol, 1.085 g/mL) in THF (800 mL) was added freshly prepared LDA (180 mL, 1.0 M, 180 mmol) at -78°C. After stirring at -78°C for 2 h, the reaction mixture was quenched with acetic acid (10.6 mL, 188 mmol) in THF (50 mL), stirred at 15°C for 16 h, poured into water (1000 mL) and extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (1500 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash column (0~10% of EtOAc in PE) to give **8.3** (13 g, 80%) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.29-4.19 (m, 2H), 2.23-2.08 (m, 1H), 1.96-1.59 (m, 8H), 1.53-1.28 (m, 17H), 1.17-1.02 (m, 5H), 0.96-0.90 (m, 5H), 0.86 (br d, J = 6.8 Hz, 2H).

Synthesis of 8.4

[0440] To a solution of **8.3** (13 g, 30.0 mmol) and DME (150 mL) was added $Rh_2(OAc)_4$ (132 mg, 0.3 mmol) in one portion at 15°C. After stirring at 15 °C for 2 h, the reaction mixture was concentrated to give **8.4** (13 g) as an oil, which was used as is.

Synthesis of 8.5

[0441] To a solution of **8.4** (13 g, 32.1) in MeOH (200 mL) was added KOH (18.0 g, 321 mmol) at 15°C. After stirring 70°C for 1 h, the reaction mixture was poured into H_2O (200 mL), and extracted with EtOAc (3 x 200 mL). The combined organic layer was washed with HCl (1M, 100 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~15% of EtOAc in PE) to give **8.5** (8.3 g, 78.3 %) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.61 (dt, J = 6.8, 13.9 Hz, 1H), 2.27-2.15 (m, 1H), 2.08-2.02 (m, 1H), 1.87-1.49 (m, 13H), 1.48-1.20 (m, 12H), 1.18-1.10 (m, 1H), 1.08 (s, 3H), 1.03-0.96 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H).

Synthesis of 8.6

[0442] To a suspension of Ph_3PEtBr (27.6 g, 74.6 mmol) in anhydrous THF (100 mL) was added t-BuOK (11.1 g, 99.6 mmol) at 15°C under N_2. After stirring at 40°C for 30 min, a solution of **8.5** (8.3 g, 24.9 mmol) in anhydrous THF (50 mL) was dropwise. After stirring at 40°C for 16 h, the mixture was cooled, poured into ice-water (150 mL), stirred for 10 min, and extracted with EtOAc (2 x 100 mL). The combine organic phase was washed with brine

(2 x 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by trituration with MeOH/H_2O (1:1, 320 mL) at reflux to give **8.6** (5.3 g, 62%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.24-5.00 (m, 1H), 2.50 (br d, J = 13.8 Hz, 1H), 2.25-2.10 (m, 1H), 2.01-1.56 (m, 10H), 1.48-1.16 (m, 14H), 1.05 (s, 3H), 0.92-0.80 (m, 10H).

Synthesis of 8.7

[0443] To a solution of **8.6** (5.3 g, 15.3 mmol) in THF (100 ml) was added BH_3·Me_2S (4.58 mL, 45.9 mmol) at 0°C. After stirring at 15°C for 16 h, the reaction mixture was cooled (0°C) and treated with sequentially EtOH (8.91 ml, 203 mmol, 0.789 g/ml), NaOH (30.5 mL, 5M, 153 mmol) and H_2O_2 (15.3 mL, 153 mmol, 1.13 g/mL, 30% in water) dropwise added slowly until the inner temperature no longer rises and the inner temperature was maintained below 30°C. After stirring at 50°C for 1 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (130 mL) and stirred at 0°C for another 1 hour. The reaction was checked by potassium iodide-starch test paper to confirm excess H_2O_2 was destroyed (did not changed to blue). The aqueous phase was extracted with DCM (3 x 50 mL). The combine organic phase was washed with saturated $Na_2S_2O_3$ (2 x 100 mL), brine (2 x 100 mL), dried over anhydrous Na_2SO_4 filtered and concentrated to give **8.7** (4.3 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H = 2.47 (br d, J = 5.2 Hz, 0.4H), 2.29 (dd, J = 3.2, 12.8 Hz, 0.6 H), 2.13 (d, J = 3.2 Hz, 3H), 1.88-1.66 (m, 3H), 1.54-1.44 (m, 6H), 1.41-1.14 (m, 13H), 1.11-0.80 (m, 13H).

Synthesis of 8.8

[0444] To a mixture of PCC (3.70 g, 17.2 mmol) and silica gel (4 g) in DCM (20 mL) was added **8.7** (2.5 g, 6.89 mmol) in DCM (30 mL) at 25°C. After stirring at 25°C for 1 h, the reaction mixture was filtered and washed with DCM (100 mL). The filtrate was collected and concentrated to give **8.8** (1.93 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H = 2.47 (br d, J = 5.2 Hz, 0.4H), 2.29 (dd, J = 3.2, 12.8 Hz, 0.6 H), 2.13 (d, J = 3.2 Hz, 3H), 1.88-1.66 (m, 3H), 1.54-1.44 (m, 6H), 1.41-1.14 (m, 13H), 1.11-0.80 (m, 13H).

Synthesis of 8.9

[0445] To a solution of **8.8** (1.93 g, 5.35 mmol) in MeOH (20 mL) at 0 °C was added MeONa (4.33 g, 80.2 mmol). After stirring at 70°C for 16 h, the reaction mixture was added to saturated NH_4Cl (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **8.9** (1.2 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H = 2.30 (dd, J =

3.2, 12.7 Hz, 1H), 2.14 (s, 3H), 1.82 (br d, J = 12.4 Hz, 2H), 1.76-1.63 (m, 5H), 1.57-1.43 (m, 7H), 1.40-1.23 (m, 10H), 1.07-0.84 (m, 12H).

Synthesis of 8.10

[0446] To a mixture of $MePPh_3Br$ (9.46 g, 26.5 mmol) in THF (20 mL) was added t-BuOK (2.96 g, 26.5 mmol) at 25°C under N_2. After stirring at 50°C for 30 mins, **8.9** (1.2 g, 3.32 mmol) in THF (10 mL) was added at 25°C. After stirring at 60°C for 3 h, the reaction mixture was cooled, poured to ice water (50 mL), and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column (0~30% of EtOAc in PE) to give **8.10** (1.1 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H = 4.80 (s, 1H), 4.61 (s, 1H), 1.83 (br d, J = 14.4 Hz, 2H), 1.70-1.57 (m, 6H), 1.53-1.43 (m, 4H), 1.40-1.22 (m, 12H), 1.19-1.04 (m, 2H), 0.99-0.87 (m, 9H), 0.82 (s, 3H).

Synthesis of 8.11

[0447] To a solution of **8.10** (500 mg, 1.39 mmol) in DCM (10 mL) was added m-CPBA (446 mg, 2.08 mmol, 80%) at 25°C. After stirring at 25°C for 2 h, the mixture was quenched with sat. $NaHCO_3$ and $Na_2S_2O_3$ (40 mL, v: v = 1:1) and extracted with DCM (2 x 20 mL). The combined organic phase was washed with sat. $NaHCO_3$ and $Na_2S_2O_3$ (50 mL, v: v = 1:1), dried over Na_2SO_4, filtered and concentrated to give **8.11** (520 mg) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.70 (br d, J = 5.2 Hz, 1H), 2.65-2.49 (m, 1H), 1.91-1.78 (m, 7H), 1.70-1.61 (m, 10H), 1.31 (br d, J = 7.6 Hz, 10H), 0.96-0.88 (m, 14H).

Synthesis of 8 & 9

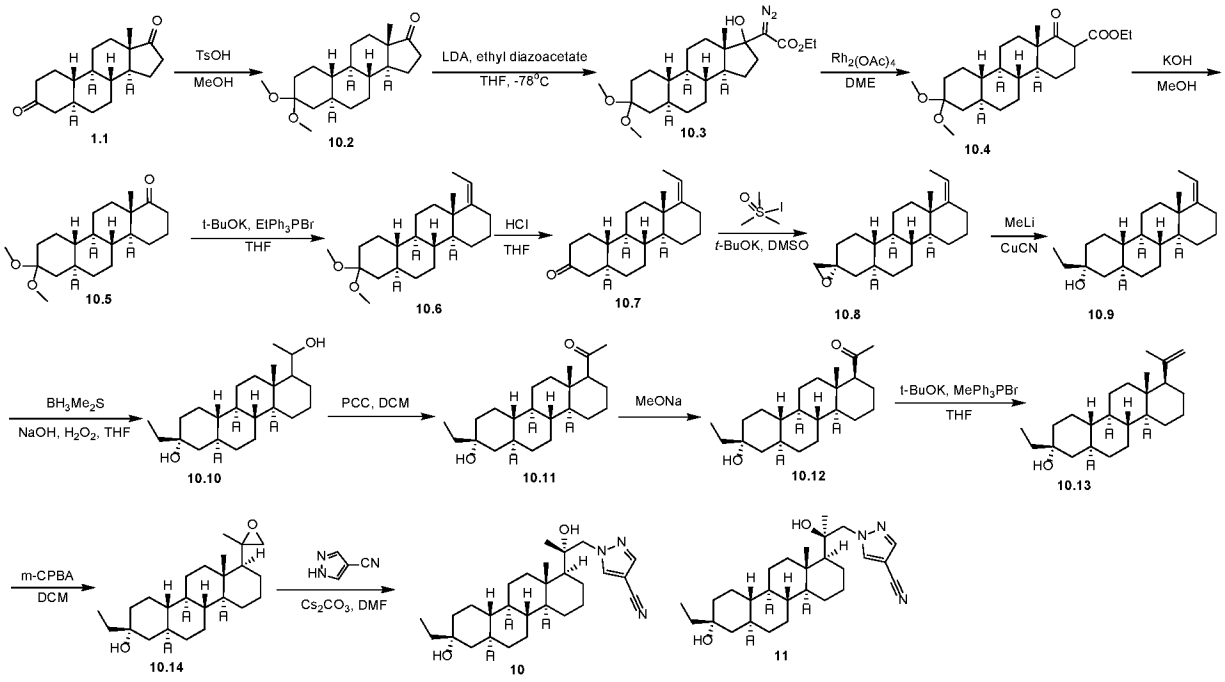
[0448] To a solution of **8.11** (300 mg, 0.8008 mmol) in DMF (5 mL) were added Cs_2CO_3 (782 mg, 2.40 mmol) and 1H-pyrazole-4-carbonitrile (186 mg, 2.00 mmol). After stirring at 130°C for 12 h, the mixture was added into saturated NH_4Cl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with LiCl (100 mL, 5% in water), brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~50% of EtOAc in PE) to afford a mixture of diastereomers **8 & 9** (165 mg) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H = 7.92 (s, 1H), 7.79 (s, 1H), 4.38-4.33 (m, 1H), 4.26-4.18 (m, 1H), 2.32 (br d, J = 13.2 Hz, 5H), 1.77-1.61 (m, 11H), 1.37-1.28 (m, 10H), 1.00-0.91 (m, 15H).

[0449] The C20 diastereomers were separated by SFC (Column DAICEL CHIRALCEL OD (250mm*30mm, 10um); Condition 0.1%NH_3H_2O EtOH; FlowRate (ml/min) 70) to give **8** (67.3 mg, 32.2%) and **9** (11 mg) as solids. **9** (11 mg) was further purified by SFC (Column DAICEL CHIRALCE OD (250mm x 30mm, 10 um); Condition 0.1%NH_3H_2O EtOH; FlowRate (ml/min) 70) to give **9** (6.5 mg) as a solid.

[0450] **8: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H = 7.92 (s, 1H), 7.79 (s, 1H), 4.39-4.32 (m, 1H), 4.26-4.20 (m, 1H), 2.43 (s, 1H), 2.32 (br d, J = 12.8 Hz, 1H), 1.91-1.64 (m, 6H), 1.55-1.18 (m, 18H), 1.03-0.82 (m, 15H). **LC-ELSD/MS** purity 99%, MS ESI calcd for $C_{29}H_{42}N_3$ [M-$2H_2O$+H]$^+$ 432.3, found 432.3. **SFC** 98.54% de

[0451] **9: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H = 7.88 (s, 1H), 7.85 (s, 1H), 4.31-4.24 (m, 1H), 4.02-3.96 (m, 1H), 3.06 (s, 1H), 2.43-2.34 (m, 1H), 1.85-1.73 (m, 2H), 1.70-1.59 (m, 4H), 1.54-1.42 (m, 12H), 1.36-1.30 (m, 3H), 1.30-1.23 (m, 5H), 1.18 (s, 1H), 1.16-1.04 (m, 2H), 1.00 (s, 1H), 0.95-0.87 (m, 6H), 0.86-0.71 (m, 3H). **LC-ELSD/MS** purity 99%, MS ESI calcd for $C_{29}H_{42}N_3$ [M-$2H_2O$+H]$^+$ 432.3, found 432.3. **SFC** 99.02% de.

Example 10 & 11: Synthesis of 1-((S)-2-((1S,4aS,4bR,6aS,8R,10aS,10bR,12aS)-8-ethyl-8-hydroxy-12a-methyloctadecahydrochrysen-1-yl)-2-hydroxypropyl)-1H-pyrazole-4-carbonitrile & 1-((R)-2-((1S,4aS,4bR,6aS,8R,10aS,10bR,12aS)-8-ethyl-8-hydroxy-12a-methyloctadecahydrochrysen-1-yl)-2-hydroxypropyl)-1H-pyrazole-4-carbonitrile



Synthesis of 10.2

[0452] To a solution of **1.1** (50 g, 182 mmol) in MeOH (600 mL) was added 4-methylbenzenesulfonic acid (6.26 g, 36.4 mmol) at 25°C. After stirring at 55°C for 16 h, the mixture was diluted with Et_3N (20 mL). The solid was filtered and the filtrate concentrated to afford **10.2** (52 g, 89.1 %) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.73-0.83 (m, 1 H), 0.91 (s, 3 H), 0.98-1.13 (m, 2 H), 1.20-1.56 (m, 16 H), 1.72-1.78 (m, 1 H), 1.80-1.86 (m, 2 H), 1.88-1.99 (m, 2 H), 2.05-2.16 (m, 2 H), 2.25-2.35 (m, 3 H), 2.38-2.51 (m, 2 H), 3.15 (s, 1 H), 3.21 (s, 1 H), 3.50 (s, 6 H).

Synthesis of 10.3

[0453] To a solution of **10.2** (4.5 g, 14.0 mmol) and ethyl diazoacetate (7.35 mL g, 1.085 g/mL, 70.0 mmol) in THF (300 mL) was added the fresh prepared LDA (67.1 mL, 1.0 M, 67.1 mmol) at -78°C. After stirring at -78°C for 2 h, the reaction was quenched with acetic acid (4.00 mL, 1.0492 g/mL, 70.0 mmol) in THF (100 mL). After stirring at 15°C for 16 h, he mixture was added to NH_4Cl(200 mL) and extracted with EtOAc (2 x 125 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~10% of EtOAc in PE) to give **10.3** (3.7 g, 60.8 %) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.77-4.64 (m, 1H), 4.25 (dq, J = 1.6, 7.2 Hz, 2H), 3.20 (s, 3H), 3.14 (s, 3H), 2.22-2.01 (m, 2H), 1.96-1.76 (m, 4H), 1.69-1.61 (m, 2H), 1.55-1.42 (m, 1H), 1.41-1.27 (m, 5H), 1.27-0.96 (m, 9H), 0.93 (s, 3H), 0.91-0.83 (m, 1H), 0.80-0.62 (m, 2H).

Synthesis of 10.4

[0454] To a solution of **10.3** (57 g, 147 mmol) and DME (500 mL) was added $Rh_2(OAc)_4$ (800 mg, 1.81 mmol) in one portion at 15°C. After stirring at 15°C for 2 h, the reaction mixture was concentrated to give **10.4** (59.7 g) as an oil, which was used as is.

Synthesis of 10.5

[0455] To a solution of **10.4** (59.7 g) in MeOH (500 mL) was added KOH (81.9 g, 1460 mmol) at 15°C. After stirring at 70°C for 1 h, the reaction mixture was poured into H_2O (500 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layer was washed with HCl (1M, 100 mL), saturated $NaHCO_3$ (100 mL), and brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~15% of

EtOAc in PE) to give **10.5** (30 g, 61.4 %) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.21 (d, J = 1.2 Hz, 3H), 3.15 (d, J = 1.6 Hz, 3H), 2.24-2.01 (m, 3H), 1.98-1.78 (m, 5H), 1.76-1.61 (m, 2H), 1.59-1.13 (m, 8H), 1.10 (d, J = 6.4 Hz, 3H), 1.08-0.82 (m, 5H), 0.78-0.62 (m, 2H).

Synthesis of 10.6

[0456] To a mixture of $EtPPh_3Br$ (99.4 g, 268 mmol) in THF (400 mL) was added t-BuOK (30.0 g, 268 mmol) at 15°C under N_2. After stirring at 15°C for 30 min, **10.5** (30 g, 89.6 mmol) in THF (100 mL) was added. After stirring at 40°C for 1 h, the mixture was poured into sat. NH_4Cl aqueous solution (400 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layer was washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **10.6** as a residue, which was used directly for the next step.

Synthesis of 10.7

[0457] To a solution of **10.6** (31 g, 89.4 mmol) in THF (300 mL) was added HCl (89.4 mL, 1 M, 89.4 mmol). After stirring at 15°C for 2 h, the mixture was poured into $NaHCO_3$ aq (200 mL) and extracted with EtOAc (2 x 150 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~3% of EtOAc in PE) to give **10.7** (14 g, 52.2%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.25-5.07 (m, 1H), 2.45-2.36 (m, 1H), 2.35-2.12 (m, 4H), 2.07 (t, J = 13.2 Hz, 1H), 1.95-1.81 (m, 3H), 1.80-1.64 (m, 5H), 1.27-1.08 (m, 9H), 0.99-0.93 (m, 2H), 0.93-0.74 (m, 6H).

Synthesis of 10.8

[0458] A stirred solution of trimethylsulfoxonium iodide (10.2 g, 46.5 mmol) and t-BuOK (6.81 g, 55.8 mmol) in DMSO (60 mL) and THF (20 mL) was heated at 40°C for 1 h under N_2. The reaction mixture was added to **10.7** (14 g, 46.5 mmol) in DMSO (20 mL). After stirring at 40°C for 30 min, the reaction was diluted with water (250 mL) to give a solid. The precipitate was filtered, dried under reduced pressure to afford **10.8** (12.5 g, 85.6%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.32-5.01 (m, 1H), 2.64 (s, 2H), 2.55-2.48 (m, 1H), 2.28-2.10 (m, 1H), 2.03-1.96 (m, 1H), 1.90-1.80 (m, 3H), 1.80-1.58 (m, 7H), 1.47-1.21 (m, 4H), 1.12 (br s, 4H), 1.10-1.01 (m, 3H), 0.95 (s, 2H), 0.92-0.64 (m, 5H).

Synthesis of 10.9

[0459] To a suspension of CuCN (4.21 g, 47.4 mmol) in THF (120 mL) at -40°C was added MeLi (59.2 mL, 94.8 mmol, 1.6 M). After stirring at -40°C for 1 h, **10.8** (5 g, 15.8 mmol) in THF (30 mL) was added at -40°C. After stirring at 25°C for 2 h, the reaction was slowly poured into 10% NH_4Cl (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4 filtered and concentrated to give **10.9** (4.5 g, 86.2%) as a solid. **^{1}H NMR** (400 MHz, CDCl3) δ_H 5.23-5.05 (m, 1H), 2.30-2.09 (m, 1H), 2.04-1.70 (m, 7H), 1.56-1.39 (m, 4H), 1.39-1.23 (m, 4H), 1.22-0.95 (m, 10H), 0.95-0.83 (m, 8H), 0.83-0.55 (m, 3H).

Synthesis of 10.10

[0460] To a solution of **10.9** (5.5 g, 16.6 mmol) in THF (100 mL) was added BH_3Me_2S (4.97 mL, 49.8 mmol, 10M) at 0°C. After stirring at 20°C for 12 h, the resulting mixture was treated with ethanol (20 mL) and NaOH aqueous (33.2 mL, 5.0 M) at 0°C. Hydrogen peroxide (19.9 mL, 10 M) was then added dropwise at 0°C. After stirring for 2 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (30 mL) and extracted with EtOAc (2×30 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **10.10** (5.5 g, 95.1%) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.95-1.73 (m, 5H), 1.72-1.55 (m, 7H), 1.54-1.39 (m, 5H), 1.21-1.04 (m, 7H), 1.04-0.96 (m, 5H), 0.94-0.84 (m, 6H), 0.83-0.55 (m, 5H).

Synthesis of 10.11

[0461] To a solution of **10.10** (5.5 g, 15.7 mmol) in DCM (100 mL) was added PCC (10.1 g, 47.0 mmol) and silica gel (12 g) at 25°C. After stirring at 25°C for 1 h, the reaction mixture was filtered and the filter cake was washed with DCM (2 x 20 mL). The combined organic layer was concentrated under reduced pressure. The residue was purified by column (15-20% of EtOAc in PE) to give **10.11** (4.4 g, 81.4%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.50-2.25 (m, 1H), 2.17-2.09 (m, 3H), 1.87-1.67 (m, 6H), 1.50-1.38 (m, 4H), 1.36-1.17 (m, 5H), 1.17-0.94 (m, 7H), 0.93-0.92 (m, 3H), 0.91-0.87 (m, 4H), 0.87-0.54 (m, 5H).

Synthesis of 10.12

[0462] To a solution of **10.11** (1.4 g, 4.03 mmol) in MeOH (50 mL) at 0°C was added MeONa (3.26 g, 60.4 mmol). After stirring at 70°C for 16 h, the reaction mixture was added

to saturated NH_4Cl (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with saturated brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **10.12** (1.2 g, 86.3%) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.31 (dd, J = 3.2, 12.8 Hz, 1H), 2.15 (s, 3H), 1.88-1.60 (m, 8H), 1.56-1.29 (m, 7H), 1.24-0.95 (m, 8H), 0.95-0.88 (m, 7H), 0.87-0.55 (m, 4H).

Synthesis of 10.13

[0463] To a mixture of $MePPh_3Br$ (6.57 g, 18.4 mmol) in THF (40 mL) was added t-BuOK (2.06 g, 18.4 mmol) at 15°C under N_2. After stirring at 15°C for 30 min, **10.12** (800 mg, 2.30 mmol) in THF (10 mL) was added. After stirring at 40°C for 2 h, the reaction mixture was poured into NH_4Cl aq (150 mL) andextracted with EtOAc (2 x 200 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (12~20% of EtOAc in PE) to give **10.13** (650 mg, 82.0%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.81 (s, 1H), 4.62 (d, J = 1.6 Hz, 1H), 1.90-1.75 (m, 4H), 1.73 (s, 3H), 1.73-1.58 (m, 5H), 1.56-1.20 (m, 8H), 1.12-0.94 (m, 7H), 0.91 (t, J = 7.6 Hz, 4H), 0.87-0.83 (m, 4H), 0.82-0.56 (m, 3H).

Synthesis of 10.14

[0464] To a solution of **10.13** (450 mg, 1.30 mmol) in DCM (15 mL) was added m-CPBA (527 mg, 85%, 2.60 mmol). After stirring at 0°C for 1 h, the mixture was quenched with $NaHCO_3$ (50 mL, sat. aq.) and $Na_2S_2O_3$ (20 mL, sat. aq.). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **10.14** (360 mg, 76.9%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.77-2.70 (m, 1H), 2.68-2.61 (m, 1H), 1.87-1.72 (m, 6H), 1.52-1.41 (m, 5H), 1.30-1.23 (m, 9H), 0.94-0.90 (m, 7H), 0.89-0.87 (m, 3H), 0.86-0.59 (m, 8H).

Synthesis of 10 & 11

[0465] To a solution of **10.14** (360 mg, 0.998 mmol) in DMF (10 mL) was added 1H-pyrazole-4-carbonitrile (185 mg, 1.99 mmol) and Cs_2CO_3 (648 mg, 1.99 mmol) at 20°C. After stirring at 130°C for 2 h, the mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was separated, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column (30~65% EtOAc in PE) to give a mixture of diastereomers **10 & 11** (200 mg, 44.2% yield) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.93 (s, 1H), 7.80 (s, 1H), 4.41-4.35 (m, 1H), 4.27-4.21 (m, 1H), 2.50 (s,

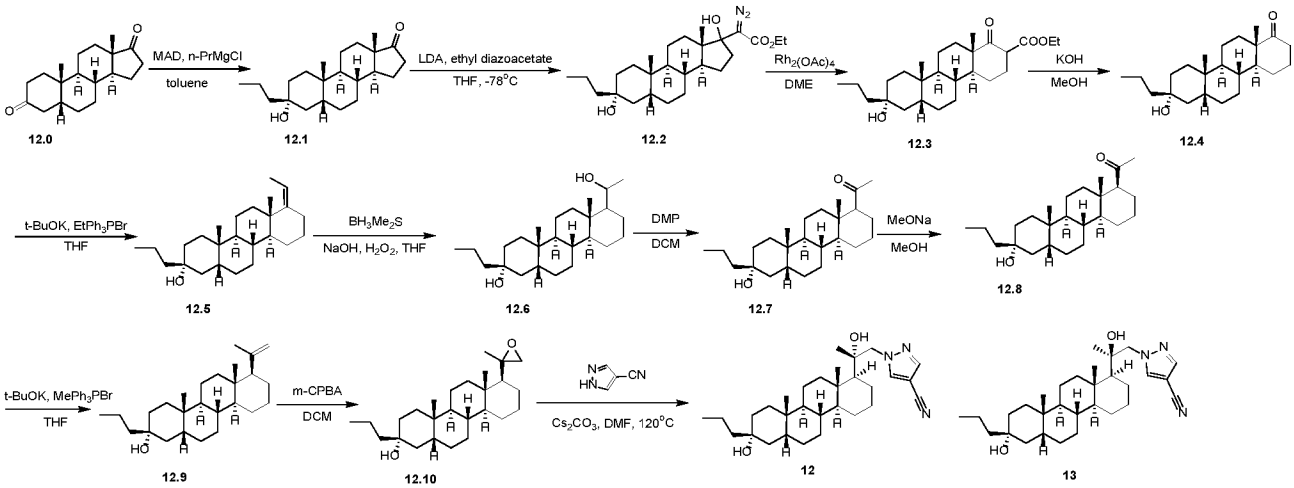
1H), 2.41-2.26 (m, 1H), 1.91-1.72 (m, 8H), 1.53-1.39 (m, 7H), 1.17-1.06 (m, 3H), 1.01 (s, 3H), 0.97 (s, 3H), 0.94-0.89 (m, 5H), 0.87-0.83 (m, 5H), 0.78-0.55 (m, 3H).

[0466] The diastereomers were separated by SFC: Column: DAICEL CHIRALCEL OJ-H 250 mm x 30 mm, 5um; Condition: 0.1% NH_3H_2O EtOH; Gradient: from 25% to 25% of B; Flow rate: 60 mL/min; Column temperature: 40°C) to afford **11** (30 mg) and **10** (130.5 mg) as solids. **11** was re-purified by SFC: Column: DAICEL CHIRALCEL OJ-H 250 mm x 30 mm, 5um; Condition: 0.1% NH_3H_2O EtOH; Gradient: from 20% to 20% of B; Flow rate: 60mL/min; Column temperature: 40°C) to afford **11** (16.9 mg) as a solid.

[0467] **10: ^{1}H NMR** (400 MHz, CDCl3) δ_H 7.93 (s, 1H), 7.80 (s, 1H), 4.40-4.35 (m, 1H), 4.26-4.21 (m, 1H), 2.47 (s, 1H), 2.35-2.29 (m, 1H), 1.91-1.59 (m, 9H), 1.53-1.35 (m, 6H), 1.33-1.23 (m, 3H), 1.18-1.03 (m, 3H), 1.01 (s, 3H), 0.99-0.95 (m, 5H), 0.91 (t, J = 7.6 Hz, 4H), 0.87-0.68 (m, 3H), 0.66-0.55 (m, 1H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{28}H_{40}N_3$ $[M-2H_2O+H]^+$ 418.3 found 418.3. **SFC**: 95% de.

[0468] **11: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.89 (s, 1H), 7.84 (s, 1H), 4.28 (d, J = 13.6 Hz, 1H), 4.01 (d, J = 13.6 Hz, 1H), 3.00 (s, 1H), 2.41-2.34 (m, 1H), 1.84-1.57 (m, 9H), 1.52-1.40 (m, 6H), 1.19 (s, 3H), 1.10-1.06 (m, 3H), 1.11-1.05 (m, 1H), 1.02 (s, 3H), 1.01-0.93 (m, 5H), 0.93-0.89 (m, 4H), 0.78-0.66 (m, 3H), 0.62-0.54 (m, 1H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{28}H_{40}N_3$ $[M-2H_2O+H]^+$ 418.3 found 418.3. **SFC**: 99% de.

Example 12 &13: Synthesis of 1-((S)-2-hydroxy-2-((1S,4aS,4bR,6aR,8R,10aS,10bS,12aS)-8-hydroxy-10a,12a-dimethyl-8-propyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile & 1-((R)-2-hydroxy-2-((1S,4aS,4bR,6aR,8R,10aS,10bS,12aS)-8-hydroxy-10a,12a-dimethyl-8 propyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile



Synthesis of 12.1

[0469] To the fresh prepared MAD (310 mmol) solution in toluene (300 mL) was added (5β)- androstane-3,17-dione, **12.0** (30 g, 104 mmol) in DCM (100 mL) dropwise at -70°C. After stirring at -70°C for 1 h under N_2, n-PrMgCl (130 mL, 260 mmol, 2M) was added dropwise at -70°C. After stirring at -70°C for 4 h, the reaction mixture was poured into saturated aqueous citric acid (1000 mL) at 10°C and extracted with EtOAc (2 x 1000 mL). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash column (0~30% of EtOAc in PE) to give **12.1** (16 g, 47.7%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.49-2.38 (m, 1H), 2.17-2.00 (m, 1H), 1.98-1.76 (m, 4H), 1.74-1.66 (m, 1H), 1.62-1.40 (m, 10H), 1.38-1.15 (m, 9H), 1.12-0.99 (m, 1H), 0.98-0.90 (m, 6H), 0.84 (s, 3H).

