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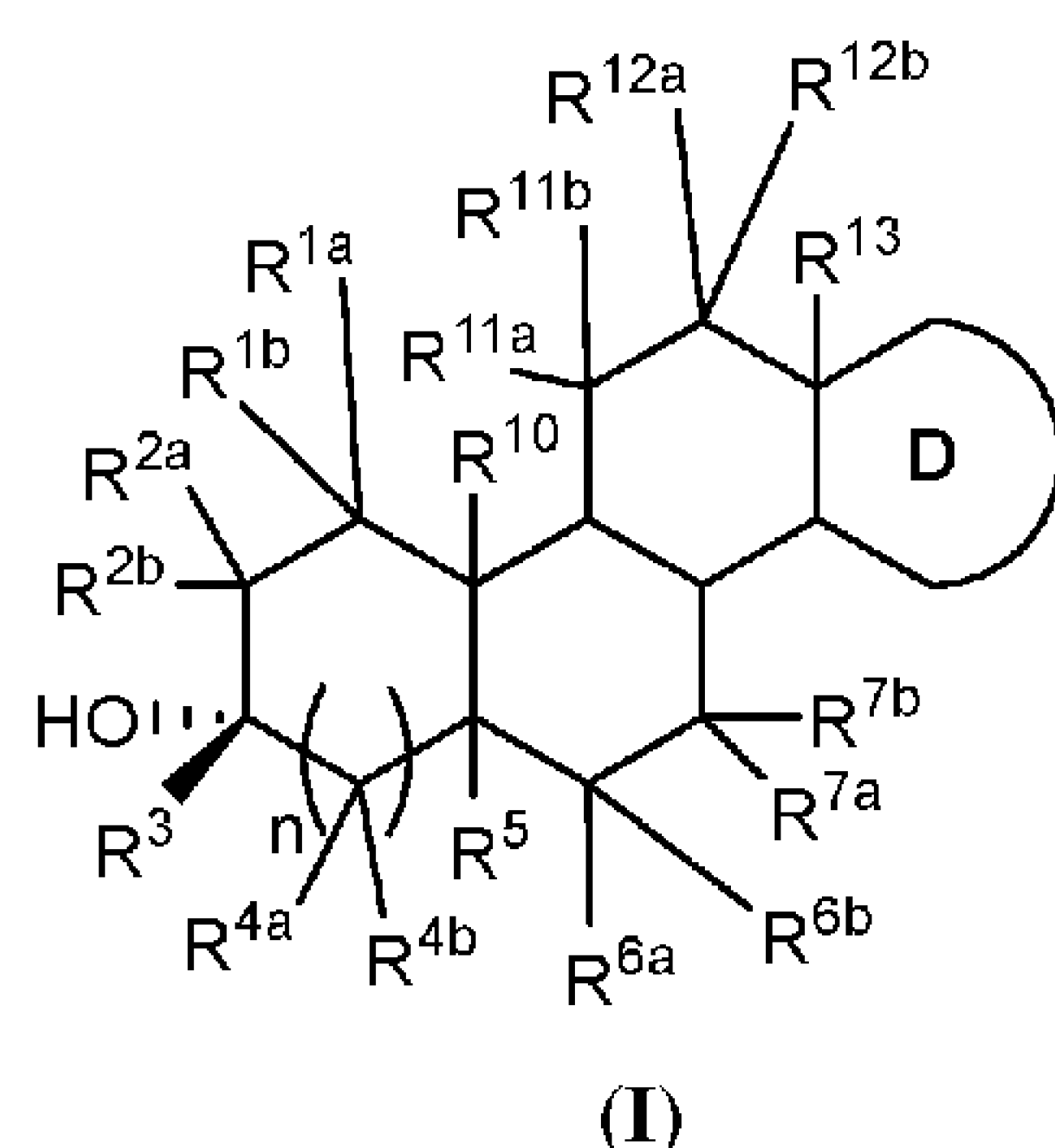
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(57) Abstract: Provided herein is a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein ring D and the substituents are defined herein. Also provided are pharmaceutical compositions comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof and methods of using the compound of Formula (I) in the treatment of CNS-related disorders.

COMPOSITIONS AND METHODS FOR TREATING CNS DISORDERS**CROSS REFERENCE TO RELATED APPLICATION**

[0001] This PCT application claims the benefit of U.S. provisional application nos. 63/118,089; 63/118,122; 63/118,086; 63/118,107, 63/118,079; and 63/118,092; all of which were filed on November 25, 2020. These documents are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to compounds, pharmaceutically acceptable salts thereof, and pharmaceutical compositions that modulate GABA activity and are useful for treating CNS-related disorders.

BACKGROUND OF THE INVENTION

[0003] 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.

[0004] 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.

[0005] 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.

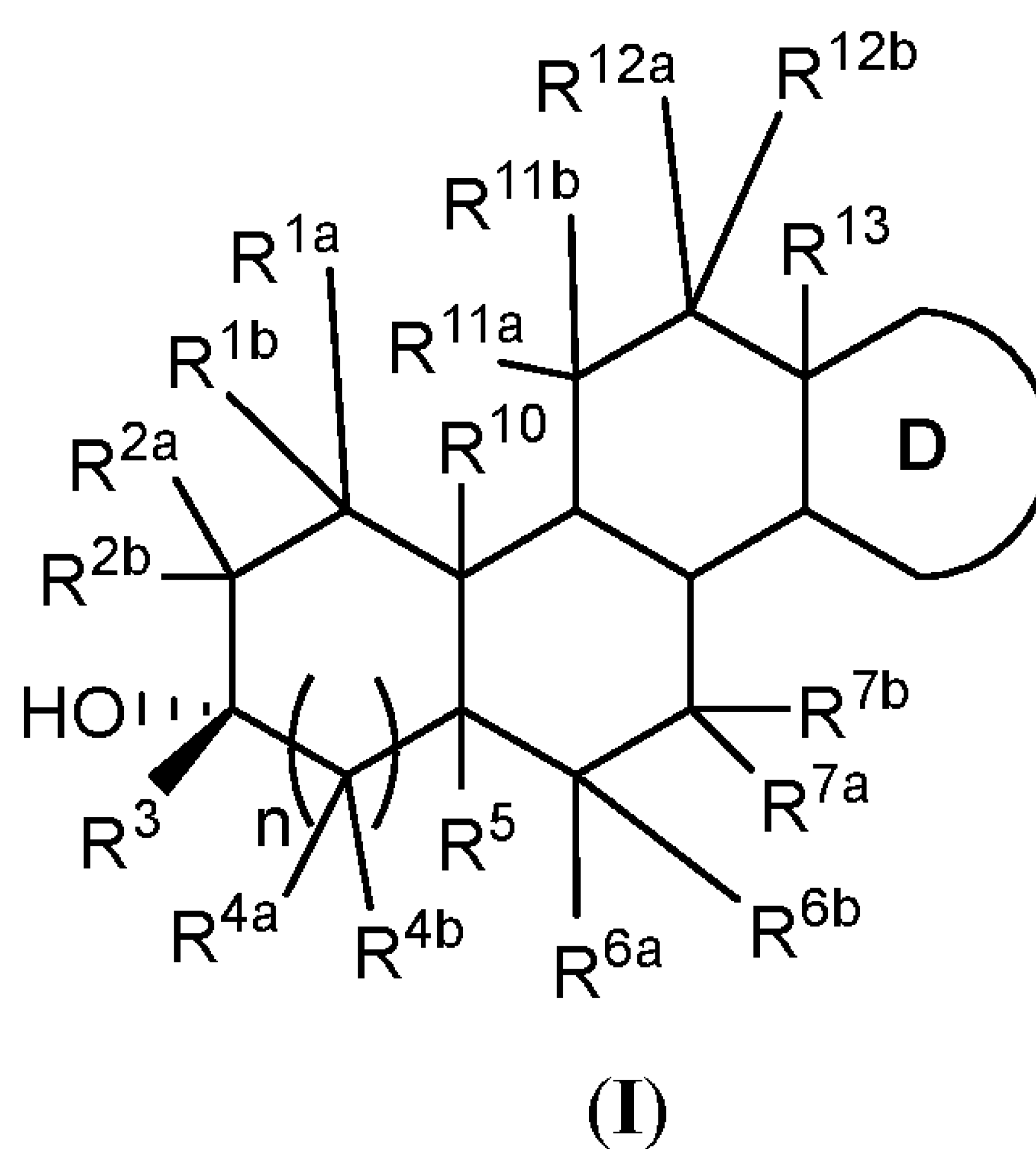
[0006] Neuroactive steroids can occur endogenously. The most potent endogenous neuroactive steroids are 3 α -hydroxy-5-reduced pregnan-20-one and 3 α -21-dihydroxy-5-reduced pregnan-20-one, metabolites of hormonal steroids progesterone and deoxycorticosterone, respectively. The ability of these steroid 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)).

[0007] 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.

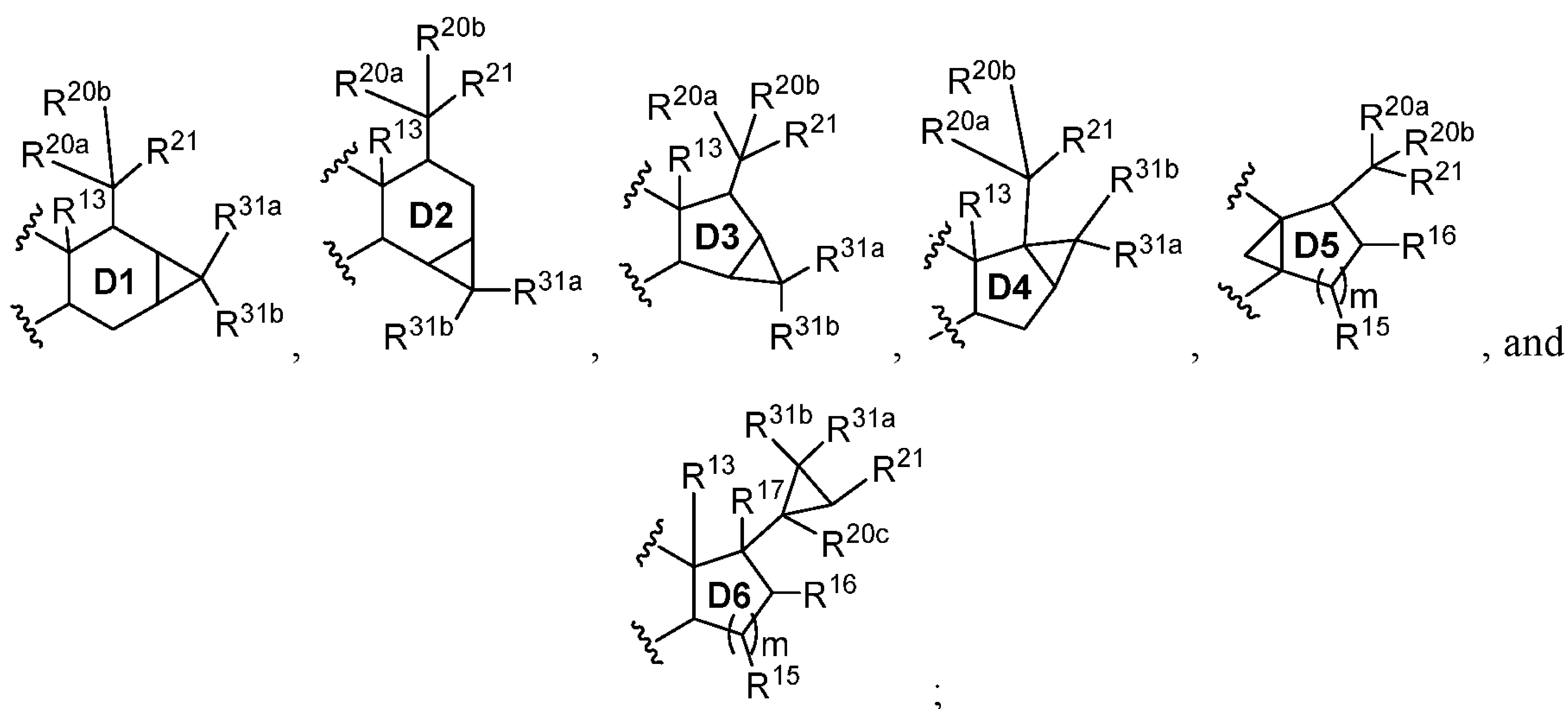
SUMMARY OF THE INVENTION

[0008] Provided herein are compounds designed, for example, to act as GABA modulators. In some embodiments, such compounds are useful as therapeutic agents for treating a CNS-related disorders.

[0009] The present invention provides a compound of Formula (I)

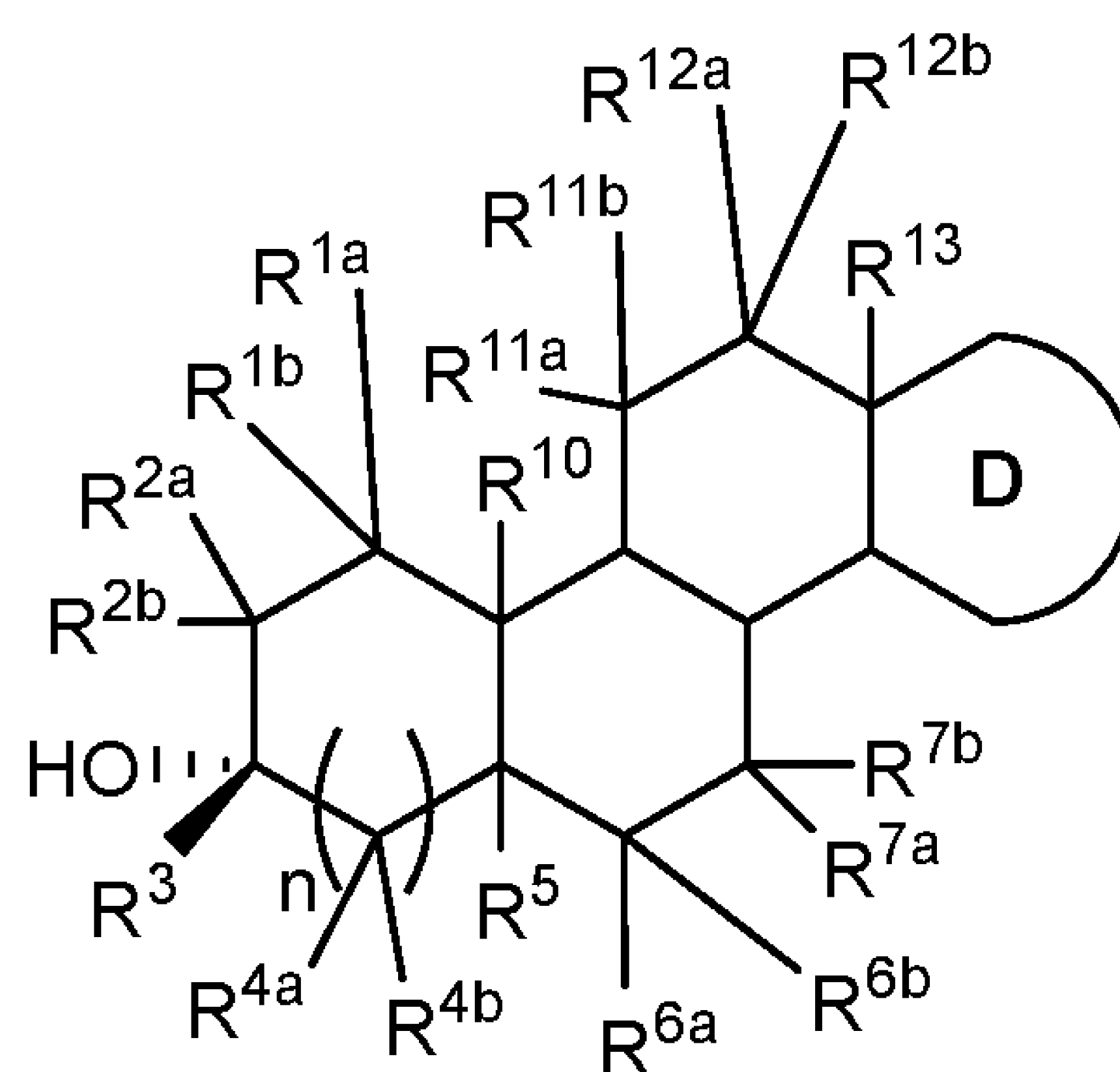


or a pharmaceutically acceptable salt thereof, wherein ring D is selected from



each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20a} , R^{20b} , R^{20c} , and R^{21} , is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'$ -, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'$ -, $-NR'S(O)_2-$, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)-$, or $-S(O)_2-$; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl-O- C_{1-6} alkyl, and an optionally substituted 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, or R^{1a} and R^{1b} taken together form oxo, or R^{2a} and R^{2b} taken together form oxo, or R^{4a} and R^{4b} taken together form oxo, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo, or R^{20a} and R^{20b} taken together form oxo; each of R^5 and R^{20c} is independently selected from $-H$ and optionally substituted C_{1-6} alkyl; R^{10} is $-H$, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} alkyl-O- C_{1-3} alkyl; each of R^{31a} and R^{31b} is independently selected from $-H$, halo, C_{1-6} alkyl, and $-OR^{32}$, wherein R^{32} is $-H$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, or S; m is 1 or 2; and n is 0, 1, or 2, provided that when one of R^{31a} and R^{31b} is $-OR^{32}$, the other of R^{31a} and R^{31b} is $-H$.

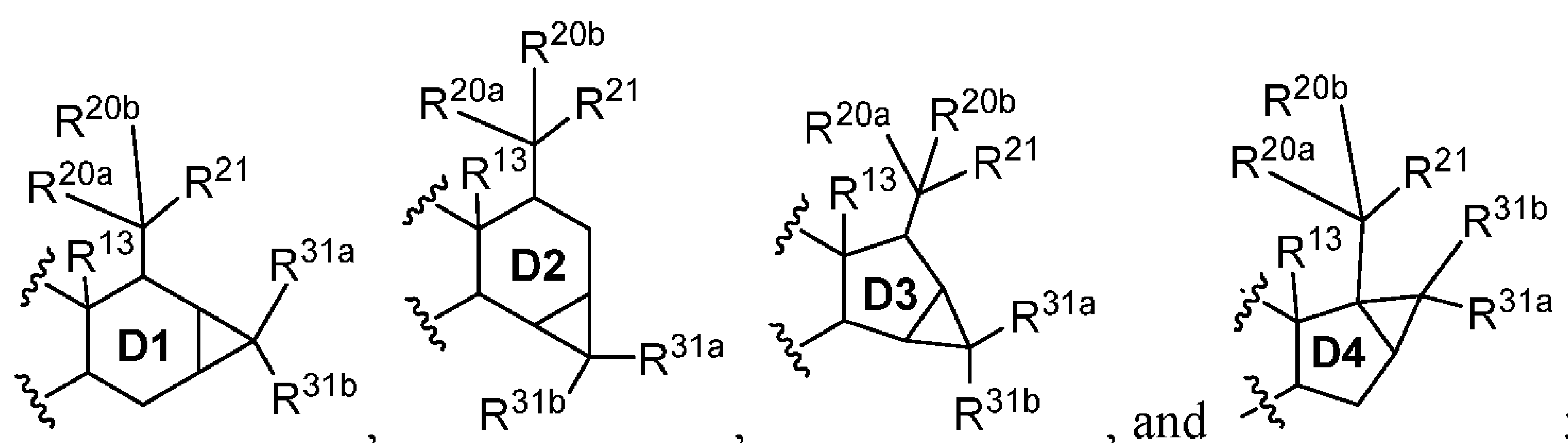
[0010] Another aspect of the present invention provides a compound of Formula (II)



(II)

or a pharmaceutically acceptable salt thereof, wherein ring D, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20a} , R^{20b} , R^{20c} , R^{21} , R^{31a} , R^{31b} , m , and n are as defined in any of the embodiments of the compound of Formula (I).

[0011] In some embodiments, ring D is a fused bicyclic ring selected from



each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{20a} , R^{20b} , and R^{21} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$, or R^{1a} and R^{1b} taken together form oxo, or R^{2a} and R^{2b} taken together form oxo, or R^{4a} and R^{4b} taken together form oxo, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo, or R^{20a} and R^{20b} taken

together form oxo; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$ or optionally substituted C_{1-6} alkyl; R^{13} is $-H$ or optionally substituted C_{1-6} alkyl; each of R^{31a} and R^{31b} is independently selected from $-H$, halo, C_{1-6} alkyl, and $-OR^{32}$, wherein R^{32} is $-H$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, or S; and n is 0, 1, or 2, provided that when one of R^{31a} and R^{31b} is $-OR^{32}$, the other of R^{31a} and R^{31b} is $-H$.

[0012] In some embodiments, each of R^{1a} and R^{1b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{1a} and R^{1b} taken together form oxo. In some embodiments, each of R^{1a} and R^{1b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{1a} and R^{1b} taken together form oxo. In some embodiments, one of R^{1a} and R^{1b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, one of R^{1a} and R^{1b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, one of R^{1a} and R^{1b} is $-H$, and the other is methyl. And, in some embodiments, each of R^{1a} and R^{1b} is $-H$.

[0013] In some embodiments, each of R^{2a} and R^{2b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{2a} and R^{2b} taken together form oxo. In some embodiments, each of R^{2a} and R^{2b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{2a} and R^{2b} taken together form oxo. In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is methyl. And, in some embodiments, each of R^{2a} and R^{2b} is $-H$.

[0014] In some embodiments, R^3 is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^3 is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^3 is $-H$, $-CH_3$, $-CH_2-CH_2-CH_3$, or $-CH_2-O-CH_3$. And, in some embodiments, R^3 is $-H$ or methyl.

[0015] In some embodiments, n is 0 and both of R^{4a} and R^{4b} are absent. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$ or C_{1-6} alkyl optionally substituted with R' , or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, n is 1, one of R^{4a} and R^{4b} is

–H, and the other is –H or C₁₋₆ alkyl optionally substituted with R'. In some embodiments, n is 1, one of R^{4a} and R^{4b} is –H, and the other is methyl. And, in some embodiments, n is 1 and each of R^{4a} and R^{4b} is –H.

[0016] In some embodiments, R⁵ is –H or methyl. In some embodiments, R⁵ is –H.

[0017] In some embodiments, each of R^{6a}, R^{6b}, R^{7a}, and R^{7b} is independently selected from –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, and –O-R', or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo. In some embodiments, each of R^{6a}, R^{6b}, R^{7a}, and R^{7b} is independently selected from –H and C₁₋₆ alkyl optionally substituted with R'. In some embodiments, two of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are –H, and the other two of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are independently selected from –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, and –O-R'. In some embodiments, three of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are –H, and the other of R^{6a}, R^{6b}, R^{7a}, and R^{7b} is –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, or –O-R'. In some embodiments, three of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are –H, and the other is –H or methyl. And, in some embodiments, each of R^{6a}, R^{6b}, R^{7a}, and R^{7b} is –H.

[0018] In some embodiments, R¹⁰ is –H, C₁₋₆ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl. In some embodiments, R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl. In some embodiments, R¹⁰ is –H, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl. And, in some embodiments, R¹⁰ is –H, methyl, or methoxymethyl.

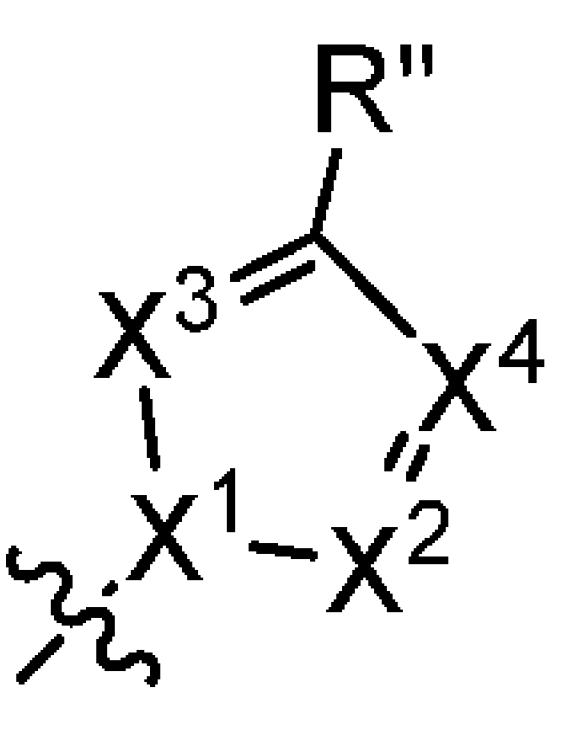
[0019] In some embodiments, each of R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, and –O-R', or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo. In some embodiments, each of R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from –H and C₁₋₆ alkyl optionally substituted with R'. In some embodiments, two of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are –H, and the other two of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are independently selected from –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, and –O-R'. In some embodiments, two of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are –H, and the other two of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are independently selected from –H or methyl. In some embodiments, three of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are –H, and the other of R^{11a}, R^{11b}, R^{12a}, and R^{12b} is –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, or –O-R'. In some embodiments, three of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are –H, and the other is –H or methyl. And, in some embodiments, each of R^{11a}, R^{11b}, R^{12a}, and R^{12b} is –H.

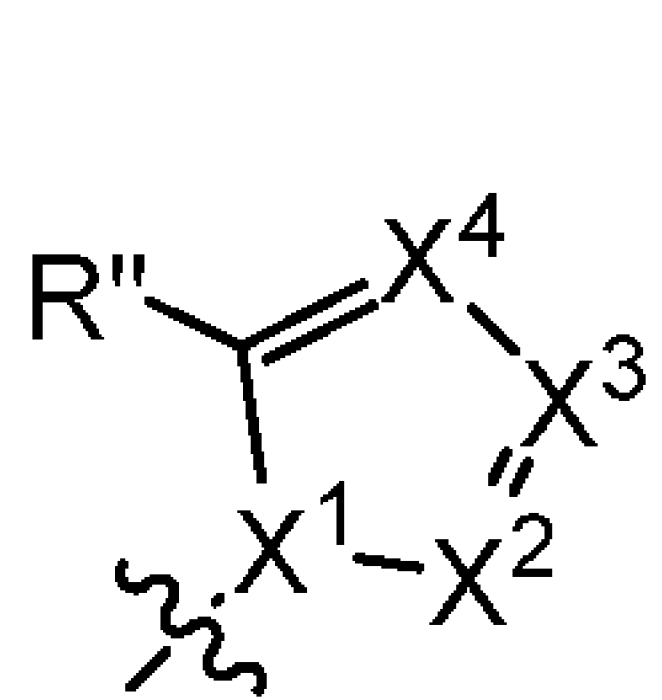
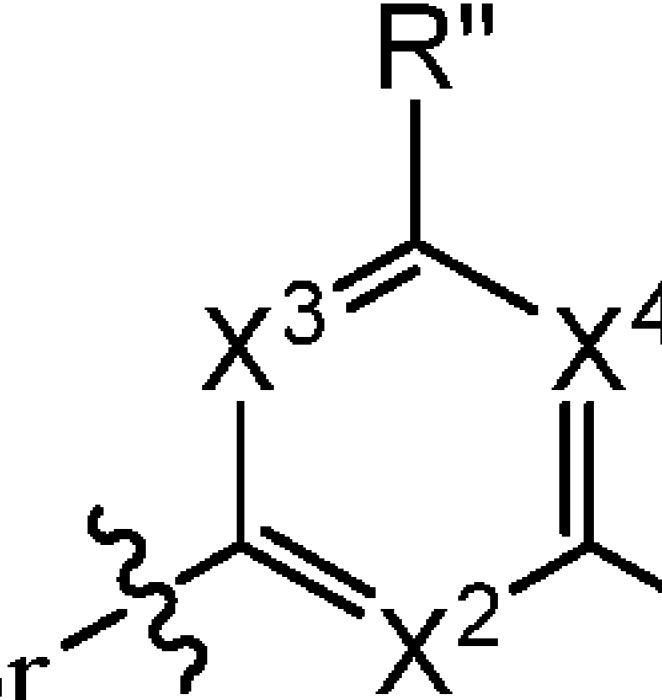
[0020] In some embodiments, R¹³ is –H, C₁₋₆ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl. In some embodiments, R¹³ is –H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl. In some embodiments, R¹³ is –H, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or

ethoxyethyl. In some embodiments, R^{13} is $-H$, methyl, or methoxymethyl. And, in some embodiments, R^{13} is methyl.

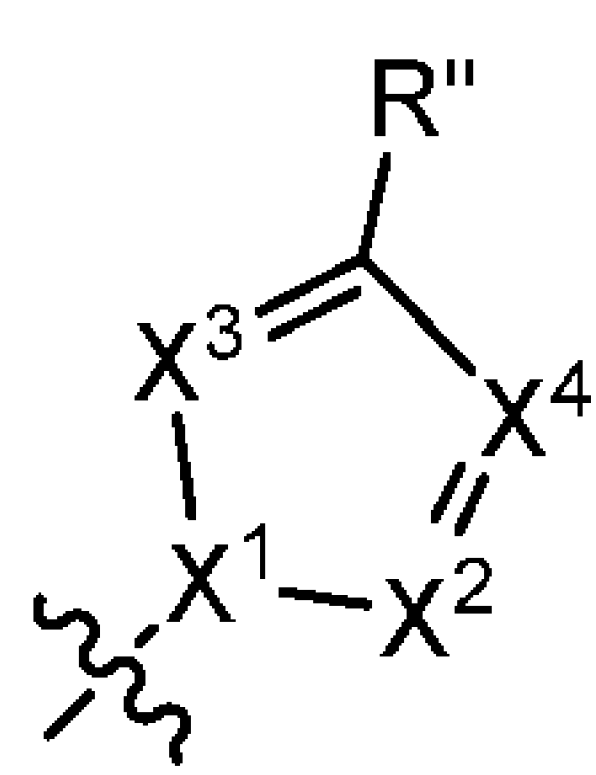
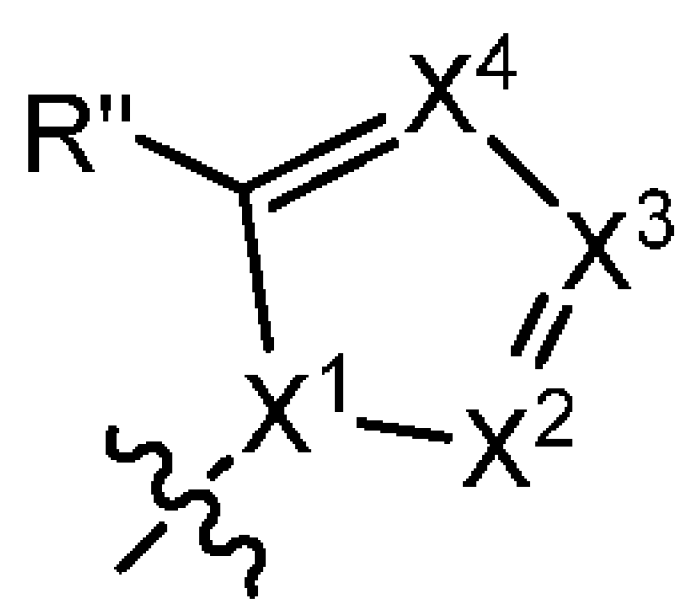
[0021] In some embodiments, each of R^{20a} and R^{20b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo. In some embodiments, each of R^{20a} and R^{20b} are independently selected from $-H$, C_{1-6} alkyl, $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo. In some embodiments, R^{20a} and R^{20b} are independently selected from $-H$, methyl, or $-OH$. In some embodiments, one of R^{20a} and R^{20b} is $-OH$, and the other is $-H$, or methyl. And, in some embodiments, R^{20a} and R^{20b} taken together form oxo.

[0022] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, $-NH-$, or $-CH_2-CH_2-CH_2-$; and R^{30} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, or $-NH-$; and R^{30} is a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond or $-CH_2-$; and R^{30} is a 5-6-membered partially unsaturated or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-2 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond or $-CH_2-$; and R^{30} is  ,

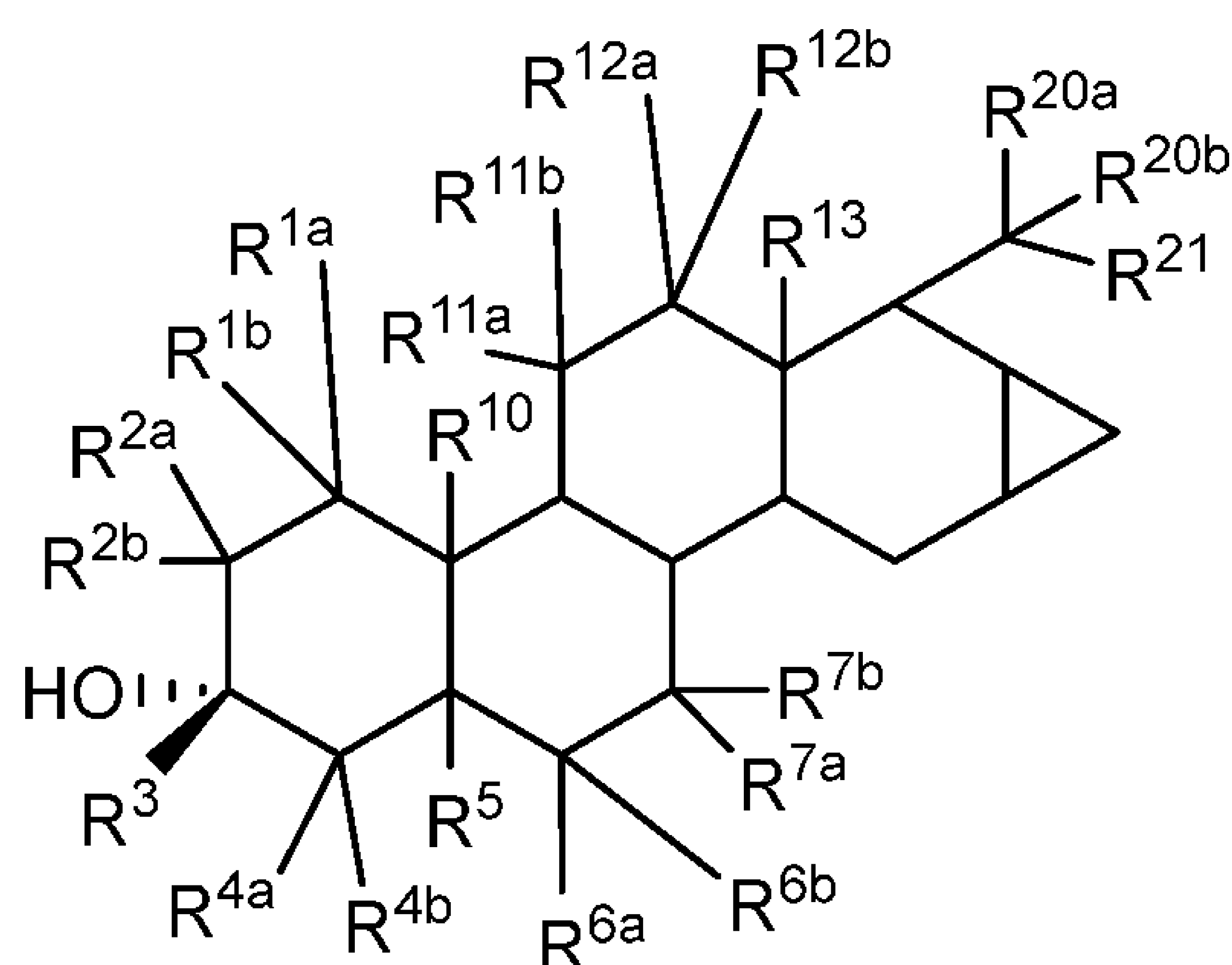
 , or  , wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'', wherein each R'' is independently selected from $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and

(ii) no greater than 2 instances of R'' are independently selected from halo, $-OH$, $-CN$, $-NO_2$,

–CF₃, –CH₃, and –CH₂OH. In some embodiments, R³⁰ is  or , X¹ is N; and each of X², X³, and X⁴ is independently selected from N and CR'', wherein each R'' is independently selected from –H, –OH, –CN, –NO₂, –CF₃, –CH₃, and –CH₂OH, provided that no greater than 2 instances of R'' are independently selected from halo, –OH, –CN, –NO₂, –CF₃, –CH₃, and –CH₂OH.

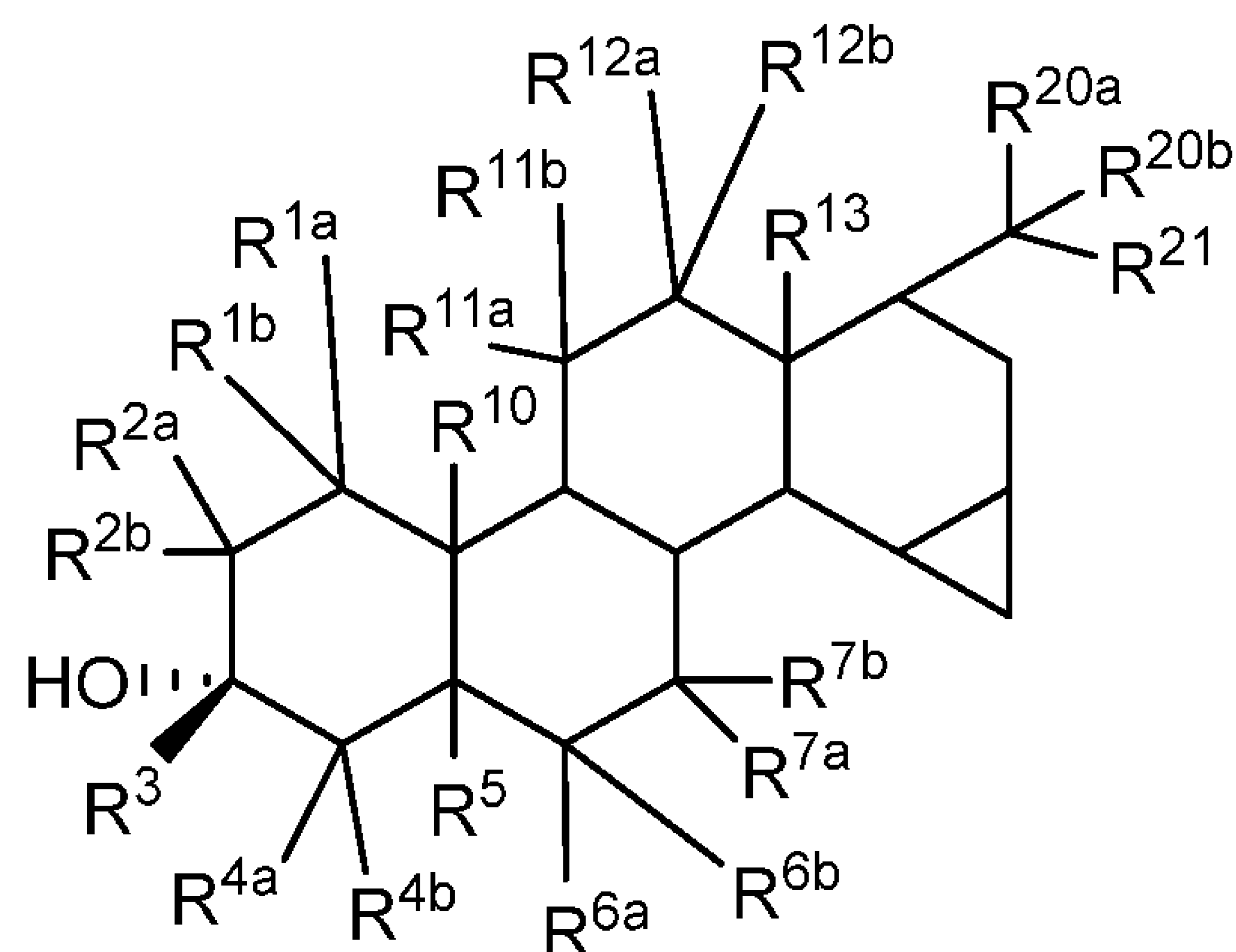
[0023] In some embodiments, each of R^{31a} and R^{31b} is independently selected from –H, halo, and C₁₋₆ alkyl, or when one of R^{31a} and R^{31b} is –H, the other is –H, halo, C₁₋₆ alkyl, or –OR³², wherein R³² is –H, C₁₋₆ alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S. In some embodiments, one of R^{31a} and R^{31b} is –H, and the other is –H, halo, C₁₋₆ alkyl, or –OR³², wherein R³² is –H, C₁₋₆ alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S. In some embodiments, each of R^{31a} and R^{31b} is independently selected from –H, halo, and C₁₋₆ alkyl. In some embodiments, one of R^{31a} and R^{31b} is –H, and the other is –OH, –O-C₁₋₆ alkyl, –O-phenyl, or –O-C₃₋₆ cycloalkyl. And, in some embodiments, each of R^{31a} and R^{31b} is –H.

[0024] Another aspect of the present invention provides a compound of Formula (II-A) or (II-B)



(II-A)

or



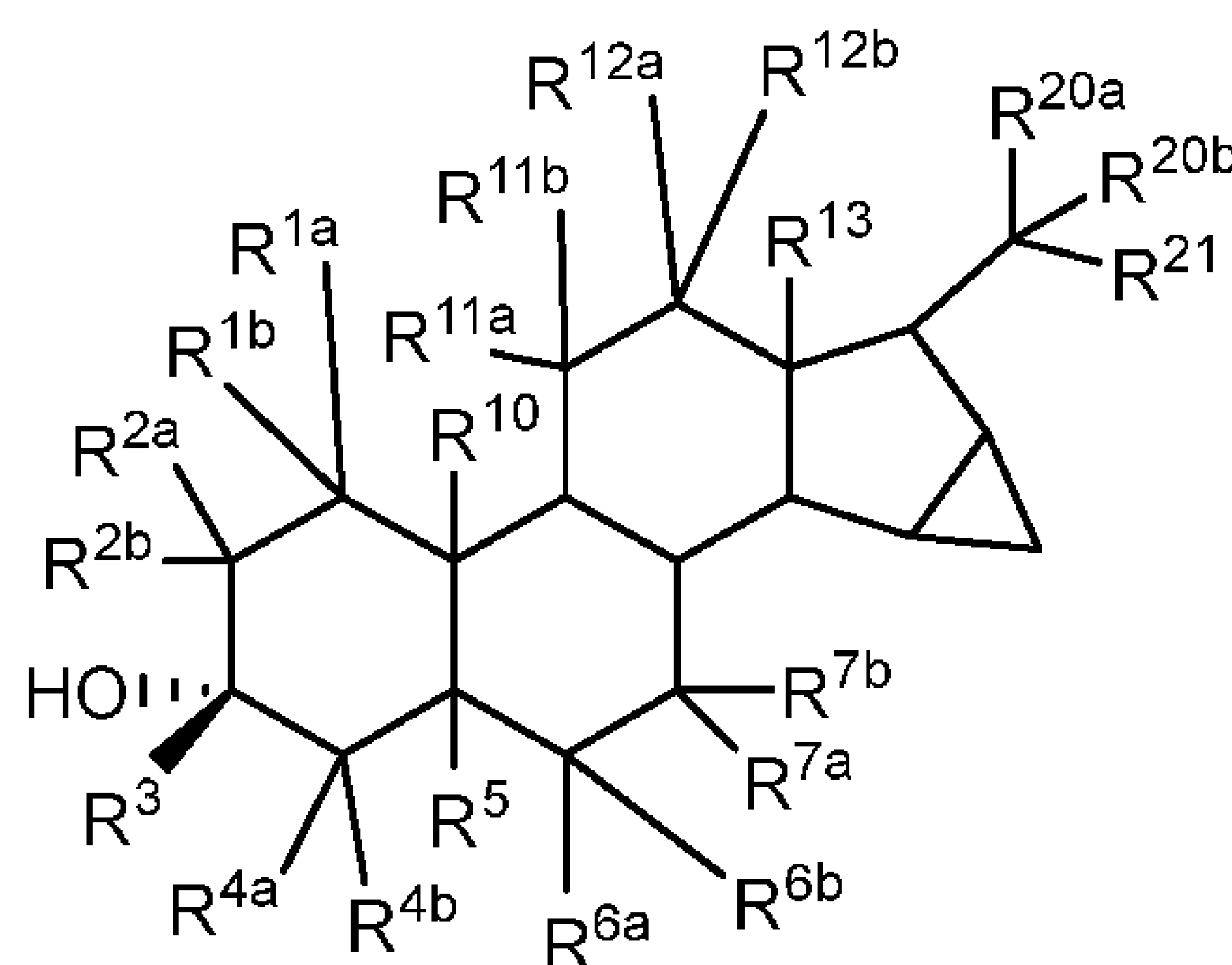
(II-B)

or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R^{4a}, R^{4b}, R⁵, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R¹⁰, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R^{20a}, R^{20b}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I) or (II).

[0025] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{20a} , R^{20b} , and R^{21} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$, or R^{20a} and R^{20b} taken together form oxo; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$ or optionally substituted C_{1-3} alkyl; and R^{13} is $-H$ or optionally substituted C_{1-3} alkyl.

[0026] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl; R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-3} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-CH_2OH$, C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-S(O)$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, or $-S(O)_2$ -; R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0027] Another aspect of the present invention provides a compound of Formula (II-C)



(II-C)

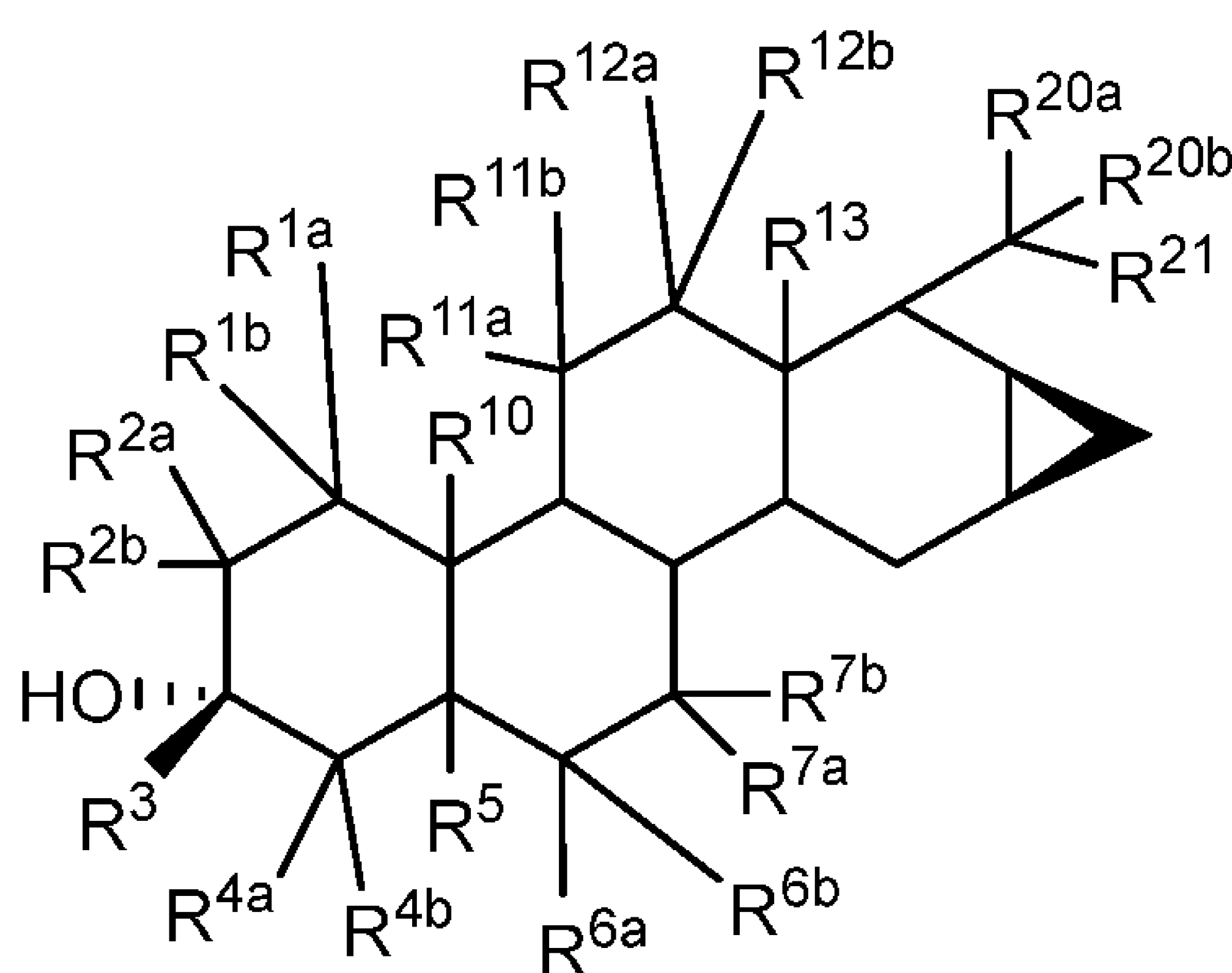
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I) or (II).

[0028] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{20a} , R^{20b} , and R^{21} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-C(O)$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; each R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$, or R^{20a} and R^{20b} taken together form oxo; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$ or optionally substituted C_{1-3} alkyl; and R^{13} is $-H$ or optionally substituted C_{1-3} alkyl.