Synthesis of 12.2

[0470] To a freshly prepared LDA (150 mmol) solution in THF (100 mL) was added a solution of **12.1** (10 g, 30.0 mmol) and ethyl diazoacetate (19.0 g, 150 mmol, 90%) in THF (200 mL) at -70°C. After stirring at -70°C for 2h, the reaction was quenched with acetic acid (8.57 mL, 150 mmol) in THF (20 mL). After warming to rt overnight, the reaction was diluted with water (300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~20% of EtOAc in PE) to give **12.2** (13 g, 97.7%) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.75-4.65(m, 1H), 4.25 (q, J=7.2 Hz, 2H), 2.20-2.09 (m, 1H), 1.93-1.76 (m, 3H), 1.72-1.35 (m, 14H), 1.34-1.24 (m, 7H), 1.23-0.99 (m, 5H), 0.96-0.91 (m, 6H), 0.89 (s, 3H).

Synthesis of 12.3

[0471] To a solution of **12.2** (13 g, 29.1 mmol) in DME (130 mL) was added $Rh_2(OAc)_4$ (300 mg, 0.6787 mmol) in one portion at 15°C. After stirring at 15°C for 16 h, the reaction was diluted with water (300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **12.3** (11 g, 90.9%) as an oil.

Synthesis of 12.4

[0472] To a solution of **12.3** (11 g, 26.2 mmol) in MeOH (110 mL) was added KOH (14.6 g, 262 mmol) at 20°C. After stirring for 3 hours at 70°C, the reaction mixture was added to saturated brine (100 mL) and extracted with DCM (2 x 200 mL). The combined organic layer was washed with HCl (200 mL, 1N), saturated $NaHCO_3$ (200 mL), saturated brine (100 mL), dried over Na_2SO_4, filtered and concentrated to give **12.4** (11 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.61 (dt, *J*=6.8, 14.0 Hz, 1H), 2.24-2.15 (m, 1H), 2.09-2.01 (m, 1H), 1.91-1.68 (m, 6H), 1.67-1.43 (m, 10H), 1.42-1.19 (m, 10H), 1.06 (s, 3H), 0.96-0.90 (m, 6H).

Synthesis of 12.5

[0473] To a mixture of $EtPPh_3Br$ (38.2 g, 103 mmol) in THF (160 mL) was added t-BuOK (11.5 g,103 mmol) at 20°C under N_2. After stirring at 40°C for 30 min, **12.4** (9.0 g, 25.9 mmol) was added at 40°C. After stirring at 40°C for 16 h, the reaction mixture was quenched with saturated NH_4Cl aqueous (150 mL) at 20°C and extracted with EtOAc (2 x 100 mL). The combined organic phase was concentrated. The residue was purified by flash column (0~20% of EtOAc in PE) to give **12.5** (4.2 g, 45.2%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δH 5.25-5.05 (m, 1H), 2.54-2.10 (m, 1H), 1.99-1.69 (m, 7H), 1.67-1.57 (m, 4H), 1.54-1.20 (m, 16H), 1.05-0.98 (m, 4H), 0.96-0.86 (m, 9H)

Synthesis of 12.6

[0474] To a solution of **12.5** (4.2 g, 11.7 mmol) in THF (40 mL) was added $BH_3.Me_2S$ (3.51 mL, 10 M, 35.1 mmol). After stirring at 15°C for 16 h, the reaction was treated sequentially with EtOH (6.73 mL, 117 mmol), NaOH (4.67 g in 23.4 mL water, 5 M, 117 mmol) dropwise and H_2O_2 (11.7 mL, 10 M, 117 mmol) dropwise at 0 °C. After stirring 70°C for 2 h, the mixture was quenched by Na_2SO_3 (100 mL, 10%) and extracted with EtOAc (2 x

100 mL). The combined organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **12.6** (4.2 g) as a solid, which was used as is.

Synthesis of 12.7

[0475] To a solution of **12.6** (4.2 g, 11.1 mmol) in DCM (50 mL) was added DMP (9.41 g, 22.2 mmol). After stirring at 20°C for 1h, the mixture was quenched by $NaHCO_3$ (100 mL, saturated) and $Na_2S_2O_3$ (100 mL, saturated). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give **12.7** (4.0 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.50-2.24 (m, 1H), 2.16-2.10 (m, 3H), 1.93-1.64 (m, 7H), 1.54-1.43 (m, 6H), 1.39-1.12 (m, 11H), 1.05-0.82 (m, 14H)

Synthesis of 12.8

[0476] To a solution of **12.7** (3.5 g, 9.34 mmol) in MeOH (80 mL) at 0°C was added MeONa (10.0 g, 186 mmol). After stirring at 80°C for 16 h, the reaction mixture was concentrated. The residue was diluted with saturated NH_4Cl (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with saturated brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **12.8** (2.2 g, 63.0%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) 2.32-2.25 (m, 1H), 2.13 (s, 3H), 1.89-1.75 (m, 3H), 1.74-1.56 (m, 5H), 1.52-1.40 (m, 6H), 1.39-1.17 (m, 10H), 1.04-0.96 (m, 2H), 0.95-0.92 (m, 4H), 0.91-0.89 (m, 6H), 0.89-0.82 (m, 1H); **LC-ELSD/MS:** purity>99%,, MS ESI calcd. for $C_{25}H_{41}O$ $[M\text{-}H2O+H]^+$ 357.3, found 357.3.

Synthesis of 12.9

[0477] To a mixture of $MePPh_3Br$ (3.78 g, 10.6 mmol) in THF (16 mL) was added t-BuOK (1.18 g, 10.6 mmol) at 20°C under N_2. After stirring at 50°C for 30 min, **12.8** (1.0 g, 2.66 mmol) was added at 50°C. After stirring at 50°C for 16 h, the reaction mixture was quenched with saturated NH_4Cl aqueous (150 mL) at 20°C and extracted with EtOAc (2 x 100 mL). The combined organic phase was concentrated. The residue was purified by flash column (0~20% of EtOAc in PE) to give **12.9** (700 mg, 70.6%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.80 (s, 1H), 4.60 (d, *J*=2.0 Hz, 1H), 1.87-1.58 (m, 12H), 1.54-1.23 (m, 17H), 1.12-0.97 (m, 3H), 0.96-0.91 (m, 4H), 0.90 (s, 3H), 0.80 (s, 3H).

Synthesis of 12.10

[0478] To a solution of **12.9** (700 mg, 1.87 mmol) in DCM (10 mL) was added m-CPBA (758 mg, 3.74 mmol). After stirring at 20°C for 1h, the mixture was quenched by $NaHCO_3$ (20 mL, saturated) and $Na_2S_2O_3$ (20 mL, saturated). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated to give **12.10** (700 mg) as a solid, which was used as is.

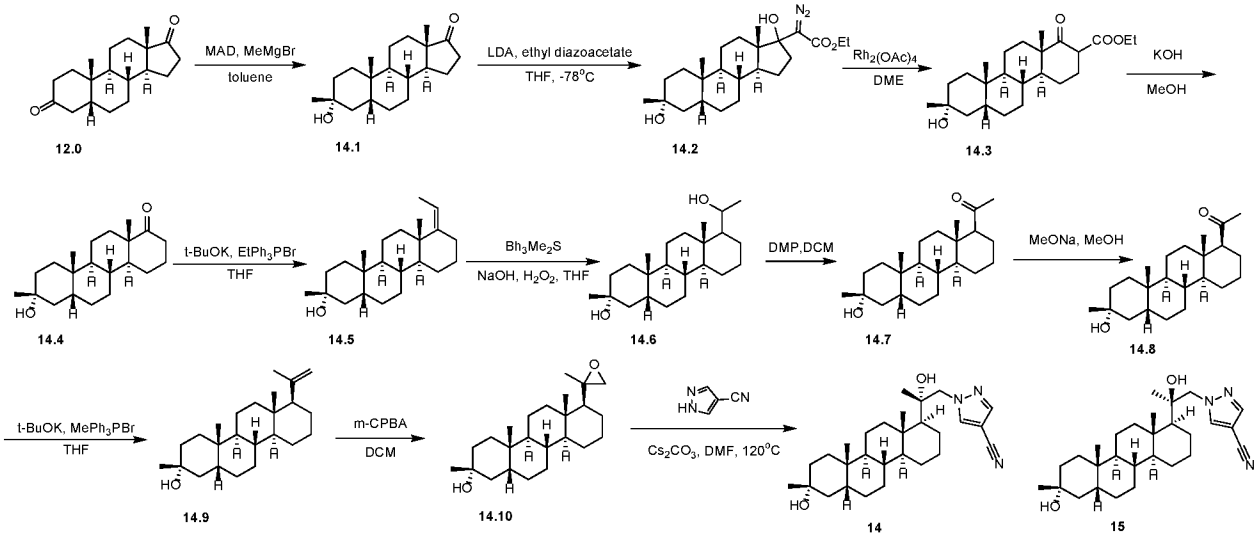
Synthesis of 12 & 13

[0479] To a solution of **12.10** (400 mg, 1.02 mmol) in DMF (20 mL) was added 1H-pyrazole-4-carbonitrile (189 mg, 2.04 mmol) and Cs_2CO_3 (668 mg, 2.04 mmol) at 20°C. After stirring at 120°C for 48 h, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column (5~40% EtOAc in PE) to give a mixture of diastereomers of **12 & 13** (350 mg, 71.2%) as a solid. **12 & 13** (350 mg, 0.7 mmol) was separated by SFC (column: DAICEL CHIRALCEL OJ-H (250mm*30mm,5um); Mobile phase: A: CO_2 B: 0.1%NH_3H_2O EtOH ; gradient: from 20% to 20% of B, FlowRate (ml/min): 60) to give **12** (41.0 mg, 11.7%) and **13** (98.4 mg, 28.1%) both as a solid.

[0480] **12: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.88 (s, 1H), 7.87 (s, 1H), 4.33-3.94 (m, 2H), 3.06 (s, 1H), 2.45-2.35 (m, 1H), 1.87-1.61 (m, 5H), 1.52-1.20 (m, 15H), 1.18 (s, 3H), 1.13-1.01 (m, 3H), 0.98 (s, 3H), 0.93 (t, *J*=7.2 Hz, 4H), 0.87 (s, 3H), 0.85-0.66 (m, 3H). **LC-ELSD/MS:** purity>99%, analytic SFC: 97.84% de; MS ESI calcd. for $C_{30}H_{44}N_3$ [M-$2H_2O$+H]$^+$ 446.4, found 446.4.

[0481] **13: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.91 (s, 1H), 7.79 (s, 1H), 4.39-4.19 (m, 2H), 2.40 (s, 1H), 2.36-2.29 (m, 1H), 1.91-1.63 (m, 7H), 1.53-1.41 (m, 7H), 1.40-1.10 (m, 13H), 0.98 (s, 3H), 0.96-0.91 (m, 7H), 0.90-0.85 (m, 4H); **LC-ELSD/MS:** purity>99%,, analytic SFC: 99.64% de; MS ESI calcd. for $C_{30}H_{44}N_3$ [M-$2H_2O$+H]$^+$ 446.4, found 446.4.

Example 14 & 15: Synthesis of 1-((S)-2-hydroxy-2-((1S,4aS,4bR,6aR,8R,10aS,10bS,12aS)-8-hydroxy-8,10a,12a-trimethyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile & 1-((R)-2-hydroxy-2-((1S,4aS,4bR,6aR,8R,10aS,10bS,12aS)-8-hydroxy-8,10a,12a-trimethyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile



Synthesis of 14.1

[0482] To the fresh prepared MAD (519 mmol) solution in toluene (1 L) was added a solution of **12.0** (50.0 g, 173 mmol) in DCM (200 mL) dropwise at -70°C. After stirring at -70°C for 1 h under N_2, MeMgBr (173 mL, 519 mmol, 3 M in ethyl ether) was added dropwise at -70°C. After stirring at -70°C for 2 h, the reaction mixture was poured into saturated aqueous citric acid (1000 mL) at 10°C and extracted with EtOAc (2 x 400 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 10/1 to 3/1) to afford **14.1** (36 g, 68%) as a solid. **^{1}HNMR** (400 MHz, $CDCl_3$) δ_H 2.48-2.38 (m, 1H), 2.13-2.02 (m, 1H), 1.98-1.85 (m, 3H), 1.83-1.69 (m, 2H), 1.63-1.43 (m, 8H), 1.39-1.14 (m, 10H), 1.12-1.02 (m, 1H), 0.97 (s, 3H), 0.84 (s, 3H).

Synthesis of 14.2

[0483] To the fresh prepared LDA (82.1 mmol) solution in THF (100 mL) was a solution of **14.1** (6 g, 19.7 mmol) and ethyl diazoacetate (12.4 g, 98.4 mmol, 90%) in THF (120 mL) at -70°C. After stirring at -70°C for 2 h, the reaction was quenched with acetic acid (5.61 mL, 98.4 mmol) in THF (15 mL), warmed to 20°C for 16 h, diluted with water (300 mL) and

extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~15% of EtOAc in PE) to give **14.2** (8.0 g, 97%) as an oil. **^{1}HNMR** (400 MHz, $CDCl_3$) δ_H 4.69 (br s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 2.18-2.08 (m, 1H), 2.04 (s, 1H), 2.01-1.93 (m, 1H), 1.91-1.78 (m, 2H), 1.76-1.63 (m, 2H), 1.60-1.38 (m, 9H), 1.35-1.29 (m, 4H), 1.28-1.23 (m, 5H), 1.14-0.98 (m, 4H), 0.94 (s, 3H), 0.89 (s, 3H).

Synthesis of 14.3

[0484] To a solution of **14.2** (8.0 g) in DME (100 mL) was added $Rh_2(OAc)_4$ (211 mg, 0.48 mmol) in one portion at 15°C. After stirring at 30°C for 12 h, the mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 60 mL). The combined organic phase was washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford **14.3** (7.7 g) as an oil. **^{1}HNMR** (400 MHz, $CDCl_3$) δ_H 12.41 (s, 1H), 4.24-4.15 (m, 2H), 3.74-2.27 (m, 2H), 2.22-2.11 (m, 1H), 1.98-1.69 (m, 5H), 1.57-1.35 (m, 8H), 1.32-1.24 (m, 9H), 1.22-1.01 (m, 7H), 0.96-0.90 (m, 3H).

Synthesis of 14.4

[0485] To a solution of **14.3** (7.7 g, 19.7 mmol) in MeOH (100 mL) was added KOH (6.62 g, 118 mmol) at 15°C. After stirring at 70°C for 1h, the reaction mixture was poured into saturated brine (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with HCl (1M, 100 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **14.4** (5.8 g, 93%) as a solid. **^{1}HNMR** (400 MHz, $CDCl_3$) δ_H 2.66-2.55 (m, 1H), 2.23-2.16 (m, 1H), 2.09-2.01 (m, 1H), 1.93-1.84 (m, 2H), 1.83-1.72 (m, 3H), 1.67-1.50 (m, 6H), 1.44-1.31 (m, 5H), 1.30-1.13 (m, 7H), 1.09-0.99 (m, 5H), 0.93 (s, 3H).

Synthesis of 14.5

[0486] To a mixture of Ph_3PEtBr (40.4 g,109 mmol) in THF (160 mL) was added t-BuOK (12.2 g, 21.8 mmol) at 20°C under N_2. After stirring at 40°C for 1 h, **14.4** (5.8 g, 18.2 mmol) was added. After stirring at 40°C for 2 h, the reaction mixture was quenched with 10% NH_4Cl aqueous (60 mL) at 20°C and extracted with EtOAc (2×100 mL). The combined organic phase was washed with brine (50 mL) dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~15% of EtOAc in PE) to give **14.5** (5.3 g, 88%) as an oil. **^{1}HNMR** (400 MHz, $CDCl_3$) δ_H 5.20-5.09 (m, 1H), 2.55-2.10 (m, 2H),

2.01-1.70 (m, 7H), 1.66-1.58 (m, 3H), 1.53-1.31 (m, 7H), 1.31-1.22 (m, 6H), 1.22-1.01 (m, 5H), 1.00-0.82 (m, 7H).

Synthesis of 14.6

[0487] To a solution of **14.5** (5.3 g, 16 mmol) in THF (80 mL) was added $BH_3.Me_2S$ (4.8 mL, 48 mmol, 10M) under N_2. After stirring at 20°C under N_2 for 12 h, the mixture was cool to 0°C and EtOH (16.5 mL, 288 mmol) and NaOH (57.6 mL, 5M, 288 mol) were added. H_2O_2 (28.8 mL, 10M, 288 mmol) was then added dropwise. After stirring at 70°C for 2 h, the mixture was cooled, poured into $Na_2S_2O_3$ (500 mL, sat.), stirred for 30 min, and extracted with EtOAc (2 x 200 mL). The combined organic layer was washed with saturated brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **14.6** (5.57 g) as a solid. **^{1}HNMR** (400 MHz, $CDCl_3$) δ_H 1.97-1.72 (m, 5H), 1.70-1.67 (m, 1H), 1.55-1.34 (m, 8H), 1.31-1.18 (m, 12H), 1.17-0.99 (m, 5H), 0.97-0.85 (m, 8H), 0.79-0.72 (m, 1H).

Synthesis of 14.7

[0488] To a solution of **14.6** (5.57 g, 15.9 mmol) in DCM (120 mL) was added DMP (13.4 g, 31.8 mmol) at 20°C. After stirring at 20°C for 1 h, the mixture was quenched by saturated $NaHCO_3$ aqueous (100 mL). The DCM phase was separated and washed with saturated $NaHCO_3/Na_2S_2O_3$ aqueous (1:1, 2 x 100 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~20% of EtOAc in PE) to give **14.7** (4.95 g, 90%) as an oil. **^{1}HNMR** (400 MHz, $CDCl_3$) δ_H 2.48-2.25 (m, 1H), 2.13 (d, J = 1.6 Hz, 3H), 1.98-1.87 (m, 1H), 1.86-1.65 (m, 5H), 1.63-1.43 (m, 8H), 1.42-1.28 (m, 5H), 1.24-1.14 (m, 5H), 1.08-0.92 (m, 3H), 0.91- 0.83 (m, 7H).

Synthesis of 14.8

[0489] To a solution of **14.7** (4.95 g, 14.2 mmol) in MeOH (80 mL) was added MeONa (15.2 g, 283 mmol) in one portion under N_2. After stirring at 80°C for 48 h, the mixture was diluted with H_2O (60 mL) and extracted with EtOAc (3 x 70 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford **14.8** (3.9 g) as a solid. **^{1}HNMR** (400 MHz, $CDCl_3$) δ_H 2.32-2.24 (m, 1H), 2.13 (s, 3H), 1.97-1.89 (m, 1H), 1.87-1.66 (m, 5H), 1.57-1.32 (m, 9H), 1.31-1.17 (m, 9H), 1.07-0.93 (m, 3H), 0.91-0.86 (m, 7H).

Synthesis of 14.9

[0490] To a mixture of $MePPh_3Br$ (12.3 g,34.6 mmol) in THF (50 mL) was added t-BuOK (3.87 g, 34.9 mmol) at 20°C under N_2. After stirring at 50°C for 1 h, **14.8** (2.0 g, 5.8mmol) was added at 50°C. After stirring at 50°C for 12 h, the reaction mixture was quenched with 10% NH_4Cl aqueous (100 mL) at 20°C and extracted with EtOAc (2×80 mL). The combined organic phase was washed with brine (40 mL) dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~10% of EtOAc in PE) to give **14.9** (1.6 g, 81%) as an oil. **^{1}HNMR** (400 MHz, $CDCl_3$) δ_H 4.80 (s, 1H), 4.60 (s, 1H), 1.98-1.89 (m, 1H), 1.86-1.74 (m, 3H), 1.69-1.55 (m, 5H), 1.54-1.47 (m, 3H), 1.47-1.36 (m, 5H), 1.30-1.24 (m, 6H), 1.17-0.92 (m, 6H), 0.90 (s, 3H), 0.89-0.84 (m, 3H), 0.80 (s, 3H).

Synthesis of 14.10

[0491] To a solution of **14.9** (1.5 g, 4.4 mmol) in DCM (30 mL) was added m-CPBA (1.76 g, 8.7 mmol, 85% purity) at 25°C under N_2. After stirring at 25°C for 4 h, the mixture was quenched by saturated $NaHCO_3$ aqueous (20 mL) and extracted with DCM (3 x 30 mL). The combined organic solution washed with saturated $NaHCO_3$/$Na_2S_2O_3$ aqueous (1:1, 30 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~20% of EtOAc in PE) to give **14.10** (1.52 g, 97%) as a solid. **^{1}HNMR** (400 MHz, $CDCl_3$) δ_H 2.73-2.62 (m, 2H), 1.87-1.72 (m, 5H), 1.68-1.58 (m, 5H), 1.50-1.30 (m, 8H), 1.25 (s, 3H), 1.22 (s, 3H), 1.07-0.96 (m, 2H), 0.93-0.88 (m, 8H), 0.87-0.71 (m, 4H).

Synthesis of 14 & 15

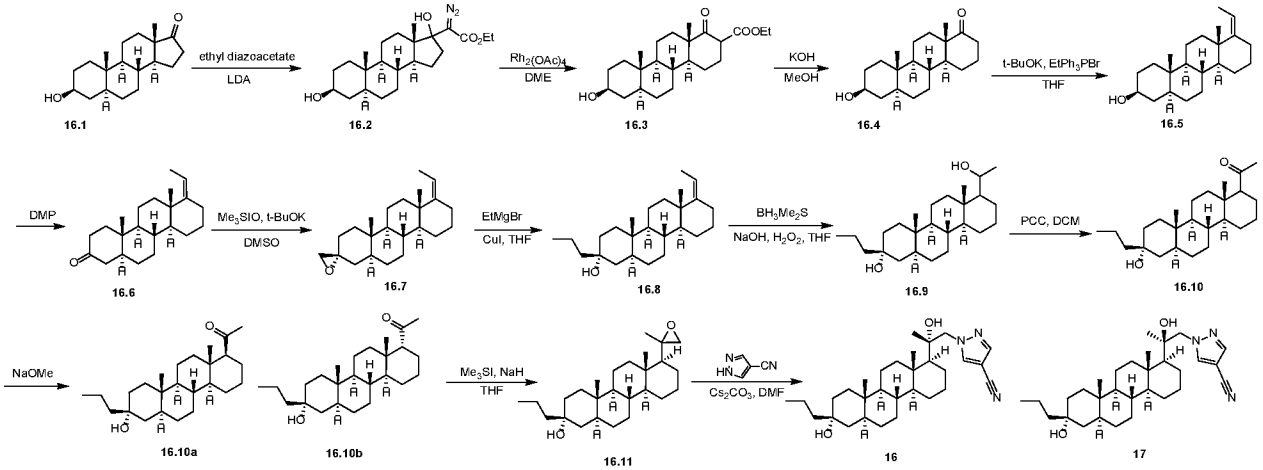
[0492] To a solution of **14.10** (1.52 g, 4.2 mmol) in DMF (30 mL) was added 1H-pyrazole-4-carbonitrile (587 mg, 6.3 mmol) and Cs_2CO_3(4.10 g, 12.6 mmol) under N_2. After stirring at 130°C for 72 h, the mixture was diluted with H_2O (40 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with H_2O (4 x 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~35% of EtOAc in PE) to give to give a mixture of diastereomers **14 & 15** (0.85 g) as a solid. **^{1}HNMR**(400 MHz, $CDCl_3$) δ_H 7.94-7.88 (m, 1H), 7.81-7.77 (m, 1H), 4.38-4.27 (m, 1H), 4.26-4.19 (m, 1H), 2.36-2.28 (m, 1H), 1.97-1.82 (m, 3H), 1.78-1.74 (m, 2H), 1.74-1.65 (m, 4H), 1.64-1.56 (m, 2H), 1.55-1.32 (m, 10H), 1.31-1.28 (m, 1H), 1.20-1.01 (m, 4H), 0.99-0.93 (m, 7H), 0.91-0.85 (m, 5H).

[0493] The diastereomers **14 & 15** (0.81 g) was separated by SFC (column: DAICEL CHIRALCEL OD-H (250mm*30mm,5um), A; CO_2; B: 0.1%NH_3H_2O EtOH; gradient: 30-30%, flow rate: 50 mL/min) to afford **14** (112 mg) and **15** (351.4 mg) both as solids.

[0494] **14: ^{1}HNMR**(400 MHz, $CDCl_3$) δ_H 7.89-7.87 (m, 1H), 7.87-7.86 (m, 1H), 4.33-4.23 (m, 1H), 4.03-3.90 (m, 1H), 3.07 (s, 1H), 2.44-2.36 (m, 1H), 1.95-1.86 (m, 1H), 1.84-1.65 (m, 4H), 1.51-1.44 (m, 3H), 1.43-1.34 (m, 5H), 1.29-1.20 (m, 6H), 1.20-1.16 (m, 4H), 1.07-0.99 (m, 2H), 0.99-0.89 (m, 5H), 0.89-0.83 (m, 4H), 0.83-0.66 (m, 3H); **LC-ELSD/MS:** purity 99%, analytic SFC: 99.74% de; MS ESI calcd. for $C_{28}H_{40}N_3$ $[M-2H_2O+H]^+$ 418.3, found 418.3.

[0495] **15: ^{1}HNMR**(400 MHz, $CDCl_3$) δ_H 7.91 (s, 1H), 7.79 (s, 1H), 4.38-4.30 (m, 1H), 4.26-4.19 (m, 1H), 2.41 (s, 1H), 2.37-2.30 (m, 1H), 1.97-1.71 (m, 6H), 1.66-1.59 (m, 1H), 1.55-1.35 (m, 9H), 1.30-1.13 (m, 8H), 1.08- 0.94 (m, 8H), 0.93-0.85 (m, 5H); **LC-ELSD/MS:** purity 99%, analytic SFC: 100% de; MS ESI calcd. for $C_{28}H_{40}N_3$ $[M-2H_2O+H]^+$ 418.3, found 418.3.

Example 16 & 17: Synthesis of 1-((S)-2-hydroxy-2-((1S,4aS,4bR,6aS,8R,10aS,10bS,12aS)-8-hydroxy-10a,12a-dimethyl-8-propyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile & 1-((R)-2-hydroxy-2-((1S,4aS,4bR,6aS,8R,10aS,10bS,12aS)-8-hydroxy-10a,12a-dimethyl-8-propyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile



Synthesis of 16.2

[0496] To a mixture of (3α,5α) 3-hydroxy-androstan-17-one, **16.1** (10 g, 34.4 mmol) in THF (100 mL) was added LDA (1 M, 160 mL, 160 mmol) at -70°C under N_2. After stirring at -70°C for 2 h, the reaction mixture was quenched with HOAc (10.2 g, 171 mmol) in THF (100 mL) at 0°C. After warming slowly to rt overnight, the reaction was diluted with water (400 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give **16.2** (15 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.82 (s, 3H), 0.91 (s, 3H), 0.95-1.01 (m, 1H), 1.05-1.15 (m, 2H), 1.26-1.33 (m, 6H), 1.35-1.52 (m, 6H), 1.54-1.73 (m, 6H), 1.74-1.92 (m, 4H), 2.11-2.22 (m, 1H), 3.55-2.60 (m, 1H), 4.20-4.28 (m, 2H), 4.69 (s, 1H).

Synthesis of 16.3

[0497] To a solution of **16.2** (10 g, 24.7 mmol) and DME (200 mL) was added $Rh_2(OAc)_4$ (196 mg, 0.4445 mmol) in one portion at 15 °C. After stirring at 15°C for 16 h under N_2, the reaction mixture was concentrated to give **16.3** (10.5 g) as solid, which was used directly for the next step without purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.65-0.88 (m, 4H), 0.93-1.12 (m, 7H), 1.21-1.38 (m, 7H), 1.37-1.28 (m, 6H), 1.64-1.88 (m, 5H), 1.91-2.36 (m, 4H), 3.51-3.63 (m, 1H), 4.12-4.26 (m, 2H).

Synthesis of 16.4

[0498] To a solution of NaOH (2.64 g, 66.0 mmol) in H_2O (20 mL) was added **16.3** (5 g, 13.2 mmol) in MeOH (100 mL) /THF (30mL). After stirring at 60°C for 16 h, the reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layer was washed with HCl (1M, 100 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by trituration with EtOAc/PE (3:1, 100 mL) at 15 °C to give **16.4** (2.5 g, 50%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.62-0.65 (m, 1H), 0.79 (s, 3H), 1.08 (s, 3H), 1.24-1.38 (m, 6H), 1.41-1.63 (m, 9H), 1.72-1.85 (m, 6H), 2.02-2.08 (m, 1H), 2.16-2.25 (m, 1H), 2.58-2.66 (m, 1H), 3.52-3.63 (m, 1H).