[0029] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl, R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-3} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-S(O)$ -,

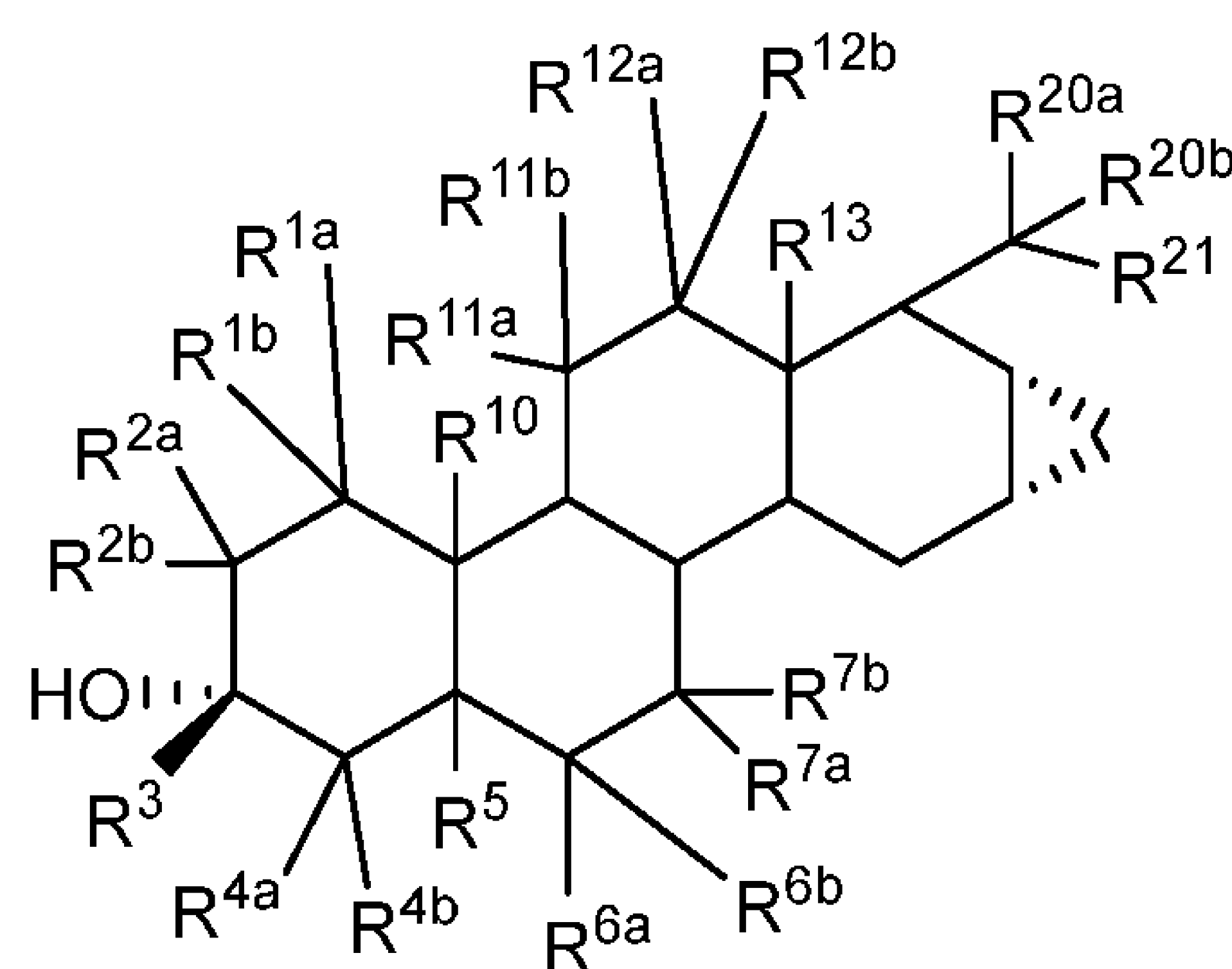
–NR'C(O)NR'–, –OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, or –S(O)₂–; R³⁰ is selected from R', halo, –CN, –NO₂, and –CF₃; and each R' is independently selected from –H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, and –CH₃.

[0030] Another aspect of the present invention provides a compound of Formula (II-A1) or (II-A2)



(II-A1)

or



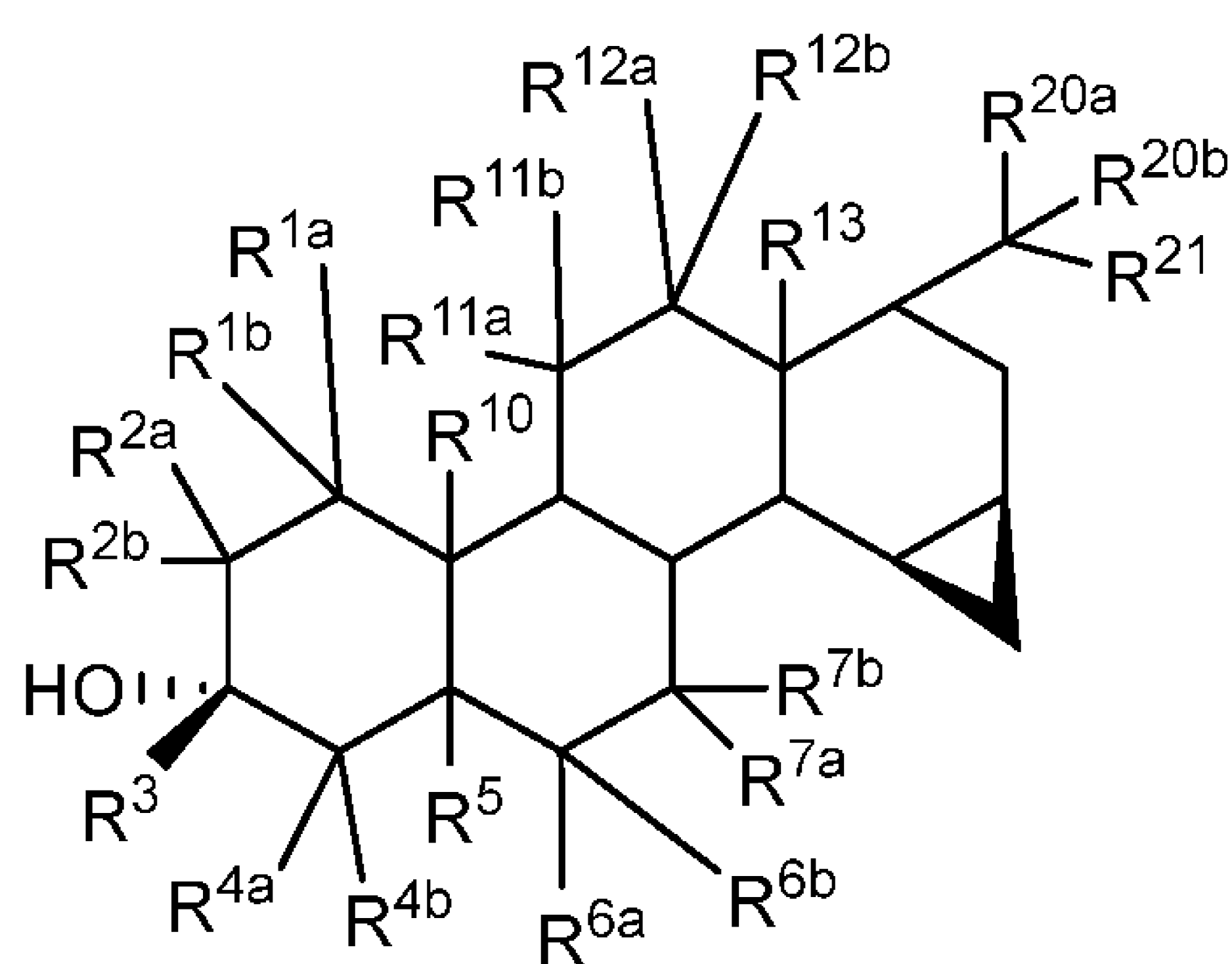
(II-A2),

or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R^{4a}, R^{4b}, R⁵, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R¹⁰, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R^{20a}, R^{20b}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (II), or (II-A).

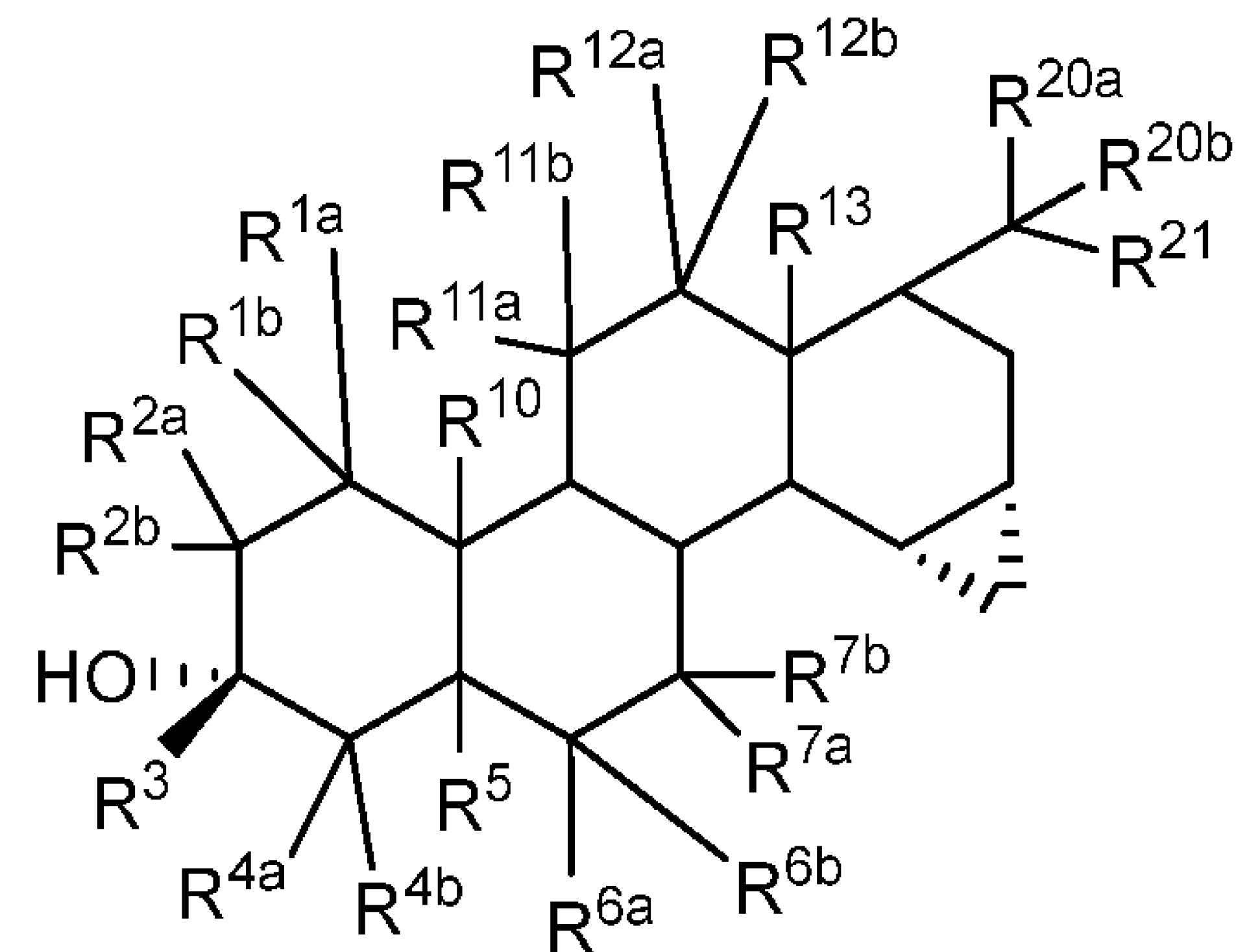
[0031] In some embodiments, each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from –H and C₁₋₆ alkyl, R³ is –H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; R⁵ is –H or C₁₋₆ alkyl; R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; R¹³ is –H or optionally substituted C₁₋₃ alkyl; each of R^{20a} and R^{20b} is independently selected from –H, –OH, –C₁₋₅ alkyl-OH, C₁₋₆ alkyl, and –NH₂, or R^{20a} and R^{20b} taken together form oxo; R²¹ is –L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by –NR'–, –S–, –O–, –OC(O)–, –C(O)O–, –C(O)–, –C(O)C(O)–, –C(O)NR'–, –NR'C(O)–, –NR'C(O)O–, –S(O)₂NR'–, –NR'S(O)₂–, –S(O)–, –C(O)NR'NR'–, –NR'C(O)NR'–, –OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, or –S(O)₂–; R³⁰ is selected from R', halo, –CN, –NO₂, and –CF₃; and each R' is independently selected from –H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is

optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, and $-\text{CH}_3$.

[0032] Another aspect of the present invention provides a compound of Formula **(II-B1)** or **(II-B2)**

**(II-B1)**

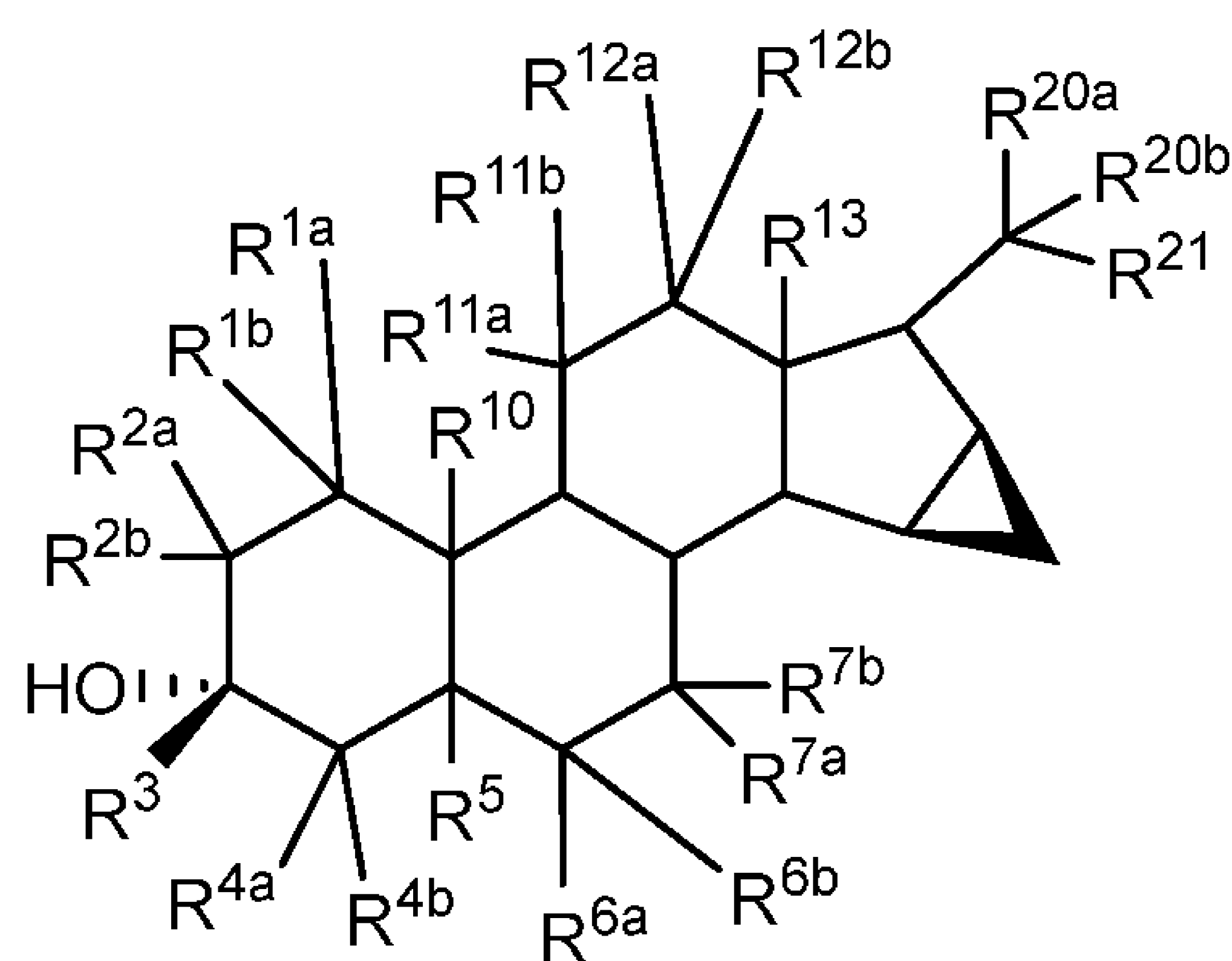
or

**(II-B2),**

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula **(I)**, **(II)**, or **(II-B)**.

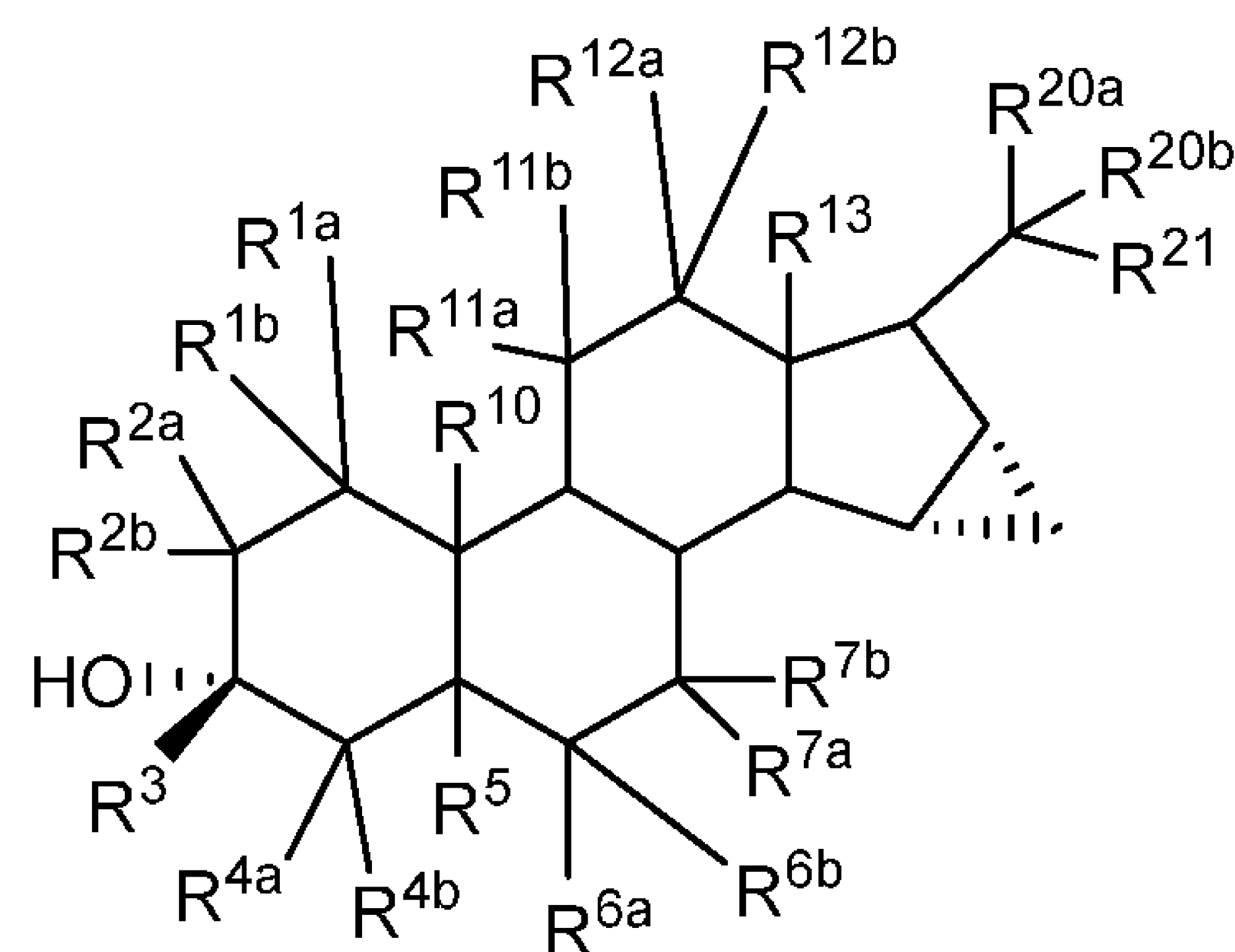
[0033] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-\text{H}$ and C_{1-6} alkyl, R^3 is $-\text{H}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-\text{H}$ or C_{1-6} alkyl; R^{10} is $-\text{H}$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-\text{H}$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{C}_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-\text{NH}_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-\text{L}^A-\text{R}^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-\text{NR}'$ -, $-\text{S}$ -, $-\text{O}$ -, $-\text{OC}(\text{O})$ -, $-\text{C}(\text{O})\text{O}$ -, $-\text{C}(\text{O})$ -, $-\text{C}(\text{O})\text{C}(\text{O})$ -, $-\text{C}(\text{O})\text{NR}'$ -, $-\text{NR}'\text{C}(\text{O})$ -, $-\text{NR}'\text{C}(\text{O})\text{O}$ -, $-\text{S}(\text{O})_2\text{NR}'$ -, $-\text{NR}'\text{S}(\text{O})_2$ -, $-\text{S}(\text{O})$ -, $-\text{C}(\text{O})\text{NR}'\text{NR}'$ -, $-\text{NR}'\text{C}(\text{O})\text{NR}'$ -, $-\text{OC}(\text{O})\text{NR}'$ -, $-\text{NR}'\text{NR}'$ -, $-\text{NR}'\text{S}(\text{O})_2\text{NR}'$ -, or $-\text{S}(\text{O})_2$ -; R^{30} is selected from R' , halo, $-\text{CN}$, $-\text{NO}_2$, and $-\text{CF}_3$; and each R' is independently selected from $-\text{H}$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, and $-\text{CH}_3$.

[0034] Another aspect of the present invention provides a compound of Formula **(II-C1)** or **(II-C2)**



(II-C1)

or

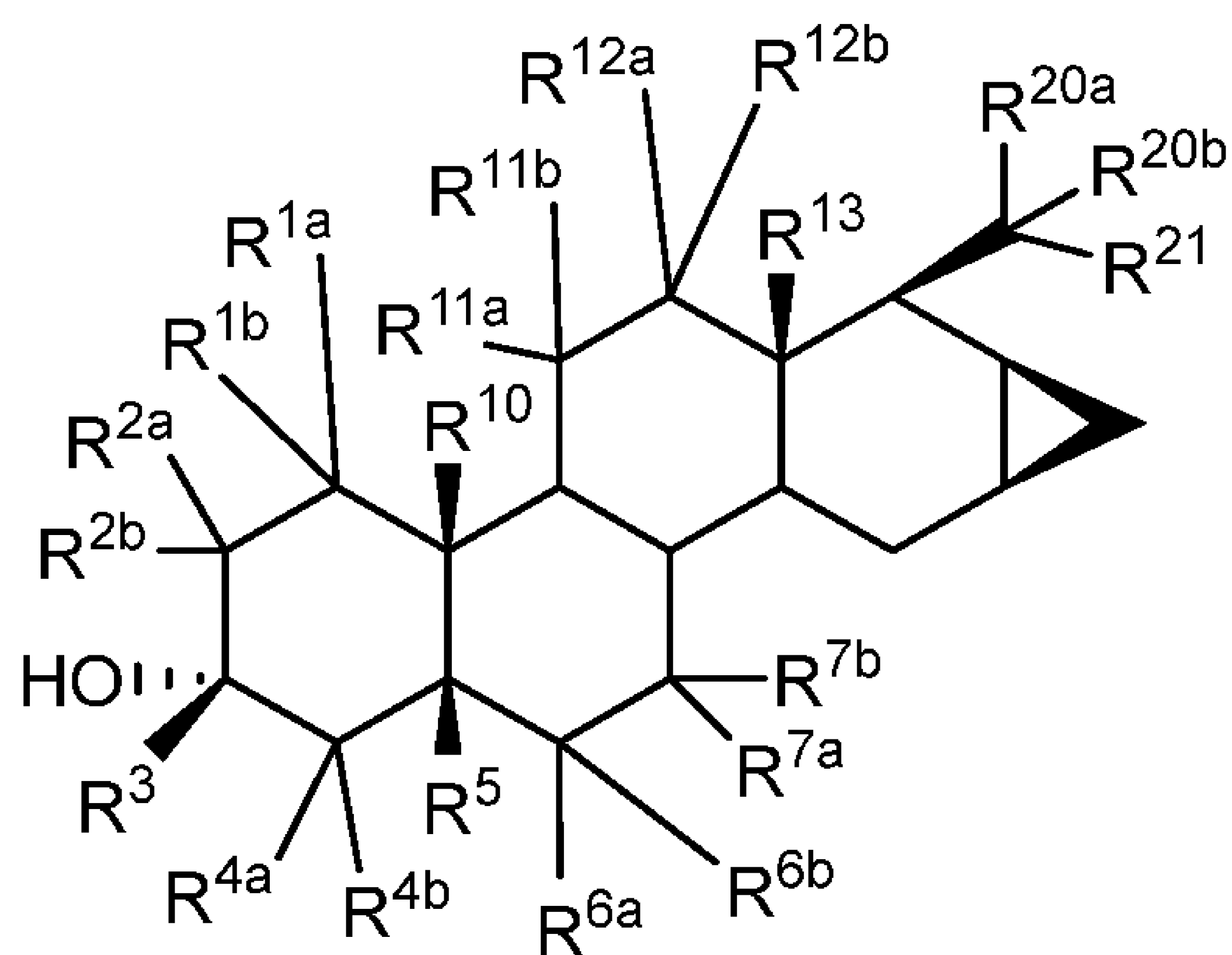


(II-C2),

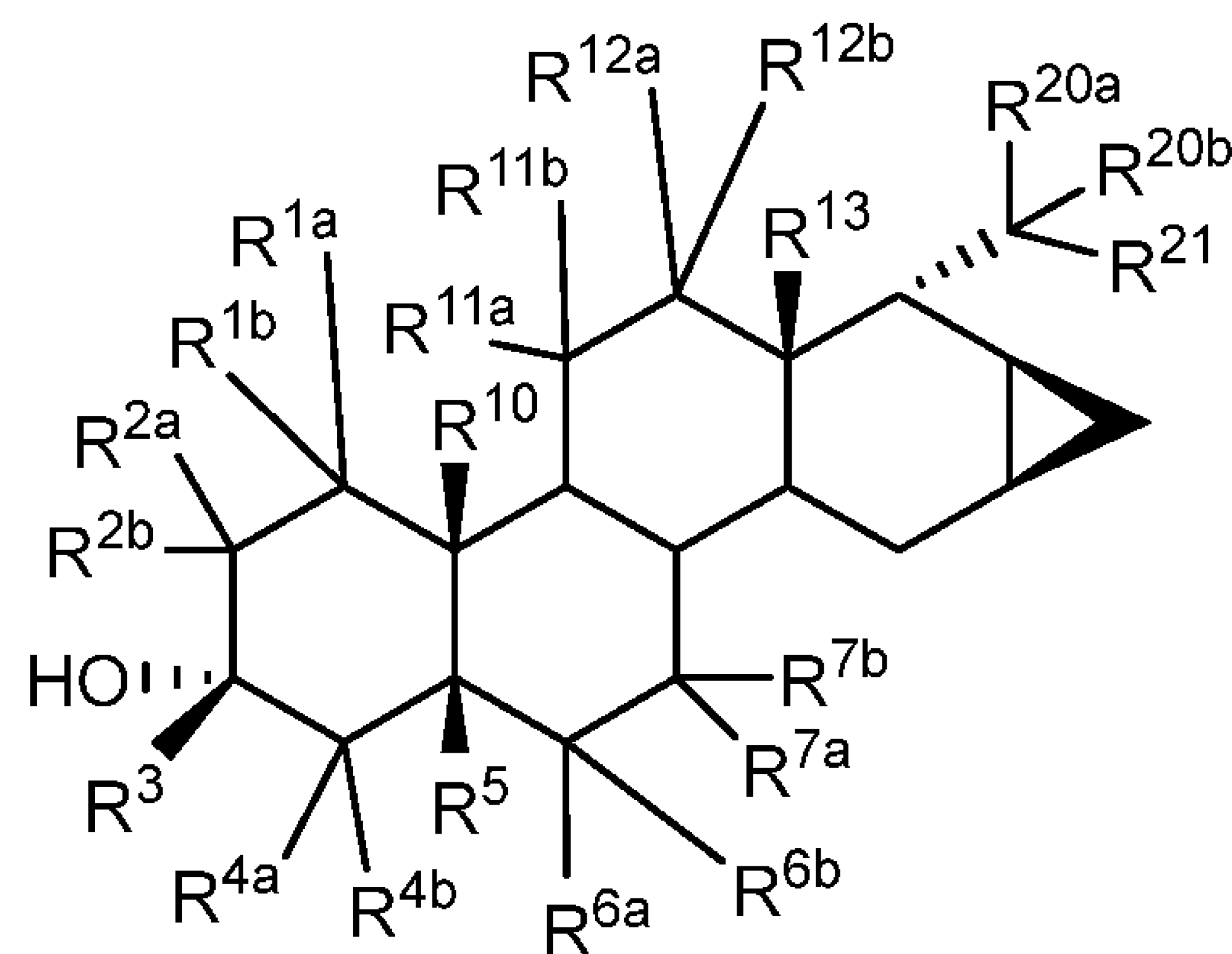
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), or (II-C).

[0035] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl, R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-S(O)$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, or $-S(O)_2$; R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

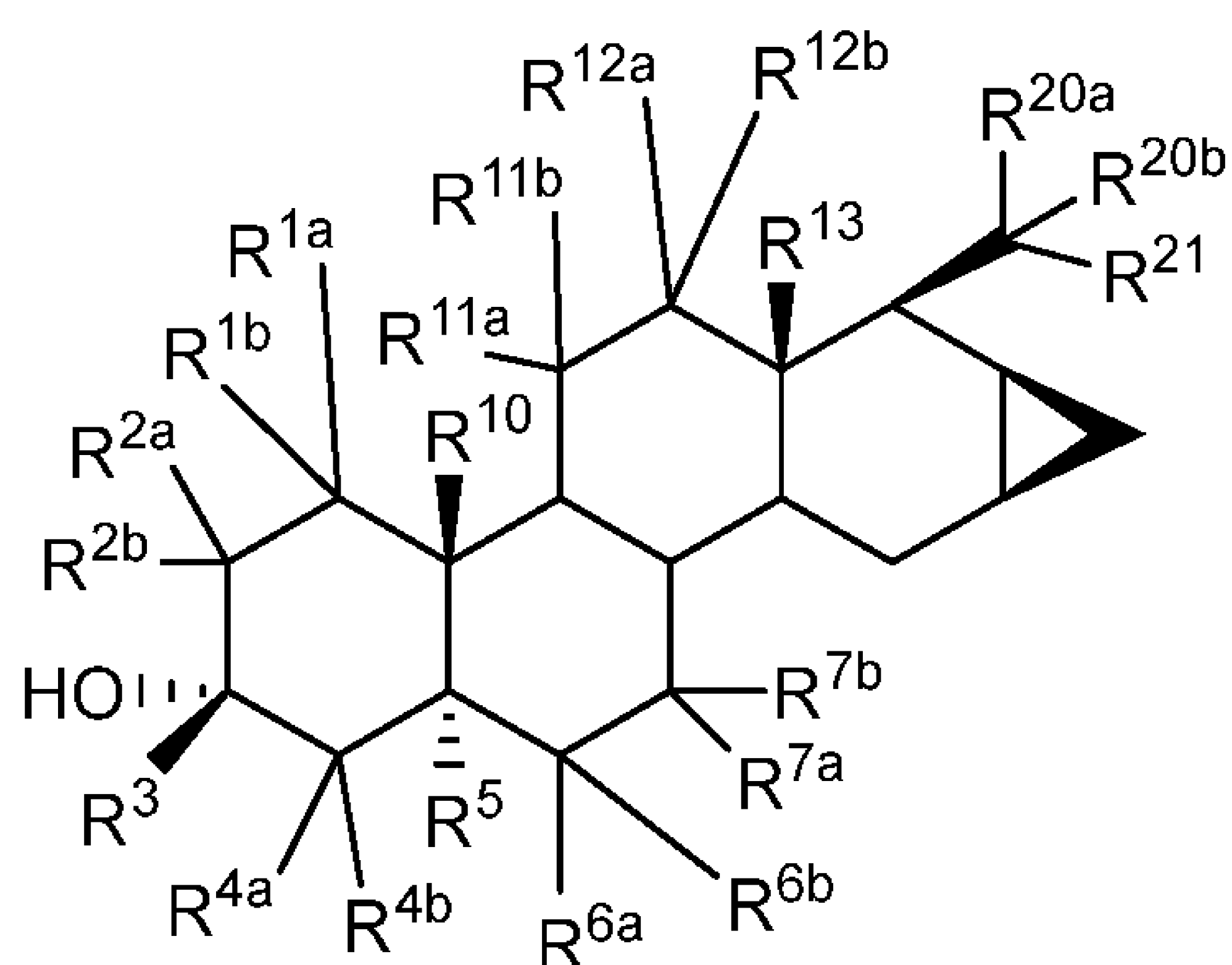
[0036] Another aspect of the present invention provides a compound of Formula (II-A1a), (II-A1b), (II-A1c) or (II-A1d)



(II-A1a),

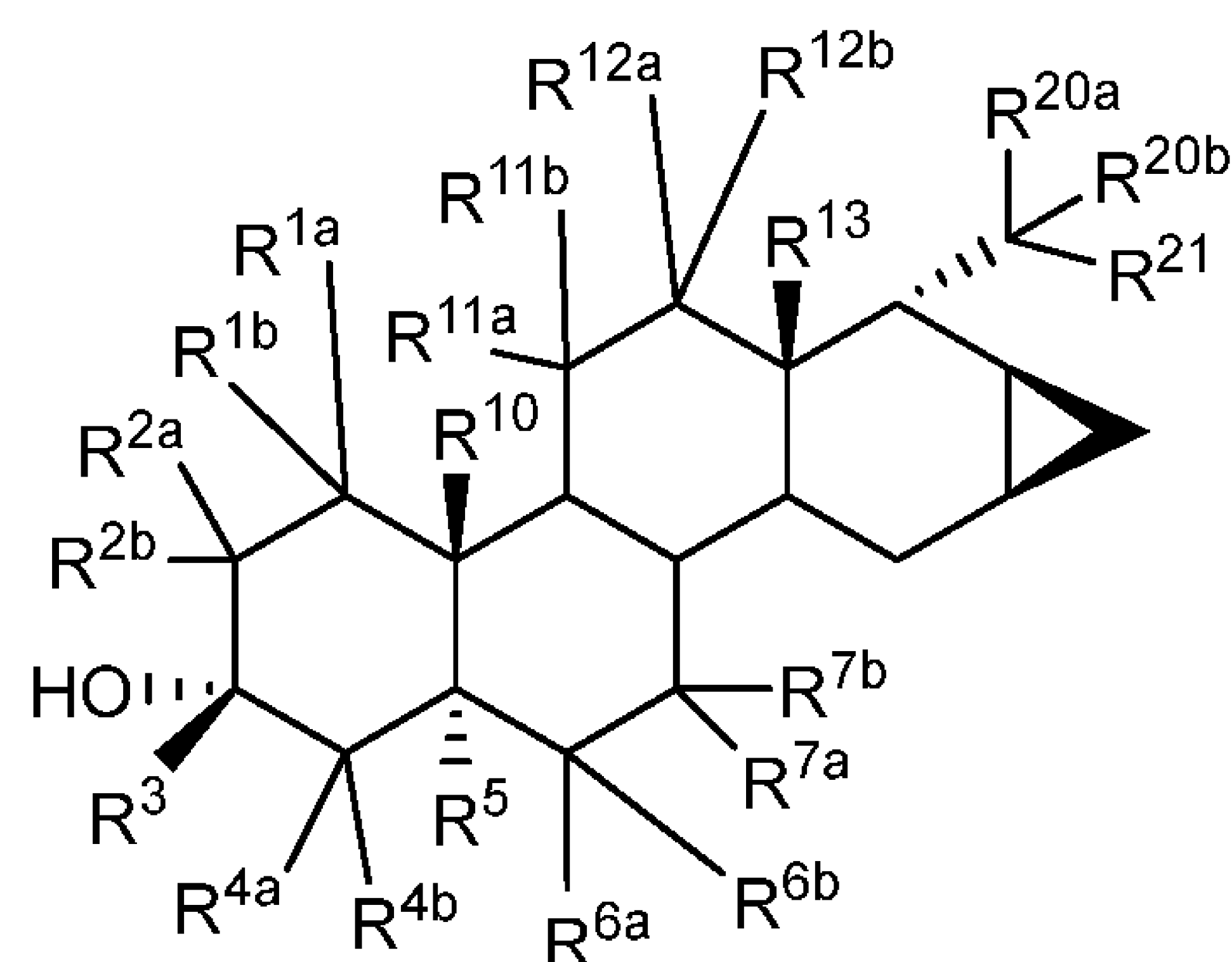


(II-A1b),



(II-A1c),

or



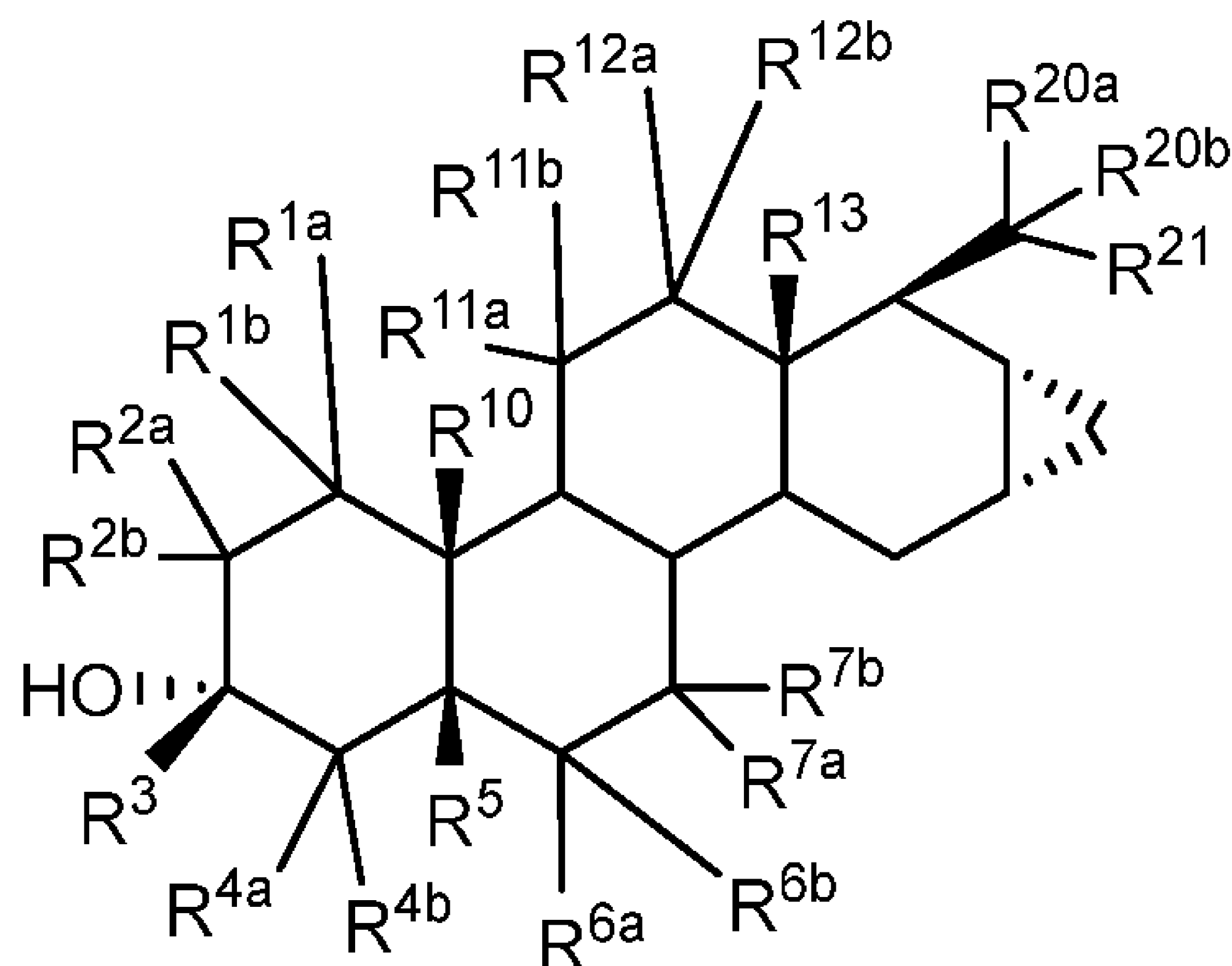
(II-A1d),

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-A), or (II-A1).

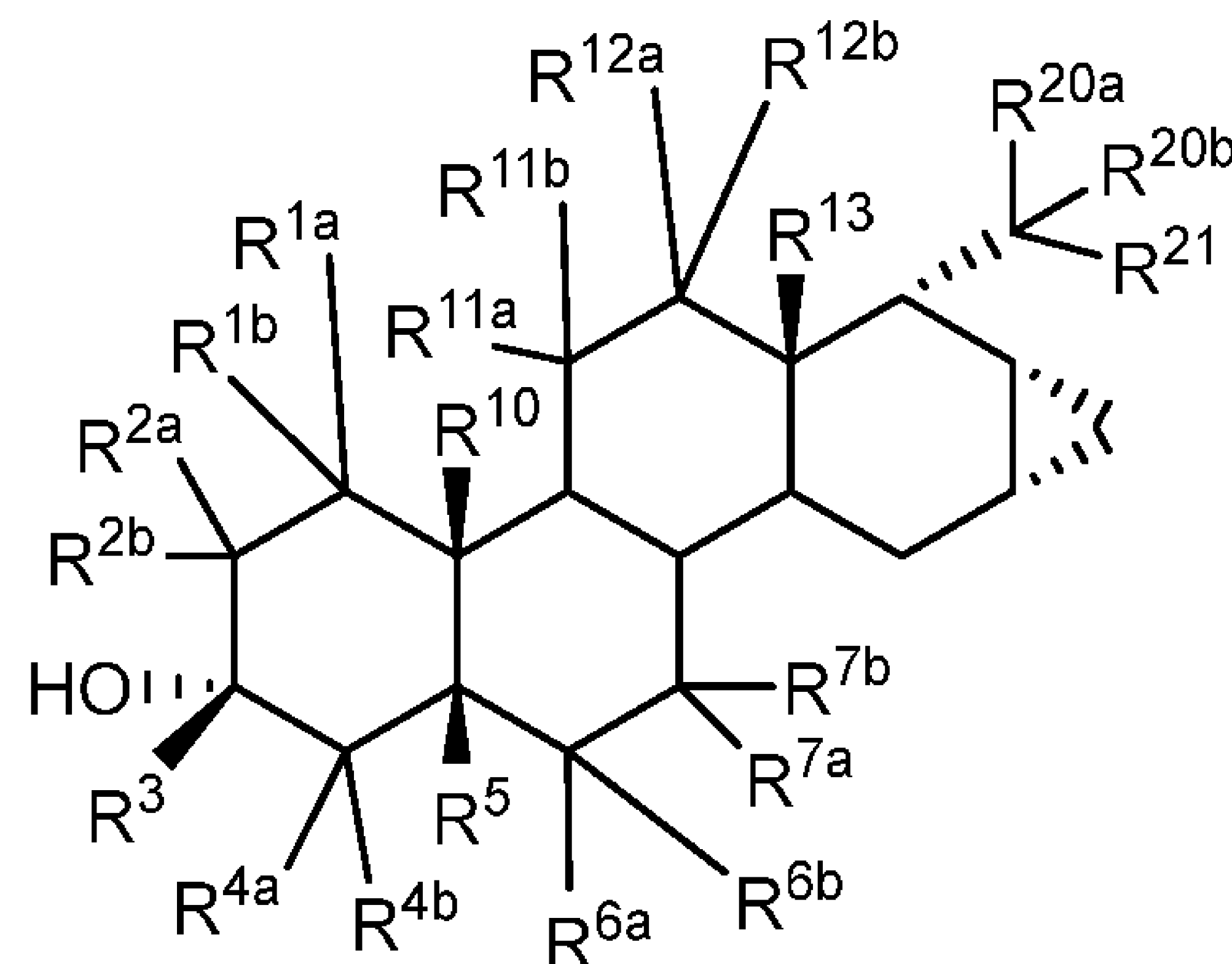
[0037] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4

nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

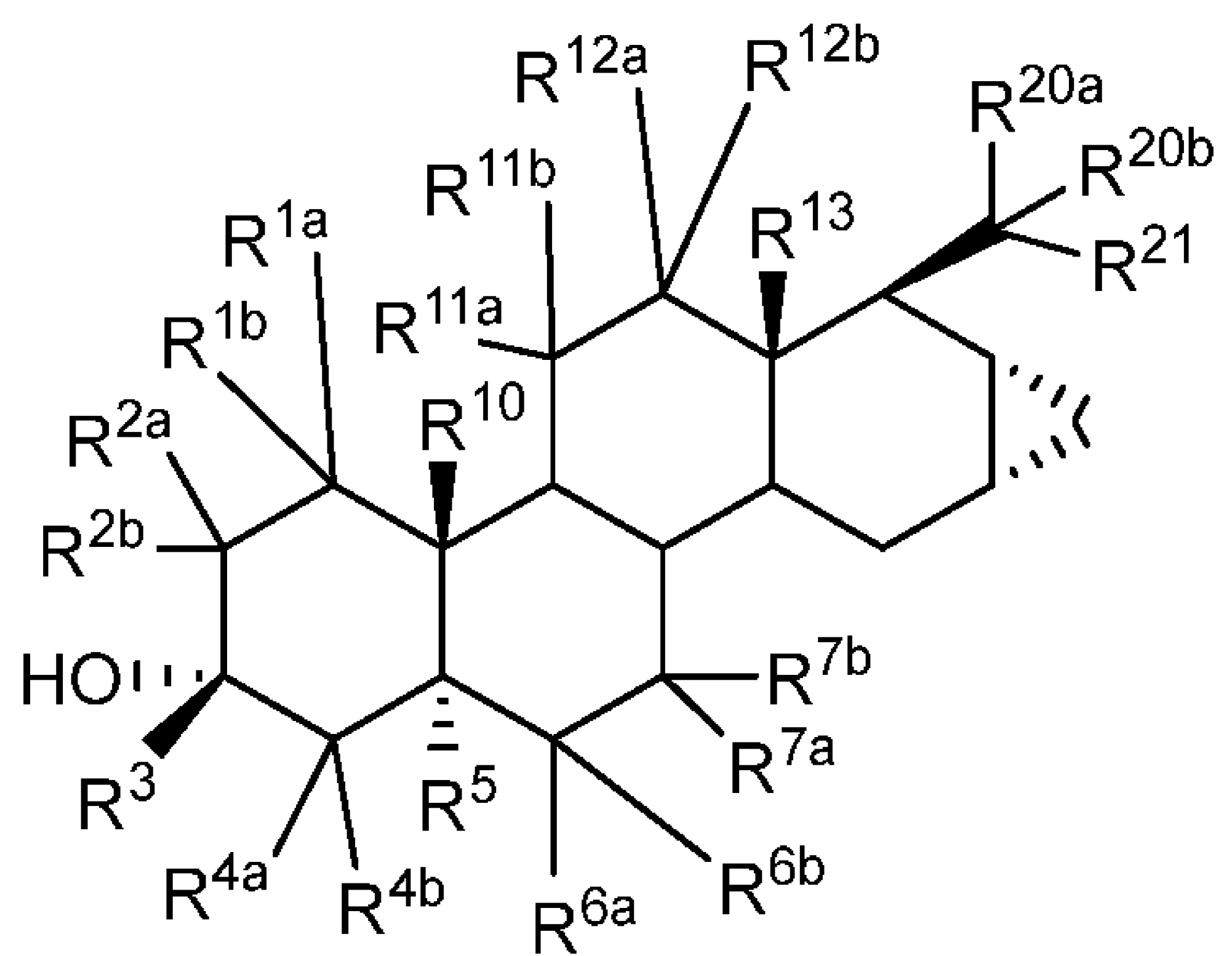
[0038] Another aspect of the present invention provides a compound of Formula (II-A2a), (II-A2b), (II-A2c) or (II-A2d)