Synthesis of 16.5

[0499] To a suspension of Ph_3PEtBr (29.1 g, 78.6 mmol) in anhydrous THF (25 mL) was added t-BuOK (8.8 g, 78.6 mmol) at 25°C under N_2. After stirring at 45°C for 30 min, a solution of **16.4** (4 g, 13.1 mmol) in anhydrous THF (25 mL) was dropwise. After stirring for 12 h, the reaction mixture was combined with another batch prepared from 4 g of **16.4**. The combined mixture was cooled and poured into ice-water (600 mL) stirred for 10 min. The aqueous phase was extracted with EtOAc (2 x 400 mL). The combine organic phase was washed with brine (2 x 400 mL), filtered and concentrated. The residue was purified by flash column (0~30% of EtOAc in PE) to give **16.5** (9 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.57-0.72 (m, 1H), 0.57-0.73 (m, 1H), 0.77-0.80 (m, 3H), 0.90-0.96 (m, 3H), 0.97-1.01 (m, 1H), 1.03-1.09 (m, 3H), 1.16-1.42 (m, 6H), 1.53-1.62 (m, 5H), 1.66-1.75 (m, 4H), 1.80-1.90 (m, 3H), 1.92-2.04 (m, 1H), 2.11-2.33 (m, 2H), 2.45-2.54 (m, 1H), 3.44-3.66 (m, 1H), 5.08-5.23 (m, 1H).

Synthesis of 16.6

[0500] To a solution of **16.5** (9 g, 28.4 mmol) in DCM (100 mL) was added DMP (24 g, 56.8 mmol). After stirring at 25°C for 2 h, the mixture was quenched with saturated $NaHCO_3$ aqueous (50 mL) at 10°C. The DCM phase was separated and washed with saturated $NaHCO_3/Na_2S_2O_3$ aqueous (1:1, 2 x 100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified with MeCN (210 mL) at 82°C to give **16.6** (8 g, 89.5%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.69-0.92 (m, 3H), 0.94 (s, 1H), 0.97-1.01 (m, 3H), 1.05-1.19 (m, 4H), 1.31-1.48 (m, 5H), 1.55-1.61 (m, 2H), 1.64-1.76 (m, 3H), 1.80-2.12 (m, 5H), 2.13-2.46 (m, 4H), 2.46-2.55 (m, 1H), 2.82 (dd, J = 16.44, 2.13 Hz, 1H), 3.27 (br d, J = 16.56 Hz, 1H), 5.10-5.24 (m, 1H).

Synthesis of 16.7

[0501] To a stirred solution of trimethylsulfoxonium iodide (11.1 g, 50.8 mmol) in DMSO (100 mL) was added t-BuOK (7.12 g, 63.5 mmol). After stirring at 25°C for 1.0 h under N_2, **16.6** (8 g, 25.4 mmol) was added. After stirring at 60°C for 12 h, the reaction was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with water (2 x 100 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column (PE/EtOAc = 0~30%) to afford **16.7** (4 g, 47.9%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H

0.81-0.84 (m, 4H), 0.93 (s, 2H), 0.95-0.98 (m, 1H), 1.03-1.07 (m, 2H), 1.22-1.38 (m, 8H), 1.38-1.46 (m, 2H), 1.62-1.69 (m, 2H), 1.70-1.78 (m, 4H), 1.79-1.94 (m, 4H), 1.98-2.09 (m, 2H), 2.11-2.23 (m, 1H), 2.46-2.54 (m, 1H), 2.59-2.64 (m, 2H), 5.11-5.21 (m, 1H).

Synthesis of 16.8

[0502] To a solution of **16.7** (4 g, 12.1 mmol) in THF (50 mL) was added CuI (1.15 g, 6.05 mmol), then EtMgBr (12.1 mL, 3 M, 36.3 mmol) at 0°C. After stirring at 0°C for 1 h, the mixture was poured into water (200 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **16.8** (3.2 g, 73.9%) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.69-0.74 (m, 3H), 0.77-0.83 (m, 1H), 0.87-0.95 (m, 5H), 1.02-1.17 (m, 5H), 1.18-1.32 (m, 8H), 1.38 (br d, J = 3.26 Hz, 4H), 1.48-1.54 (m, 1H), 1.58 (br t, J = 2.64 Hz, 5H), 1.62-1.70 (m, 3H), 1.71-1.77 (m, 2H), 1.79-1.94 (m, 2H), 2.10-2.26 (m, 1H), 2.49 (br d, J = 14.05 Hz, 1H), 5.10-5.20 (m, 1H).

Synthesis of 16.9

[0503] To a solution of **16.8** (3.2 g, 8.92 mmol) in THF (30 ml) was added $BH_3.Me_2S$ (2.67 ml, 26.7 mmol) at 25°C. After stirring at 45°C for 2 h, the reaction mixture was cooled and quenched by EtOH (4.10 g, 89.2 mmol, 0.789 g/ml) at 0°C and then NaOH (1.78 mL, 5M, 8.92 mmol) H_2O_2 (10.1 g, 89.2 mmol, 1.13 g/mL, 30% in water) was added slowly until the inner temperature no longer rises and the inner temperature was maintained below 30°C. After stirring at 60°C for 1 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (100 mL) and stirred at 0°C for 1 hour. The reaction was checked by potassium iodide-starch test paper to confirm excess H_2O_2 was destroyed (did not changed to blue). The aqueous phase was extracted with DCM (3 x 100 mL). The combine organic phase was washed with saturated $Na_2S_2O_3$ (2 x 100 mL), brine (2 x 100 mL), dried over anhydrous Na_2SO_4 filtered and concentrated to give **16.9** (3.5 g) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.61-0.66 (m, 3H), 0.70 (s, 1H), 0.68-0.72 (m, 1H), 0.72-0.78 (m, 2H), 0.81-0.89 (m, 5H), 0.90 (s, 1H), 0.93-1.01 (m, 1H), 1.03 (d, J = 6.27 Hz, 1H), 1.09 (br d, J = 6.53 Hz, 2H), 1.13-1.25 (m, 9H), 1.26 (br s, 1H), 1.31 (br d, J = 3.01 Hz, 4H), 1.39 (br d, J = 3.76 Hz, 2H), 1.45 (br d, J = 11.29 Hz, 2H), 1.47-1.64 (m, 6H), 1.71-1.87 (m, 2H), 2.55 (s, 1H).

Synthesis of 16.10

[0504] To a solution of **16.9** (3.5 g, 9.29 mmol) in DCM (100 mL) at 25°C was added silica gel (3.98 g) and PCC (3.98 g, 18.5 mmol). After stirring at 25°C for 2 h, the resulting mixture was filtered through a pad of silica gel and the filter cake was washed with DCM (40 mL x 5). The combined filtrates were concentrated to give **16.10** (2.5 g, 71.8%) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.63 (d, J = 1.00 Hz, 3H), 0.69-0.81 (m, 3H), 0.85 (br d, J = 0.75 Hz, 6H), 1.01-1.11 (m, 2H), 1.19 (t, J = 7.15 Hz, 5H), 1.29-1.33 (m, 4H), 1.35-1.49 (m, 7H), 1.54 (s, 3H), 1.56-1.81 (m, 4H), 2.06 (d, J = 5.27 Hz, 3H), 2.22 (dd, J = 12.80, 3.26 Hz, 1H), 2.39 (d, J = 5.27 Hz, 1H).

Synthesis of 16.10a & 16.10b

[0505] To a solution of **16.10** (250 mg, 0.667 mmol) in MeOH (10 mL, 0.667 mmol) was added methoxysodium (718 mg, 13.3 mmol) in one portion. After stirring at 70°C for 12 h, the mixture was cooled and concentrated in reduced pressure at 25°C. The residue was poured into ice-water (20 mL) and stirred for 20 min. The aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by pre-HPLC (Column:Welch Xtimate C18 150*25mm*5um; Condition: water (0.225% FA)-ACN; Begin B: 80%; End B:100%) to afford **16.10a** (22 mg, 8.8%) and **16.10b** (6.1 mg, 2.44%) as solids.

[0506] **16.10: ^{1}H NMR** (400 MHz, $CDaCl_3$) δ_H 0.72 (s, 3H), 0.76-0.88 (m, 3H), 0.90-1.01 (m, 7H), 1.13-1.20 (m, 1H), 1.22 (br d, J = 4.02 Hz, 1H), 1.23-1.26 (m, 3H), 1.28 (br s, 1H), 1.29-1.33 (m, 2H), 1.38-1.44 (m, 5H), 1.45-1.62 (m, 9H), 1.65-1.79 (m, 1H), 1.80-1.90 (m, 2H), 2.16 (s, 3H), 2.31 (dd, J = 12.67, 3.14 Hz, 1H),. **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{25}H_{41}O_1$ $[M\text{-}H_2O+H]^+$ 357.3 found 357.3.

[0507] **16.10b: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.67-0.72 (m, 4H), 0.78-0.86 (m, 2H), 0.88-0.95 (m, 8H), 1.08-1.16 (m, 2H), 1.17-1.24 (m, 5H), 1.24-1.31 (m, 5H), 1.36-1.38 (m, 4H), 1.41-1.46 (m, 4H), 1.51 (br d, J = 3.76 Hz, 2H), 1.66-1.88 (m, 2H), 2.12 (s, 3H), 2.46 (d, J = 5.27 Hz, 1H),. **LC-ELSD/MS** purity 98%, MS ESI calcd. for $C_{25}H_{41}O_1$ $[M\text{-}H_2O+H]^+$ 357.3 found 357.3.

Synthesis of 16.11

[0508] To a stirred solution of trimethylsulfanium (108 mg, 0.532 mmol) in DMSO (5 mL) was added NaH (21.1 mg, 0.532 mmol) at 25°C. After stirring for 1.0 h under N_2. **16.10a** (100 mg, 0.266 mmol) was added. After stirring at 60°C for 12 h, the mixture was poured into water (10 mL), stirred for 20 min, and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **16.11** (180 mg) as an oil. The residue was purified by flash column (0~30% of EtOAc in PE) to give **16.12** (60 mg) as a solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.71 (s, 3H), 0.74-0.84 (m, 4H), 0.85-0.97 (m, 8H), 1.13 (br d, J = 12.55 Hz, 3H), 1.22 (s, 5H), 1.27-1.34 (m, 3H), 1.38 (br d, J = 3.51 Hz, 4H), 1.41-1.53 (m, 5H), 1.59-1.69 (m, 1H), 1.73 (br d, J = 12.55 Hz, 1H), 1.70-1.77 (m, 1H), 1.82 (br s, 2H), 1.91-1.98 (m, 1H), 2.37 (s, 1H), 2.63 (d, J = 4.77 Hz, 1H), 2.70-2.73 (m, 1H).

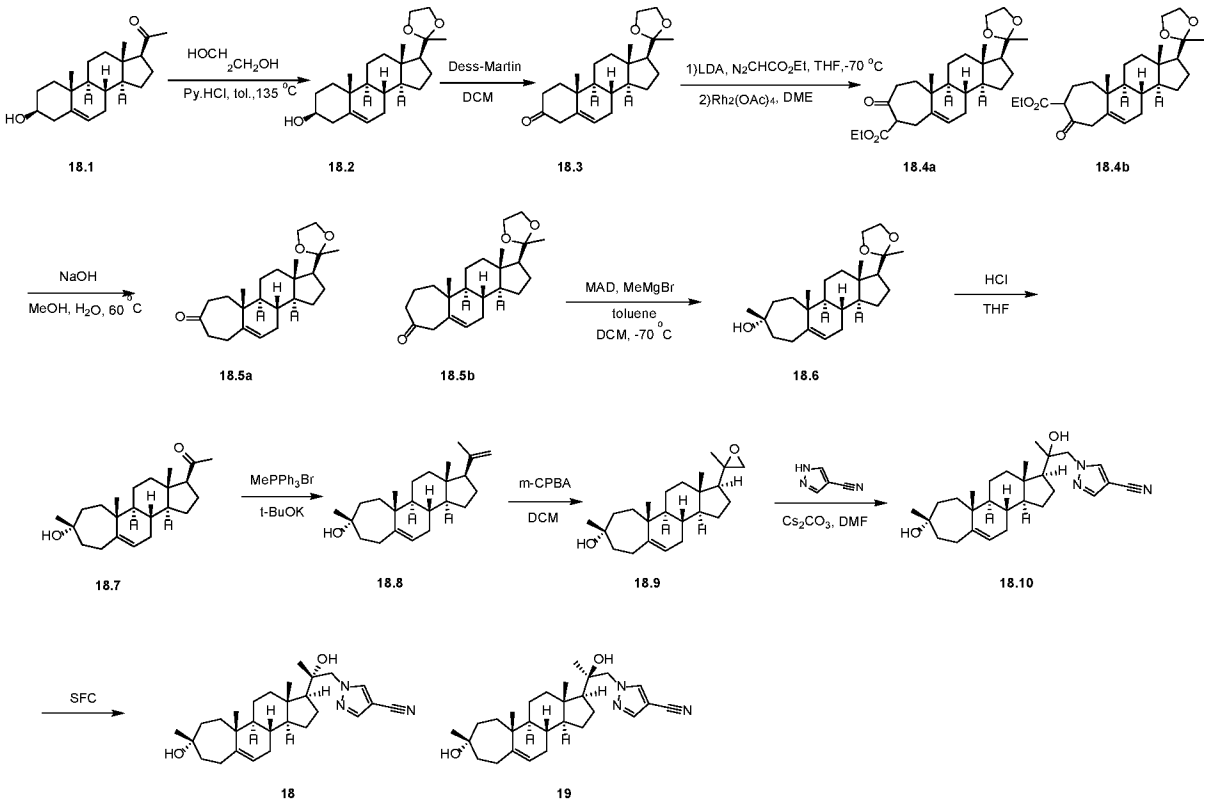
Synthesis of 16 & 17

[0509] To a solution of **16.11** (60 mg, 0.154 mmol) in DMF (3 mL) was added 1H-pyrazole-4-carbonitrile (28.6 mg, 0.308 mmol) and Cs_2CO_3 (100 mg, 0.308 mmol) at 20°C. After stirring at 130°C for 12 h, the mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was separated, concentrated to give mixture of diastereomers **16 & 17** (30 mg) as a solid. The diastereomers were separated by SFC (Column: DAICEL CHIRALPAK AD (250mm*30mm, 10um); Condition: 0.1%NH_3H_2O IPA; Begin B:60%; End B:60%) to afford **16** (5.1 mg, 17.0%) and **17** (2.6 mg, 8.369%) as solids.

[0510] **16: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.68 (s, 3H), 0.73-0.94 (m, 7H), 0.99 (s, 3H), 1.06-1.28 (m, 14H), 1.35-1.52 (m, 11H), 1.66 (br d, J = 16.06 Hz, 1H), 1.80 (br t, J = 13.80 Hz, 2H), 2.37 (br d, J = 12.05 Hz, 1H), 2.98 (s, 1H), 3.92-4.32 (m, 2H), 7.86 (d, J = 19.58 Hz, 2H),. **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{30}H_{44}N_3$ $[M-2H_2O+H]^+$ 446.4 found 446.4. **SFC** 100% de.

[0511] **17: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 0.63 (s, 3H), 0.69-0.86 (m, 7H), 0.88 (s, 3H), 0.92 (s, 3H), 1.01-1.24 (m, 11H), 1.27-1.42 (m, 10H), 1.61-1.84 (m, 4H), 2.25 (br d, J = 12.55 Hz, 1H), 2.38 (s, 1H), 4.11-4.34 (m, 2H), 7.64-7.91 (m, 2H),. **LC-ELSD/MS** purity 99%, MS ESI calcd. For $C_{30}H_{44}N_3$ $[M-2H_2O+H]^+$ 446.3 found 446.3.

Example 18 & 19: 1-((S)-2-hydroxy-2-((1S,3aS,3bS,8S,10aR,10bS,12aS)-8-hydroxy-8,10a,12a-trimethyl-1,2,3,3a,3b,4,6,7,8,9,10,10a,10b,11,12,12a-hexadecahydrocyclohepta[a]cyclopenta[f]naphthalen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (18) & 1-((R)-2-hydroxy-2-((1S,3aS,3bS,8S,10aR,10bS,12aS)-8-hydroxy-8,10a,12a-trimethyl-1,2,3,3a,3b,4,6,7,8,9,10,10a,10b,11,12,12a-hexadecahydrocyclohepta[a]cyclopenta[f]naphthalen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (19)



Synthesis of 18.2

[0512] To a solution of **18.1** (50.0 g, 157 mmol) in toluene (500 mL) was added pyridine.HCl (3.61 g, 31.4 mmol) and ethane-1,2-diol (48.7 g, 785 mmol). The mixture was stirred at 135°C for 48 hrs to remove water by Dean-Stark trap. The mixture was concentrated under reduced pressure. The residue was triturated from EtOAc (150 mL) to give the product **18.2** (35.0 g, 62%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.35 (d, J = 5.2 Hz, 1H), 4.03-3.83 (m, 4H), 3.58-3.47 (m, 1H), 2.34-2.17 (m, 2H), 2.10-1.92 (m, 2H), 1.88-1.61 (m, 6H), 1.53-1.43 (m, 5H), 1.30 (s, 3H), 1.23-1.06 (m, 3H), 1.01 (s, 3H), 0.96-0.84 (m, 3H), 0.78 (s, 3H).

Synthesis of 18.3

[0513] To a solution of **18.2** (10.0 g, 27.7 mmol) in DCM (200 mL) was added Dess-Martin reagent (35.2 g, 83.1 mmol). The reaction mixture was stirred at 20 °C for 1 hr. The reaction mixture was quenched with saturated $NaHCO_3$ (500 mL) and saturated $Na_2S_2O_3$ (200 mL) at 0°C and stirred for 20 min. The mixture was extracted with DCM (2 x 200 mL). The combined organic layer was washed with saturated $NaHCO_3$ (2 x 200 mL) and saturated brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give the product **18.3** (11.0 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.40-5.30 (m, 1H), 4.02-3.87 (m, 4H), 3.28 (d, J = 16.4 Hz, 1H), 2.82 (dd, J = 2.0, 16.4 Hz, 1H), 2.53-2.42 (m, 1H), 2.34-2.26 (m, 1H), 2.13-1.99 (m, 3H), 1.85-1.68 (m, 4H), 1.55-1.42 (m, 4H), 1.31-1.24 (m, 6H), 1.19 (s, 3H), 1.08-1.00 (m, 2H), 0.81 (s, 3H).

Synthesis of 18.4a and 18.4b

[0514] A cold (-70 °C) LDA solution (139 mL, 1.0 M, 139 mmol, fresh prepared) was added to a stirred solution of **18.3** (10.0 g, 27.8 mmol) and ethyl diazoacetate (15.8 g, 139 mmol) in THF (160 mL) at -70°C. The mixture was stirred at -70°C for 2h. Then acetic acid (8.34 g, 139 mmol) in THF (40 mL) was added, the mixture was then warmed to 20°C and stirred for 16 hrs. Water (300 mL) and PE (200 mL) was added, the organic phase was separated and the aqueous phase was extracted with EtOAc (150 mL). The combined organic layers were washed with saturated brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give the product (13 g), which was used directly in next step. To a solution of the product (12 g, 25.3 mmol) in DME (100 mL) was added $Rh_2(OAc)_4$ (335 mg, 0.76 mmol). The reaction mixture was stirred at 25 °C for 16 hrs to give a solution. The reaction mixture was concentrated. The residue was purified by silica gel chromatography (0-20% of EtOAc in PE) to give the mixture product **18.4a** and **18.4b** (6.80 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 12.8-12.6 (m, 0.2H), 5.69-5.44 (m, 1H), 4.29-4.10 (m, 2H), 4.04-3.82 (m, 4H), 3.44-3.17 (m, 0.8H), 2.99-2.65 (m, 1H), 2.48-1.96 (m, 4H), 1.85-1.61 (m, 6H), 1.55-1.40 (m, 3H), 1.34-1.14 (m, 12H), 1.02-0.96 (m, 3H), 0.79 (s, 3H).

Synthesis of 18.5a and 18.5b

[0515] To a mixture of **18.4a** and **18.4b** (6.80 g, 15.2 mmol) in MeOH (150 mL) was added H_2O (50 mL) and NaOH (6.08 g, 152 mmol). The reaction mixture was stirred at 60 °C for 16 hrs to give a mixture. The reaction mixture was concentrated. Then H_2O (150 mL) was

added. The mixture was extracted with EtOAc (3 x 150 mL). The combined organic phase was washed with saturated brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (0-2% of EtOAc in DCM) to give the product **18.5a** (1.5 g, 26%) and the product **18.5b** (900 mg, 16%).

[0516] **18.5a: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.57 (d, J = 4.4 Hz, 1H), 4.04-3.82 (m, 4H), 2.67-2.56 (m, 1H), 2.49-2.25 (m, 4H), 2.20-1.97 (m, 3H), 1.84-1.59 (m, 7H), 1.56-1.37 (m, 3H), 1.30 (s, 3H), 1.26-1.03 (m, 4H), 1.00 (s, 3H), 0.79 (s, 3H).

[0517] **18.5b:^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.56 (d, J = 4.4 Hz, 1H), 4.05-3.83 (m, 4H), 3.25 (d, J = 14.0 Hz, 1H), 2.82 (d, J = 14.4 Hz, 1H), 2.65-2.53 (m, 1H), 2.24-2.01 (m, 3H), 1.89-1.60 (m, 7H), 1.57-1.39 (m, 4H), 1.30 (s, 3H), 1.28-1.02 (m, 5H), 0.99 (s, 3H), 0.79 (s, 3H).

Synthesis of 18.6

[0518] To a solution of BHT (10.6 g, 48.3 mmol) in toluene (100 mL) under nitrogen at 0°C was added trimethylaluminum (2 M in toluene, 12.0 mL, 24.1 mmol) dropwise. The mixture was stirred at 25°C for 1 h and used directly as a solution of MAD without further purification. To the MAD solution was added a solution of **18.5a** (3.0 g, 8.0 mmol) in anhydrous DCM (20 mL) drop-wise at -70°C. After stirring at -70°C for 1h under N_2, MeMgBr (8.03 mL, 24.1 mmol, 3M in ethyl ether) was added dropwise at -70°C. The resulting solution was stirred at -70°C for another 2h. The reaction mixture was poured into saturated aqueous citric acid (100 mL) below 10°C and extracted with EtOAc (2 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give product. The product was purified together with another batch (from 300 mg of **18.5a**). The residue was triturated from PE (20 mL) at 20°C to give **18.6** (3.3 g), which was used without further purification and used directly for the next step.

Synthesis of 18.7

[0519] To a solution of **18.6** (3.30 g, 8.5 mmol) in THF (50 mL) was added 12M HCl (3 mL, 36.0 mmol). The reaction mixture was stirred at 20°C for 16 hours to give a solution. The reaction mixture was diluted with H_2O (50 mL) and adjust to pH = 9 with solid Na_2CO_3 (20 g). The product was extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give the product. The product was purified by flash column (20~100% of EtOAc in PE) to provide **18.7** (600 mg) as a solid.

[0520] **18.7:^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.40 (d, J = 3.6 Hz, 1H), 2.53 (t, J = 8.8 Hz, 1H), 2.28-2.17 (m, 2H), 2.12 (s, 3H), 2.10-2.01 (m, 2H), 1.92-1.50 (m, 8H), 1.49-1.32 (m, 6H), 1.30-1.19 (m, 7H), 0.91 (s, 3H), 0.63 (s, 3H).

Synthesis of 18.8

[0521] To a mixture of $MePPh_3Br$ (7.75g, 21.7 mol) in THF (30 mL) was added t-BuOK (2.43 g, 21.7 mol) at 25°C under N_2. The resulting mixture was stirred at 50°C for 30 min. Compound **18.7** (2.50 g, 7.25 mol) was added in portions keeping the temperature below 50°C. The reaction mixture was stirred at 60°C for 16 hours to give a suspension. The reaction mixture was quenched with 10% NH_4Cl aqueous (50 mL) at 25°C. The organic layer was separated. The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic phase was concentrated under reduced pressure to give a solid, which was purified by silica gel chromatography (0-50% of EtOAc in PE) to give **18.8** (2.50 g, 99%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.50-5.41 (m, 1H), 4.85 (s, 1H), 4.71 (s, 1H), 2.10-1.94 (m, 3H), 1.93-1.77 (m, 4H), 1.76 (s, 3H), 1.75-1.64 (m, 3H), 1.63-1.56 (m, 2H), 1.55-1.31 (m, 6H), 1.31-1.26 (m, 2H), 1.25 (s, 3H), 1.24-1.05 (m, 5H), 0.89 (s, 3H), 0.59 (s, 1H).

Synthesis of 18.9

[0522] To a solution **18.8** (300 mg, 0.875 mmol) in DCM (5 mL), was added m-CPBA (188 mg, 0.875 mmol). The resulting mixture was stirred at 20°C for 2 h. The mixture was quenched with saturated $NaHCO_3$ aqueous (100 mL) at 20°C. The DCM phase was separated and washed with saturated $NaHCO_3$/$Na_2S_2O_3$ aqueous (1:1, 2 x 100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **18.9** (350 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.46 (s, 1H), 4.85 (s, 1H), 4.70 (s, 2H), 2.89 (d, J=4.4 Hz, 1H), 2.59-2.48 (m, 1H), 2.59-2.48 (m, 1H), 2.32 (d, J=4.8 Hz, 1H), 2.26-2.17 (m, 2H), 2.00-1.79 (m, 6H), 1.70-1.64 (m, 4H), 0.98 (s, 8H), 0.89 (s, 2H), 0.81 (s, 1H), 0.69 (s, 3H), 0.58 (s, 5H).

Synthesis of 18 and 19

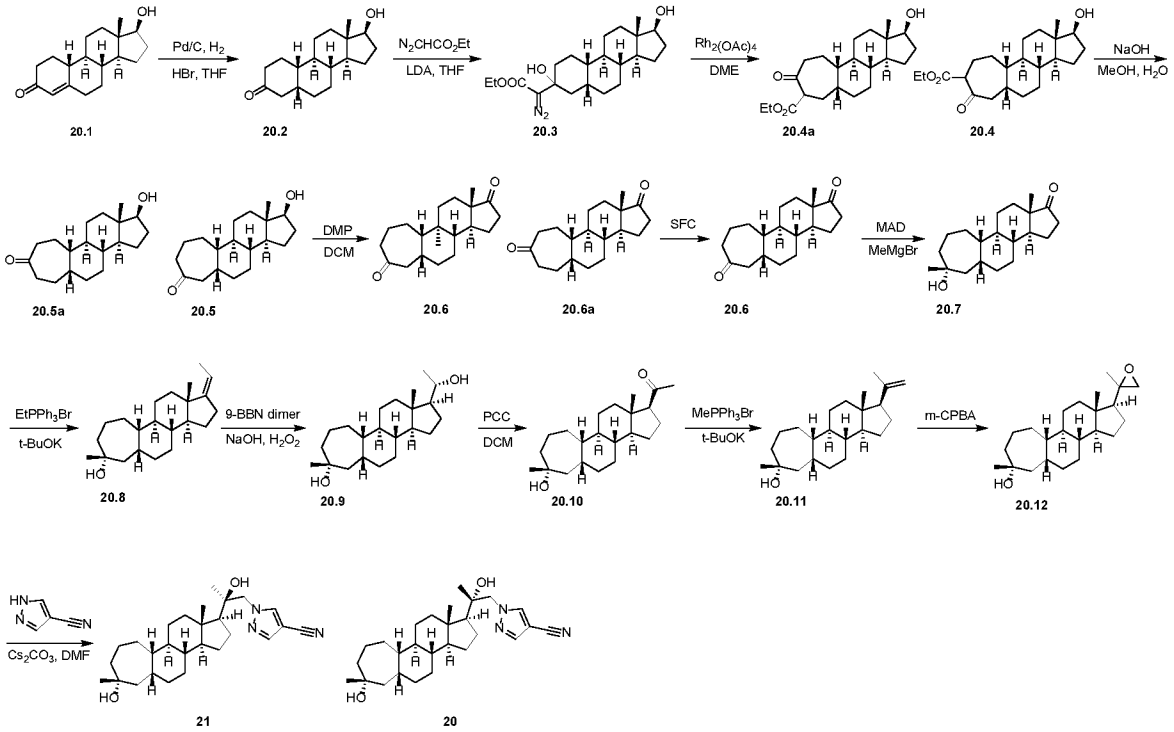
[0523] A solution of **18.9** (350 mg, 0.98 mmol), Cs_2CO_3 (957 mg, 2.92 mmol) and 1H-pyrazole-4-carbonitrile (181 mg, 1.95 mmol) in DMF (10 mL) was stirred at 120°C for 16 hours. The mixture was added into saturated NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with LiCl (50 mL, 3% in water), saturated brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and

concentrated. The residue was purified by silica gel chromatography (0-20% of acetone in DCM) to yield **18.10** (70mg) which was purified by SFC (Column: Phenomenex-Cellulose-2 (250 mm* 30 mm, 10 um); Condition: 0.1%NH_3H_2O EtOH; Begin B: 45%; End B: 45%; Gradient Time(min): n/a; 100%B Hold Time(min): n/a; Flow Rate(ml/min); 70) to afford **18** (40.3 mg, 57.6%) and **19** (17.3 mg, 24.7%).

[0524] **18: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.82 (s, 1H), 5.46 (d, *J*=4.0 Hz, 1H), 4.36 (d, *J*=13.6 Hz, 1H), 4.09 (d, *J*=13.6 Hz, 1H), 2.50 (s, 1H), 2.11-1.94 (m, 3H), 1.93-1.84 (m, 2H), 1.82-1.63 (m, 4H), 1.61-1.55 (m, 2H), 1.54-1.34 (m, 6H), 1.28-1.25 (m, 2H), 1.25 (s, 3H), 1.23-1.00 (m, 4H), 0.98 (s, 3H), 0.94 (s, 3H), 0.89 (s, 3H).**LCMS** purity≥99%, MS ESI calcd. for $C_{28}H_{38}N_3$ $[M-2H_2O+H]^+$ 416.3, found 416.3.

[0525] **19: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.83 (s, 1H), 5.48 (d, *J*=4.0 Hz, 1H), 4.23-4.16 (m, 1H), 4.07-4.00 (m, 1H), 2.31 (s, 1H), 2.16-1.85 (m, 6H), 1.79-1.67 (m, 3H), 1.65-1.57 (m, 4H), 1.56-1.35 (m, 8H), 1.32-1.28 (m, 2H), 1.27 (s, 3H), 1.26-1.13 (m, 4H), 1.13 (s, 3H), 1.11-1.04 (m, 1H), 0.92 (d, *J*=2.4 Hz, 6H).**LCMS** purity≥99%, MS ESI calcd. for $C_{28}H_{38}N_3$ $[M-2H_2O+H]^+$ 416.3, found 416.3.

Example 20 & 21: 1-((S)-2-hydroxy-2-((1S,3aS,3bR,5aR,7R,10aS,10bR,12aS)-7-hydroxy-7,12a-dimethyloctadecahydrocyclohepta[a]cyclopenta[f]naphthalen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (20) & 1-((R)-2-hydroxy-2-((1S,3aS,3bR,5aR,7R,10aS,10bR,12aS)-7-hydroxy-7,12a-dimethyloctadecahydrocyclohepta[a]cyclopenta[f]naphthalen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (21)



Synthesis of 20.2

[0526] To a solution of **20.1** (10 g, 36.4 mmol) in THF (50 mL) was added Pd/C (1 g, dry) and HBr (0.5 mL). The reaction mixture was degassed under reduced pressure and purged with H_2 for five times. The mixture was stirred at 20°C for 16 hrs under H_2. The reaction mixture was filtered through a pad of Celite and washed with THF (5 x 20 mL). The filtrate was concentrated. The residue was triturated from petroleum ether (10 mL) at 20°C to give **20.2** (10.31 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.75-3.65 (m, 2H), 2.61-2.54 (m, 1H), 2.23-2.04 (m, 6H), 1.87-1.62 (m, 6H), 1.52-1.46 (m, 3H), 1.29-1.07 (m, 7H), 0.77 (s, 3H).

Synthesis of 20.3

[0527] To a solution of diisopropylamine (27.9 g, 276 mmol) in anhydrous THF (110 mL) under nitrogen at -70°C was added n-BuLi (2.5 M in hexane, 110 mL, 276 mmol) dropwise. The mixture was stirred at -70°C for 20 min. To a solution of **20.2** (20 g, 55.4 mmol) in THF (600 mL) was added ethyl diazoacetate (31.4 g, 276 mmol) under N_2 atmosphere. Then the freshly prepared LDA (276 mmol) was added dropwise at -70°C. The mixture was stirred at -70°C for 4 hours. Then acetic acid (22.0 g, 276 mmol) in THF (100 mL) was added to quench the reaction at -70°C. The mixture was then warmed to 25°C and stirred for 12 h. Water (200 mL) was added. The aqueous solution was extracted with EtOAc

(2 x 600 mL). The combined organic layer was washed with brine (1000 mL), dried over Na_2SO_4, and concentrated to give **20.3** (40.0 g).

Synthesis of 20.4 & 20.4a

[0528] To a solution of **20.3** (30.0 g) in DME (300 mL) was added $Rh_2(OAc)_4$ (373 mg, 0.84 mmol) at 25°C. The reaction mixture was stirred at 40°C for 12 hours. The reaction mixture was concentrated under reduced pressure to give **20.4 & 20.4a** (30.0 g).

Synthesis of 20.5 & 20.5a

[0529] To a mixture of **20.4 & 20.4a** (30.0 g, 82.7 mmol) in MeOH/THF /H_2O (200 mL/200 mL/50 mL) was added NaOH (33.0 g, 827 mmol). The reaction mixture was stirred at 70°C for 12 hour. The reaction mixture was extracted with ethyl acetate (2 x 500 mL). The combined organic phase was washed with water (500 mL), brine (600 mL), dried over Na_2SO_4, filtered and concentrated to give **20.5 & 20.5a** (20.0 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.67 (br s, 1 H), 3.05 (t, J=12.67 Hz, 1 H), 2.37-2.52 (m, 2 H), 1.82-2.14 (m, 6 H), 1.62-1.78 (m, 6 H), 0.94-1.46 (m, 8 H), 0.77 (s, 3 H).

Synthesis of 20.6 & 20.6a

[0530] A solution of **20.5 & 20.5a** (20.0 g, 68.8 mmol) in DCM (300 mL) was added DMP (58 g, 137 mmol) under N_2. The reaction mixture was stirred at 15°C under N_2 for 2 hrs to get a mixture. The mixture was poured into saturated aqueous $NaHCO_3$ (500 mL), then saturated aqueous $Na_2S_2O_3$ (500 mL) was added. The aqueous phase was extracted with DCM (3 x 200 mL). The combined organic phase was washed with brine (2 x 500 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column (0~20% of EtOAc in PE) to give **20.6 & 20.6a** (14.5 g, 73.2%), which was purified by SFC (Column DAICEL CHIRALPAK IC(250 mm* 50 mm, 10 um) Condition 0.1%$NH_3.H_2O$ ETOH Begin B 40% End B 40% Gradient Time (min) 100%B Hold Time (min) Flow Rate(ml/min) 200 Injections 500) to afford **20.6a** (3.8 g) as solid and **20.6** (9 g) as solid, which was re-purified by flash column (0~30% of EtOAc in PE) to give **20.6** (3.5 g, 24.3%). The **20.6a** was purified by flash column (0~20% of EtOAc in PE) to give **20.6a** (3.5 g, 13.1 mmol).

[0531] **20.6: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.04 (t, J=12.55 Hz, 1 H), 2.35-2.55 (m, 3 H), 1.91-2.17 (m, 5 H), 1.50-1.88 (m, 10 H), 0.99-1.45 (m, 7 H), 0.90 (s, 3 H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for C19H29O2 [M+H]+ 289.3 found 289.3.

[0532] **20.6a:** **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.24-2.63 (m, 5 H), 1.88-2.17 (m, 5 H), 1.63-1.86 (m, 6 H), 1.06-1.60 (m, 10 H), 0.90 (s, 3 H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{19}H_{29}O_2$ $[M+H]^+$ 289.3 found 289.3.

Synthesis of 20.7

[0533] To a solution of 2,6-di-tert-butyl-4-methylphenol (15.9 g, 72.6 mmol) in toluene (40 mL) was added dropwise $AlMe_3$ (18.1 mL, 36.3 mmol, 2 M in toluene) at 0°C. The mixture was stirred at 25°C for 30 min. A solution of **20.6** (3.5 g, 12.1 mmol) in anhydrous DCM (5 mL) was added dropwise to MAD (36.3 mmol) solution at -70°C. After stirring at -70°C for 1 h, MeMgBr (12.1 mL, 36.3 mmol, 3 M in ethyl ether) was added dropwise at -70°C and stirred at -70°C for 1 h. The reaction mixture was poured into saturated aqueous citric acid (50 mL) below 10°C. The aqueous solution extracted with EtOAc (3 x50 mL). The combined organic layers were washed with brine (80 mL), dried by Na_2SO_4, and evaporated under reduced pressure to give the product. The product was purified by flash column (10~30% of EtOAc in PE) to give **20.7** (1.8 g). Compound **20.7** (200 mg) was purified by flash column (0~30% of EtOAc in PE) to give **20.7** (14.3 mg).

20.7: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.44 (dd, J=19.20, 8.16 Hz, 1 H), 1.75-2.16 (m, 8 H), 1.58-1.66 (m, 2 H), 1.41-1.53 (m, 4 H), 0.95-1.40 (m, 13 H), 0.89 (s, 3 H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{20}H_{31}O$ $[M-H_2O+H]^+$ 287.3 found 287.3.

Synthesis of 20.8

[0534] To a solution of t-BuOK (2.19 g, 19.6 mmol) in THF (20 mL) was added $EtPPh_3Br$ (7.27 g, 19.6 mmol) at 40°C under N_2. The mixture was stirred at 40°C for 30 min to give solution. Then compound **20.7** (2.0 g, 6.56 mmol) in THF (10 ml) was added. The mixture was stirred at 40°C for 30 min to give solution. The mixture was poured into water (30 mL) and stirred for 20 min. The aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic phase was washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~10% of EtOAc in PE) to give **20.8** (1.6.0 g, 77.2%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.05-5.24 (m, 1 H), 1.95-2.43 (m, 5 H), 1.61-1.94 (m, 8 H), 1.15-1.53 (m, 15 H), 0.92-1.14 (m, 4 H), 0.89 (s, 3 H).

Synthesis of 20.9

[0535] To a solution of **20.8** (1.6 g, 5.05 mmol) in THF (30 mL) was added 9-BBN dimer (2.44 g, 10.1 mmol) under N_2. The reaction mixture was stirred at 50°C under N_2 for 2 hrs to get a mixture and cooled to 0°C. To the reaction mixture was added ethanol (4.40 mL, 75.7 mmol) and NaOH (15.1 mL, 5 M, 75.7 mmol). Subsequently, H_2O_2 (8.56 g, 30%, 75.7 mmol) was added dropwise at 15°C. The mixture was stirred at 50°C for 2 hours. Saturated aqueous $Na_2S_2O_3$ (50 mL) was added and the mixture was stirred at 0°C for another 1 hour. The reaction was checked by potassium iodide-starch test paper to confirm excess H_2O_2 was destroyed. The aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic phase was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **20.9** (1.0 g).

Synthesis of 20.10

[0536] To a solution of **20.9** (1.0 g, 2.98 mmol) in DCM (30 mL) was added DMP (1.44 g, 5.96 mmol) under N_2. The reaction mixture was stirred at 15°C under N_2 for 2 hrs to get a mixture. The mixture was added saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous $Na_2S_2O_3$ (50 mL) was added. The aqueous phase was extracted with DCM (3 x 40 mL). The combined organic phase was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column (0~20% of EtOAc in PE) to give **20.10** (0.8 g, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.55 (t, *J*=8.91 Hz, 1 H), 2.16 (br d, *J*=9.29 Hz, 1 H), 2.12 (s, 3 H), 1.95-2.05 (m, 2 H), 1.71-1.92 (m, 4 H), 1.37-1.70 (m, 10 H), 0.87-1.35 (m, 13 H), 0.63 (s, 3 H).

Synthesis of 20.11

[0537] To a solution of t-BuOK (1.0 g, 9.00 mmol) in THF (20 mL) was added $MePPh_3Br$ (3.21 g, 9.00 mmol) at 50°C under N_2. The mixture was stirred at 50°C for 30 min to give solution. **20.10** (1.0 g, 3.00 mmol) in THF (10 ml) was added. The mixture was stirred at 50°C for 30 min to give solution. The mixture was poured into water (30 mL) and stirred for 20 min. The aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~10% of EtOAc in PE) to give **20.11** (800 mg, 80.7%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.85 (s, 1 H), 4.71 (s, 1 H), 1.77-

2.05 (m, 6 H), 1.62-1.71 (m, 3 H), 1.35-1.60 (m, 9 H), 1.08-1.33 (m, 12 H), 0.83-1.03 (m, 4 H), 0.58 (s, 3 H).

Synthesis of 20.12

[0538] To a solution of **20.11** (150 mg, 0.4537 mmol) in DCM (10 mL) was added m-CPBA (156 mg, 0.9074 mmol, 80%) at 0°C. The solution was stirred at 25°C for 1 h to give a suspension. The mixture was quenched with sat. $NaHCO_3$ and $Na_2S_2O_3$ (40 mL, 1:1) and extracted with DCM (3 x 20 mL). The combined organic phase was washed with sat. $NaHCO_3$ and $Na_2S_2O_3$ (60 mL, 1:1), dried over Na_2SO_4, filtered and concentrated to give **20.12** (220 mg).

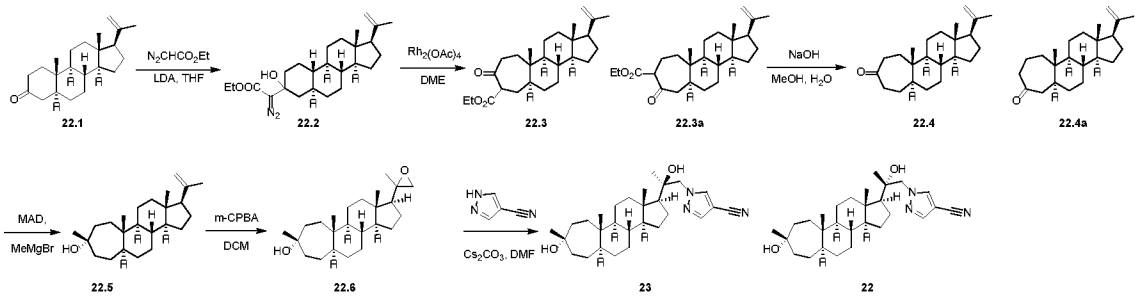
Synthesis of 20 and 21

[0539] A mixture of **20.12** (220 mg, 0.6348 mmol), Cs_2CO_3 (619 mg, 1.90 mmol) and 1H-pyrazole-4-carbonitrile (117 mg, 1.26 mmol) in DMF (10 mL) was stirred at 130°C for 12 hours to give a suspension. The mixture was poured into saturated NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with LiCl (50 mL, 5% in water), brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column (0~50% of EtOAc in PE) to afford **20 & 21** (300 mg). The diastereomers were purified by SFC (Column DAICEL CHIRALPAK AD-H (250 mm* 30 mm, 5 um) Condition 0.1%NH_3H_2O ETOH Begin B 40 End B 40 Gradient Time (min) 100%B Hold Time (min) Flow Rate (ml/min) 60) to afford **21** (51.2 mg, 16%, Rt = 4.210 min) as a solid and **20** (124.2 mg, 39.8%, Rt = 4.855 min).

[0540] **21: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.90 (s, 1 H), 7.81 (s, 1 H), 4.11-4.25 (m, 1 H), 3.93-4.08 (m, 1 H), 2.29 (s, 1 H), 1.75-2.11 (m, 6 H), 1.64-1.72 (m, 3 H), 1.35-1.52 (m, 5 H), 0.93-1.31 (m, 13 H), 0.89 (s, 3 H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{27}H_{38}N_3$ $[M-2H_2O+H]^+$ 404.3 found 404.3. **SFC** 100% de.

[0541] **20: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.94 (s, 1 H), 7.82 (s, 1 H), 4.36 (d, J=13.76 Hz, 1 H), 4.09 (d, J=13.76 Hz, 1 H), 2.49 (s, 1 H), 1.93-2.06 (m, 2 H), 1.62-1.90 (m, 7 H), 1.36-1.57 (m, 9 H), 1.01-1.33 (m, 12 H), 0.98 (s, 3 H), 0.94 (s, 3 H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{27}H_{38}N_3$ $[M-2H_2O+H]^+$ 404.3 found 404.3. **SFC** 100% de.

Example 22 & 23: 1-((S)-2-hydroxy-2-((1S,3aS,3bR,5aS,8S,10aS,10bS,12aS)-8-hydroxy-8,10a,12a-trimethyloctadecahydrocyclohepta[a]cyclopenta[f]naphthalen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (22) & 1-((R)-2-hydroxy-2-((1S,3aS,3bR,5aS,8S,10aS,10bS,12aS)-8-hydroxy-8,10a,12a-trimethyloctadecahydrocyclohepta[a]cyclopenta[f]naphthalen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (23)



Synthesis of 22.2

[0542] To a solution of **22.1** (13 g, 41.3 mmol) in THF (400 mL) was added ethyl diazoacetate (23.5 g, 206 mmol) under N_2 followed by LDA (206 mmol) at -70°C. After stirring at -70°C for 4 h, a solution of acetic acid (16.4 g, 206 mmol) in THF (100 mL) was added to quench the reaction at -70°C. The mixture was then warmed to 25°C stirred for 12 h and treated with water (200 mL). The aqueous solution was extracted with diethyl ether (2 x 300 mL). The combined organic layer was washed with brine (300 mL), dried over Na_2SO_4, and concentrated to give **22.2** (17 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.88-4.79 (m, 1H), 4.75-4.67 (m, 1H), 4.37-4.19 (m, 4H), 3.52-3.28 (m, 1H), 2.01-1.82 (m, 3H), 1.75 (s, 11H), 1.47-1.31 (m, 7H), 0.99-0.63 (m, 7H), 0.55 (s, 3H).

Synthesis of 22.3 & 22.3a

[0543] To a solution of **22.2** (17 g, 41.0 mmol) in DME (50 mL) was added $Rh_2(OAc)_4$ (271 mg, 0.615 mmol) at 25°C. The reaction mixture was stirred at 40°C for 2 hours. The reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **22.3 & 22.3a** (16 g).

Synthesis of 22.4 & 22.4a

[0544] To a mixture of **22.3 & 22.3a** (16 g, 5.54 mmol) in MeOH/THF /H_2O (200 mL/100 mL/50 mL) was added NaOH (15.9 g, 399 mmol). The reaction mixture was stirred at 70°C for 12 hour. The reaction mixture was extracted with ethyl acetate (4 x 500 mL). The combined organic phase was washed with water (500 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the product, which was purified by flash column (0~10% of EtOAc in PE) to give **22.4 & 22.4a** (13 g). The mixture of **22.4 & 22.4a** was purified by SFC (Column: DAICEL CHIRALPAK AD (250 mm* 50 mm, 10 um); Condition: 0.1%NH_3H_2O ETOH; Begin B 30% End B 30%; Flow Rate (ml/min): 200) to give **22.4** (3.3 g) and **22.4a** (3.0 g).

[0545] **22.4: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.84 (s, 1H), 4.70 (s, 1H), 2.63-2.39 (m, 3H), 2.35-2.26 (m, 1H), 2.06-1.95 (m, 2H), 1.75 (s, 10H), 1.41-1.10 (m, 10H), 0.98-0.86 (m, 1H), 0.81 (s, 4H), 0.56 (s, 3H). **LC-ELSD/MS** purity 99%, MS ESI calcd for $C_{23}H_{37}O$ $[M+H]^+$ 329.3, found 329.3, $C_{23}H_{35}$ $[M-H_2O+H]^+$ 311.3, found 311.3.

[0546] **22.4a: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.84 (s, 1H), 4.70 (s, 1H), 2.81 (dd, J = 11.2, 15.2 Hz, 1H), 2.53-2.30 (m, 2H), 2.12-1.90 (m, 3H), 1.89-1.81 (m, 1H), 1.75 (s, 10H), 1.49-1.00 (m, 9H), 0.88 (s, 4H), 0.82-0.73 (m, 1H), 0.56 (s, 3H). **LC-ELSD/MS** purity 99%, MS ESI calcd for $C_{23}H_{37}O$ $[M+H]^+$ 329.3, found 329.3, $C_{23}H_{35}$ $[M-H_2O+H]^+$ 311.3, found 311.3.

Synthesis of 22.5

To a solution of 2,6-di-tert-butyl-4-methylphenol (12.8 g,58.4 mmol) in toluene (40 mL) was added dropwise $AlMe_3$ (14.6 mL, 29.2 mmol, 2 M in toluene) at 0°C. The mixture was stirred at 25°C for 30 min and used as a MAD solution. To a solution of **22.4** (3.2 g, 9.74 mmol) in anhydrous DCM (20 mL) was added dropwise to a MAD (29.2 mmol) solution at -70°C. After stirring at -70°C for 1 h, MeMgBr (9.73 mL, 29.2 mmol, 3M in ethyl ether) was added dropwise at -70°C and stirred at -70°C for 1 h. The reaction mixture was poured into saturated aqueous citric acid (15 mL) below 10°C. The aqueous solution was extracted with EtOAc (3 x100 mL). The combined organic layer was washed with brine (200 mL), dried by Na_2SO_4, and evaporated under reduced pressure to give the product. The product was purified by flash column (10~30% of EtOAc in PE) to give **22.4** (1.1 g, recovered) and **22.5** (2.0 g). **^{1}H NMR**

(400 MHz, $CDCl_3$) δ_H 4.90-4.78 (m, 1H), 4.74-4.65 (m, 1H), 2.07-1.96 (m, 1H), 1.75 (s, 13H), 1.46-1.24 (m, 5H), 1.20 (s, 11H), 0.82-0.79 (m, 1H), 0.75 (s, 3H), 0.55 (s, 3H).

Synthesis of 22.6

[0547] To a solution of **22.5** (300 mg, 0.87 mmol) in DCM (6 mL) was added m-CPBA (352 mg, 85%, 1.74 mmol) at 15°C. After stirring at 15°C for 1 hour to give a solution, the mixture was quenched with saturated $NaHCO_3$ aqueous (10 mL) at 15°C. The DCM phase was separated and washed with saturated $NaHCO_3/Na_2S_2O_3$ aqueous (1:1, 2 x 10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **22.6** (300 mg).

Synthesis of 22 & 23

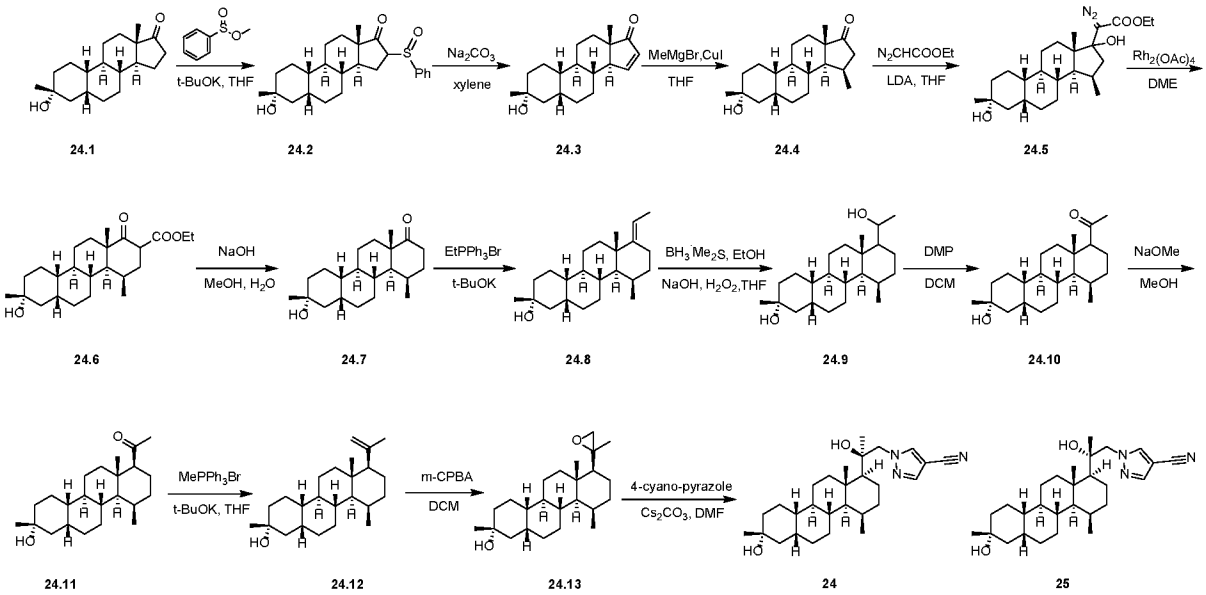
[0548] A solution of **22.6** (300 mg, 0.8319 mmol), Cs_2CO_3 (811 mg, 2.49 mmol) and 1H-pyrazole-4-carbonitrile (154 mg, 1.66 mmol) in DMF (10 mL) was stirred at 130°C for 12 hours to give a solution. The mixture was poured into saturated NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with LiCl (100 mL, 5% in water), brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column (0~30% of EtOAc in PE) to afford **22 & 23** (260 mg).

[0549] **22 & 23** (260 mg) was purified by SFC (Column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); Condition: 0.1%NH_3H_2O IPA; Begin B 50% End B 50%; Flow Rate (ml/min) 70) to afford **23** (50.6 mg, 19.5%, Rt = 1.627 min) and **22** (72.4 mg, 27.9%, Rt = 1.247 min).

[0550] **22: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.92 (s, 1H), 7.81 (s, 1H), 4.35 (d, J = 14.0 Hz, 1H), 4.08 (d, J = 13.6 Hz, 1H), 2.48 (s, 1H), 2.05-1.97 (m, 1H), 1.92-1.81 (m, 1H), 1.80-1.56 (m, 8H), 1.44-1.24 (m, 7H), 1.22-0.87 (m, 17H), 0.76 (s, 4H). **LC-ELSD/MS** purity 99%, MS ESI calcd for $C_{28}H_{40}N_3O_2$ $[M-2H_2O+H]^+$ 418.3, found 418.3. **SFC** 100% de.

[0551] **23: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.88 (s, 1H), 7.80 (s, 1H), 4.20-4.11 (m, 1H), 4.04-3.97 (m, 1H), 2.27 (s, 1H), 2.08-1.99 (m, 1H), 1.96-1.82 (m, 2H), 1.75-1.56 (m, 7H), 1.20 (s, 16H), 1.09 (s, 4H), 0.86 (s, 4H), 0.76 (s, 4H). **LC-ELSD/MS** purity 99%, MS ESI calcd for $C_{28}H_{40}N_3O_2$ $[M-2H_2O+H]^+$ 418.3, found 418.3. **SFC** 99% de.

Example 24 & 25: 1-((R)-2-hydroxy-2-((1S,4R,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-4,8,12a-trimethyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (24) & 1-((S)-2-hydroxy-2-((1S,4R,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-4,8,12a-trimethyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (25)



Synthesis of 24.2

[0552] To a solution of t-BuOK (3.86 g, 34.4 mmol) in THF (110 mL) was added **24.1** (5.0 g, 17.2 mmol) at 25°C under N_2. The mixture was stirred at 25°C for 10 min. Then methyl benzenesulfinate (5.37 g, 34.4 mmol) was added. The mixture was stirred at 30°C for 0.5 h. The mixture was quenched with H_2O (200 mL) and extracted with EtOAc (200 x 3 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **24.2** (8.7 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.70-7.45 (m, 10H), 3.52-3.42 (m, 1H), 3.25 (t, J = 11.6 Hz, 1H), 2.43-2.29 (m, 1H), 1.86-1.75 (m, 7H), 1.64-1.58 (m, 3H), 1.42-1.34 (m, 8H), 0.93 (s, 3H).

Synthesis of 24.3

[0553] To a mixture of **24.2** (8.7 g, 20.9 mmol) in xylene (110 mL) was added Na_2CO_3 (33.1 g, 313 mmol) in portions. The reaction mixture was stirred at 130 °C for 12 hours under N_2. The mixture was filtered and concentrated. The residue was purified by silica gel chromatography (0-15% of EtOAc in PE) to give the product **24.3** (3.7 g, 61.4%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.52 (d, J = 6.0 Hz, 1H), 6.10-5.93 (m, 1H), 2.41-2.30 (m, 1H), 1.90-

1.67 (m, 7H), 1.62-1.48 (m, 4H), 1.45-1.37 (m, 5H), 1.35-1.30 (m, 2H), 1.28 (s, 3H), 1.26-1.23 (m, 1H), 1.07 (s, 3H).

Synthesis of 24.4

[0554] To a solution of MeMgBr (17.0 mL, 51.2 mmol, 3M) in THF (30 mL) was added CuI (7.31 g, 38.4 mmol) at 0°C and stirred at 0°C for 1 hour, then **24.3** (3.7 g, 12.8 mmol) in THF (40 mL) was added at 0°C. After stirring at 0°C for 3 hours, the mixture was poured into saturated NH_4Cl (200 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0%~70% of EtOAc in PE) to give **24.4** (3.40 g, 87.4 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.54-2.36 (m, 2H), 2.30-2.18 (m, 1H), 1.93-1.79 (m, 3H), 1.77-1.61 (m, 4H), 1.55-1.46 (m, 3H), 1.44-1.35 (m, 5H), 1.27 (s, 4H), 1.10 (d, J = 7.3 Hz, 3H), 1.03 (s, 3H), 0.93-0.80 (m, 4H).

Synthesis of 24.5

[0555] LDA (27.7 mL, 55.5 mmol) (2M in THF) was added to a stirred solution of **24.4** (3.4 g, 11.1 mmol) and ethyl diazoacetate (7.03 g, 55.5 mmol, 90%) in THF (70 mL) at -70°C. The mixture was stirred at -70°C for 2 hours. Then acetic acid (3.17 mL, 55.5 mmol) in THF (30 mL) was added and the mixture was warmed to 20°C for 16 hours. Subsequently, water (300 mL) was added. The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **24.5** (4.64 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.79 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 4.00-3.85 (m 2H), 2.46 (s, 3H), 1.91-1.59 (m, 7H), 1.50-1.29 (m, 9H), 1.26 (s, 5H), 1.24-0.87 (m, 14H), 0.83 (t, J = 6.7 Hz, 3H), 0.52 (s, 3H).

Synthesis of 24.6

[0556] To a solution of **24.5** (6.64 g) in DME (100 mL) was added $Rh_2(OAc)_4$ (121 mg, 0.275 mmol) in one portion at 20°C. The mixture was stirred at 20°C for 16 hours. The mixture was treated with H_2O (200 mL). The mixture was extracted with EtOAc (3 x 150 mL). The combined organic phase was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **24.6** (4.29 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.23-4.19 (m, 2H), 2.30-2.16 (m, 2H), 1.93-1.64 (m, 8H), 1.62-1.51 (m, 3H), 1.48-1.36 (m, 9H), 1.35-1.28 (m, 11H), 1.23 (s, 3H), 1.08 (d, J = 7.3 Hz, 3H), 1.04-0.94 (m, 2H), 0.84 (d, J = 7.3 Hz, 2H).