(II-A2a),

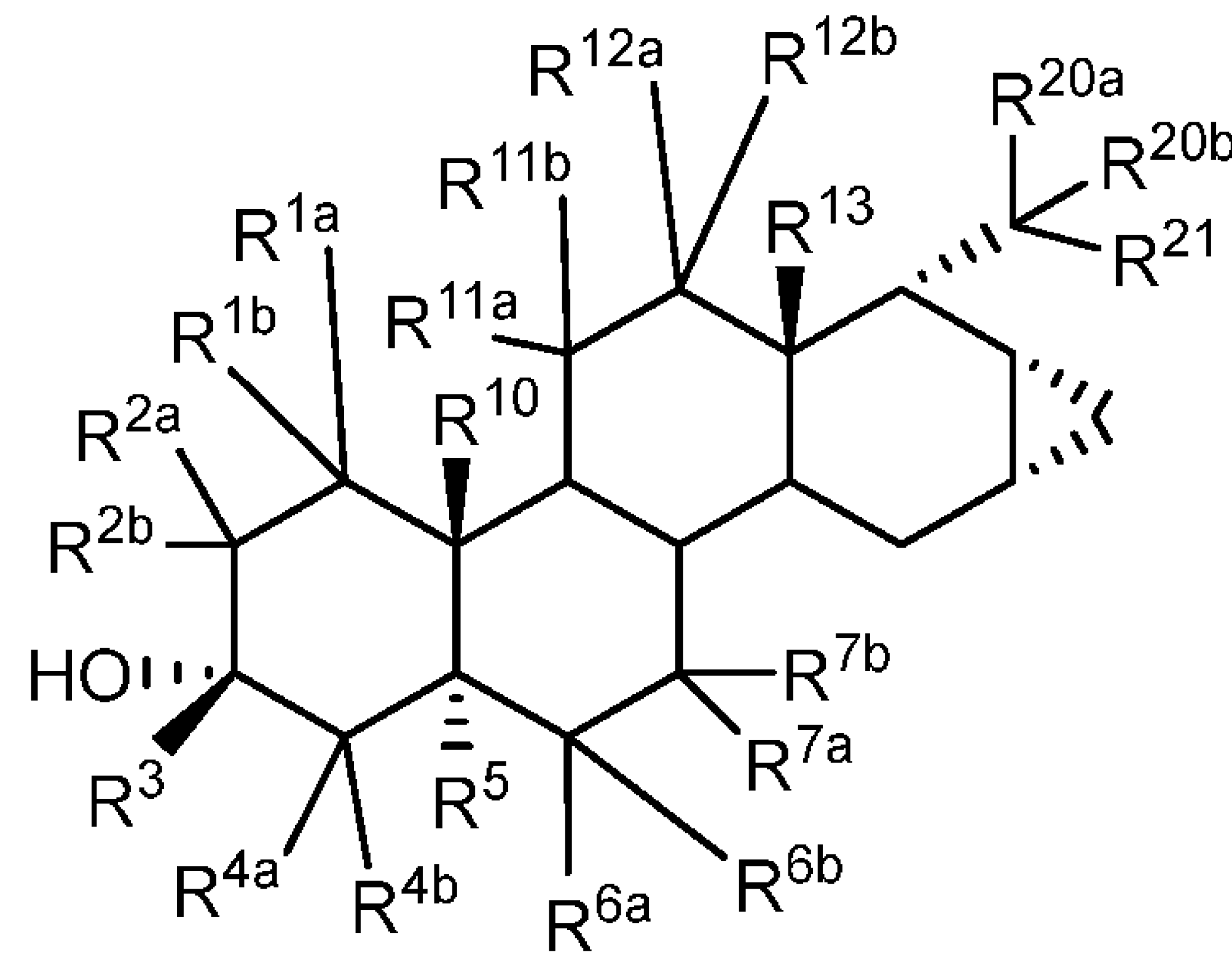


(II-A2b),



(II-A2c),

or



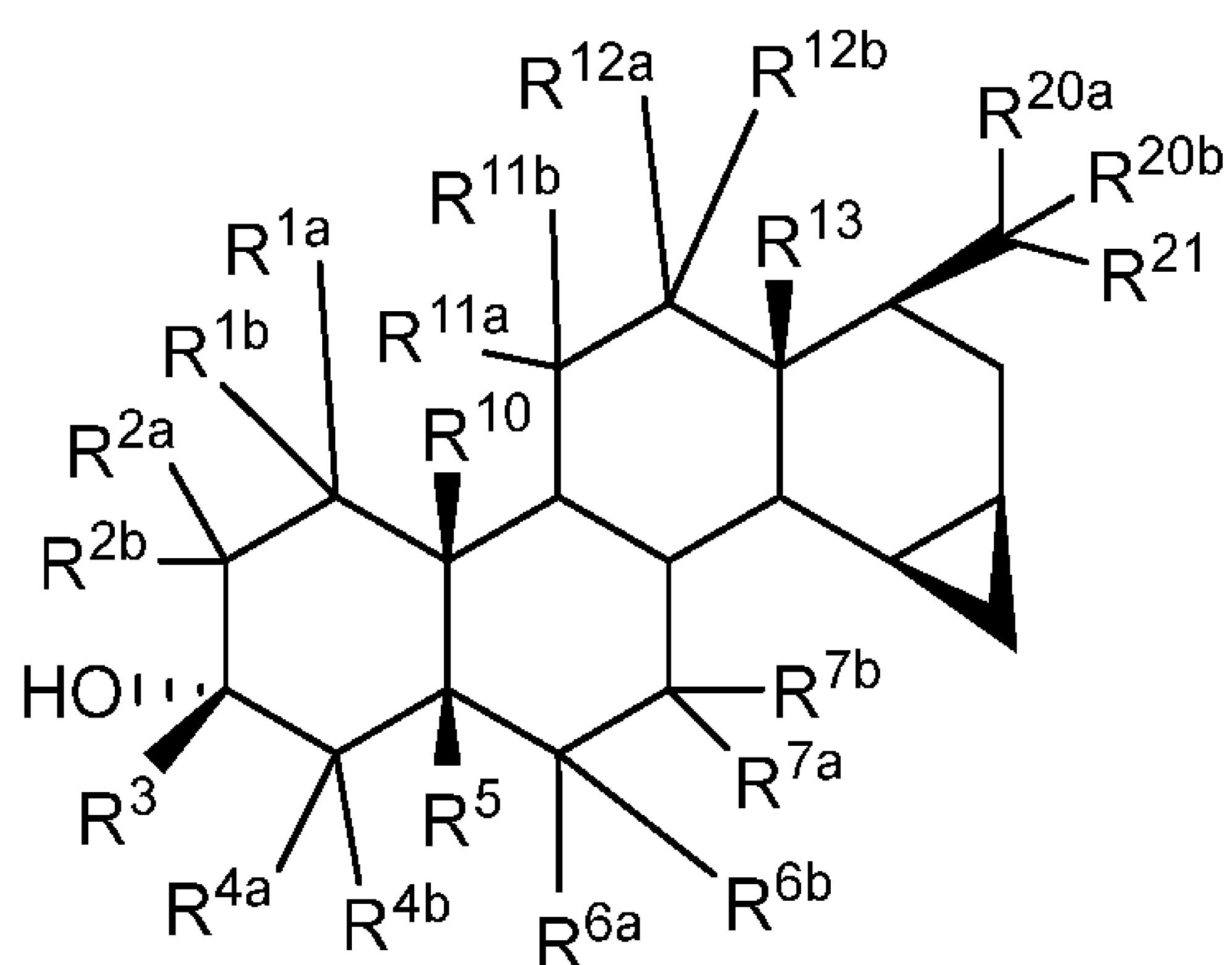
(II-A2d),

or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R^{4a}, R^{4b}, R⁵, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R¹⁰, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R^{20a}, R^{20b}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-A), or (II-A2).

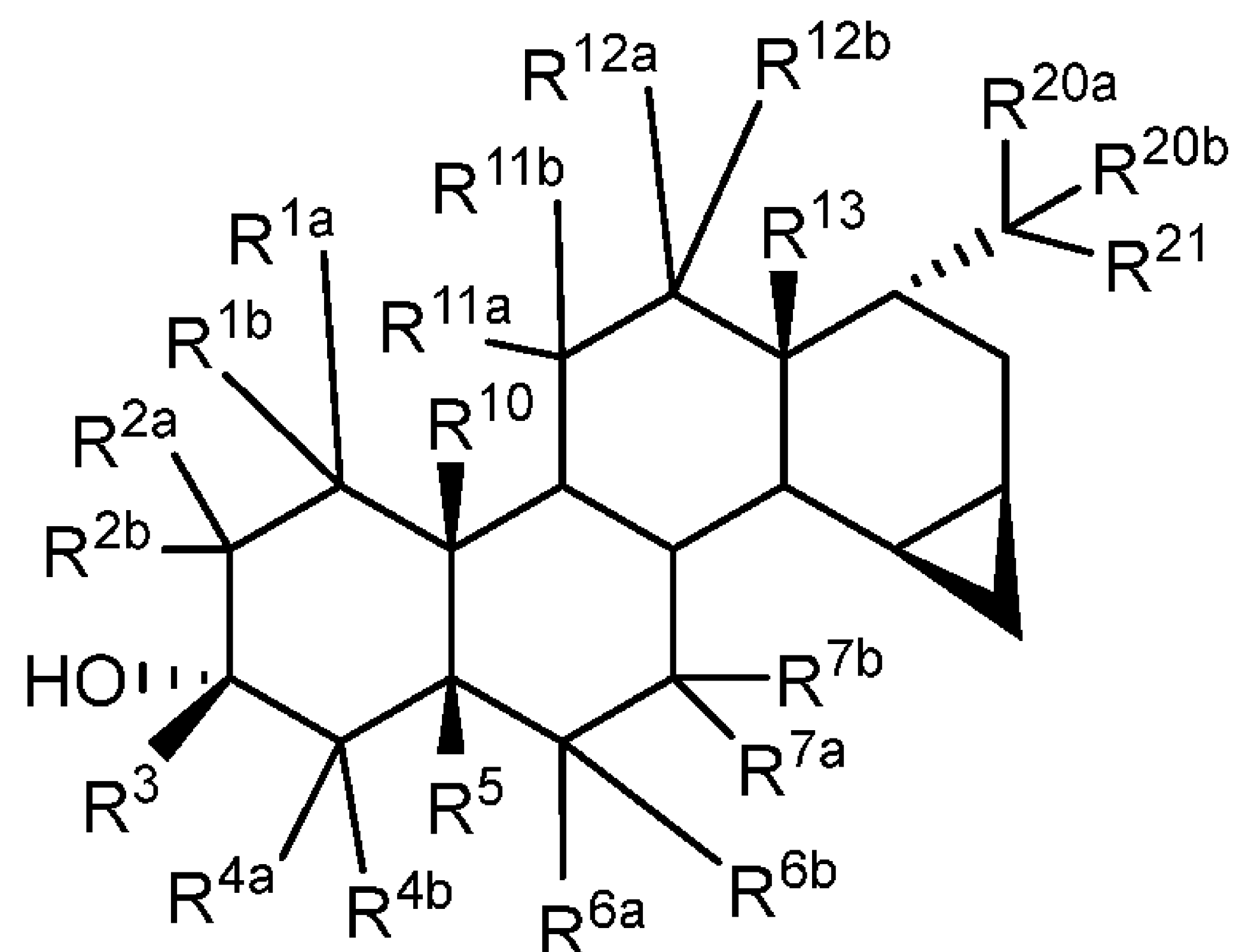
[0039] In some embodiments, each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from -H and C₁₋₆ alkyl, R³ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; R⁵ is -H or C₁₋₆ alkyl; R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; R¹³ is -H or optionally substituted C₁₋₃ alkyl; each of R^{20a} and R^{20b} is independently selected from -H, -OH, -C₁₋₅ alkyl-OH, C₁₋₆ alkyl, and -NH₂, or R^{20a} and R^{20b} taken together form oxo; R²¹ is -L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by -NR'-, -S-, -O-, -OC(O)-, -C(O)O-, -C(O)-, -C(O)C(O)-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)O-, -S(O)₂NR'-, -NR'S(O)₂-, -C(O)NR'NR'-, -NR'C(O)NR'-,

–OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, –S(O)–, or –S(O)₂–; R³⁰ is selected from R', halo, –CN, –NO₂, and –CF₃; and each R' is independently selected from –H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, and –CH₃.

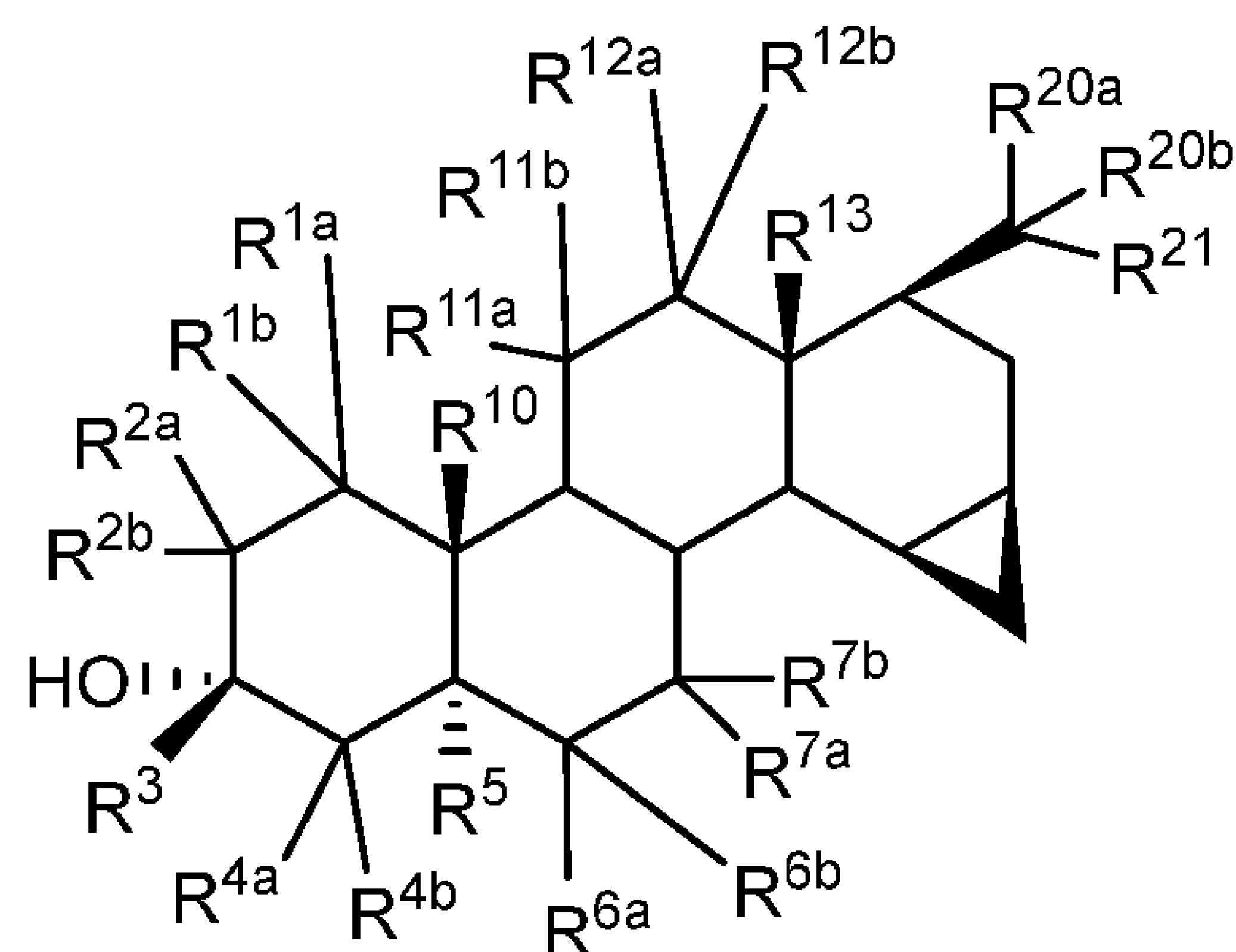
[0040] Another aspect of the present invention provides a compound of Formula (II-B1a), (II-B1b), (II-B1c) or (II-B1d)



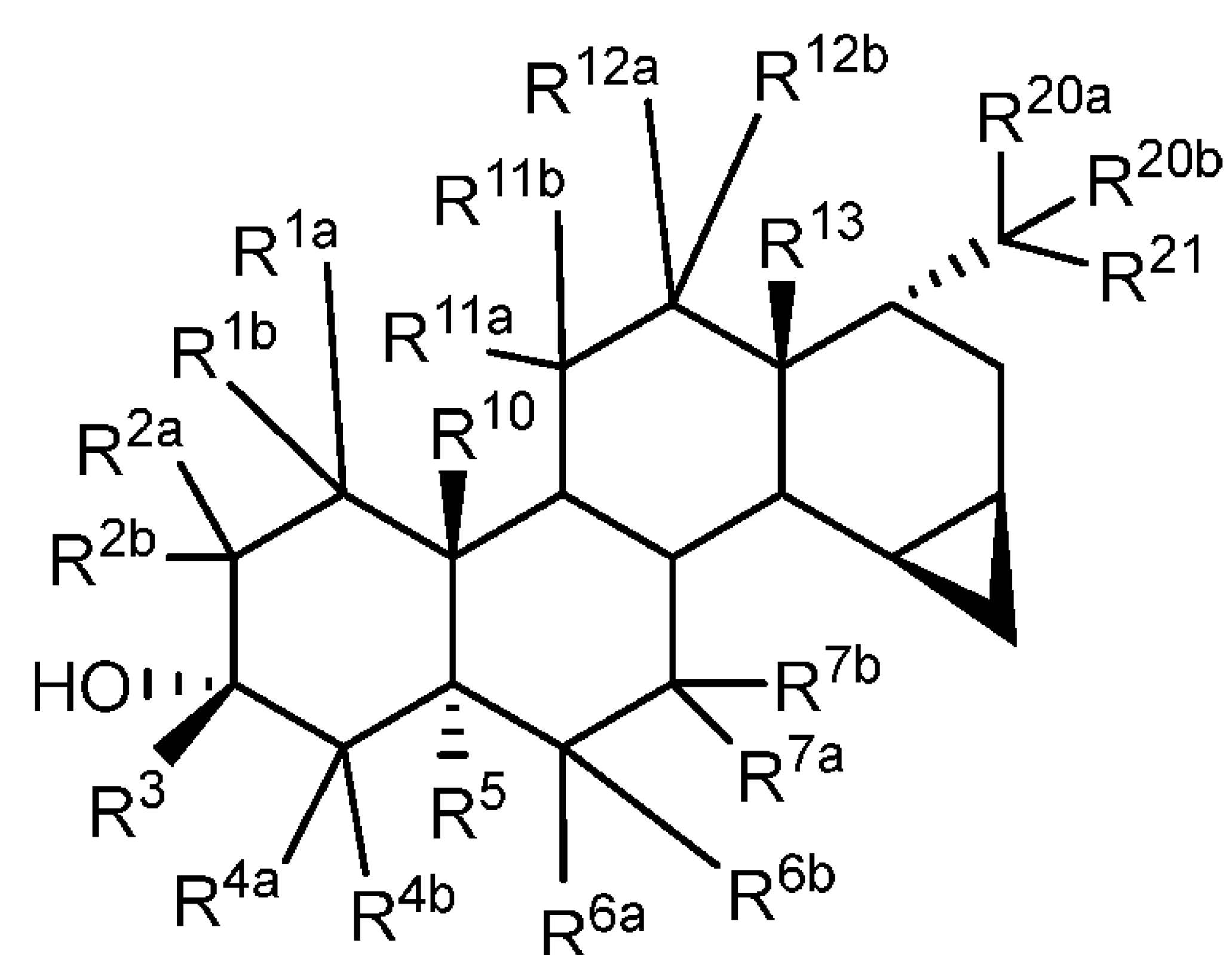
(II-B1a),



(II-B1b),



(II-B1c),



(II-B1d),

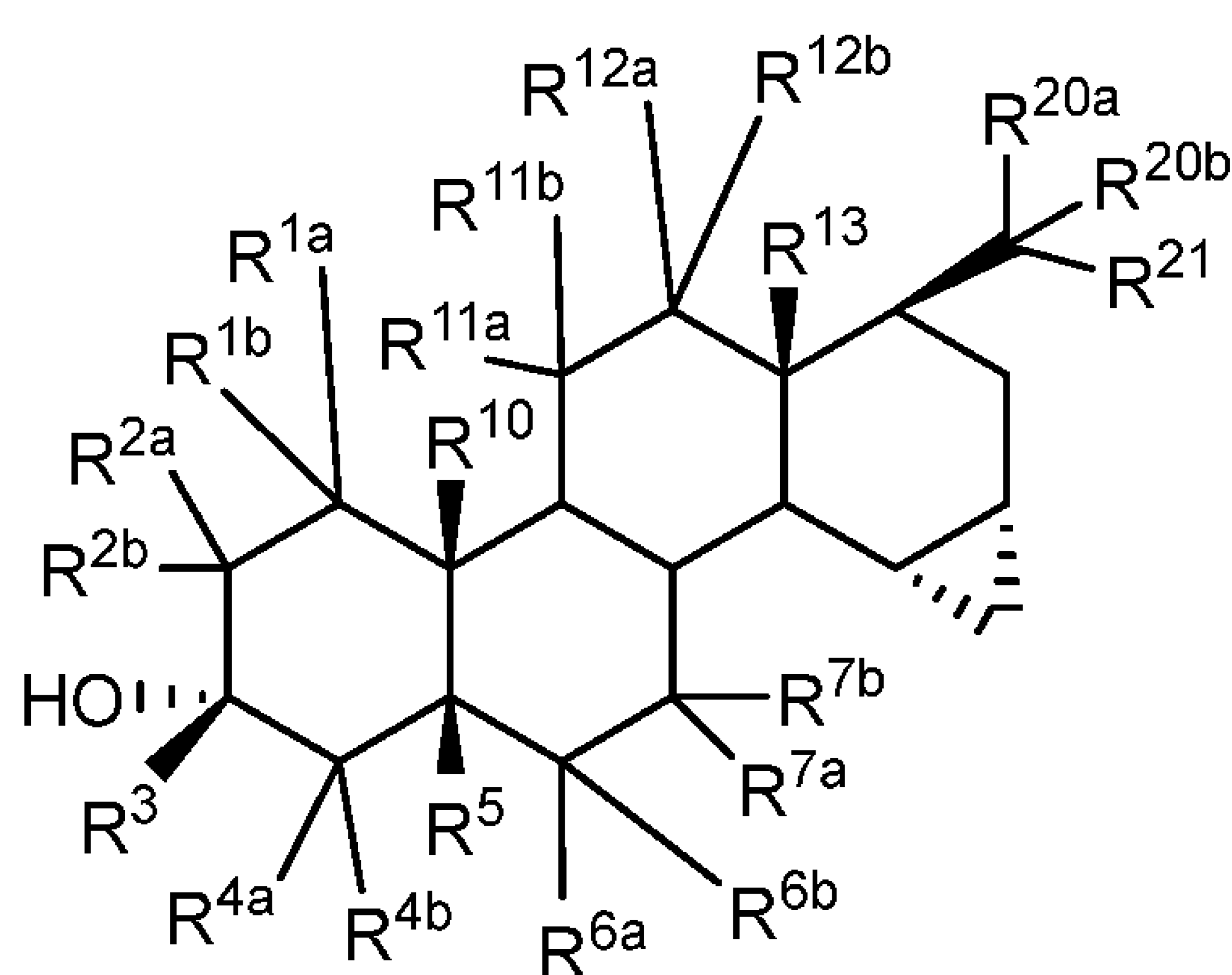
or

or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R^{4a}, R^{4b}, R⁵, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R¹⁰, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R^{20a}, R^{20b}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-B), or (II-B1).

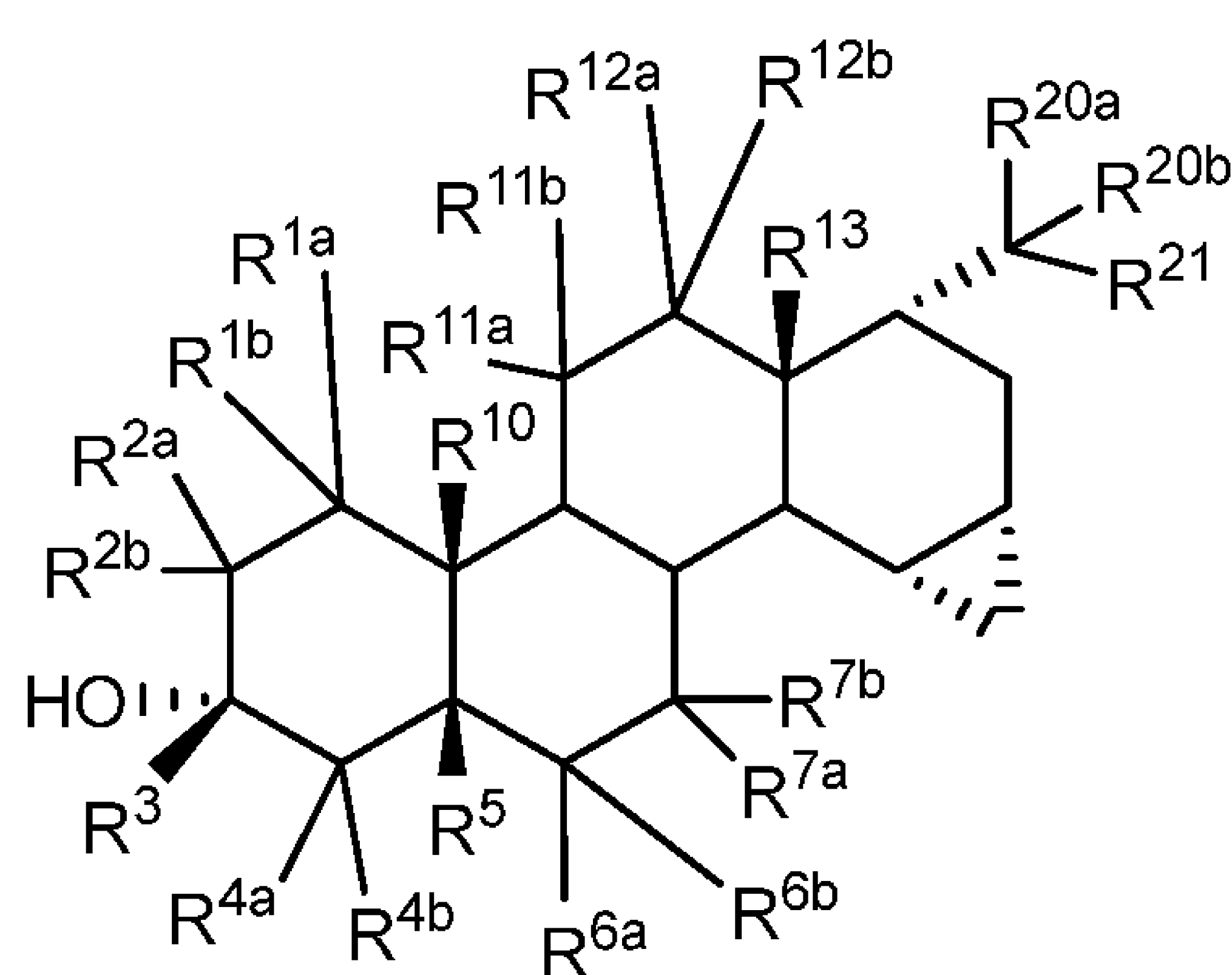
[0041] In some embodiments, each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from –H and C₁₋₆ alkyl, R³ is –H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; R⁵ is –H or C₁₋₆ alkyl; R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; R¹³ is –H or optionally substituted C₁₋₃ alkyl; each of R^{20a} and R^{20b} is independently selected from –H, –OH, –C₁₋₅ alkyl-OH, C₁₋₆ alkyl, and –NH₂, or R^{20a} and R^{20b} taken together form oxo; R²¹ is –L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃

alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'-$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'-$, $-NR'S(O)_2-$, $-C(O)NR'NR'-$, $-NR'C(O)NR'-$, $-OC(O)NR'-$, $-NR'NR'-$, $-NR'S(O)_2NR'-$, $-S(O)-$, or $-S(O)_2-$; R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