0Synthesis of 24.7

[0557] To a mixture of **24.6** (4.29 g) in MeOH (50 mL) was added H_2O (130 mL) and KOH (3.66 g, 65.3 mmol). The reaction mixture was stirred at 60 °C for 2 hours to give a mixture. The reaction mixture was concentrated. Then H_2O (200 mL) was added. The mixture was extracted with EtOAc (3 x 150 mL). The combined organic phase was washed with saturated brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (0-60% of EtOAc in PE) to give **24.7** (2.0 g, 57.6 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.85-2.72 (m, 1H), 2.22-2.10 (m, 2H), 1.90-1.82 (m, 3H), 1.80-1.70 (m, 4H), 1.68-1.53 (m, 3H), 1.51-1.27 (m, 10H), 1.26 (s, 3H), 1.16 (s, 3H), 1.06 (d, J = 7.2 Hz, 3H), 1.03-0.95 (m, 1H)

Synthesis of 24.8

[0558] To a mixture of $EtPPh_3Br$ (7.68 g, 20.7 mmol) in THF (50 mL) was added t-BuOK (2.32 g, 20.7 mmol) at 20°C under N_2. The resulting mixture was stirred at 60°C for 30 min. **24.7** (1.1 g) in THF (20 mL) was added in portions below 60°C. The reaction mixture was stirred at 60°C for 16 hours. The reaction mixture was quenched with 10% NH_4Cl aqueous (20 mL) at 15°C. The organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (2 x 20 mL), filtered, concentrated under reduced pressure. The residue was purified by flash column (0 ~5% ethyl acetate in PE) to give **24.8** (1 g, 87.7 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.34-5.01 (m, 1H), 2.41 (d, J = 14.1 Hz, 1H), 2.34-1.96 (m, 3H), 1.94-1.85 (m, 1H), 1.82-1.69 (m, 4H), 1.67-1.57 (m, 5H), 1.45-1.30 (m, 8H), 1.26 (s, 6H), 1.23-1.04 (m, 4H), 1.01 (s, 3H), 0.95-0.84 (m, 6H).

Synthesis of 24.9

[0559] A solution of **24.8** (2.0 g, 6.05 mmol) in THF (30 mL) was added $BH_3{\cdot}Me_2S$ (2.42 mL, 24.2 mmol, 10 M) stirred at 25°C for 16 hours. To the resulting mixture was added ethanol (6.05 mL, 60.5 mmol, 10 M) at 15°C, followed by NaOH aqueous (12.1 mL, 5.0 M, 60.5 mmol) at 0°C. Hydrogen peroxide (6.05 mL, 10 M, 60.5 mmol) was added dropwise at 0°C. The reaction mixture was stirred at 70°C for 1 hour. The mixture was cooled to 15°C and $Na_2S_2O_3$ (100 mL, sat. aq.) was added. The aqueous was extracted with EtOAc (100 mL X 3). The combined organic layer was washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column

(0~50% of EtOAc in PE) to give **24.9** (1.8 g, 85.7 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.17-4.08 (m, 1H), 2.98 (s, 1H), 2.03-1.74 (m, 5H), 1.72-1.32 (m, 14H), 1.31-1.23 (m, 8H), 1.20-1.11 (m, 3H), 1.09-0.92 (m, 5H), 0.90-0.74 (m, 4H).

Synthesis of 24.10

[0560] To a solution of **24.9** (1.75 g, 5.02 mmol) in DCM (40 mL) was added Dess-martin reagent (4.24 g, 10.0 mmol) at 25°C. The reaction mixture was stirred at 25°C for 20 min. The mixture was quenched by saturated $NaHCO_3$ aqueous (30 mL) at 10°C. The DCM phase was separated and washed with saturated $NaHCO_3$/$Na_2S_2O_3$ aqueous (1:1, 3 x 50 mL), brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column (0~60% ethyl acetate in PE) to give **24.10** (1.1 g, 63.5 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.51-2.44 (m, 1H), 2.26 (dd, J = 2.9, 12.7 Hz, 1H), 2.16-2.11 (m, 3H), 2.04-1.73 (m, 6H), 1.70-1.46 (m, 9H), 1.44-1.29 (m, 7H), 1.26-1.22 (m, 3H), 1.20-1.02 (m, 3H), 1.00 (d, J = 4.5 Hz, 3H), 0.83 (dd, J = 3.1, 7.4 Hz, 3H).

Synthesis of 24.11

[0561] To a solution of **24.10** (1.1 g, 3.17 mmol) in MeOH (10 mL) at 0°C was added MeONa (3.42 g, 63.4 mmol) and the reaction was stirred at 80°C for 16 hours. Then the residue was poured into saturated NH_4Cl (100 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with saturated brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **24.11** (1.0 g, 91.7 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.26 (dd, J = 3.0, 12.8 Hz, 1H), 2.15 (s, 3H), 2.04-1.97 (m, 1H), 1.90-1.82 (m, 2H), 1.81-1.75 (m, 2H), 1.71-1.57 (m, 4H), 1.50-1.30 (m, 10H), 1.27 (s, 6H), 1.09-1.00 (m, 2H), 0.99 (s, 3H), 0.97-0.92 (m, 1H), 0.83 (d, J = 7.5 Hz, 3H). **LC-ELSD/MS** purity: 99%, MS ESI calcd. for $C_{23}H_{38}O_2$ $[M-H_2O+H]^+$ 329.2, found $C_{23}H_{38}O_2$ $[M-H_2O+H]^+$ 329.3.

Synthesis of 24.12

[0562] To a mixture of $MePPh_3Br$ (7.36 g, 20.7 mmol) in THF (80 mL) was added t-BuOK (2.32 g, 20.7 mmol) at 20°C under N_2. The resulting mixture was stirred at 60°C for 30 min. Compound **24.11** (900 mg, 2.59 mmol) in THF (10 mL) was added in portions below 60°C. The reaction mixture was stirred at 60°C for 16 hours. The reaction mixture was quenched with 10% NH_4Cl aqueous (200 mL) at 15°C. The organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic phase was

washed with brine (2 x 50 mL), filtered, concentrated under reduced pressure. The residue was purified by flash column (0 ~20% ethylacetate in PE) to give **24.12** (770 mg, 86.3 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.80 (s, 1H), 4.62 (d, J = 2.0 Hz, 1H), 2.01-1.59 (m, 12H), 1.55-1.46 (m, 3H), 1.43-1.28 (m, 7H), 1.26 (s, 5H), 1.22-1.15 (m, 1H), 1.08-0.92 (m, 4H), 0.90 (s, 3H), 0.82 (d, J = 7.5 Hz, 3H).

Synthesis of 24.13

[0563] To a mixture of **24.12** (300 mg, 0.8706 mmol) in DCM (5 ml) was added m-CPBA (374 mg, 1.74 mmol, 80% purity). The mixture was stirred at 25 °C for 12 hours. Saturated aqueous $NaHCO_3$ (30 mL) and $Na_2S_3O_3$ (30 mL) was added and the mixture was stirred for another 5 mins. The aqueous phase was extracted with DCM (3 x 30 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **24.13** (180 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.73 (d, J = 5.0 Hz, 1H), 2.65 (d, J = 4.8 Hz, 1H), 2.05-1.82 (m, 3H), 1.80-1.72 (m, 3H), 1.71-1.61 (m, 5H), 1.55-1.46 (m, 4H), 1.42-1.29 (m, 6H), 1.26 (s, 4H), 1.25 (s, 3H), 1.23-1.03 (m, 4H), 1.00 (s, 3H), 0.97-0.88 (m, 3H), 0.80 (d, J = 7.3 Hz, 3H).

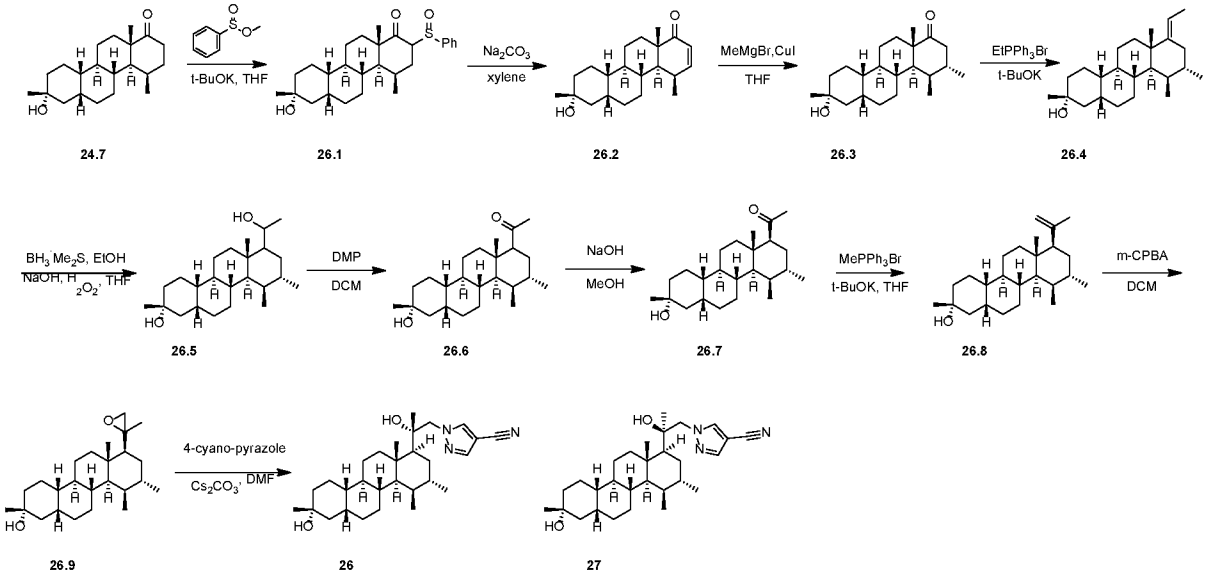
Synthesis of 24 and 25

[0564] To a solution of **24.13** (180 mg, 0.4991 mmol) in DMF (5 mL) was added 1H-pyrazole-4-carbonitrile (138 mg, 1.49 mmol) and Cs_2CO_3 (488 mg, 1.49 mmol) at 25°C. The mixture was stirred at 145°C for 48 hours. The mixture was washed with water (5 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine (30 mL x 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column (0%-70% of EtOAc in PE) to give **24** (49.6 mg, 21.9 %) and **25** (20 mg). Compound **25** (20 mg) was further purified by SFC (column: DAICEL CHIRALCEL OD-H (250 mm*30 mm, 5 um); Mobile phase: A: CO_2 B: 0.1%NH_3H_2O IPA; gradient: from 50% to 50% of B. Flow Rate (ml/min): 80) to give **25** (9.4 mg, 4.15 %).

[0565] 24: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.91 (s, 1H), 7.79 (s, 1H), 4.49-4.12 (m, 2H), 2.41 (s, 2H), 2.07-2.00 (m, 1H), 1.91-1.84 (m, 1H), 1.81-1.73 (m, 2H), 1.70-1.59 (m, 5H), 1.48-1.31 (m, 7H), 1.27 (s, 7H), 1.11 (s, 3H), 1.07-1.03 (m, 1H), 1.01 (s, 5H), 0.81 (d, J = 7.5 Hz, 3H). **LC-ELSD/MS** purity: 99%, MS ESI calcd. for $C_{28}H_{43}N_3O_2$ $[M-2H_2O+H]^+$ 418.3, found $C_{28}H_{43}N_3O_2$ $[M-2H_2O+H]^+$ 418.4.

[0566] 25: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.87 (d, J = 1.8 Hz, 2H), 4.30 (d, J = 13.9 Hz, 1H), 4.01 (d, J = 13.9 Hz, 1H), 3.11 (s, 1H), 2.44 (d, J = 5.6 Hz, 1H), 2.10-1.92 (m, 1H), 1.91-1.80 (m, 1H), 1.79-1.70 (m, 2H), 1.68-1.57 (m, 3H), 1.52-1.28 (m, 9H), 1.25 (s, 6H), 1.20 (s, 3H), 1.17-1.12 (m, 1H), 1.10 (s, 3H), 1.02-0.83 (m, 5H), 0.79 (d, J = 7.5 Hz, 3H), 0.70 (d, J = 11.6 Hz, 1H). **LC-ELSD/MS** purity: 99%, MS ESI calcd. for $C_{28}H_{43}N_3O_2$ [M-$2H_2O$+H]$^+$ 418.3, found $C_{28}H_{43}N_3O_2$ [M-$2H_2O$+H]$^+$ 418.3.

Example 26 & 27: 1-((S)-2-hydroxy-2-((1S,3S,4R,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-3,4,8,12a-tetramethyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (26) & 1-((R)-2-hydroxy-2-((1S,3S,4R,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-3,4,8,12a-tetramethyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (27)



Synthesis of 26.1

[0567] To a solution of t-BuOK (4.64 g, 41.4 mmol) in THF (80 mL) was added **24.7** (6.6 g, 20.7 mmol) at 25°C under N_2. The mixture was stirred at 25°C for 10 min. Then methyl benzenesulfinate (6.46 g, 41.4 mmol) was added. The mixture was stirred at 30°C for 0.5 h. The mixture was quenched by H_2O (100 mL) and extracted with EtOAc (3 x 80 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **26.1** (9.16 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.81-7.60 (m, 2H), 7.57-7.41 (m, 3H), 4.28 (dd, J = 13.9, 5.4 Hz, 1H), 3.85 (dd, J = 13.8, 5.8 Hz, 1H), 3.79-3.69 (m, 1H),

3.60-3.42 (m, 1H), 2.45-2.13 (m, 1H), 1.96-1.58 (m, 6H), 1.54-1.30 (m, 6H), 1.28-1.23 (m, 5H), 1.08 (s, 1H), 1.05-0.90 (m, 3H).

Synthesis of 26.2

[0568] To a mixture of **26.1** (9.16 g, 20.6 mmol) in xylene (100 mL) was added Na_2CO_3 (32.7 g, 309 mmol) in portions. The reaction mixture was stirred at 140°C for 12 hrs under N_2. The mixture was filtered and concentrate. The residue was purified by silica gel chromatography (0-30% of EtOAc in PE) to give the **26.2** (5.2 g, 79.8 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.86 (dd, J = 5.3, 10.0 Hz, 1H), 5.99-5.79 (m, 1H), 2.76-2.49 (m, 1H), 2.02-1.57 (m, 8H), 1.45-1.30 (m, 8H), 1.28 (s, 4H), 1.13-1.09 (m, 6H), 1.05-0.80 (m, 3H).

Synthesis of 26.3

[0569] To a solution of MeMgBr (8.39 mL, 25.2 mmol, 3M) in THF (20 mL) was added CuI (3.59 g, 18.9 mmol) at 0°C and stirred at 0°C for 1 hour, then **26.2** (2.0 g, 6.31 mmol) in THF (20 mL) was added at 0°C. After stirring at 0°C for 3 hours, the mixture was poured into saturated NH_4Cl (100 mL) and extracted with EtOAc (3 x 100mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0%~30% of EtOAc in PE) to give **26.3** (1.92 g, 91.8 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.76 (dd, J = 5.0, 14.3 Hz, 1H), 2.11-2.04 (m, 1H), 2.00-1.85 (m, 3H), 1.84-1.56 (m, 9H), 1.44-1.30 (m, 9H), 1.27 (s, 4H), 1.17-1.09 (m, 5H), 1.06 (d, J = 7.3 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H).

Synthesis of 26.4

[0570] To a mixture of $EtPPh_3Br$ (16.0 g, 43.2 mmol) in THF (70 mL) was added t-BuOK (4.84 g, 43.2 mmol) at 20°C under N_2. The resulting mixture was stirred at 50°C for 30 min. Compound **26.3** (1.8 g, 5.17 mmol) in THF (20 mL) was added in portions below 50°C. The reaction mixture was stirred at 80°C for 16 hours. The reaction mixture was quenched with 10% NH_4Cl aqueous (200 mL) at 15°C. The organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic phase was washed with brine (2 x 100 mL), filtered and concentrated under reduced pressure. The residue was purified by flash column (0%~20% of EtOAc in PE) to give **26.4** (1.5 g, 80.6 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.39-5.16 (m, 1H), 2.42-2.26 (m, 1H), 2.24-2.15 (m, 1H), 1.96-1.87 (m, 1H), 1.82-1.57 (m, 10H), 1.56 (s, 5H), 1.54-1.47 (m, 2H), 1.43-1.29 (m, 7H),

1.27 (s, 5H), 1.25-1.17 (m, 3H), 1.06-1.02 (m, 1H), 1.00 (s, 3H), 0.94 (d, J = 7.3 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H).

Synthesis of 26.5

[0571] A solution of **26.4** (500 mg, 4.35 mmol) in THF (30 mL) was added $BH_3{\cdot}Me_2S$ (1.73 mL, 17.4 mmol 10 M) stirred at 25°C for 16 hours. To the resulting mixture was added ethanol (4.34 mL, 43.4 mmol, 10 M) at 15°C, followed by NaOH aqueous (8.68 mL, 5.0 M, 43.4 mmol) at 0°C. Hydrogen peroxide (4.34 mL 10 M, 43.4mmol) was added dropwise at 0°C. The reaction mixture was stirred at 80°C for 1 hour. The mixture was cooled to 15°C and $Na_2S_2O_3$ (150 mL, sat. aq.) was added. The aqueous layer was extracted with EtOAc (100 mL x 3).The combined organic layer was washed brine (2 x 50 mL), dried overNa_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column (0~30% of EtOAc in PE) to give **26.5** (1.3 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.98 (t, J = 6.0 Hz, 1H), 1.91-1.78 (m, 3H), 1.71-1.55 (m, 8H), 1.51-1.36 (m, 13H), 1.27 (d, J = 3.3 Hz, 11H), 1.20 (d, J = 6.3 Hz, 5H), 1.11 (s, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 7.3 Hz, 5H), 0.87-0.78 (m, 5H).

Synthesis of 26.6

[0572] To a solution of **26.5** (1 g, 2.75 mmol) in DCM (10 mL) was added Dess-martin reagent (2.33 g, 5.50 mmol) at 25°C. The reaction mixture was stirred at 25°C for 20 min. The mixture was quenched with saturated $NaHCO_3$ aqueous (50 mL) at 10°C. The DCM phase was separated and washed with saturated $NaHCO_3$/$Na_2S_2O_3$ aqueous (1:1, 3 x 50 mL), brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column (0~30% ethyl acetate in PE) to give **26.6** (740 mg, 74.6%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.54 (dd, J = 6.3, 10.0 Hz, 1H), 2.14 (s, 3H), 1.88-1.77 (m, 3H), 1.68-1.52 (m, 10H), 1.49-1.26 (m, 12H), 1.25 (s, 3H), 1.24-1.18 (m, 2H), 1.14 (s, 3H), 1.09-0.99 (m, 3H), 0.96 (d, J = 6.8 Hz, 4H), 0.91-0.87 (m, 3H).

Synthesis of 26.7

[0573] To a solution of **26.6** (640 mg, 1.77 mmol) in MeOH (20 mL) at 0°C was added MeONa (1.91 g, 35.4 mmol). After stirring at 80°C for 16 hours, the mixture was poured into saturated NH_4Cl (100 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with saturated brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~25% ethyl

acetate in PE) to give **26.7** (300 mg, 47.0%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.52 (d, J = 10.5 Hz, 1H), 2.14 (s, 3H), 2.12-2.04 (m, 1H), 1.95-1.73 (m, 5H), 1.69-1.59 (m, 3H), 1.53-1.31 (m, 9H), 1.27 (s, 5H), 1.23-1.14 (m, 3H), 1.03 (d, J = 7.3 Hz, 3H), 0.97 (s, 4H), 0.86 (d, J = 7.5 Hz, 3H).

Synthesis of 26.8

[0574] To a mixture of $MePPh_3Br$ (2.36 g, 6.65 mmol) in THF (20 mL) was added t-BuOK (746 mg, 6.65 mmol) at 20°C under N_2. The resulting mixture was stirred at 80°C for 30 min. Compound **26.7** (300 mg, 0.8319 mmol) in THF (5 mL) was added in portions below 80°C. The reaction mixture was stirred at 80°C for 16 hours. The reaction mixture was quenched with 10% NH_4Cl aqueous (50 mL) at 15°C. The organic layer was separated. The aqueous layer was extracted with EtOAc (3x 50 mL). The combined organic phase was washed with brine (2 x 30 mL), filtered and concentrated under reduced pressure. The residue was purified by flash column (0 ~20% EA in PE) to give **26.8** (130 mg, 43.6 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.81 (s, 1H), 4.64 (s, 1H), 2.09-1.99 (m, 2H), 1.93-1.75 (m, 4H), 1.72 (s, 3H), 1.68-1.59 (m, 3H), 1.55-1.31 (m, 9H), 1.26 (s, 6H), 1.22-1.16 (m, 2H), 1.13-1.06 (m, 2H), 1.04 (d, J = 7.3 Hz, 3H), 0.88 (s, 3H), 0.85 (d, J = 7.5 Hz, 3H).

Synthesis of 26.9

[0575] To a mixture of **26.8** (130 mg, 0.36 mmol) in DCM (5 ml） was added m-CPBA (156 mg, 0.725 mmol, 80% purity). The mixture was stirred at 25 °C for 12 hours. Saturated aqueous $NaHCO_3$ (30 mL) and $Na_2S_3O_3$ (30 mL) were added and the mixture was stirred for another 5 mins. The aqueous phase was extracted with DCM (3 x 30 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **26.9** (150 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.75 (d, J = 4.8 Hz, 1H), 2.65 (d, J = 4.8 Hz, 1H), 2.04-1.94 (m, 1H), 1.92-1.77 (m, 4H), 1.70-1.58 (m, 4H), 1.56-1.31 (m, 8H), 1.27 (s, 4H), 1.24 (s, 3H), 1.21-1.07 (m, 4H), 1.03-1.00 (m, 2H), 0.99-0.94 (m, 6H), 0.84 (d, J = 7.5 Hz, 3H).

Synthesis of 26 and 27

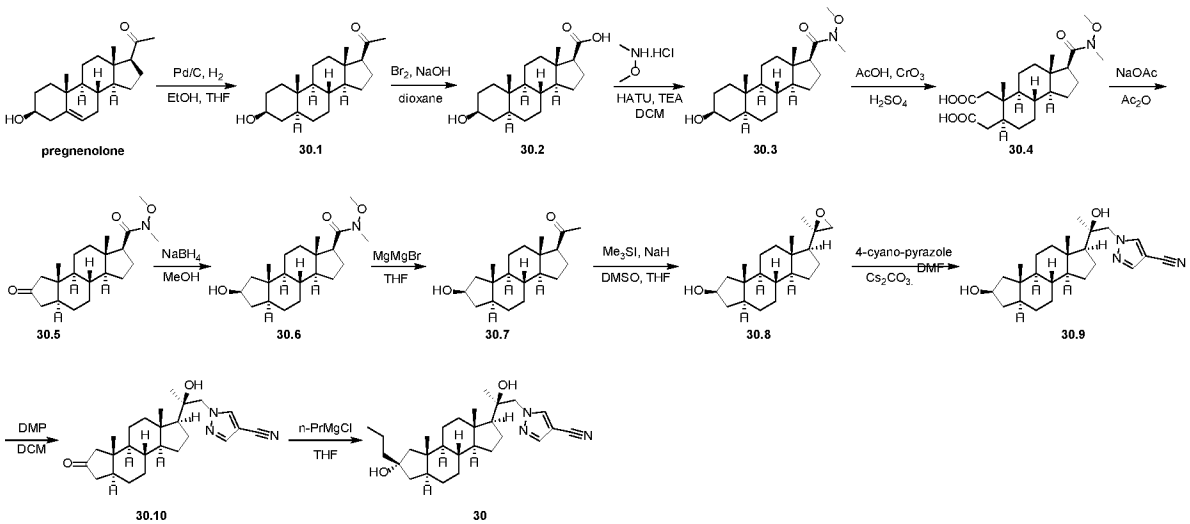
[0576] To a solution of **26.9** (150 mg, 0.4004 mmol) in DMF (5 mL) was added 1H-pyrazole-4-carbonitrile (111 mg, 1.20 mmol) and Cs_2CO_3 (390 mg, 1.20 mmol) at 25°C. The mixture was stirred at 145°C for 16 hours. The mixture was washed with water (5 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine (30

mL x 2), dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by column (0%-70% of EtOAc in PE) to give a mixture of **26 & 27** (180 mg). The was purified by SFC (column: DAICEL CHIRALCEL OJ-H (250 mm* 30 mm, 5 um); Mobile phase: A: CO_2 B: 0.1%NH_3H_2O ETOH; gradient: from 20% to 20% of B. Flow Rate (ml/min): 70) to give **26** (5.1 mg, 2.72 %) and **27** (29.7 mg, 15.8 %).

[0577] 26: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.87 (s, 2H), 4.32-3.94 (m, 2H), 3.36 (s, 1H), 2.46 (d, J = 8.3 Hz, 1H), 1.95-1.57 (m, 8H), 1.52-1.27 (m, 10H), 1.25 (s, 4H), 1.20 (s, 3H), 1.09 (s, 3H), 1.08-0.98 (m, 3H), 0.96-0.87 (m, 3H), 0.83 (dd, J = 5.1, 7.2 Hz, 5H).**LC-ELSD/MS** purity: 99%, MS ESI calcd. for $C_{29}H_{45}N_3O_2$ $[M-2H_2O+H]^+$ 432.3, found $C_{29}H_{45}N_3O_2$ $[M-2H_2O+H]^+$ 432.4.

[0578] 27: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.91 (s, 1H), 7.79 (s, 1H), 4.44-4.16 (m, 2H), 2.44-2.36 (m, 2H), 1.93-1.57 (m, 10H), 1.54-1.29 (m, 10H), 1.27 (s, 4H), 1.24-1.18 (m, 2H), 1.10 (s, 3H), 1.03 (d, J = 7.3 Hz, 3H), 0.99 (s, 4H), 0.84 (d, J = 7.5 Hz, 3H). **LC-ELSD/MS** purity: 99%, MS ESI calcd. for $C_{29}H_{45}N_3O_2$ $[M-2H_2O+H]^+$ 432.3, found $C_{29}H_{45}N_3O_2$ $[M-2H_2O+H]^+$ 432.3.

Example 30: 1-((R)-2-hydroxy-2-((1S,3aS,3bR,5aS,7S,8aS,8bS,10aS)-7-hydroxy-8a,10a-dimethyl-7-propylhexadecahydrodicyclopenta[a,f]naphthalen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (30)



Synthesis of 30.1

[0579] To a solution of pregnanolone (50 g, 157 mmol) in EtOH (250 mL) and THF (250 mL) was added Pd/C (5 g, <1% water). Then the solution was hydrogenated under 30 psi of

hydrogen at 25°C for 16 hrs. The reaction was worked up with another 3 batches from 50 g of pregnanolone. The mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to afford **30.1** (188 g, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.70-3.50 (m, 1H), 2.60-2.45 (m, 1H), 2.25-1.90 (m, 5H), 1.80-1.50 (m, 8H), 1.45-1.05 (m, 10H), 1.00-0.50 (m, 9H).

Synthesis of 30.2

[0580] Liquid bromine (45.0 g, 282 mmol) was added slowly to stirring NaOH aqueous (376 mL, 3 M, 1129 mmol) at 0°C. When all the bromine was dissolved, the mixture was diluted with cold dioxane (90 mL) and added slowly to a stirred solution of **30.1** (30 g, 94.1 mmol) in dioxane (210 mL) and water (90 mL). After stirring at 25°C for 5 h, the remaining oxidizing reagent was quenched with $Na_2S_2O_3$ (300 mL, aq.) and the mixture was then heated to 80°C until the solid material was dissolved. The solution was acidified with HCl (3 M, 50 mL) and a solid was precipitated. The solid was filtered and washed with water (3 x 100 mL) to give a solid, which was dried under reduced pressure to afford **30.2** (28 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.66-3.51 (m, 1H), 2.37 (t, J = 9.2 Hz, 1H), 2.13-2.00 (m, 2H), 1.88-1.77 (m, 3H), 1.75-1.64 (m, 4H), 1.60-1.57 (m, 1H), 1.47-1.32 (m, 3H), 1.32-1.20 (m, 6H), 1.16-1.04 (m, 2H), 1.04-0.84 (m, 2H), 0.81 (s, 3H), 0.73-0.65 (m, 4H).

Synthesis of 30.3

[0581] A mixture of **30.2** (28 g, 87.3 mmol), N, O-dimethylhydroxylamine hydrochloride (16.9 g, 174 mmol), HATU (39.5 g, 104 mmol) and Et_3N (50.4 mL, 349 mmol) in anhydrous DCM (350 mL) was stirred at 25 °C for 18 h. Then the mixture was treated with water (200 mL) and extracted with DCM (2 x 400 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (PE/EtOAc = 5/1) to afford **30.3** (24 g, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.65-3.52 (m, 4H), 3.18 (s, 3H), 2.23-2.09 (m, 1H), 1.84-1.62 (m, 7H), 1.60-1.50 (m, 2H), 1.42-1.34 (m, 2H), 1.33-1.22 (m, 6H), 1.19-1.03 (m, 2H), 1.00-0.84 (m, 3H), 0.79 (s, 3H), 0.73-0.65 (m, 4H).

Synthesis of 30.4

[0582] Concentrated H_2SO_4 (35.1 mL) was diluted with H_2O (140 mL). CrO_3 (31.5 g, 316 mmol) was added. The fresh prepared reagent was added to a solution of **30.3** (24 g, 66.0 mmol) in AcOH (300 mL). After stirring at 70°C for 3 h to give a green solution, the mixture

was diluted with water (300 mL) and extracted with DCM (3 x 300 mL). The combined organic phase was washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **30.4** (30 g), which was used directly for next step without further purification.

Synthesis of 30.5

[0583] To a solution of **30.4** (30 g) in Ac_2O (250 mL) was added NaOAc (23.9 g, 292 mmol). After stirring at 130°C for 16 h to give a solution, the reaction mixture was quenched with water (100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (10%~20% of EtOAc in PE) to give **30.5** (8 g).

Synthesis of 30.6

[0584] To a solution of **30.5** (8 g, 23.0 mmol) in MeOH (100 mL) was added $NaBH_4$ (2.61 g, 69.0 mmol) at 25°C. After stirring at 25°C for 30 min, the reaction was quenched with water (100 mL) and extracted with DCM (2 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column (15%~20% of EtOAc in PE) to give **30.6** (5.9 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.47-4.31 (m, 1H), 3.63 (s, 3H), 3.19 (s, 3H), 2.80-2.76 (m, 1H), 2.24-2.06 (m, 2H), 1.85-1.64 (m, 5H), 1.60-1.43 (m, 7H), 1.32-1.23 (m, 3H), 1.21-1.04 (m, 2H), 1.02-0.93 (m, 2H), 0.90 (s, 3H), 0.74 (s, 3H).

Synthesis of 30.7

[0585] To a solution of **30.6** (5.9 g, 16.8 mmol) in THF (100 mL) was added MeMgBr (16.7 mL, 50.4 mmol, 3M) at -78°C under N_2. The reaction was warmed to 25°C and stirred at 25°C for 1 h. Then the reaction was quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column (10%~15% of EtOAc in PE) to give **30.7** (4.2 g, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.46-4.35 (m, 1H), 2.53 (t, J = 9.0 Hz, 1H), 2.26-2.02 (m, 5H), 2.03-1.94 (m, 1H), 1.75-1.58 (m, 3H), 1.55-1.47 (m, 3H), 1.46-1.37 (m, 5H), 1.36-1.27 (m, 1H), 1.27-1.09 (m, 4H), 0.91 (s, 3H), 0.88-0.79 (m, 1H), 0.79-0.70 (m, 1H), 0.61 (s, 3H).

Synthesis of 30.8

[0586] To a solution of trimethylsulfonium iodide (141 mg, 1.84 mmol) in DMSO (2 mL) was added NaH (73.5 mg, 1.84 mmol, 60 % in oil) in THF (1 mL) and stirred at 0°C for 1.0 h under N_2.. Subsequently a solution of **30.7** (222.9 mg, 0.73 mmol) in DMSO (2 mL) was added at 0°C. After stirring at 25°C for 16 hrs, the reaction was treated with water (5 mL) and extracted with EtOAc (2 x 5 mL). The combined organic phase was washed with water (2 x 5 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give **30.8** (900 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.40-4.39 (m, 1H), 3.68-3.49 (m, 1H), 3.25 (s, 1H), 2.61 (s, 1H), 2.49 (s, 1H), 2.33 (s, 1H), 2.04 (s, 3H), 1.75-1.65 (m, 4H), 1.52-1.45 (m, 4H), 1.37 (s, 10H), 0.79 (s, 7H)

Synthesis of 30.9

[0587] To a solution of **30.8** (900 mg, 2.82 mmol) in DMF (10 mL) was added 4-cyanopyrazole (1.04 g, 11.2 mmol) and Cs_2CO_3 (2.75 g, 8.46 mmol). After stirring at 120°C for 16 hrs under N_2, the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was concentrated to give **30.9** (200 mg), which was purified by SFC (Column: DAICEL CHIRALPAK AS (250 mm*30 mm, 10 um); Condition: 0.1%NH3H2O ETOH; Begin B: 35%; End B: 35%) to afford (100 mg, 50.2%). The solid was triturated from MeCN (2 mL) at 25°C to give **30.9** (84 mg, 84.0%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.88 (s, 1H), 7.80 (s, 1H), 4.45-4.35 (m, 1H), 4.18-4.12 (m, 1H), 4.04-3.98 (m, 1H), 2.26 (s, 1H), 2.04 (s, 4H), 1.75-1.65 (m, 3H), 1.45-1.31 (m, 6H), 1.26-1.14 (m, 4H), 1.11-0.97 (m, 5H), 0.89 (d, *J*=13.6 Hz, 8H), 0.74-0.66 (m, 1H). **LC-ELSD/MS** purity 99%, MS ESI calcd for $C_{25}H_{34}N_3$ $[M-2H_2O+H]^+$ 376.3 found 376.3, analytic **SFC** 100% de.

Synthesis of 30.10

[0588] To a solution of **30.9** (34 mg, 0.083 mmol) in DCM (1 mL) was added Dess-Martin reagent (70 mg, 0.16 mmol) at 20°C. After stirring at 20°C for 15 mins, the mixture was poured into saturated $NaHCO_3$/$Na_2S_2O_3$ aqueous (1:1, 20 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give product, which was purified by prep-HPLC (column: Phenomenex Gemini-NX 80 mm* 40 mm* 3 um, condition: water (0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN, begin B: 51, end B: 81, gradient time: 8 min, 100%B Hold Time: 2.3 min, flow rate: 30 mL/min) to give **30.10** (5.8 mg, 38.9%). **^{1}H**

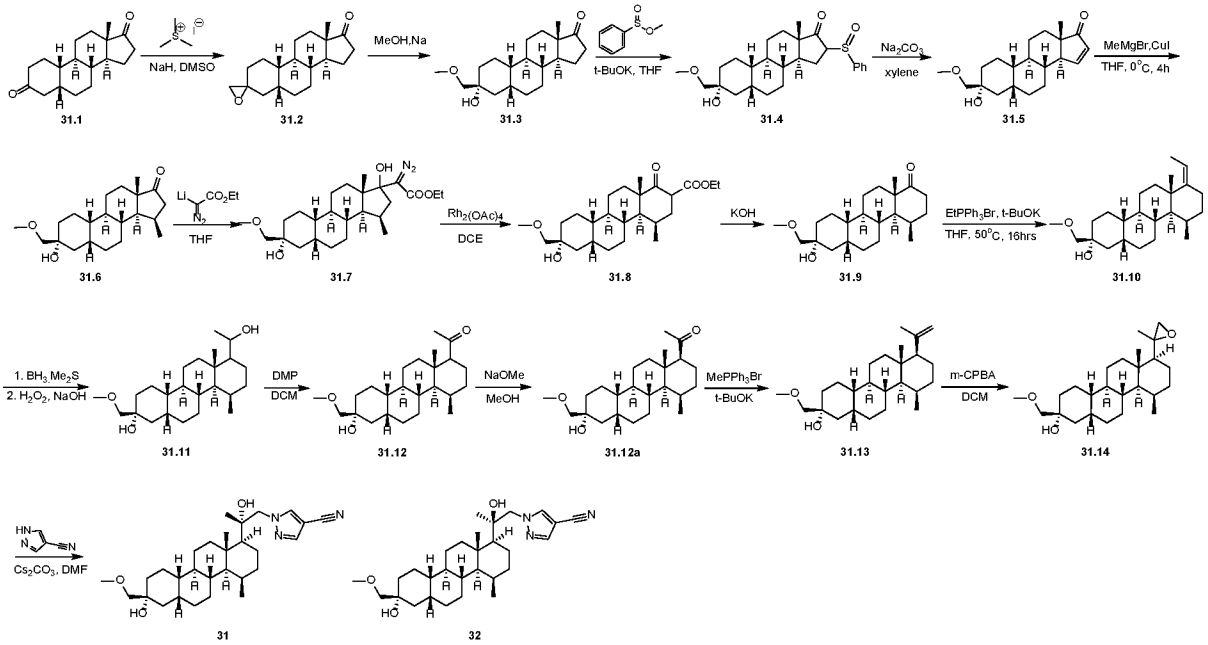
NMR (400 MHz, $CDCl_3$) δ_H 7.88 (s, 1H), 7.80 (s, 1H), 4.21-4.11 (m, 1H), 4.05-3.96 (m, 1H), 2.35 (s, 1H), 2.22-1.82 (m, 7H), 1.81-1.62 (m, 5H), 1.52-1.40 (m, 4H), 1.35-1.15 (m, 3H), 1.09 (s, 3H), 1.05-0.95 (m, 2H), 0.89 (s, 3H), 0.84 (s, 3H). **LC-ELSD/MS** purity 99%, MS ESI calcd for $C_{25}H_{34}N_3O$ $[M-H_2O+H]^+$ 392.4 found 392.4.

Synthesis of 30

[0589] To a solution of *n*-PrMgCl (0.73 ml, 1.46 mmol, 2 M in ether) in THF (1 mL) was added a solution of **30.10** (100 mg, 0.24 mmol) in THF (1 mL) dropwise at -40°C under N_2. After stirring for 2 hrs at -40°C, the mixture was poured into NH_4Cl (1 mL) and extracted with EtOAc (2 x 5 mL). The combined organic phase was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **30** (68 mg), which was purified by SFC (Column: DAICEL CHIRALPAK AS (250 mm* 30 mm, 10 um); Condition: 0.1%NH_3H_2O ETOH; Begin B: 25%; End B: 25%) to afford (6.6 mg, 9.72%).

[0590] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.89 (s, 1H), 7.80 (s, 1H), 4.21-4.10 (m, 1H), 4.06-3.96 (m, 1H), 2.28 (s, 1H), 2.10-1.97 (m, 1H), 1.95-1.80 (m, 1H), 1.78-1.75 (m, 1H), 1.72-1.59 (m, 5H), 1.54-1.36 (m, 9H), 1.35-1.13 (m, 8H), 1.09 (s, 3H), 0.95-0.91 (m, 6H), 0.87 (s, 3H), 0.75-0.65 (m, 1H). **LC-ELSD/MS** purity 99%, MS ESI calcd for $C_{28}H_{40}N_3$ $[M-2H_2O+H]^+$ 418.4 found 418.4, analytic **SFC** 100% de.

Example 31 & 32: 1-((S)-2-hydroxy-2-((1S,4R,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8-(methoxymethyl)-4,12a-dimethyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (31) & 1-((R)-2-hydroxy-2-((1S,4R,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-8-(methoxymethyl)-4,12a-dimethyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (32)



Synthesis of 31.2

[0591] A stirred solution of iodotrimethyl-4-sulfane (27.1 g, 133.0 mmol) and NaH (5.31 g, 133.0 mmol, 60%) in DMSO (300 mL) was cooled at 0°C for 1 h under N_2. The mixture was added to a solution of **31.1** (35 g, 127.0 mmol) in DMSO (100 mL) at 25°C for 16 hrs. The reaction was treated with water (300 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phase was washed with water (2 x 200 mL), brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **31.2** (40 g).

Synthesis of 31.3

[0592] To a freshly prepared MeONa (693.0 mmol) in MeOH (400 mL) was added **31.2** (20 g, 69.3 mmol) and the resulting mixture was stirred at 70°C for 16 hrs. The reaction was treated with water (200 mL). The aqueous phase was extracted with EtOAc (2 x 200 mL). The combined organic phase was washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column (0~30% of EtOAc in PE) to give **31.3** (10 g, 47.8%). **H NMR** (400 MHz, $CDCl_3$) δ_H 3.41-3.36 (m, 5H), 2.61 (s, 1H), 1.97-1.73 (m, 5H), 1.68-1.33 (m, 10H), 1.32-0.99 (m, 8H), 0.91-0.81 (m, 3H).

Synthesis of 31.4

[0593] To a solution of t-BuOK (13.2 g, 118 mmol) in THF (400 mL) was added **31.3** (19 g, 59.2 mmol) at 15°C under N_2. The mixture was stirred at 15°C for 10 min. Then methyl

benzenesulfinate (14.9 mL, 118 mmol) was added. The mixture was stirred at 30°C for 0.5 h. The mixture was quenched with H_2O (500 mL) and extracted with EtOAc (2 x 300 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **31.4** (27 g).

Synthesis of 31.5

[0594] To a mixture of **31.4** (27 g, 60.7 mmol) in xylene (300 mL) was added Na_2CO_3 (98.2 g, 910 mol) in portions. After stirring at at 125°C for 12 hrs under N_2, the mixture was filtered and concentrated. The residue was purified by silica gel chromatography (0~30% of EtOAc in PE) to give **31.6** (6.2 g, 32.1%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.52 (br d, J = 5.8 Hz, 1H), 6.02 (dd, J = 3.1, 5.9 Hz, 1H), 3.47-3.29 (m, 5H), 2.61 (br s, 1H), 2.37 (br d, J = 10.0 Hz, 1H), 1.91-1.58 (m, 11H), 1.53-1.29 (m, 7H), 1.07 (s, 3H).

Synthesis of 31.6

[0595] To a solution of MeMgBr (19.4 mL, 58.2 mmol, 3 M) in THF (40 mL) was added CuI (11.0 g, 58.2 mmol) at 0°C. After stirring at 0°C for 1 hour, **31.5** (6.2 g, 19.4 mmol) in THF (40 mL) was added at 0°C. After stirring at 0°C for 3 hours, the mixture was poured into saturated NH_4Cl (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column (0%~40% of EtOAc in PE) to give **31.6** (4.5 g, 69.4%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.46-3.34 (m, 5H), 2.53-2.19 (m, 3H), 1.88-1.56 (m, 10H), 1.53-1.29 (m, 8H), 1.24-1.17 (m, 2H), 1.10 (d, J = 7.3 Hz, 3H), 1.03 (s, 3H).

Synthesis of 31.7

[0596] To a solution of **31.6** (4.5 g, 13.4 mmol) and ethyl diazoacetate (6.11 g, 53.6 mmol) in THF (150 mL) was added a freshly prepared LDA (53.6 mL, 1.0 M, 53.6 mmol) at -78°C. After stirring at -78°C for 3 h, acetic acid (3.21 g, 53.6 mmol) in THF (50 mL) was added. Then the resulting reaction mixture was stirred at 15°C for 16 h. The mixture was poured into water (150 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give **31.7** (9.0 g).

Synthesis of 31.8

[0597] To a solution of **31.7** (9.0 g) in DME (100 mL) was added $Rh_2(OAc)_4$ (220 mg, 0.5 mmol) in one portion at 15°C. After stirring at 15°C for 12 hours, the mixture was concentrated to give **31.8** (9 g).

Synthesis of 31.9

[0598] To a solution of **31.8** (9 g) in MeOH (100 mL) was added KOH (11.9 g, 213 mmol) at 15°C. After stirring at at 70°C for 1 h, the reaction mixture was poured into H_2O (50 mL), and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column (0~15% of EtOAc in PE) to give **31.9** (2.3 g, 30.9%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.47-3.30 (m, 5H), 2.79 (ddd, J = 7.7, 12.1, 14.4 Hz, 1H), 2.22-2.10 (m, 2H), 1.93-1.47 (m, 13H), 1.46-1.28 (m, 7H), 1.16 (s, 3H), 1.06 (d, J = 7.5 Hz, 3H), 0.99-0.74 (m, 2H).

Synthesis of 31.10

[0599] To a suspension of Ph_3PEtBr (12.2 g, 32.9 mmol) in anhydrous THF (80 mL) was added t-BuOK (3.69 g, 32.9 mmol) at 15°C under N_2 and the suspension was stirred at 60°C for 30 min. Then a solution of **31.9** (2.3 g, 6.59 mmol) in anhydrous THF (50 mL) was dropwise. After stirring at 60°C for 16 h, the mixture was cooled and poured into ice-water (100 mL) and stirred for 10 min. The aqueous phase was extracted with EtOAc (2 x 100 mL). The combine organic phase was washed with brine (2 x 200 mL), filtered, concentrated and purified by flash column (0~10% of EtOAc in PE) to give **31.10** (1.9 g, 80.1%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.26-5.03 (m, 1H), 3.45-3.30 (m, 5H), 2.55 (br s, 1H), 2.40 (td, J = 3.4, 14.0 Hz, 1H), 2.29-2.18 (m, 1H), 2.15-2.01 (m, 2H), 1.89 (br d, J = 13.8 Hz, 1H), 1.80-1.58 (m, 9H), 1.50-1.13 (m, 11H), 1.09-1.03 (m, 1H), 1.00 (s, 3H), 0.90 (dd, J = 7.4, 15.7 Hz, 4H).

Synthesis of 31.11

[0600] To a solution of **31.10** (1.8 g, 4.99 mmol) in THF (50 mL) was added $BH_3.Me_2S$ (14.9 mL , 14.9 mmol, 1 M in THF) at 25°C. After stirring at 50°C for 16 hours, the reaction mixture was cooled and quenched with EtOH (3.18 mL, 2.29 g, 49.9 mmol) at 0°C, followed by adding NaOH (9.97 mL, 5M, 49.9 mmol) very slowly. After the addition, H_2O_2 (4.98 mL, 49.9 mmol, 10 M in water) was added slowly until the inner temperature no longer rised and

the inner temperature was maintained below 30°C. The mixture was stirred at 50°C for another 1 h. The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with saturated $Na_2S_2O_3$ (2 x 100 mL), brine (2 x 100 mL), drive over anhydrous Na_2SO_4, filtered and concentrated to give **31.11** (1.8 g).

Synthesis of 31.12

[0601] To a solution of **31.11** (1.8 g, 4.93 mmol) in DCM (50 mL) was added Dess-Martin reagent (4.18 g, 9.86 mmol). After stirring at 25°C for 30 mins, the mixture was quenched by saturated $NaHCO_3$ aqueous (30 mL). The DCM phase was separated and washed with saturated $NaHCO_3/Na_2S_2O_3$ aqueous (1:1, 2 x 30 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **31.12** (1.8 g).

Synthesis of 31.12a

[0602] To a solution of **31.12** (1.9 g, 5.04 mmol) in MeOH (100 mL) at 0°C was added MeONa (4.08 g, 75.6 mmol). After stirring at 70°C for 16 h, the residue was poured into saturated NH_4Cl (100 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **31.12a** (2.1 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.45-3.34 (m, 5H), 2.60 (br s, 1H), 2.28 (dd, J = 2.9, 12.6 Hz, 1H), 2.16 (s, 3H), 2.05-1.61 (m, 9H), 1.48-1.14 (m, 12H), 1.08-0.94 (m, 6H), 0.84 (d, J = 7.5 Hz, 3H).

Synthesis of 31.13

[0603] To a suspension of $MePh_3PBr$ (3.28 g, 9.29 mmol) in anhydrous THF (20 mL) was added t-BuOK (1.04 g, 9.29 mmol) at 15°C under N_2. Ater stirring at 60°C for 30 min, then a solution of **31.12a** (350 mg, 0.93 mmol) in anhydrous THF (10 mL) was added dropwise. After stirring at 60°C for 16 h, the mixture was cooled and poured into ice-water (50 mL) and stirred for 10 min. The aqueous phase was extracted with EtOAc (2 x 50 mL).The combined organic phase was washed with brine (100 mL), filtered, concentrated and purified by flash column (0~10% of EtOAc in PE) to give **31.13** (280 mg, 80.4%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.80 (s, 1H), 4.62 (d, J = 2.0 Hz, 1H), 3.47-3.23 (m, 5H), 2.55 (br s, 1H), 2.01 (br d, J = 5.0 Hz, 1H), 1.90-1.57 (m, 11H), 1.49-1.14 (m, 10H), 1.11-0.91 (m, 4H), 0.89 (s, 3H), 0.88-0.84 (m, 2H), 0.82 (d, J = 7.5 Hz, 3H).

Synthesis of 31.14

[0604] To a solution **31.13** (280 mg, 0.747 mmol) in DCM (5 mL) was added $NaHCO_3$ (125 mg, 1.49 mmol). Then m-CPBA (301 mg, 1.49 mmol) was added to the mixture at 0°C under N_2. After stirring at 25 °C for 0.5 h, the mixture was quenched with saturated $NaHCO_3$ (20 mL), the mixture was extracted with DCM (2 x 20 mL). The combined organic layer was washed with $Na_2S_2O_3$ (2 x 20 mL, sat.), brine (2 x 40 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give **31.14** (200 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.40 (s, 5H), 2.74 (d, J = 4.8 Hz, 1H), 2.65 (d, J = 4.8 Hz, 1H), 2.11-1.81 (m, 2H), 1.80-1.47 (m, 13H), 1.44-1.34 (m, 4H), 1.26 (s, 6H), 1.00 (s, 3H), 0.98-0.91 (m, 2H), 0.81 (d, J = 7.5 Hz, 3H).

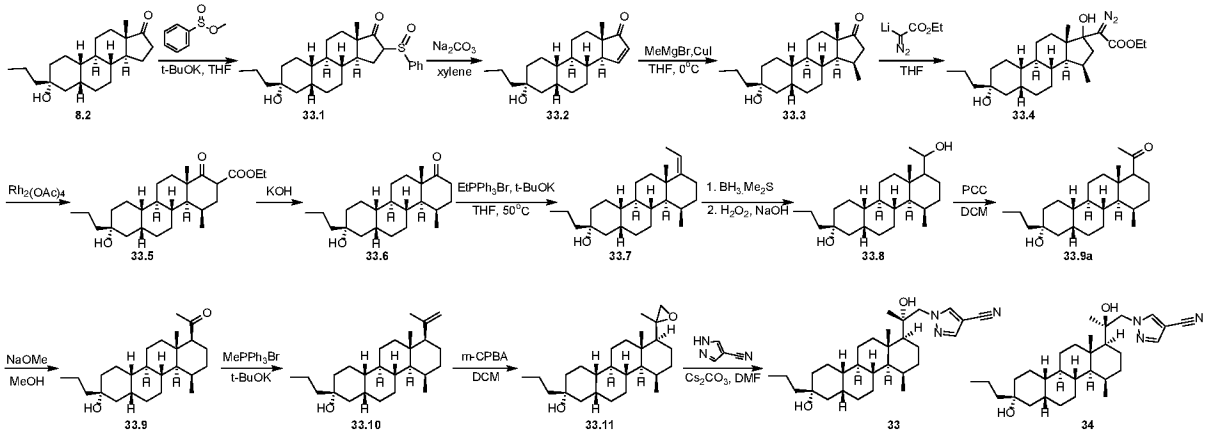
Synthesis of 31 & 32

[0605] To a solution of **31.14** (200 mg, 0.512 mmol) in DMF (3 mL) was added 1H-pyrazole-4-carbonitrile (94.8 mg, 1.02 mmol) and Cs_2CO_3 (498 mg, 1.53 mmol) at 20 °C. After stirring at 130 °C for 72 hours, to the mixture was added water (20 mL) and the mixture was extracted with EtOAc (2 x 30 mL). The organic layer was separated, concentrated and purified by flash column (0~30% EtOAc in PE) to give **31 & 32** (140 mg). The two diastereomers were purified by SFC (Column: DAICEL CHIRALCEL OD-H (250 mm*30 mm, 5 um), Condition: 0.1% NH_3H_2O ETOH Begin B 35% End B 35%, Gradient Time (min) 100%B, Hold Time (min), Flow Rate (ml/min) 60, Injections 60) to afford **31** (Peak 1, Rt = 3.513 min, 8.1 mg) and **32** (Peak 2, Rt = 3.933 min, 56.9 mg). Compound **31** was further purified by SFC (Column: DAICEL CHIRALCEL OD-H (250 mm*30 mm, 5 um), Condition: 0.1% NH_3H_2O ETOH Begin B 35% End B 35%, Gradient Time (min) 100%B, Hold Time (min), Flow Rate (ml/min) 60, Injections 60) to afford **31** (Peak 1, Rt = 1.598 min, 4.2 mg).

[0606] **31** **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.88 (d, J = 1.5 Hz, 2H), 4.30 (d, J = 13.8 Hz, 1H), 4.03 (d, J = 13.8 Hz, 1H), 3.43-3.35 (m, 5H), 2.53-2.39 (m, 1H), 2.05-1.92 (m, 1H), 1.88-1.80 (m, 1H), 1.77-1.65 (m, 3H), 1.64-1.47 (m, 3H), 1.46-1.24 (m, 9H), 1.20 (s, 5H), 1.11 (s, 3H), 1.06-0.85 (m, 6H), 0.80 (d, J = 7.5 Hz, 3H), 0.76-0.71 (m, 1H)**. LC-ELSD/MS** purity 99%, MS ESI calcd. For $C_{28}H_{38}N_3$ $[M\text{-}2H_2O\text{-}MeOH+H]^+$ 416.3 found 416.3. **SFC** 99% de.

[0607] **32** **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.92 (s, 1H), 7.80 (s, 1H), 4.45-4.35 (m, 1H), 4.30-4.21 (m, 1H), 3.41 (s, 5H), 2.59 (s, 1H), 2.37 (s, 2H), 2.11-1.97 (m, 1H), 1.90-1.82 (m, 1H), 1.78-1.62 (m, 5H), 1.57-1.54 (m, 7H), 1.48-1.32 (m, 6H), 1.31-1.15 (m, 4H), 1.11 (s, 3H), 1.02 (s, 3H), 0.82 (d, J = 7.4 Hz, 3H). **LC-ELSD/MS** purity 99%, MS ESI calcd. For $C_{28}H_{38}N_3$ $[M\text{-}2H_2O\text{-}CH_3OH+H]^+$ 416.3 found 416.3. **SFC** 99% de.

Example 33 & 34: 1-((S)-2-hydroxy-2-((1S,4R,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-4,12a-dimethyl-8-propyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (33) & 1-((R)-2-hydroxy-2-((1S,4R,4aS,4bR,6aR,8R,10aS,10bR,12aS)-8-hydroxy-4,12a-dimethyl-8-propyloctadecahydrochrysen-1-yl)propyl)-1H-pyrazole-4-carbonitrile (34)



Synthesis of 33.1

[0608] To a solution of t-BuOK (14.6 g, 131 mmol) in THF (250 mL) was added **8.2** (21 g, 65.9 mmol) at 25°C under N_2. After stirring at 25°C for 10 min, methyl benzenesulfinate (20.4 g, 131 mmol) was added. The mixture was stirred at 30°C for 0.5 h. The mixture was quenched by H_2O (200 mL) and extracted with EtOAc (3 x 200 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **33.1** (40 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.70-7.56 (m, 5H), 3.57-3.55 (m, 1H), 2.47-2.43 (m, 1H), 2.35-1.66 (m, 8H), 1.62-1.29 (m, 12H), 1.28-0.93 (m, 11H).

Synthesis of 33.2

[0609] To a mixture of **33.1** (40 g, 90.3 mmol) in xylene (200 mL) was added Na_2CO_3 (143 g, 1.35 mmol) in portions. After stirring at 130°C for 12 hrs under N_2, the mixture was filtered and concentrated, the residue was purified by silica gel chromatography (0-15% of

EtOAc in PE) to give the product **33.2** (7.8 g, 27%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.53-7.51 (dd, J = 6Hz, 1H), 6.03-6.01 (m, 1H), 2.38-2.35 (m, 1H), 1.88-1.50 (m, 10H), 1.49-1.20 (m, 13H), 1.07 (s, 3H), 0.94 (t, J = 7.6Hz, 3H).

Synthesis of 33.3

[0610] To a solution of MeMgBr (24.6 mL, 73.8 mmol, 3 M) in THF (100 mL) was added CuI (14.0 g, 73.8 mmol) at 0°C. After stirring at 0°C for 1 hour, then **33.2** (7.8 g, 24.6 mmol) in THF (100 mL) was added at 0°C. After stirring at 0°C for 3 hours, the mixture was poured into saturated NH_4Cl (100 mL) and extracted with EtOAc (2 x 500 mL). The combined organic layer was washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column (0~20% of EtOAc in PE) to give **33.3** (6.5 g, 79.4%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.50-2.21 (m, 3H), 1.87-1.44 (m, 13H), 1.43-1.14 (m, 11H), 1.10-1.08 (m, 3H), 1.03 (s, 3H), 0.94 (t, J = 7.2Hz, 3H).

Synthesis of 33.4

[0611] To a solution of **33.3** (6.5 g, 19.5 mmol) and ethyl diazoacetate (11.1 g, 97.5 mmol) in THF (600 mL) was added a freshly prepared LDA (48.7 mL, 2 M, 97.5 mmol) at -78°C. After stirring at -78°C for 2 hrs, then acetic acid (5.85 g, 97.5 mmol) in THF (20 mL) was added. After stirring at 15°C for 16 hrs, the mixture was poured into water (1000 mL). The aqueous phase was extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (1500 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give **33.4** (13 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.27-4.22 (m, 2H), 2.27-2.20 (m, 1H), 1.99-1.52 (m, 7H), 1.48-1.33 (m, 9H), 1.32-1.06 (m, 14H), 1.03-0.97 (m, 6H), 0.93 (t, J = 7.2Hz, 3H).

Synthesis of 33.5

[0612] To a solution of **33.4** (13 g) in DME (300 mL) was added $Rh_2(OAc)_4$ (385 mg, 0.873 mmol) in one portion at 15°C. After stirring at 15°C for 12 hours, the mixture was concentrated to give **33.5** (12.5 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.48-4.11 (m, 2H), 2.31-1.56 (m, 5H), 1.50-1.33 (m, 7H), 1.31-1.17 (m, 15H), 1.16-1.01 (m, 8H), 0.88-0.85 (m, 3H), 0.78-0.76 (m, 2 H).

Synthesis of 33.6

[0613] To a mixture of **33.5** (12.5 g, 29.8 mmol) in MeOH (150 mL) was added KOH (9.98 g, 178 mmol). After stirring at 70°C for 2 hrs to give a mixture, the reaction mixture was concentrated. Then H_2O (300 mL) was added. The mixture was extracted with EtOAc (3 x 200 mL). The combined organic phase was washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column (0-20% of EtOAc in PE) to give **33.6** (4.5 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.84-2.75 (m, 1H), 2.18-2.12 (m, 2H), 1.88-1.52 (m, 11H), 1.49-1.21 (m, 13H), 1.16 (s, 3H), 1.10-0.97 (m, 5H), 0.93 (t, J = 7.2Hz; 3H).

Synthesis of 33.7

[0614] To a suspension of $EtPPh_3Br$ (10.6 g, 28.8 mmol) in anhydrous THF (150 mL) was added t-BuOK (3.23 g, 28.8 mmol) at 15°C under N_2. After stirring at 60°C for 30 mins, a solution of **33.6** (2 g, 5.77 mmol) in anhydrous THF (50 mL) was added. The reaction mixture was stirred for 16 hrs. The mixture was cooled and poured into ice-water (200 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL). The combine organic phase was washed with brine (2 x 100 mL), filtered, concentrated and purified by flash column (0~10% of EtOAc in PE) to give **33.7** (1.3 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.18-5.13 (m, 1H), 2.42-2.38 (m, 1H), 2.27-2.00 (m, 2H), 1.88-1.58 (m, 7H), 1.56-1.41 (m, 6H), 1.40-1.16 (m, 13H), 1.09-0.83 (m, 12H).