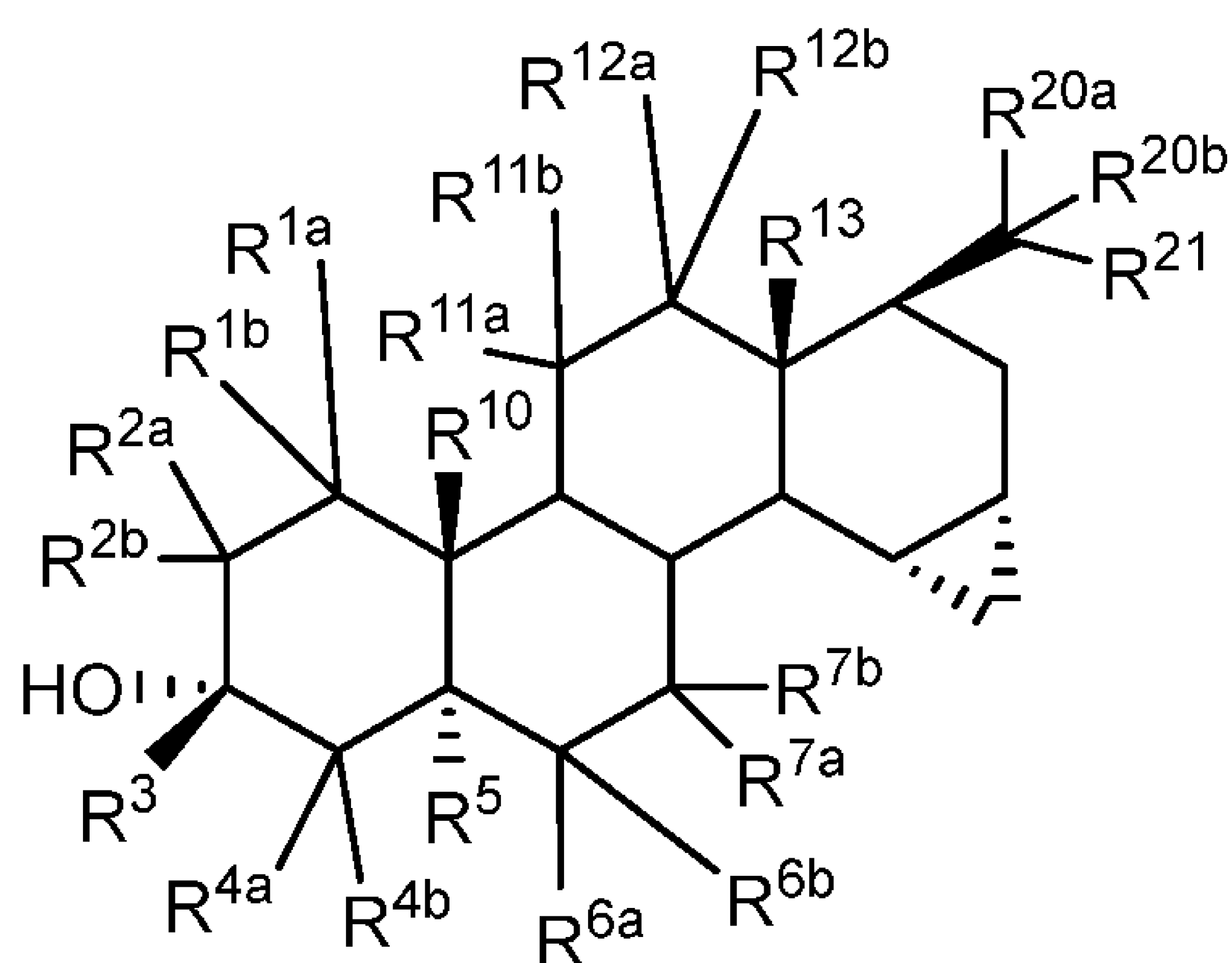
[0042] Another aspect of the present invention provides a compound of Formula (II-B2a), (II-B2b), (II-B2c) or (II-B2d)



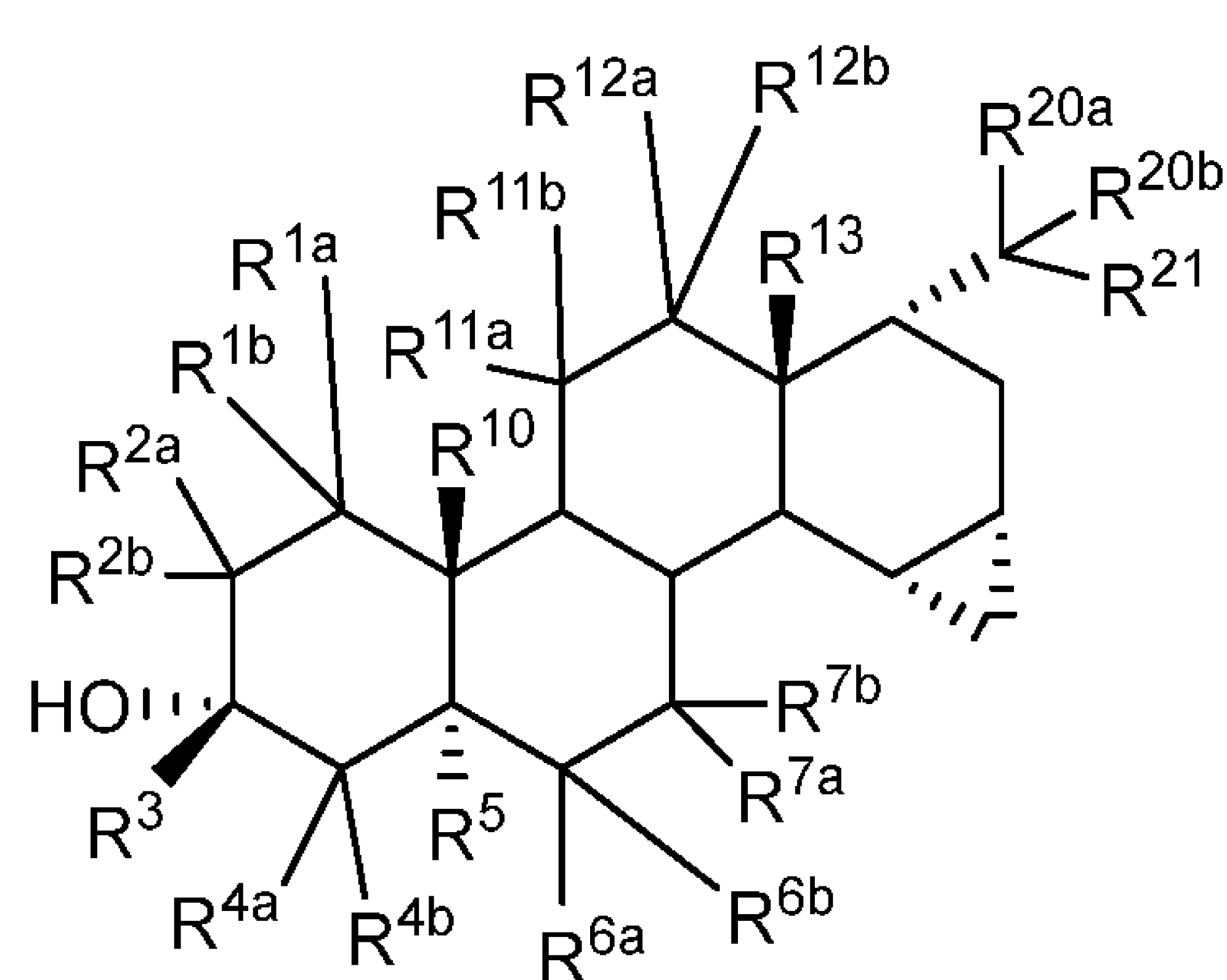
(II-B2a),



(II-B2b),



(II-B2c),



(II-B2d),

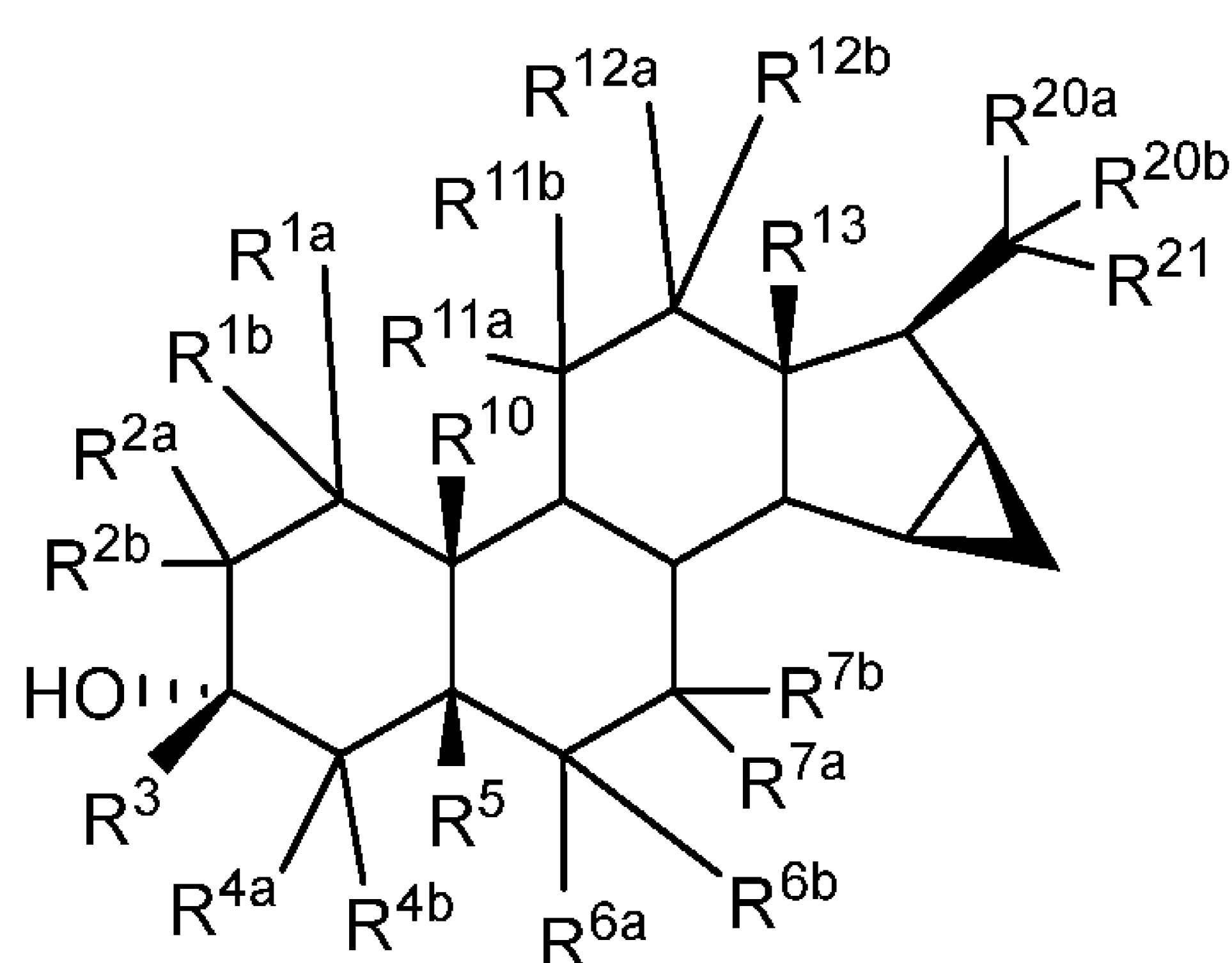
or

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-B), or (II-B2).

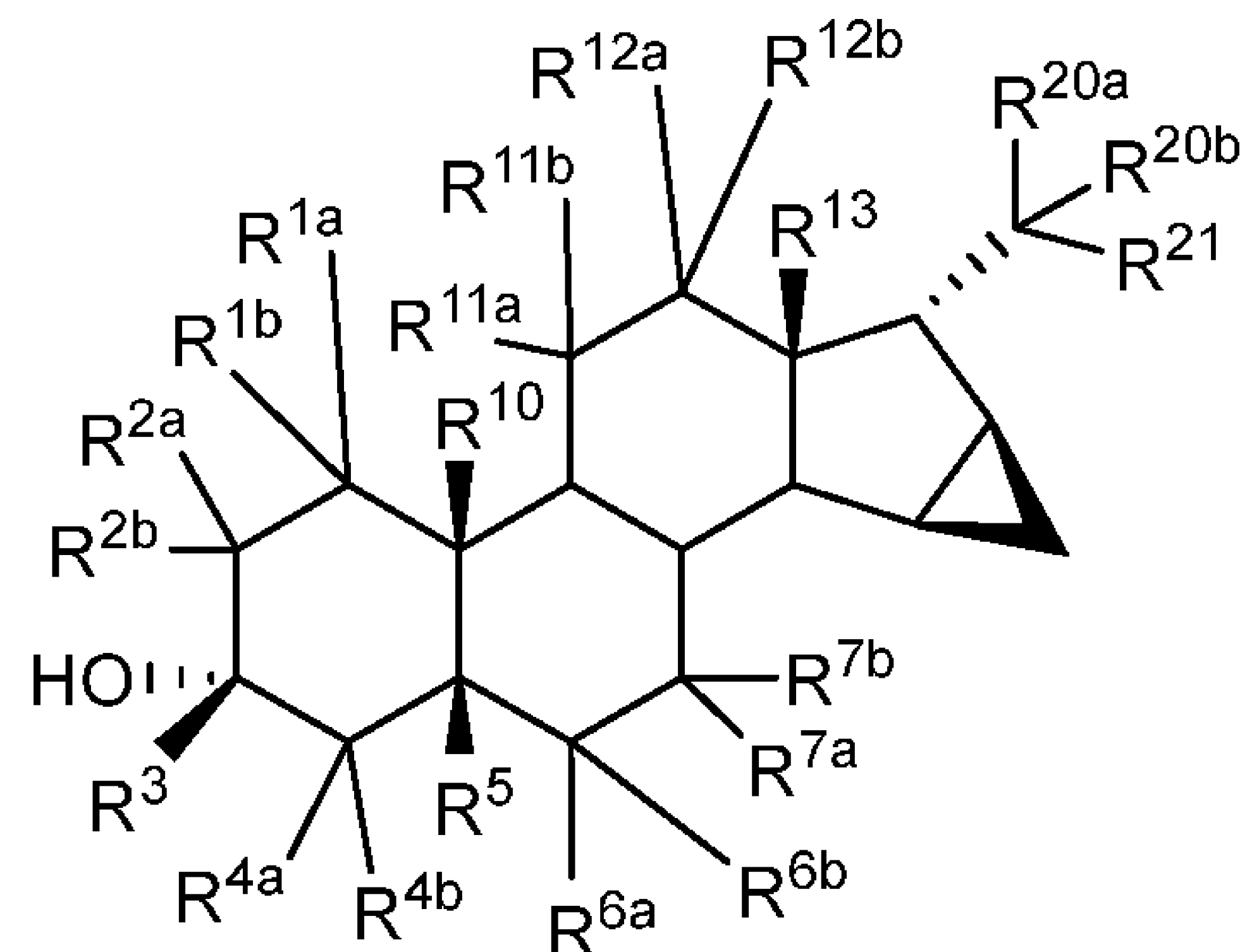
[0043] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl-O- C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl-O- C_{1-3} alkyl;

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'$ -, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'$ -, $-NR'S(O)_2-$, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)-$, or $-S(O)_2-$; R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

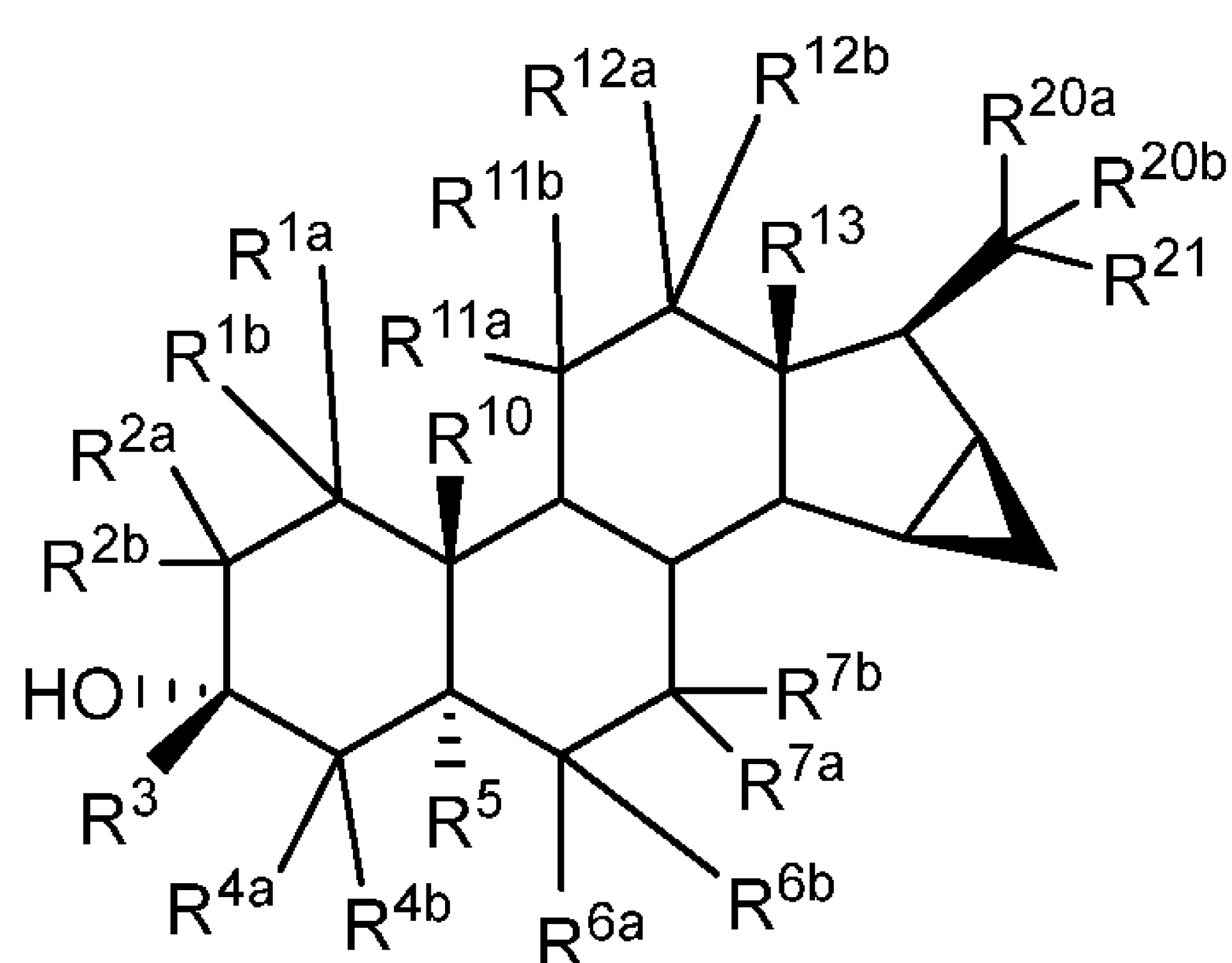
[0044] Another aspect of the present invention provides a compound of Formula (II-C1a), (II-C1b), (II-C1c) or (II-C1d)



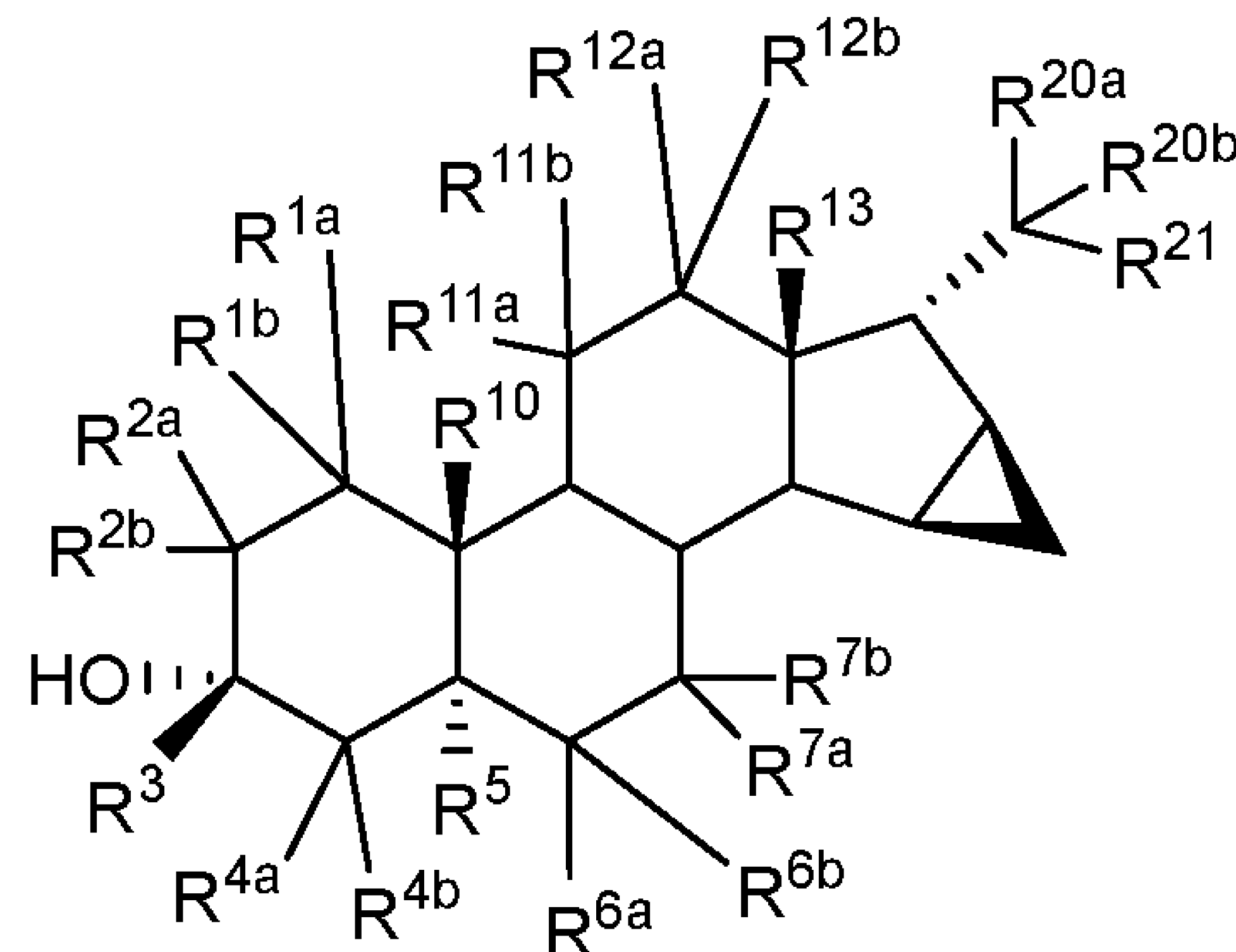
(II-C1a),



(II-C1b),



(II-C1c),



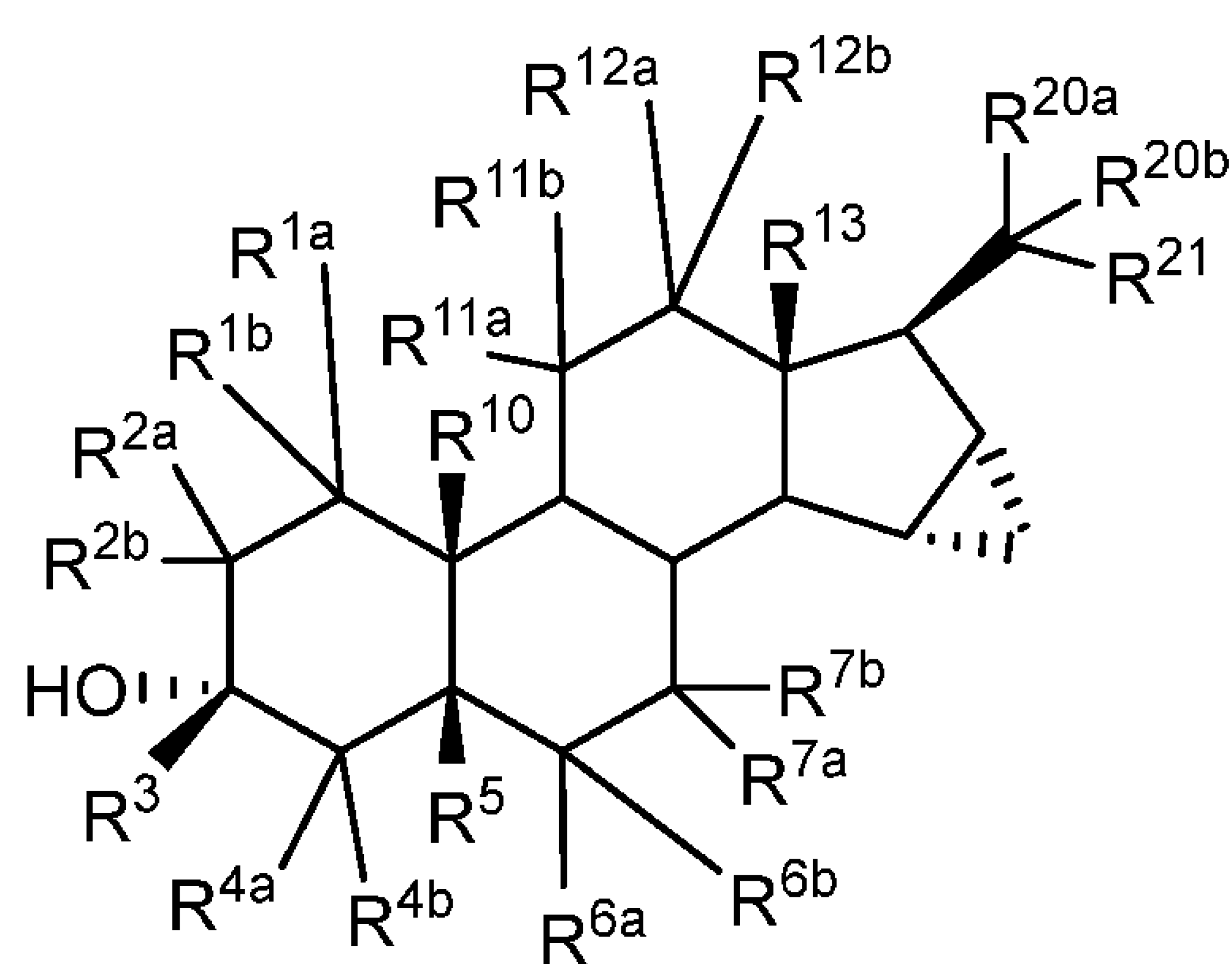
(II-C1d),

or

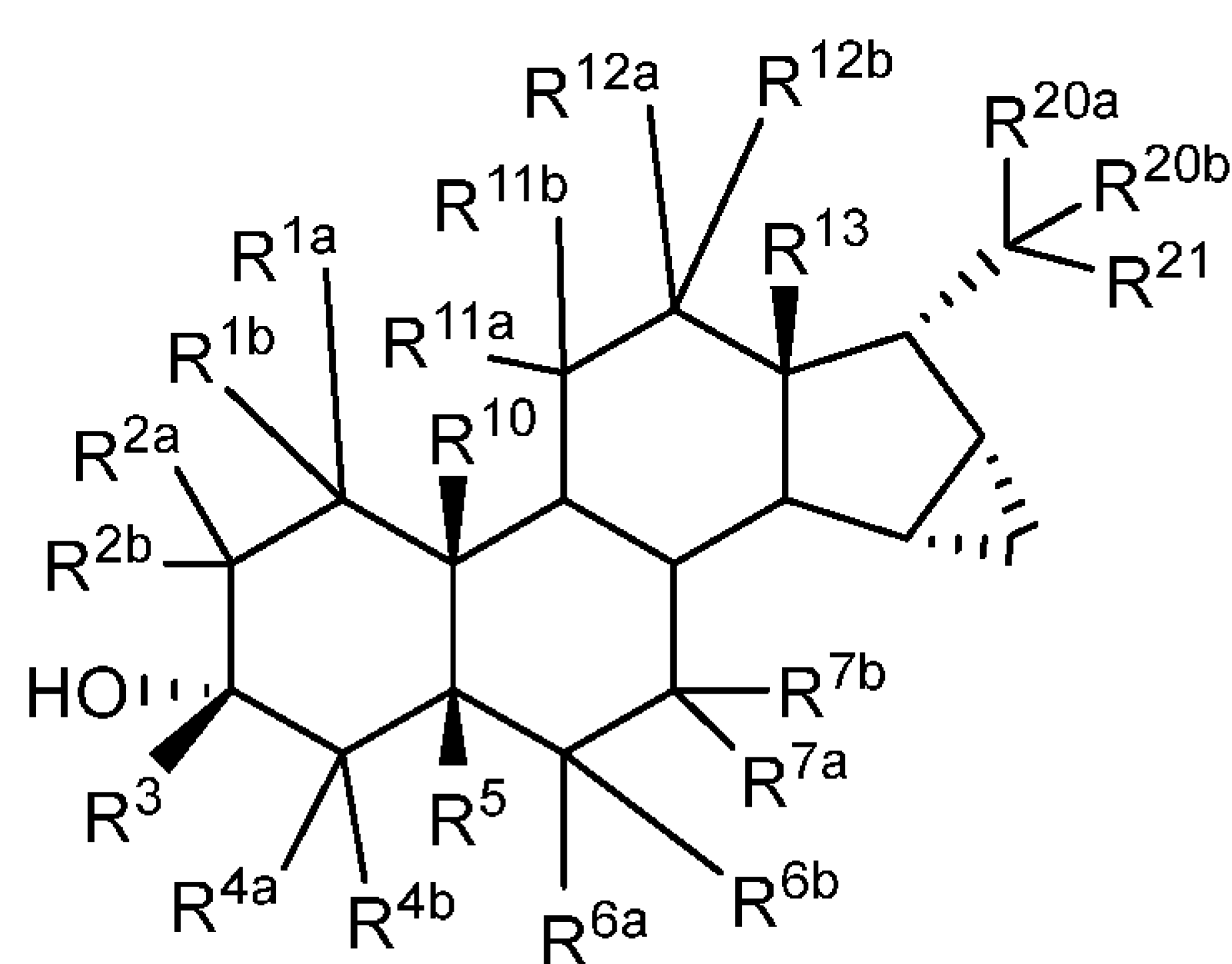
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4a} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-C), or (II-C1).

[0045] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

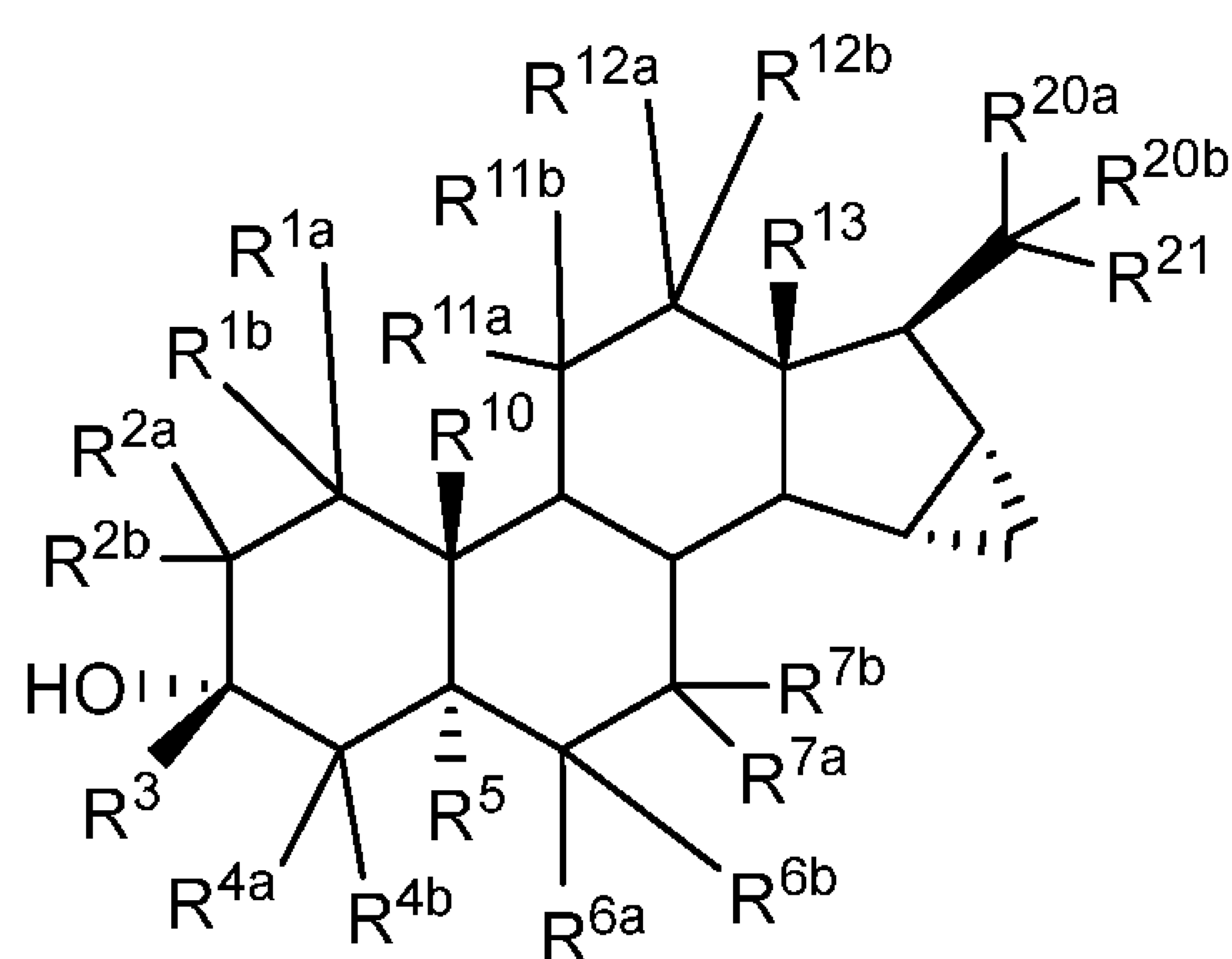
[0046] Another aspect of the present invention provides a compound of Formula (II-C2a), (II-C2b), (II-C2c) or (II-C2d)



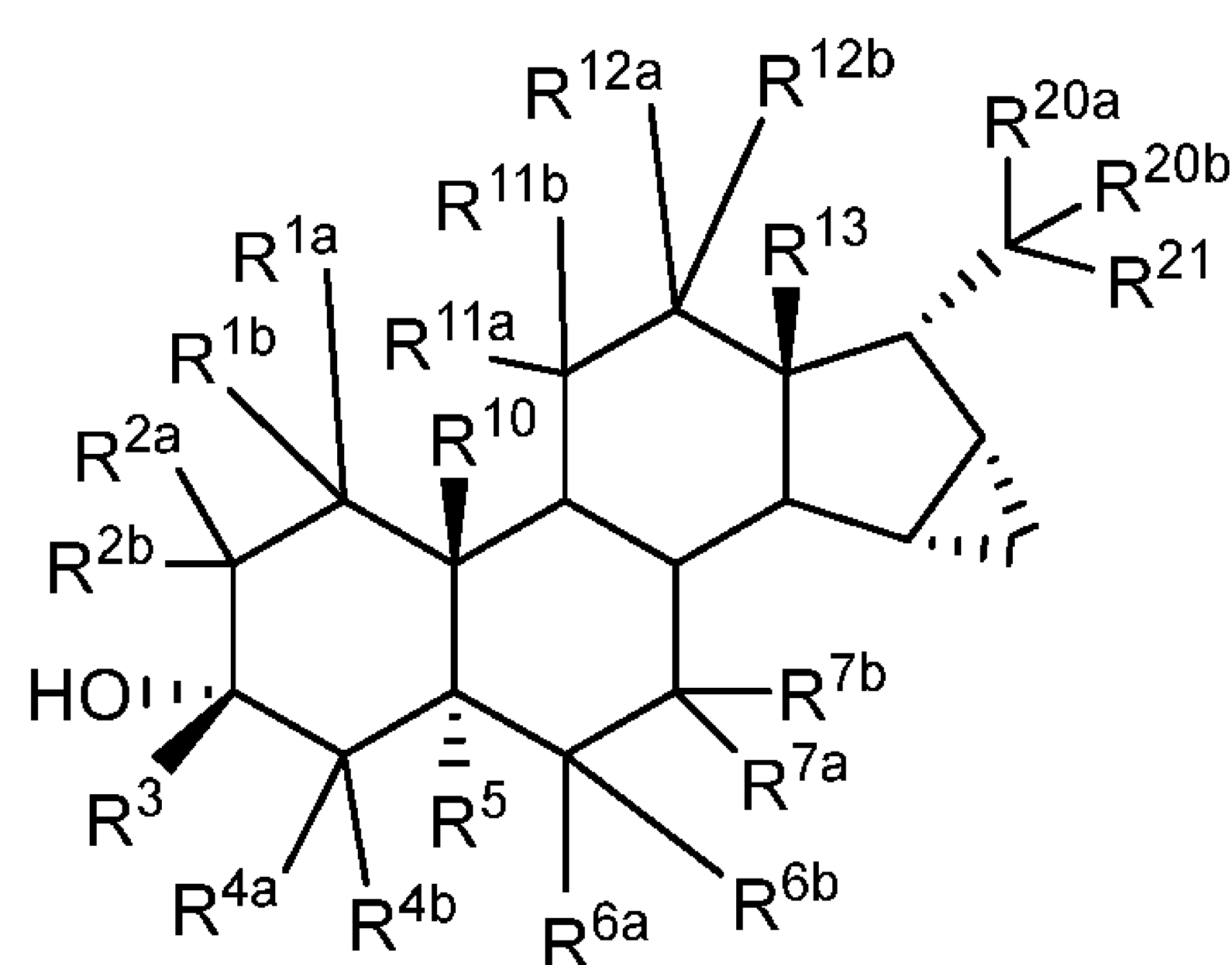
(II-C2a),



(II-C2b),



(II-C2c),



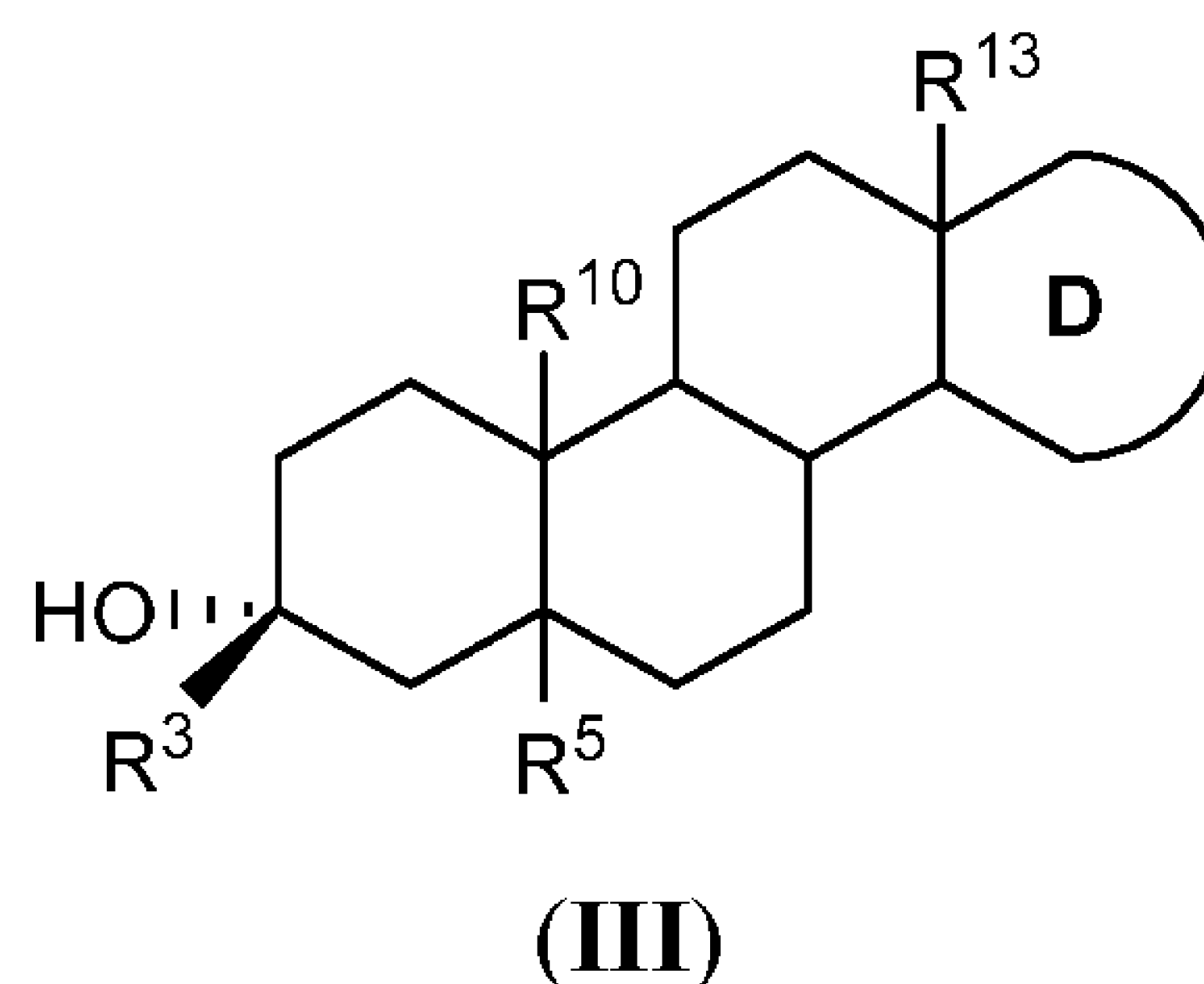
(II-C2d),

or

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-C), or (II-C2).

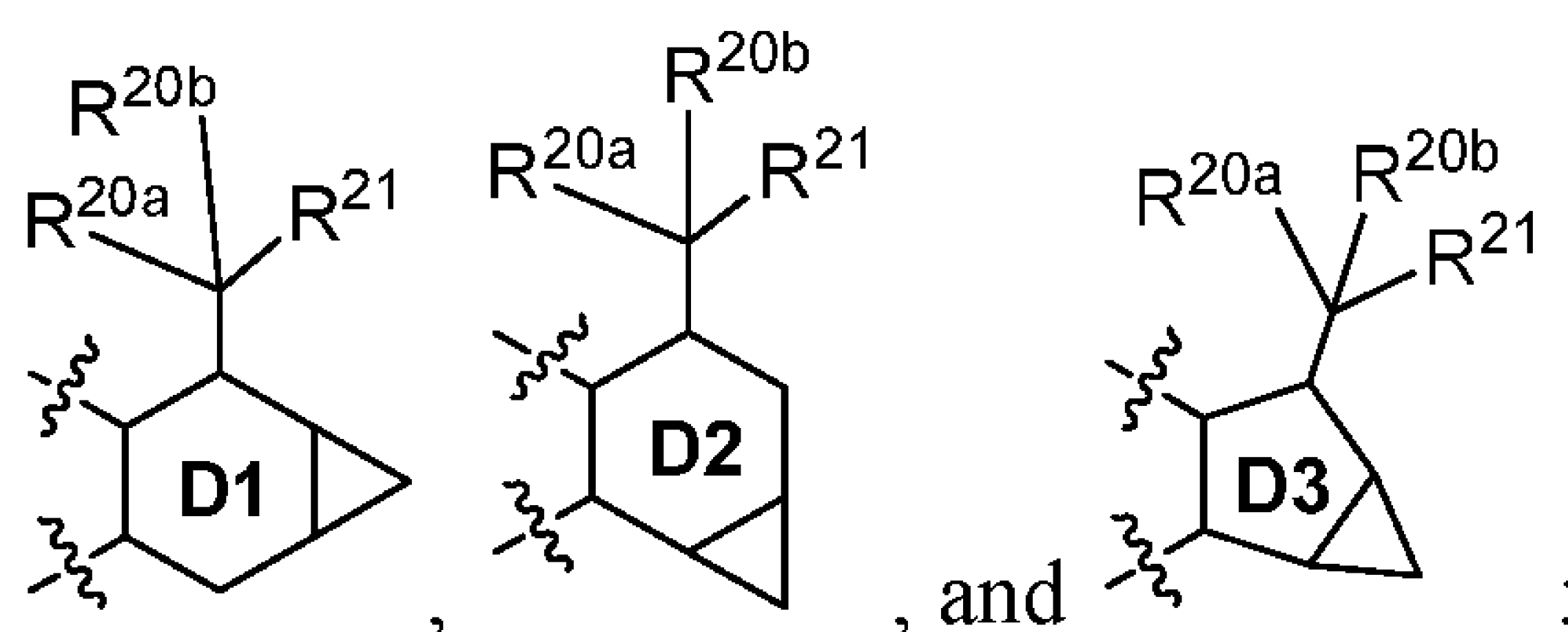
[0047] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, or $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-S(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, or $-S(O)_2$ -, R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0048] Another aspect of the present invention provides a compound of Formula (III)



or a pharmaceutically acceptable salt thereof, wherein ring D, R^3 , R^5 , R^{10} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20a} , R^{20b} , R^{20c} , R^{21} , R^{31a} , R^{31b} and m are as defined in any of the embodiments of the compounds of Formula (I) or (II).

[0049] In some embodiments, Ring D is a fused bicyclic ring selected from



R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^{13} is $-H$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently $-H$, $-OH$, C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

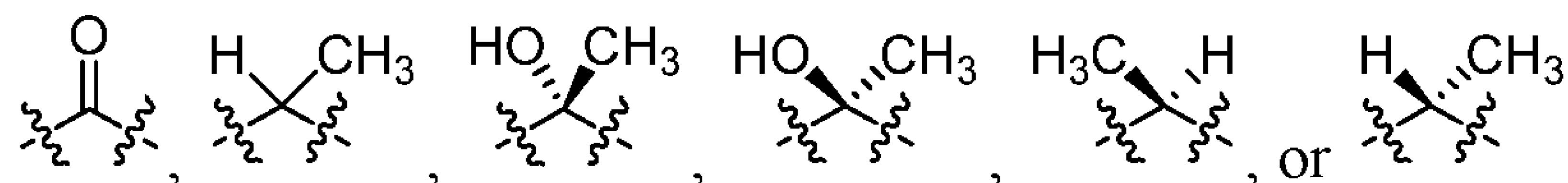
[0050] In some embodiments, R^3 is C_{1-6} alkyl or C_{1-6} alkyl- O - C_{1-6} alkyl. In some embodiments, R^3 is methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, neopentyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^3 is $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, or $-CH_2-O-CH_3$. And, in some embodiments, R^3 is $-CH_3$.

[0051] In some embodiments, R^5 is $-H$ or C_{1-3} alkyl. In some embodiments, R^5 is $-H$ or methyl.

[0052] In some embodiments, R^{10} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^{10} is $-H$ or methyl.

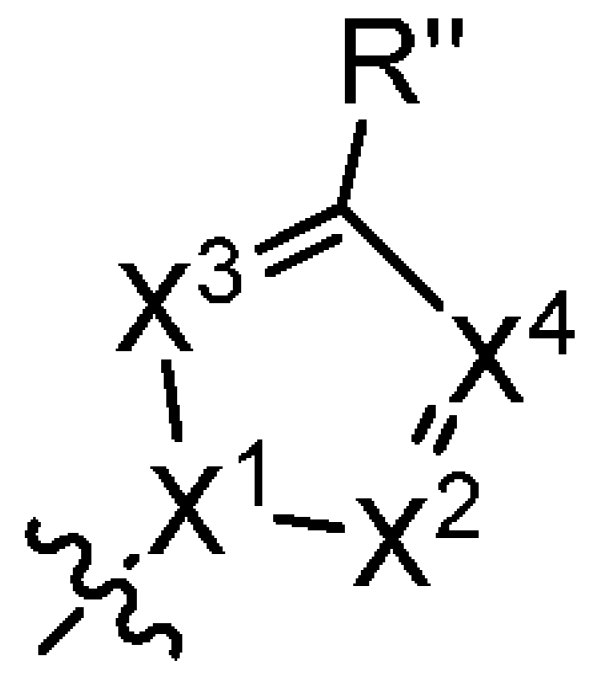
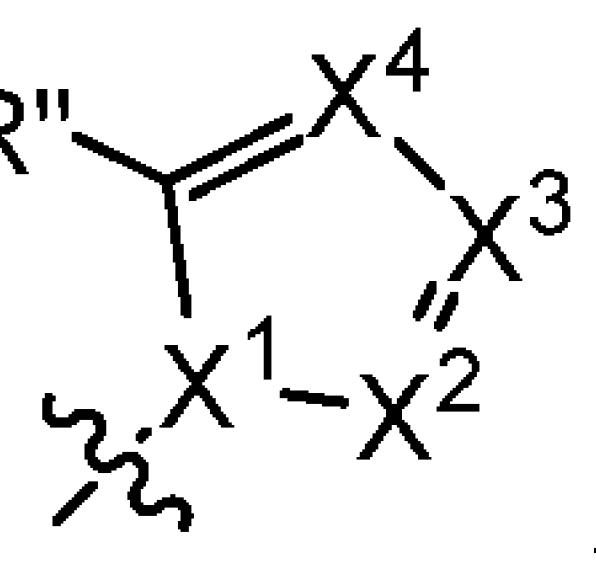
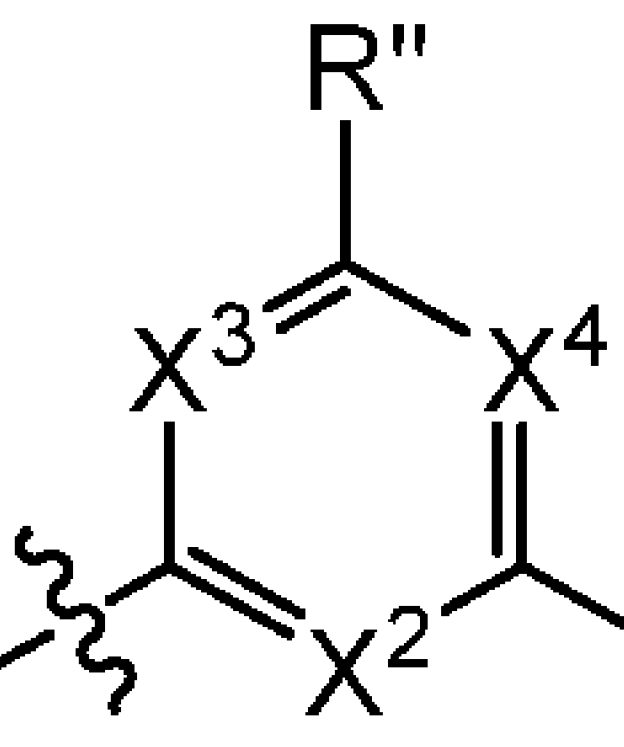
[0053] In some embodiments, R^{13} is C_{1-6} alkyl. In some embodiments, R^{13} is methyl, ethyl, or propyl. In some embodiments, R^{13} is $-H$ or methyl. And, in some embodiments, R^{13} is methyl.