Synthesis of 33.8

[0615] To a solution of **33.7** (1.3 g, 3.62 mmol) in THF (30 mL) was added $BH_3.Me_2S$ (2.17 mL, 21.7 mmol, 10 M). After stirring at 25°C for 16 hours, the mixture was added ethanol (4.22 mL, 72.4 mmol) at 15°C, followed by NaOH aqueous (14.4 mL, 5.0 M, 72.4 mmol) at 0°C. Hydrogen peroxide (7.24 mL, 10 M, 72.4 mmol) was added dropwise at 0°C. The reaction mixture was stirred at 70°C for 1 hour. The mixture was cooled to 15°C and $Na_2S_2O_3$ (100 mL, sat. aq.) was added. The aqueous was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash column (0~50% of EtOAc in PE) to give **33.8** (1.4 g).**^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.14-4.05 (m, 1H), 2.04-1.41 (m, 15H), 1.40-1.08 (m, 15H), 1.05-0.77 (m, 13H).

Synthesis of 33.9

[0616] To a solution of **33.8** (1.2 g, 3.18 mmol) in DCM (20 mL) was added DMP (2.69 g, 6.36 mmol) at 25°C. After stirring at 25°C for 30 mins, the mixture was quenched by saturated $NaHCO_3$ aqueous (30 mL) and extracted with DCM (3 x 100 mL). The combined organic layer was washed with NaS_2O_3 (3 x 100 mL) and concentrated. The residue was purified by flash column (0~15% of EtOAc in PE) to give **33.9a** (800 mg). To a solution of **33.9a** (800 mg, 2.13 mmol) in MeOH (20 mL) at 0°C was added MeONa (1.72 g, 31.9 mmol). After stirring at 70°C for 16 hrs, then the mixture was added saturated NH_4Cl (100 mL). The aqueous phase was extracted with EtOAc (2 x 200 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column (0~15% of EtOAc in PE) to give **33.9** (600 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.28-2.24 (m, 1H), 2.14-2.11 (m, 3H), 2.02-1.97 (m, 1H), 1.96-1.58 (m, 7H), 1.50-1.28 (m, 9H), 1.27-1.00 (m, 8H), 0.99 (s, 3H), 0.95-0.82 (m, 10H).

Synthesis of 33.10

[0617] To a mixture of $MePPh_3Br$ (4.71 g, 13.2 mmol) in THF (50 mL) was added t-BuOK (1.48 g, 13.2 mmol) at 20°C under N_2. After stirring at 60°C for 30 min, **33.9** (500 mg, 1.33 mmol) in THF (10 mL) was added in portions below 60°C. The reaction mixture was stirred at 60°C for 16 hours. The reaction mixture was quenched with 10% NH_4Cl aqueous (100 mL) at 15°C and extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine (100 mL), filtered, concentrated under reduced pressure and purified by flash column (0~5% ethyl acetate in PE) to give **33.10** (380 mg, 76.7 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.79 (s, 1H), 4.62 (s, 1H), 2.04-1.96 (m, 1H), 1.85-1.70 (m, 6H), 1.668-1.47 (m, 7H), 1.46-1.13 (m, 12H), 1.09-0.89 (m, 11H), 0.88-0.81 (m, 5H).

Synthesis of 33.11

[0618] To a solution **33.10** (190 mg, 0.509 mmol) in DCM (10 mL) was added $NaHCO_3$ (84.8 mg, 1.01mmol) and then m-CPBA (203 mg, 1.01 mmol) at 0°C under N_2. After stirring at 25°C for 0.5 h, the mixture was quenched with saturated $NaHCO_3$ (20 mL) and extracted with DCM (2 x 20 mL). The organic layer was washed with $Na_2S_2O_3$ (2 x 20 mL), brine (2 x 40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **33.11** (400 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.74-2.64 (m, 2H), 2.04-1.41 (m, 10H),

1.40-1.27 (m, 10H), 1.24 (s, 3H), 1.21-1.02 (m, 4H), 0.99 (s, 3H), 0.96-0.91 (m, 7H), 0.84-0.75 (m, 5H).

Synthesis of 33 & 34

[0619] To a solution of **33.11** (400 mg, 1.02 mmol) in DMF (10 mL) was added 1H-pyrazole-4-carbonitrile (284 mg, 3.06 mmol) and Cs_2CO_3 (997 mg, 3.06 mmol). After stirring at 145°C for 72 hrs, the mixture was quenched with water (5 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine (30 mL x 2), dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by column (0~20% of EtOAc in PE) to give **33 & 34** (500 mg), which was purified by SFC twice (Column DAICEL CHIRALCEL OD-H (250 mm* 30 mm, 5 um); Condition 0.1%NH_3H_2O ETOH; Begin B 40%; End B 40%) to give **33** (Peak 1, 17.7 mg, Rt = 3.654 min, 3.5%) and **34** (Peak 2, 82.9 mg, Rt = 4.288 min, 16.5%).

[0620] **33: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.86 (d, J = 2Hz, 2H), 4.31-4.27 (m, 1H), 4.02-3.99 (m, 1H), 3.10 (s, 1H), 2.45-2.43 (m, 1H), 2.00-1.92 (m, 1H), 1.82-1.44 (m, 10H), 1.39-1.13 (m, 15H), 1.10 (s, 3H), 1.00-0.82 (m, 8H), 0.79-0.69 (m, 4H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{30}H_{44}N_3$ $[M-2H_2O+H]^+$ 446.4, found 446.4. analytic **SFC** 100% de.

[0621] **34: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.90 (s, 1H), 7.79 (s, 1H), 4.40-4.37 (m, 1H), 4.27-4.23 (m, 1H), 2.41-2.38 (m, 2H), 2.06-2.01 (m, 1H), 1.85-1.59 (m, 7H), 1.58-1.45 (m, 8H), 1.41-1.16 (m, 12H), 1.10 (s, 3H), 1.07-1.03 (m, 1H), 1.01s (s, 3H), 0.93 (t, J = 7.2Hz, 3H), 0.82-0.80 (m, 3H). **LC-ELSD/MS** purity 99%, MS ESI calcd. for $C_{30}H_{44}N_3$ $[M-2H_2O+H]^+$ 446.4, found 446.4. analytic **SFC** 98% de.

Steroid Inhibition of TBPS Binding

[0622] [^{35}S]-t-Butylbicyclophosphorothionate (TBPS) binding assays using rat brain cortical membranes in the presence of 5 mM GABA has been described (Gee et al, J. Pharmacol. Exp. Ther. 1987, 241, 346-353; Hawkinson et al, Mol. *Pharmacol.* 1994, **46**, 977-985; Lewin, A.H et al., *Mol. Pharmacol.* 1989, ***35, 189-194***).

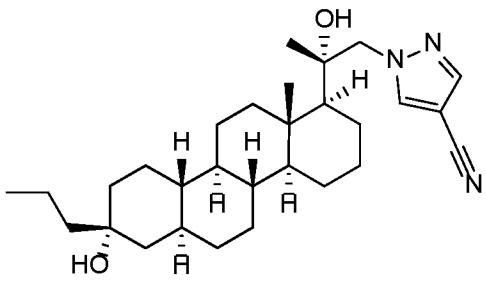
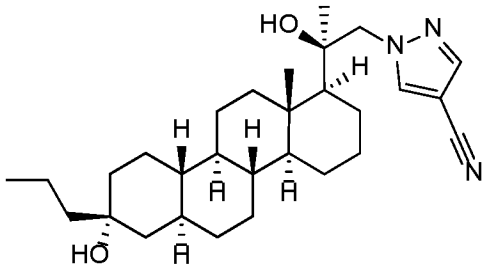
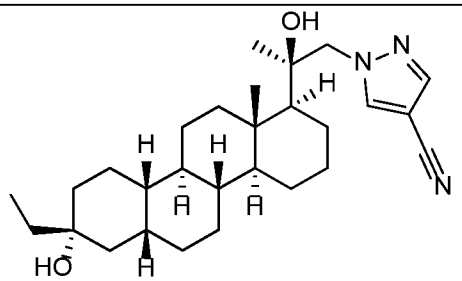
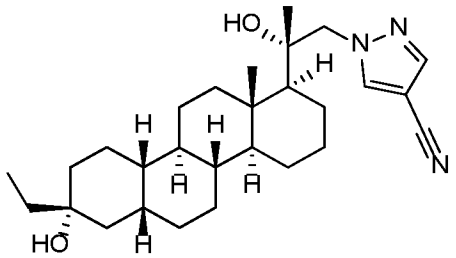
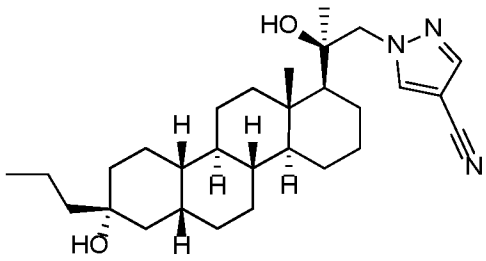
[0623] Briefly, cortices are rapidly removed following decapitation of carbon dioxide-anesthetized Sprague-Dawley rats (200-250 g). The cortices are homogenized in 10 volumes of ice-cold 0.32 M sucrose using a glass/teflon homogenizer and centrifuged at 1500 x *g* for

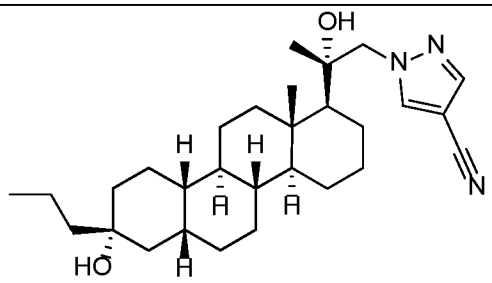
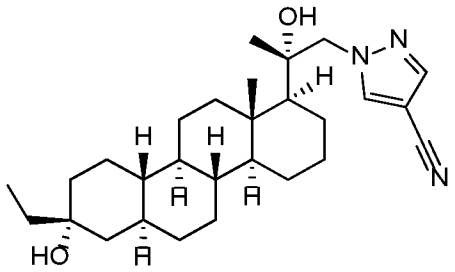
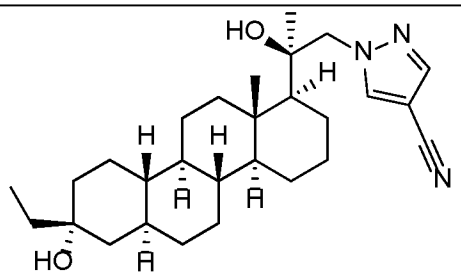
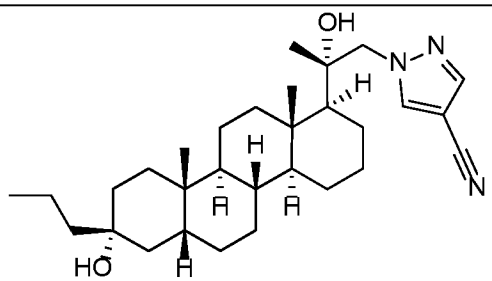
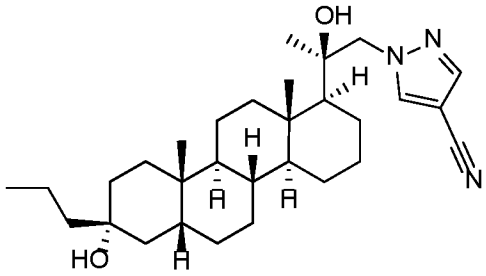
10 min at 4 °C. The resultant supernatants are centrifuged at 10,000 x *g* for 20 min at 4 °C to obtain the P2 pellets. The P2 pellets are resuspended in 200 mM NaCl/50 mM Na-K phosphate pH 7.4 buffer and centrifuged at 10,000 x *g* for 10 min at 4 °C. This washing procedure is repeated twice and the pellets are resuspended in 10 volumes of buffer. Aliquots (100 mL) of the membrane suspensions are incubated with 3 nM [^{35}S]-TBPS and 5 mL aliquots of test drug dissolved in dimethyl sulfoxide (DMSO) (final 0.5%) in the presence of 5 mM GABA. The incubation is brought to a final volume of 1.0 mL with buffer. Nonspecific binding is determined in the presence of 2 mM unlabeled TBPS and ranged from 15 to 25 %. Following a 90 min incubation at room temp, the assays are terminated by filtration through glass fiber filters (Schleicher and Schuell No. 32) using a cell harvester (Brandel) and rinsed three times with ice-cold buffer. Filter bound radioactivity is measured by liquid scintillation spectrometry. Non-linear curve fitting of the overall data for each drug averaged for each concentration is done using Prism (GraphPad). The data are fit to a partial instead of a full inhibition model if the sum of squares is significantly lower by F-test. Similarly, the data are fit to a two component instead of a one component inhibition model if the sum of squares is significantly lower by F-test. The concentration of test compound producing 50% inhibition (IC_{50}) of specific binding and the maximal extent of inhibition (I_{max}) are determined for the individual experiments with the same model used for the overall data and then the means $\pm$ SEM.s of the individual experiments are calculated. Picrotoxin serves as the positive control for these studies as it has been demonstrated to robustly inhibit TBPS binding.

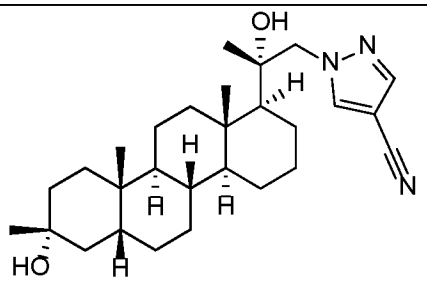
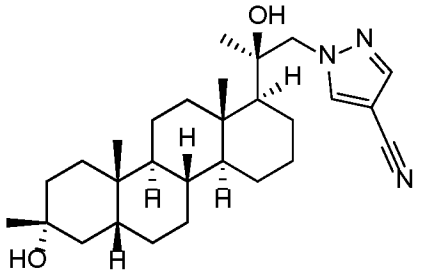
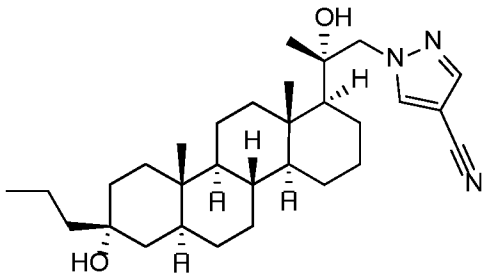
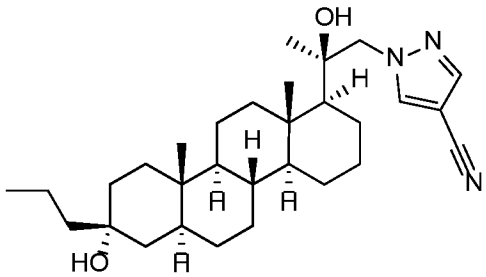
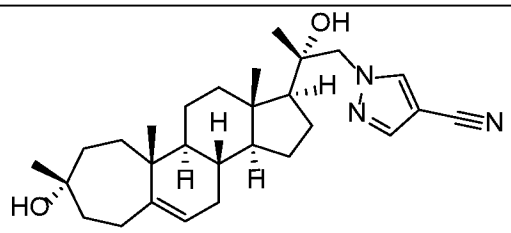
[0624] Various compounds are or can be screened to determine their potential as modulators of [^{35}S]-TBPS binding *in vitro*. These assays are or can be performed in accordance with the above.

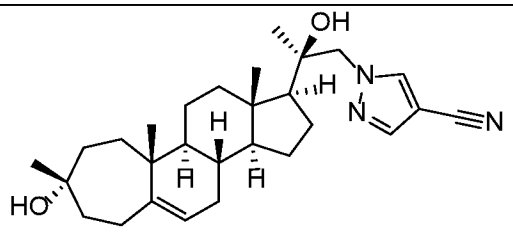
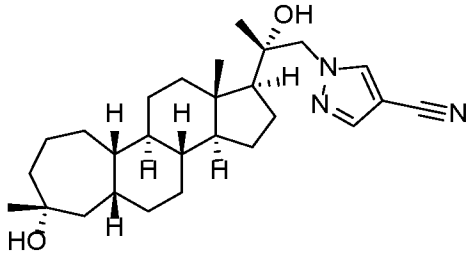
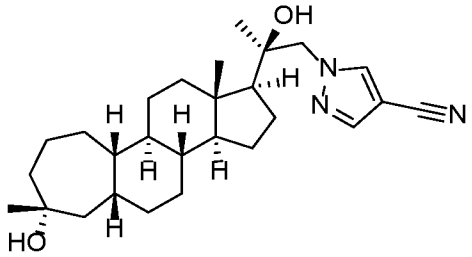
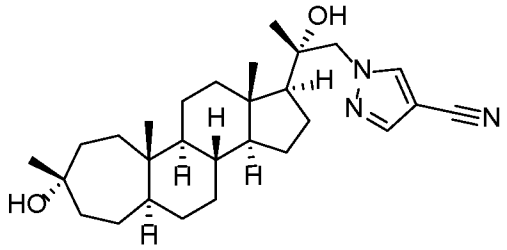
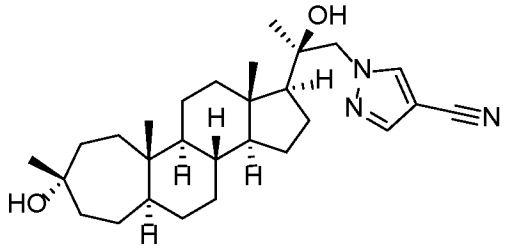
[0625] In **Table 2** below, A indicates a TBPS IC_{50} (μM) < 0.1 μM, B indicates a TBPS IC_{50} (μM) of 0.1 μM to < 1.0 μM, C indicates a TBPS IC_{50} (μM) of ≥ 1.0 μM.

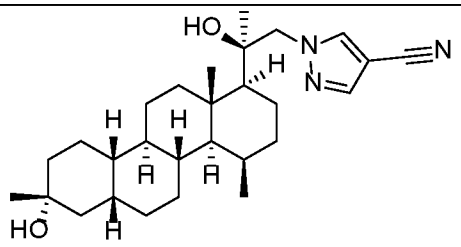
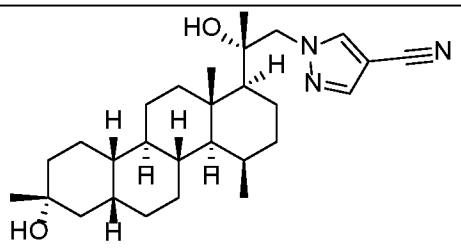
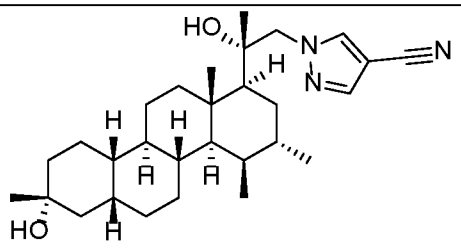
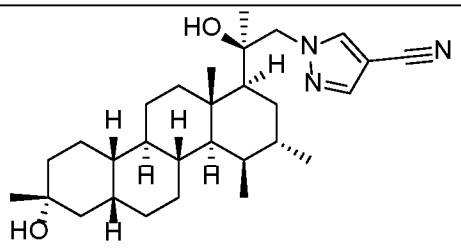
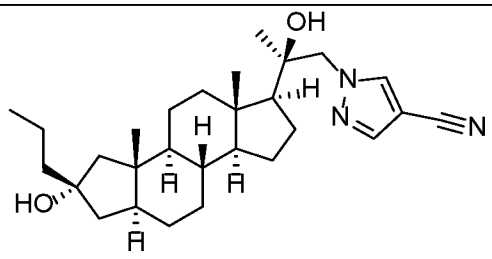
Table 2.

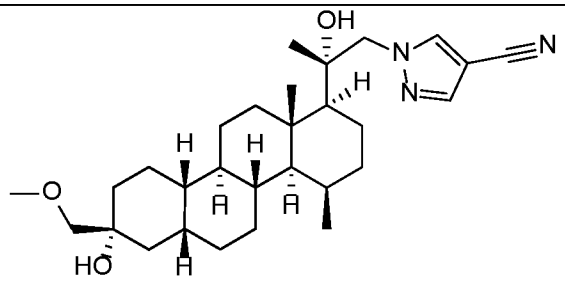
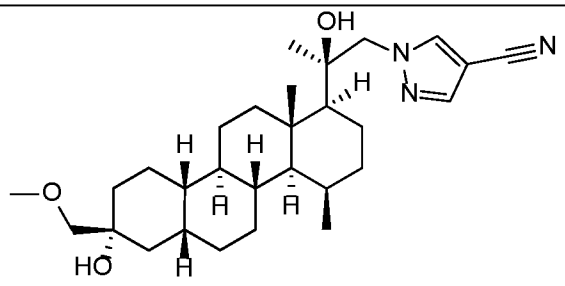
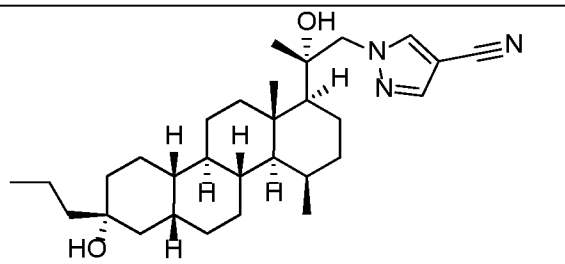
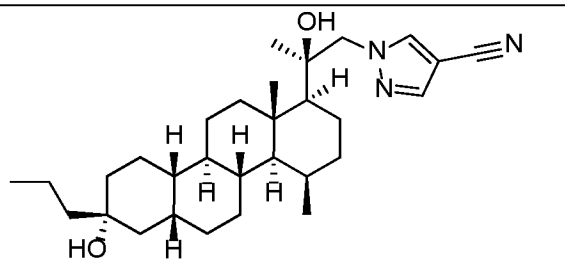
Example No.	STRUCTURE	IC_{50} (μM)
1		B
2		B
6		B
7		B
8		B

9		A
10		B
11		B
12		A
13		B

14		A
15		B
16		B
17		C
18		B

19		A
20		A
21		B
22		C
23		B

24		A
25		A
26		A
27		A
30		C

31		A
32		A
33		A
34		A

Equivalents and Scope

[0626] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is

present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[0627] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub–range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0628] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[0629] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above

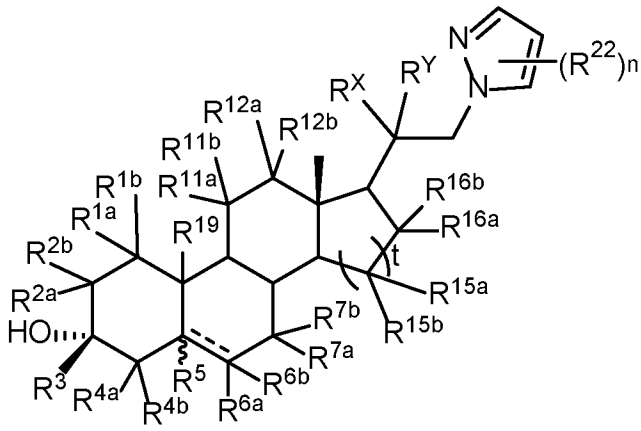
Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

5

CLAIMS

What is claimed:

1. A compound of Formula **I**:



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

------ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl,

substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})\ N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, -

$OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})\ N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

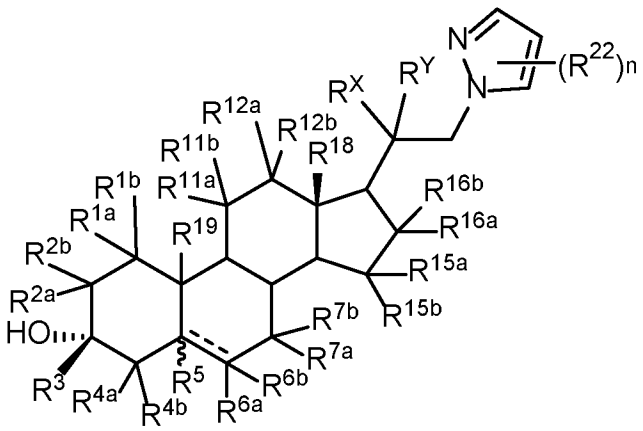
R^{19} is hydrogen or substituted or unsubstituted alkyl;

n is 0, 1, 2, or 3; and

t is 2 or 3.

2. The compound of claim 1, wherein t is 2.

3. A compound of Formula **II**:



(II)

or a pharmaceutically acceptable salt thereof;

wherein:

------ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-}

$_{6}$alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

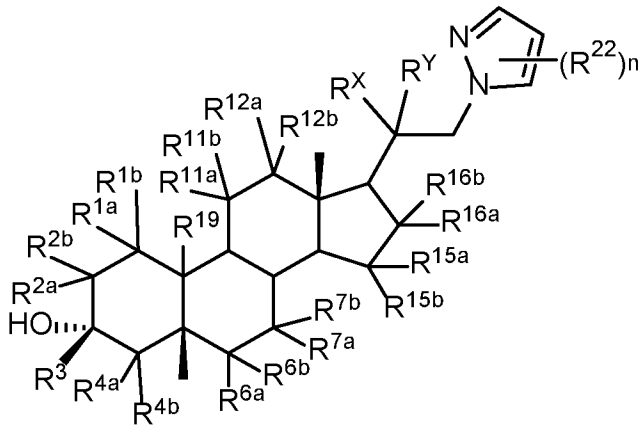
each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, $-OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})\ N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

R^{19} is hydrogen or substituted or unsubstituted alkyl;

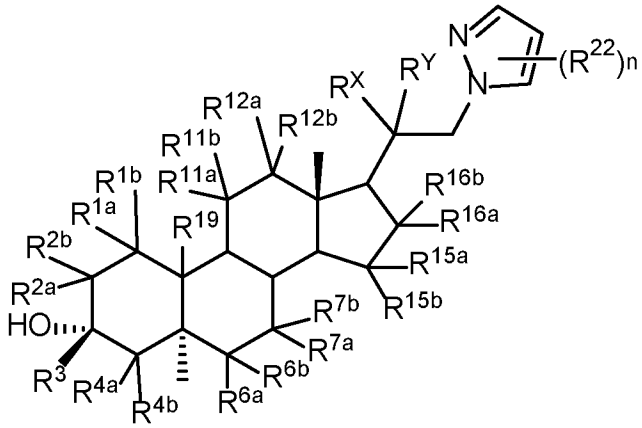
R^{18} is substituted or unsubstituted alkyl; and

n is 0, 1, 2, or 3; provided that when R^5 is hydrogen, R^{18} is not $-CH_3$.

4. The compound of claim 3, wherein the compound of Formula **II** is a compound of Formula **IIIa** or Formula **IIIb**:



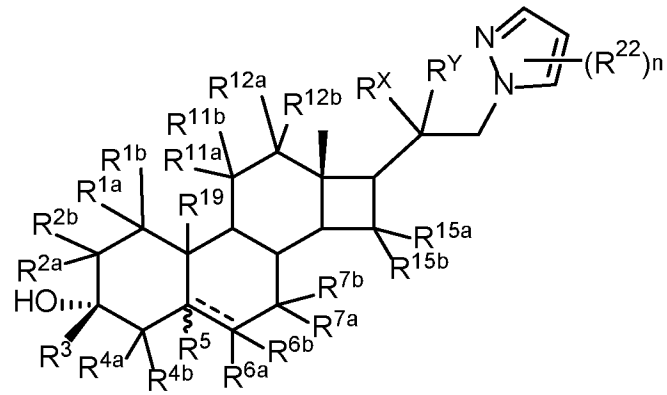
(IIIa)



(IIIb)

or a pharmaceutically acceptable salt thereof.

5. A compound of Formula **V**:



(V)

or a pharmaceutically acceptable salt thereof;

wherein:

------ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, -OR^{Q1}, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-}

$_{6}$alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

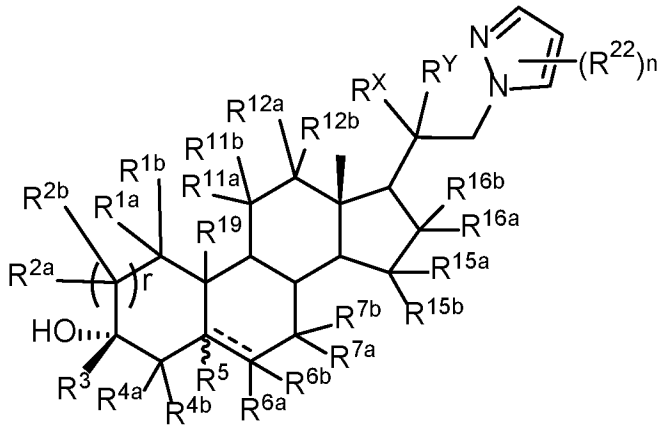
each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

each of R^{15a} or R^{15b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, $-OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})\ N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

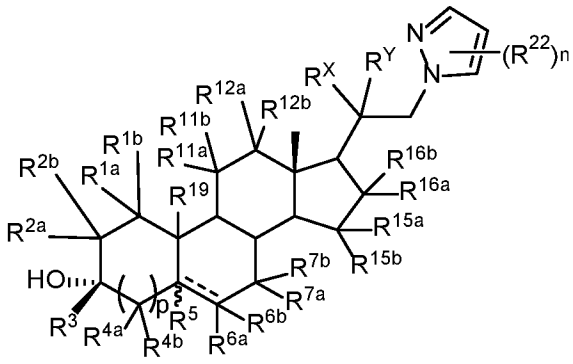
R^{19} is hydrogen or substituted or unsubstituted alkyl; and

n is 0, 1, 2, or 3.

6. A compound of Formula **VIa** or **VIb**:



(VIa)



(VIb)

or a pharmaceutically acceptable salt thereof;

wherein:

------ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, -

$S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})\ N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR^{C3}, -$N(R^{C3})_2$, -SR^{C3}, -$C(=O)R^{C3}$, -$C(=O)OR^{C3}$, -$C(=O)SR^{C3}$, -$C(=O)N(R^{C3})_2$, -$OC(=O)R^{C3}$, -$OC(=O)OR^{C3}$, -$OC(=O)N(R^{C3})_2$, -$OC(=O)SR^{C3}$, -$OS(=O)_2R^{C3}$, -$OS(=O)_2OR^{C3}$, -$OS(=O)_2N(R^{C3})_2$, -$N(R^{C3})C(=O)R^{C3}$, -$N(R^{C3})C(=NR^{C3})R^{C3}$, -$N(R^{C3})C(=O)OR^{C3}$, -$N(R^{C3})C(=O)N(R^{C3})_2$, -$N(R^{C3})C(=NR^{C3})\ N(R^{C3})_2$, -$N(R^{C3})S(=O)_2R^{C3}$, -$N(R^{C3})S(=O)_2OR^{C3}$, -$N(R^{C3})S(=O)_2N(R^{C3})_2$, -$SC(=O)R^{C3}$, -$SC(=O)OR^{C3}$, -$SC(=O)SR^{C3}$, -$SC(=O)N(R^{C3})_2$, -$S(=O)_2R^{C3}$, -$S(=O)_2OR^{C3}$, or -$S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

R^{19} is hydrogen or substituted or unsubstituted alkyl;

r is 2 or 3;

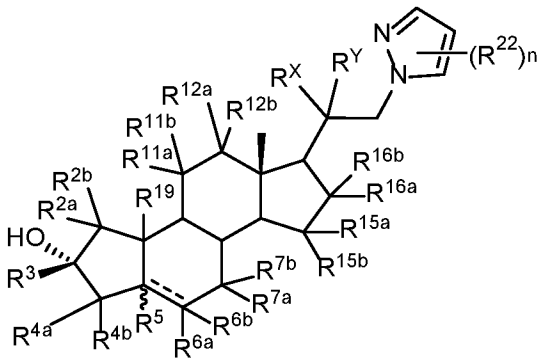
p is 2 or 3; and

n is 0, 1, 2, or 3.

7. The compound of claim 6, wherein p is 2.

8. The compound of claim 6, wherein r is 2.

9. A compound of Formula **VII**:



(VII)

or a pharmaceutically acceptable salt thereof;

wherein:

------ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting

group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})\ N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

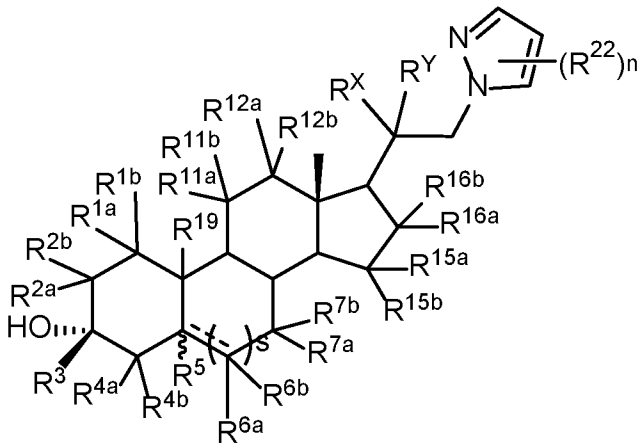
each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, $-OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})\ N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, -

$SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

R^{19} is hydrogen or substituted or unsubstituted alkyl; and

n is 0, 1, 2, or 3.

10. A compound of Formula **VIII**:



(VIII)

or a pharmaceutically acceptable salt thereof;

wherein:

------ represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, -NO_2, -CN, -OR^{GA}, -$N(R^{GA})_2$, -$C(=O)R^{GA}$, -$C(=O)OR^{GA}$, -$OC(=O)R^{GA}$, -$OC(=O)OR^{GA}$, -$C(=O)N(R^{GA})_2$, -$N(R^{GA})C(=O)R^{GA}$, -$OC(=O)N(R^{GA})_2$, -$N(R^{GA})C(=O)OR^{GA}$, -$N(R^{GA})C(=O)N(R^{GA})_2$, -$SR^{GA}$, -$S(=O)R^{GA}$, -$S(=O)_2R^{GA}$, -$S(=O)_2OR^{GA}$, -$OS(=O)_2R^{GA}$, -$S(=O)_2N(R^{GA})_2$, -$N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, -NO_2, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR^{A1}, -$N(R^{A1})_2$, -SR^{A1}, -$C(=O)R^{A1}$, -$C(=O)OR^{A1}$, -$C(=O)SR^{A1}$, -$C(=O)N(R^{A1})_2$, -$OC(=O)R^{A1}$, -$OC(=O)OR^{A1}$, -$OC(=O)N(R^{A1})_2$, -$OC(=O)SR^{A1}$, -$OS(=O)_2R^{A1}$, -$OS(=O)_2OR^{A1}$, -$OS(=O)_2N(R^{A1})_2$, -$N(R^{A1})C(=O)R^{A1}$, -$N(R^{A1})C(=NR^{A1})R^{A1}$, -$N(R^{A1})C(=O)OR^{A1}$, -$N(R^{A1})C(=O)N(R^{A1})_2$, -$N(R^{A1})C(=NR^{A1})N(R^{A1})_2$, -$N(R^{A1})S(=O)_2R^{A1}$, -$N(R^{A1})S(=O)_2OR^{A1}$, -$N(R^{A1})S(=O)_2N(R^{A1})_2$, -$SC(=O)R^{A1}$, -$SC(=O)OR^{A1}$, -$SC(=O)SR^{A1}$, -$SC(=O)N(R^{A1})_2$, -$S(=O)_2R^{A1}$, -$S(=O)_2OR^{A1}$, or -$S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

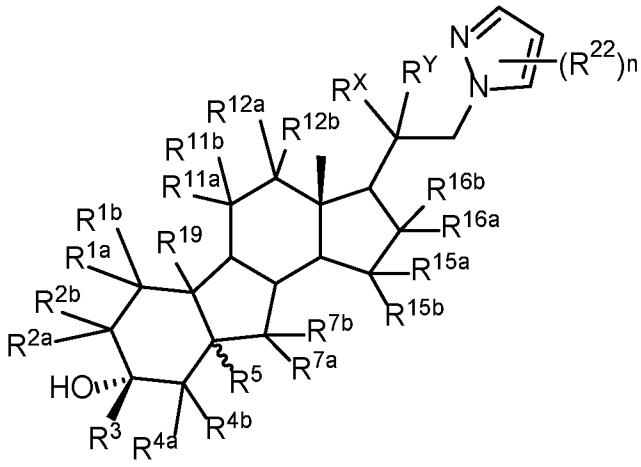
each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, $-OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})\ N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

R^{19} is hydrogen or substituted or unsubstituted alkyl;

s is 2; and

n is 0, 1, 2, or 3.

11. A compound of Formula **IX**:



(IX)

or a pharmaceutically acceptable salt thereof;

wherein:

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, $-S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting

group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})\ N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

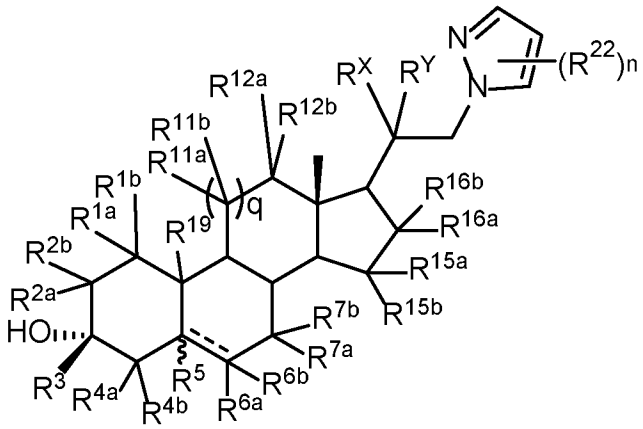
each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{C3}$, $-N(R^{C3})_2$, $-SR^{C3}$, $-C(=O)R^{C3}$, $-C(=O)OR^{C3}$, $-C(=O)SR^{C3}$, $-C(=O)N(R^{C3})_2$, $-OC(=O)R^{C3}$, $-OC(=O)OR^{C3}$, $-OC(=O)N(R^{C3})_2$, $-OC(=O)SR^{C3}$, $-OS(=O)_2R^{C3}$, $-OS(=O)_2OR^{C3}$, $-OS(=O)_2N(R^{C3})_2$, $-N(R^{C3})C(=O)R^{C3}$, $-N(R^{C3})C(=NR^{C3})R^{C3}$, $-N(R^{C3})C(=O)OR^{C3}$, $-N(R^{C3})C(=O)N(R^{C3})_2$, $-N(R^{C3})C(=NR^{C3})\ N(R^{C3})_2$, $-N(R^{C3})S(=O)_2R^{C3}$, $-N(R^{C3})S(=O)_2OR^{C3}$, $-N(R^{C3})S(=O)_2N(R^{C3})_2$, $-SC(=O)R^{C3}$, $-SC(=O)OR^{C3}$, $-SC(=O)SR^{C3}$, $-SC(=O)N(R^{C3})_2$, $-S(=O)_2R^{C3}$, $-S(=O)_2OR^{C3}$, or $-S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or

unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

R^{19} is hydrogen or substituted or unsubstituted alkyl; and

n is 0, 1, 2, or 3.

12. A compound of Formula **X**:



(X)

or a pharmaceutically acceptable salt thereof;

wherein:

represents a single or double bond, provided if a double bond is present, then one of R^{6a} or R^{6b} is absent and R^5 is absent;

R^X is selected from the group consisting of halo, -OH, $-OR^{Q1}$, and substituted or unsubstituted alkyl, wherein R^{Q1} is substituted or unsubstituted alkyl;

R^Y is halo or substituted or unsubstituted alkyl; or

R^Y and R^X may join together with the intervening atoms to form a substituted or unsubstituted carbocyclyl or a substituted or unsubstituted heterocyclyl;

R^3 is selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is hydrogen or methyl;

each instance of R^{22} is independently selected from the group consisting of halogen, $-NO_2$, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, $-C(=O)R^{GA}$, $-C(=O)OR^{GA}$, $-OC(=O)R^{GA}$, $-OC(=O)OR^{GA}$, $-C(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)R^{GA}$, $-OC(=O)N(R^{GA})_2$, $-N(R^{GA})C(=O)OR^{GA}$, $-N(R^{GA})C(=O)N(R^{GA})_2$, $-SR^{GA}$, $-S(=O)R^{GA}$, $-S(=O)_2R^{GA}$, $-S(=O)_2OR^{GA}$, $-OS(=O)_2R^{GA}$, -

$S(=O)_2N(R^{GA})_2$, $-N(R^{GA})S(=O)_2R^{GA}$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocylyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each instance of R^{GA} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocylyl, substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, and a nitrogen protecting group when attached to nitrogen, or two R^{GA} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclyl or heteroaryl ring;

each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)SR^{A1}$, $-C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-OC(=O)SR^{A1}$, $-OS(=O)_2R^{A1}$, $-OS(=O)_2OR^{A1}$, $-OS(=O)_2N(R^{A1})_2$, $-N(R^{A1})C(=O)R^{A1}$, $-N(R^{A1})C(=NR^{A1})R^{A1}$, $-N(R^{A1})C(=O)OR^{A1}$, $-N(R^{A1})C(=O)N(R^{A1})_2$, $-N(R^{A1})C(=NR^{A1})\ N(R^{A1})_2$, $-N(R^{A1})S(=O)_2R^{A1}$, $-N(R^{A1})S(=O)_2OR^{A1}$, $-N(R^{A1})S(=O)_2N(R^{A1})_2$, $-SC(=O)R^{A1}$, $-SC(=O)OR^{A1}$, $-SC(=O)SR^{A1}$, $-SC(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, or $-S(=O)_2N(R^{A1})_2$, wherein each instance of R^{A1} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{3-6}carbocyclyl, or substituted or unsubstituted 3- to 6- membered heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{A1} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

each of R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, halogen, cyano, $-NO_2$, -OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; or R^{6a} and R^{6b} are joined to form an oxo (=O) group;

each of R^{15a}, R^{15b}, R^{16a}, and R^{16b} is independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR^{C3}, -$N(R^{C3})_2$, -SR^{C3}, -$C(=O)R^{C3}$, -$C(=O)OR^{C3}$, -$C(=O)SR^{C3}$, -$C(=O)N(R^{C3})_2$, -$OC(=O)R^{C3}$, -$OC(=O)OR^{C3}$, -$OC(=O)N(R^{C3})_2$, -$OC(=O)SR^{C3}$, -$OS(=O)_2R^{C3}$, -$OS(=O)_2OR^{C3}$, -$OS(=O)_2N(R^{C3})_2$, -$N(R^{C3})C(=O)R^{C3}$, -$N(R^{C3})C(=NR^{C3})R^{C3}$, -$N(R^{C3})C(=O)OR^{C3}$, -$N(R^{C3})C(=O)N(R^{C3})_2$, -$N(R^{C3})C(=NR^{C3})$ $N(R^{C3})_2$, -$N(R^{C3})S(=O)_2R^{C3}$, -$N(R^{C3})S(=O)_2OR^{C3}$, -$N(R^{C3})S(=O)_2N(R^{C3})_2$, -$SC(=O)R^{C3}$, -$SC(=O)OR^{C3}$, -$SC(=O)SR^{C3}$, -$SC(=O)N(R^{C3})_2$, -$S(=O)_2R^{C3}$, -$S(=O)_2OR^{C3}$, or -$S(=O)_2N(R^{C3})_2$, wherein each instance of R^{C3} is independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted carbocyclyl, or substituted or unsubstituted heterocyclyl, an oxygen protecting group when attached to oxygen, a nitrogen protecting group when attached to nitrogen, and a sulfur protecting group when attached to sulfur, or two R^{C3} groups are taken with the intervening atoms to form a substituted or unsubstituted heterocyclic ring;

R^{19} is hydrogen or substituted or unsubstituted alkyl;

q is 2; and

n is 0, 1, 2, or 3.

13. The compound of any one of claims 1-8 and 10-12, wherein R^{1a} and R^{1b} are both hydrogen.

14. The compound of any one of claims 1-13, wherein R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{7a}, R^{7b}, R^{11a}, R^{11b} R^{12a}, and R^{12b} are hydrogen.

15. The compound of any one of claims 1-10 and 12-14, wherein R^{6a} and R^{6b} are both hydrogen.

16. The compound of any one of claims 1-15, wherein each R^{15a} and R^{15b} is independently hydrogen or substituted or unsubstituted alkyl.

17. The compound of any one of claims 1-16, wherein each R^{15a} and R^{15b} is independently hydrogen or methyl.

18. The compound of any one of claims 1-17, wherein R^{15a} and R^{15b} are both hydrogen.

19. The compound of any one of claims 1-4 and 6-18, wherein R^{16a} and R^{16b} are both hydrogen.

20. The compound of any one of claims 1-19, wherein R^3 is substituted or unsubstituted C_{1-6}alkyl.

21. The compound of any one of claims 1-20, wherein R^3 is methyl, ethyl, or n-propyl.

22. The compound of any one of claims 1-21, wherein R^{19} is hydrogen or unsubstituted C_{1-6}alkyl.

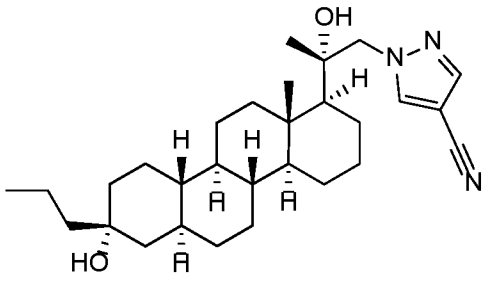
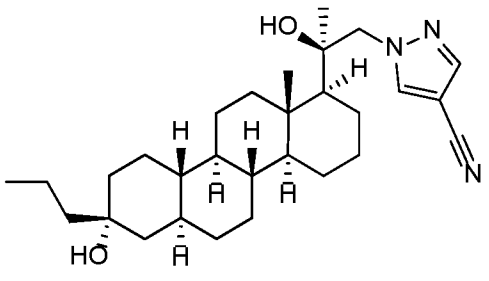
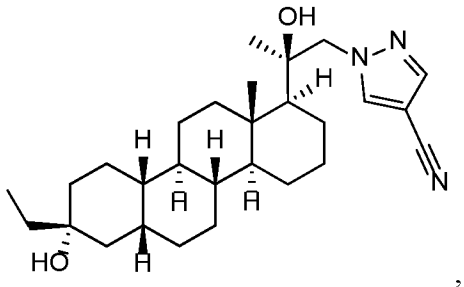
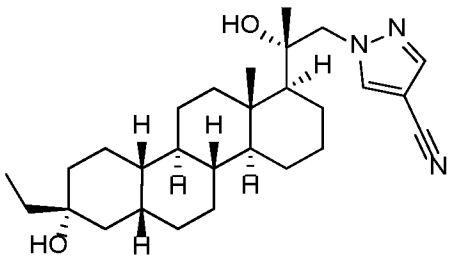
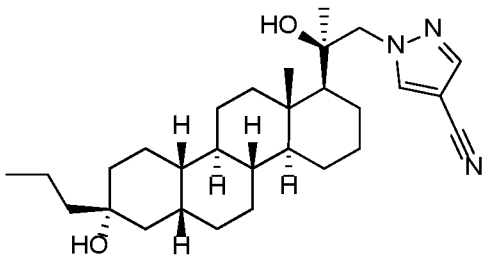
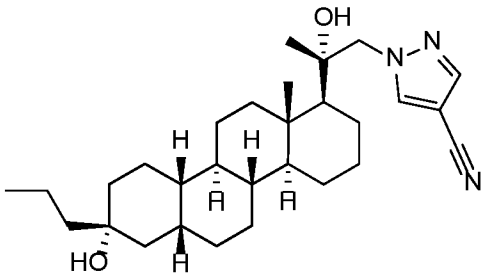
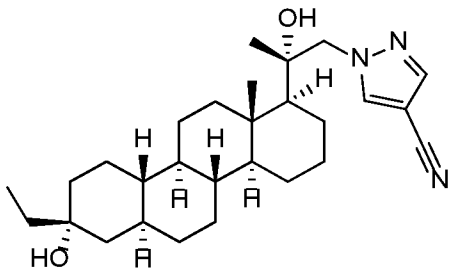
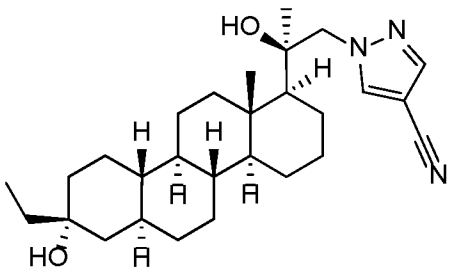
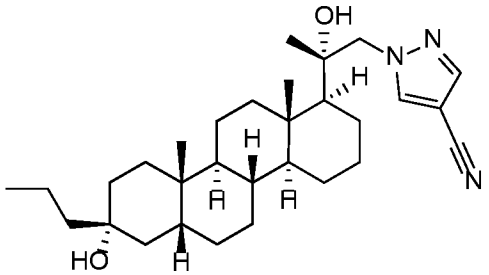
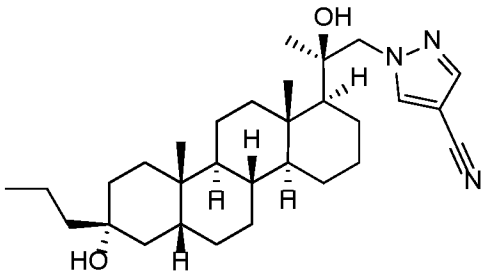
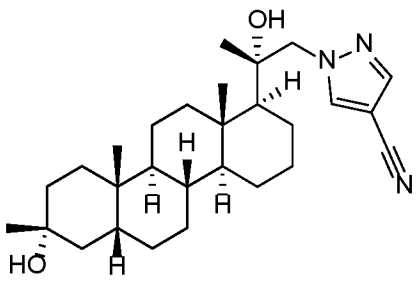
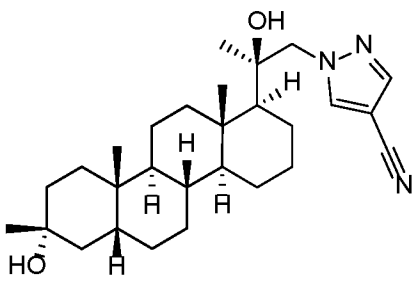
23. The compound of any one of claims 1-22, wherein R^X is -OH.

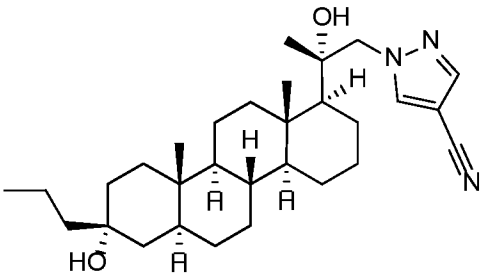
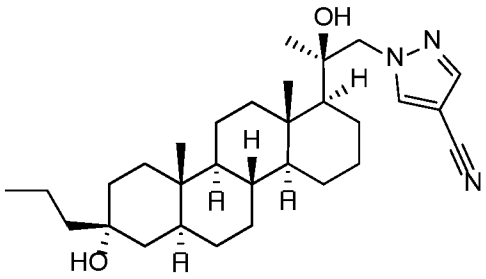
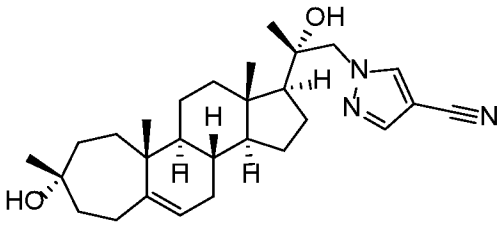
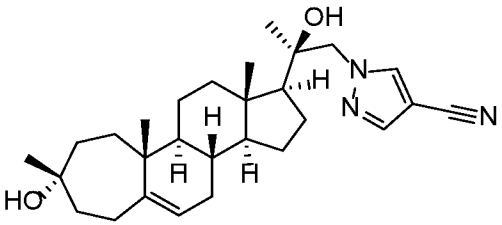
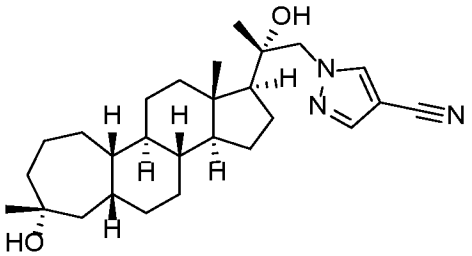
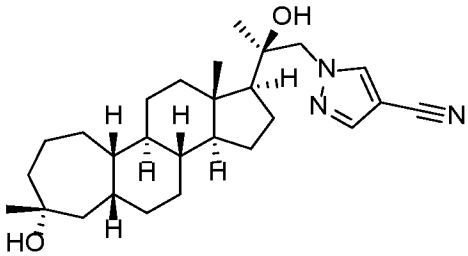
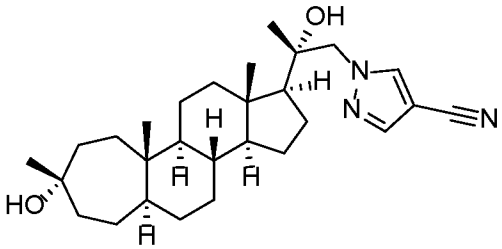
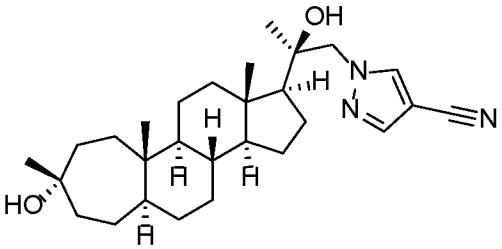
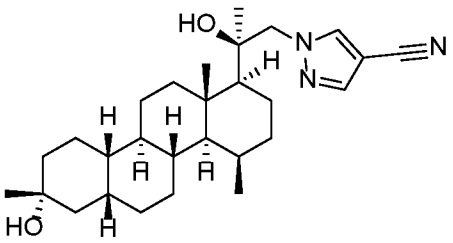
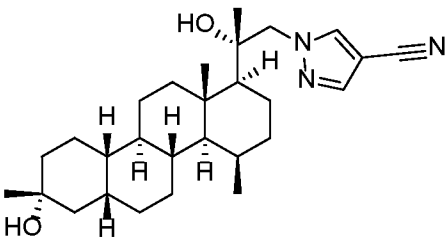
24. The compound of any one of claims 1-23, wherein R^Y is unsubstituted C_{1-3} alkyl.

25. The compound of any one of claims 1-24, wherein R^{22} is independently for each occurrence halogen, -CN, $-OR^{GA}$, $-N(R^{GA})_2$, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{3-6} carbocylyl; wherein each instance of R^{GA} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted C_{3-6} carbocylyl.

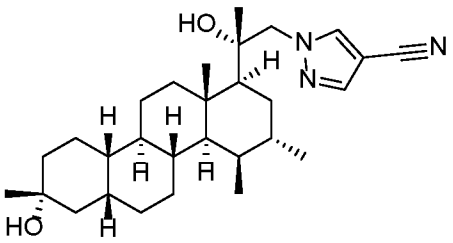
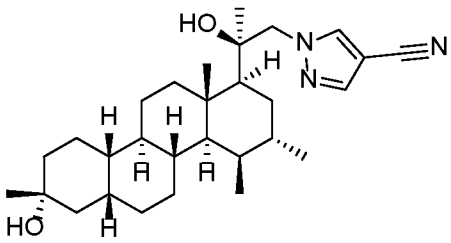
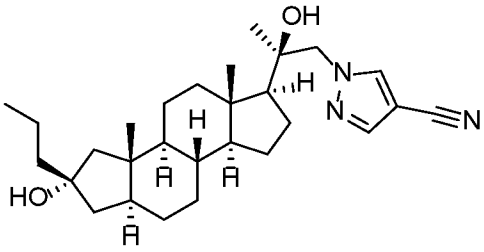
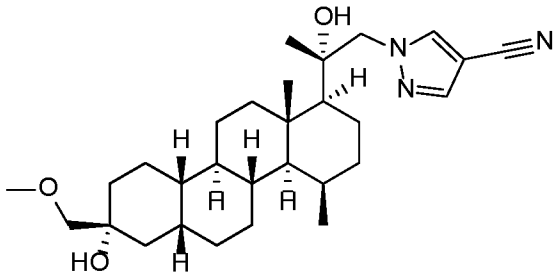
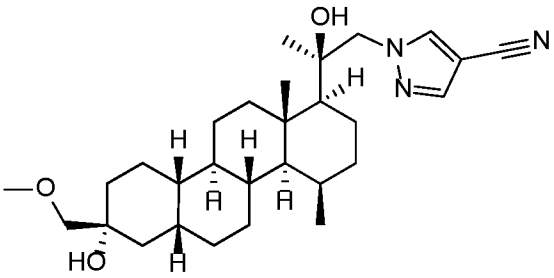
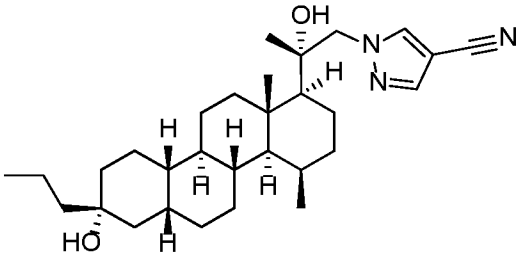
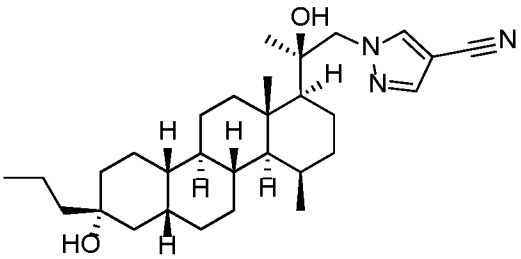
26. The compound of any one of claims 1-3 and 5-25, wherein R^5 is a hydrogen in the *alpha* or *beta* configuration.

27. The compound of any one of claims 1-26, wherein the compound is selected from the group consisting of:


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, or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising a compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

29. A method of modulating a $GABA_A$ receptor in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-27 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 28.

30. A method of treating a CNS-related disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-27 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 28.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/040153

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07J63/00 C07J61/00 A61P25/24 A61K31/58
ADD.

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)
C07J A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2014/169833 A1 (SAGE THERAPEUTICS INC [US]; BOTELLA GABRIEL MARTINEZ [US] ET AL.) 23 October 2014 (2014-10-23)	3,4, 28-30
A	Abstract; claims; examples.	1,2,5-27

Y	WO 2005/105822 A2 (CHANG PING W [US]; ZHONG NING [US] ET AL.) 10 November 2005 (2005-11-10)	3,4, 28-30
A	Abstract; claims 72, 81, 82; pages 29-30, paragraph 57.	1,2,5-27

Y	WO 2009/142594 A1 (UMECRINE AB [SE]; BAECKSTROEM TORBJOERN [SE] ET AL.) 26 November 2009 (2009-11-26)	3,4, 28-30
A	Abstract; page 5, lines 5-11; page 20, compound UC2010.	1,2,5-27

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 2020	23/09/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Weisbrod, Thomas

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	WO 2019/126761 A1 (SAGE THERAPEUTICS INC [US]) 27 June 2019 (2019-06-27) Abstract; claims; pages 96-119, table I-1. -----	1-30
Y,P	WO 2020/118060 A1 (SAGE THERAPEUTICS INC [US]) 11 June 2020 (2020-06-11) Abstract; claims; examples. -----	1-30

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Information on patent family members

International application No
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