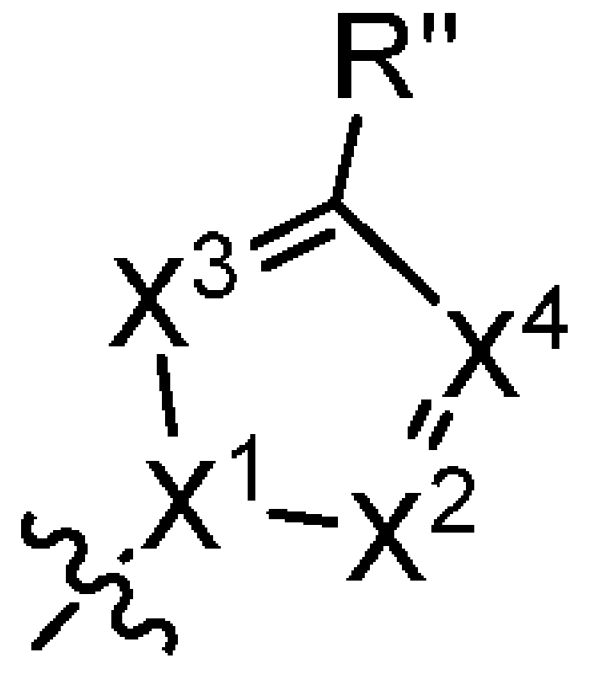
[0054] In some embodiments, R^{20a} and R^{20b} taken together form oxo. In some embodiments, one of R^{20a} and R^{20b} is $-H$, and the other of R^{20a} and R^{20b} is C_{1-6} alkyl. In some embodiments, one of R^{20a} and R^{20b} is C_{1-6} alkyl, and the other of R^{20a} and R^{20b} is $-OH$. In some embodiments, one of R^{20a} and R^{20b} is methyl, ethyl, or propyl, and the other of R^{20a} and R^{20b} is $-OH$. In some embodiments, R^{20a} , R^{20b} , and the carbon to which they are attached form

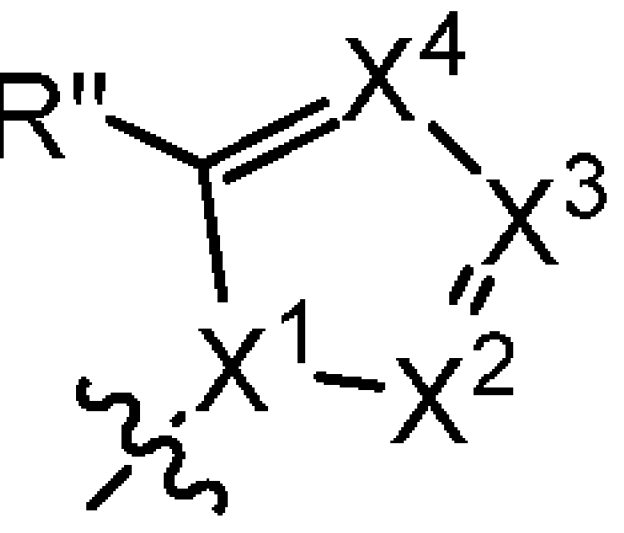


[0055] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-3} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6 membered ring of R^{30} is optionally

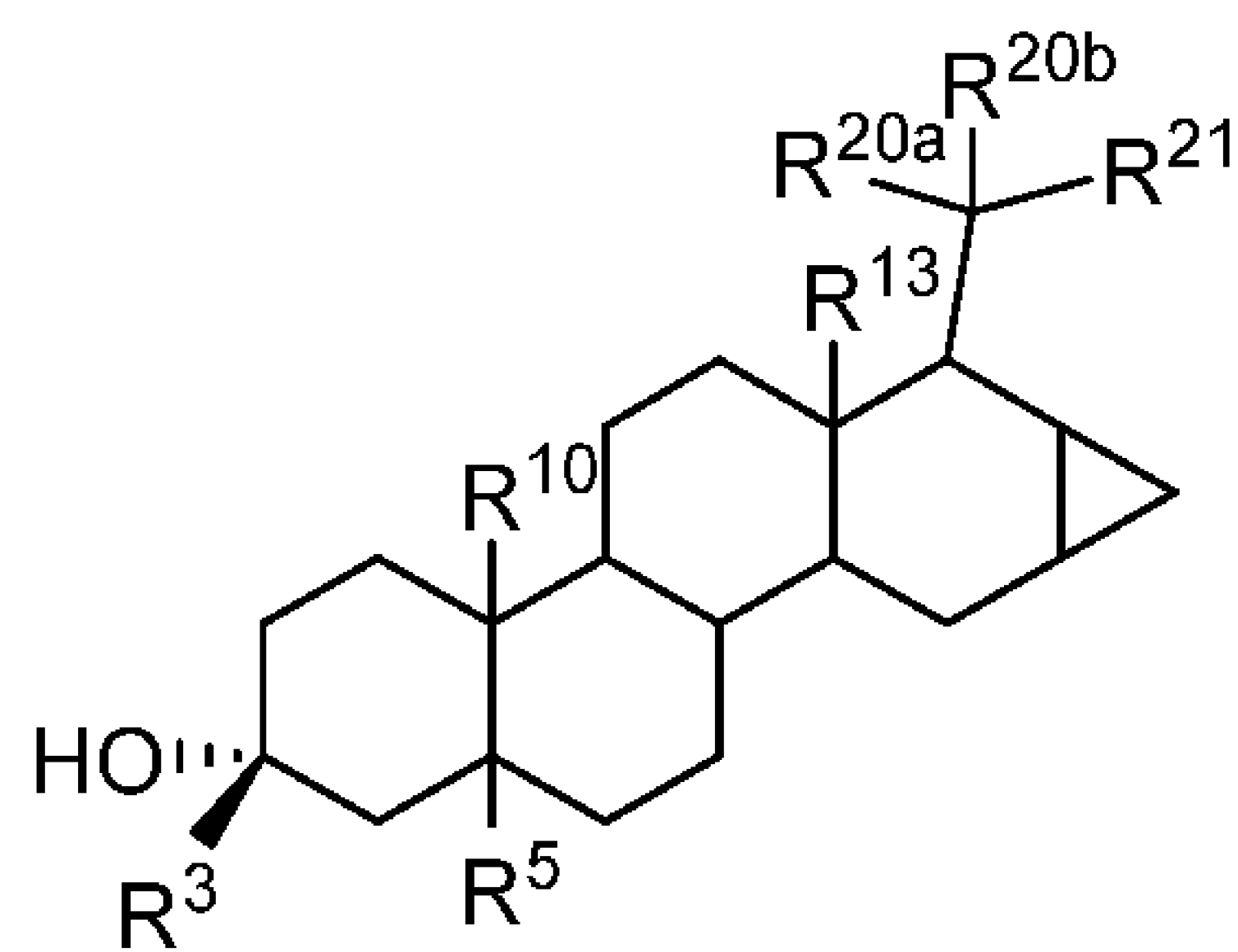
substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, or $-\text{N}(\text{H})-$; and R^{30} is $-\text{H}$ or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, or $-\text{N}(\text{H})-$; and R^{30} is a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, $-\text{CH}_2-$, or

$-\text{N}(\text{H})-$; and R^{30} is , , or , wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from

halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, R^{30} is 

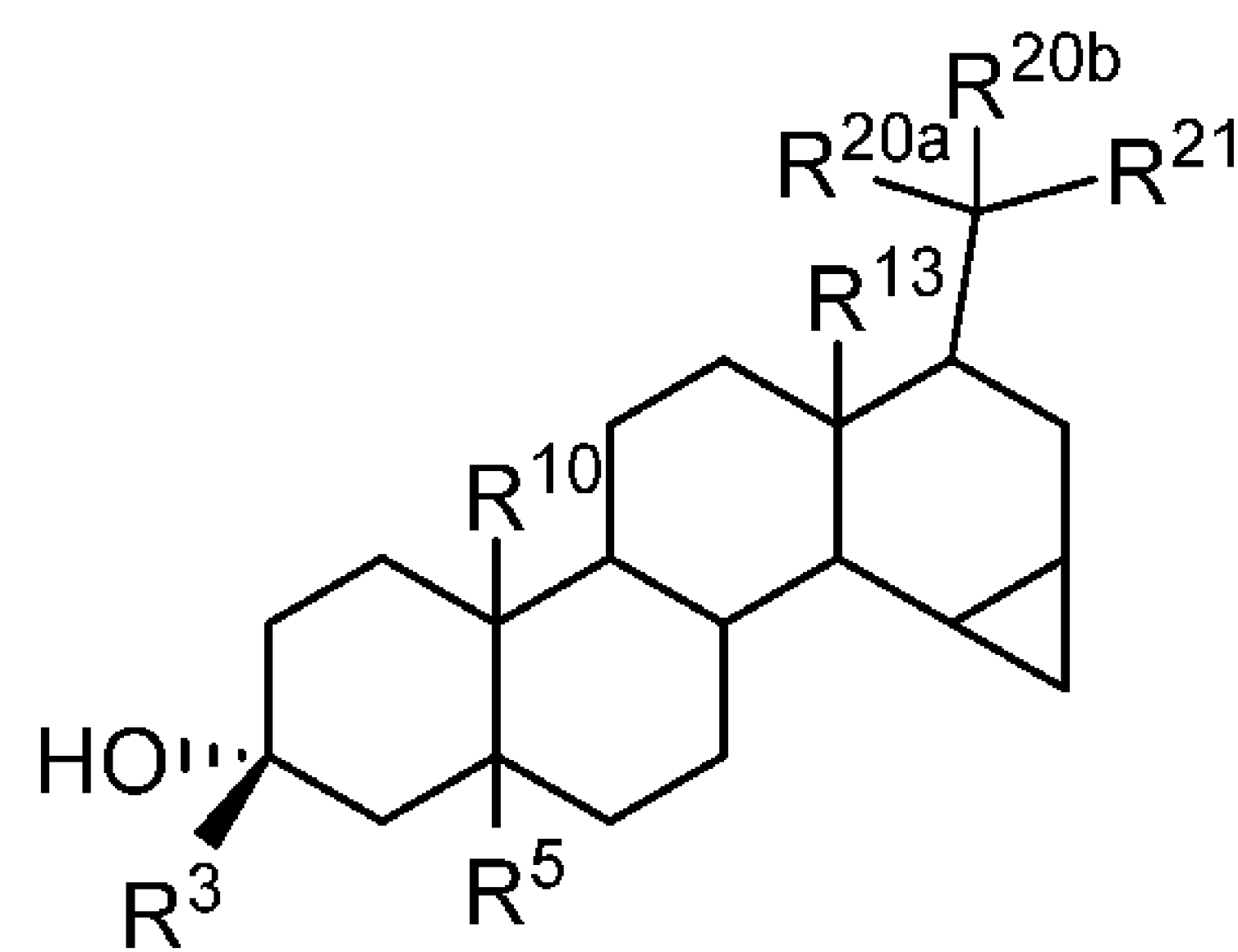
or , X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N or CR'' , wherein each R'' is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$, provided that no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$.

[0056] Another aspect of the present invention provides a compound of Formula (III-A) or (III-B)



(III-A)

or

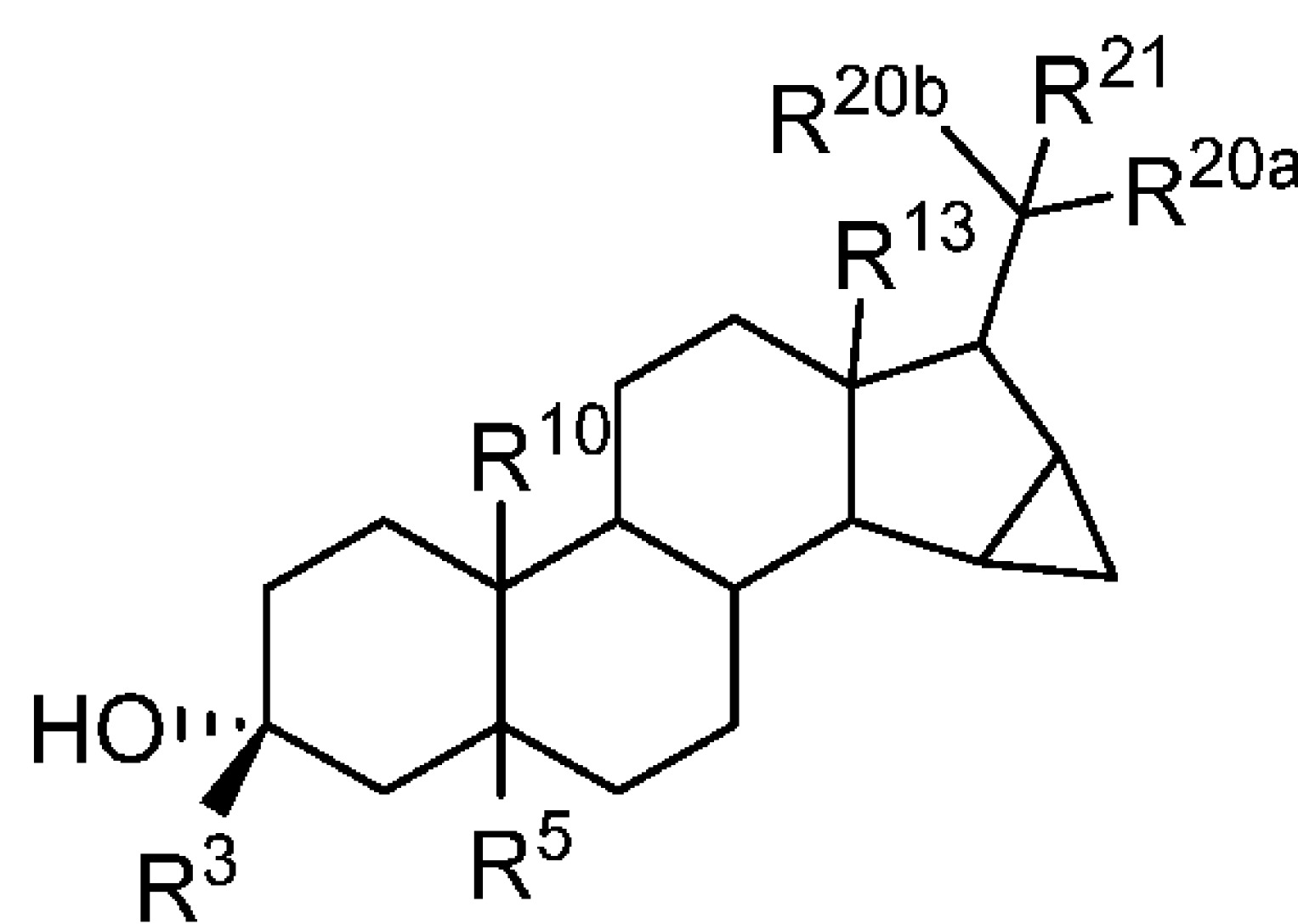


(III-B)

or a pharmaceutically acceptable salt thereof, wherein R³, R⁵, R¹⁰, R¹³, R^{20a}, R^{20b}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (II), or (III).

[0057] In some embodiments, R³ is methyl; R⁵ is -H; R¹⁰ is -H; R¹³ is -H or methyl; each of R^{20a} and R^{20b} is independently selected from -H, -OH, and methyl, or R^{20a} and R^{20b} taken together form oxo; R²¹ is -L^A-R³⁰; L^A is a bond, -NH-, or -CH₂-; R³⁰ is independently selected from pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C₁₋₆ alkyl, or cyano.

[0058] Another aspect of the present invention provides a compound of Formula (III-C)

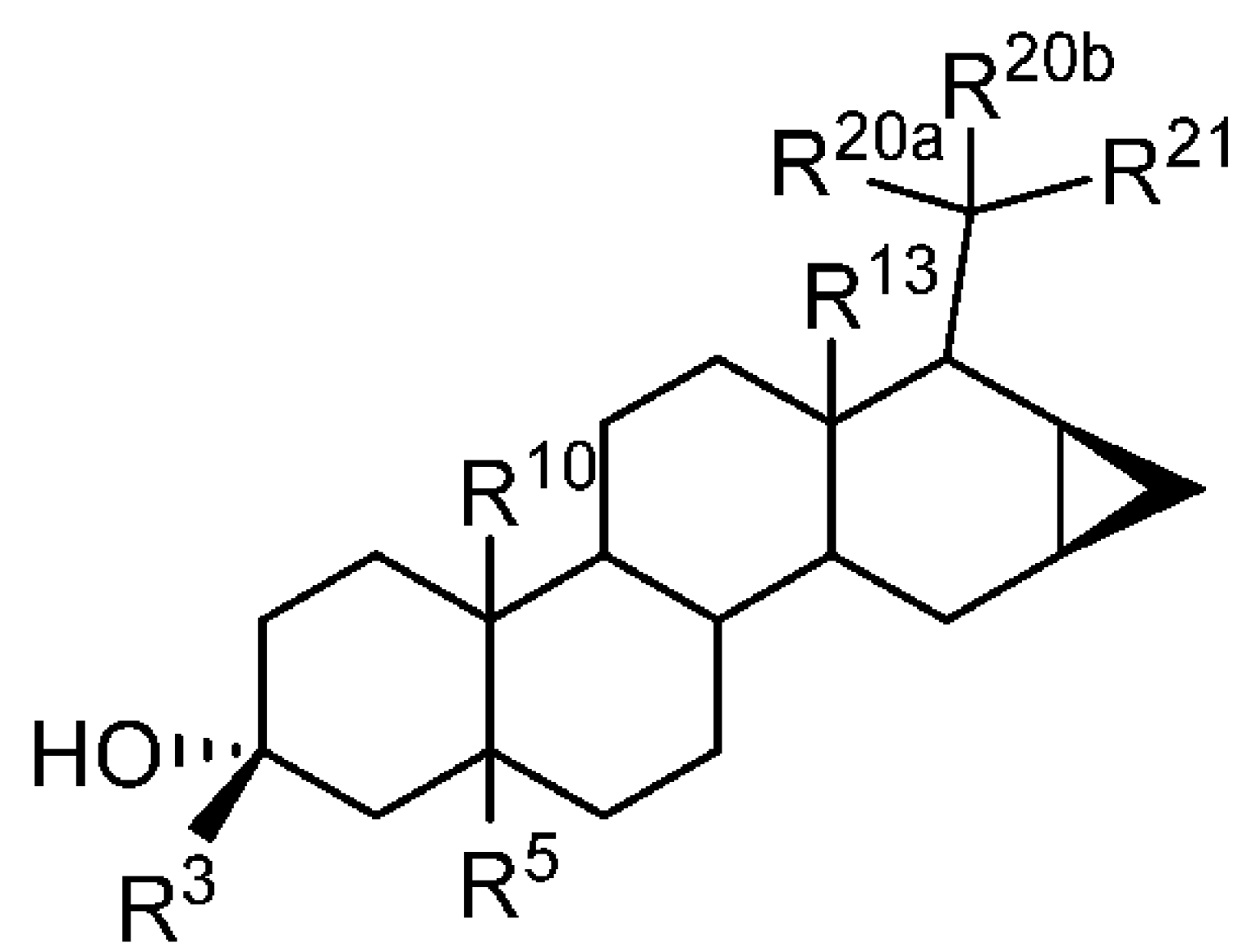


(III-C)

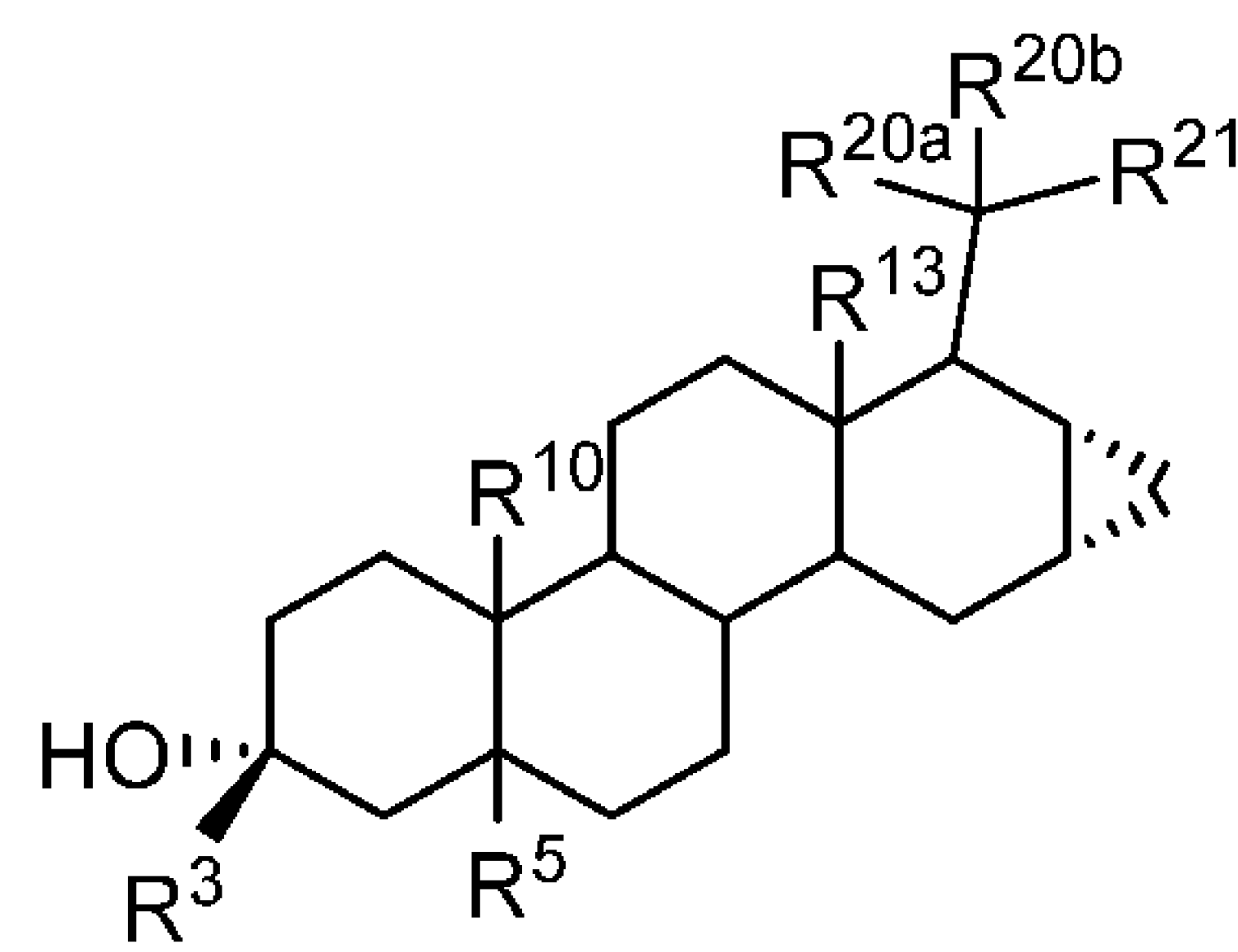
or a pharmaceutically acceptable salt thereof, wherein R³, R⁵, R¹⁰, R¹³, R^{20a}, R^{20b}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (II), or (III).

[0059] In some embodiments, R³ is methyl, ethyl, propyl, or methoxymethyl; R⁵ is -H; R¹⁰ is -H; R¹³ is -H or methyl; each of R^{20a} and R^{20b} is independently selected from -H, -OH, and methyl, or R^{20a} and R^{20b} taken together form oxo; R²¹ is -L^A-R³⁰; L^A is a bond, -NH-, or -CH₂-; R³⁰ is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C₁₋₆ alkyl, or cyano.

[0060] Another aspect of the present invention provides a compound of Formula (III-A1) or (III-A2)



(III-A1)

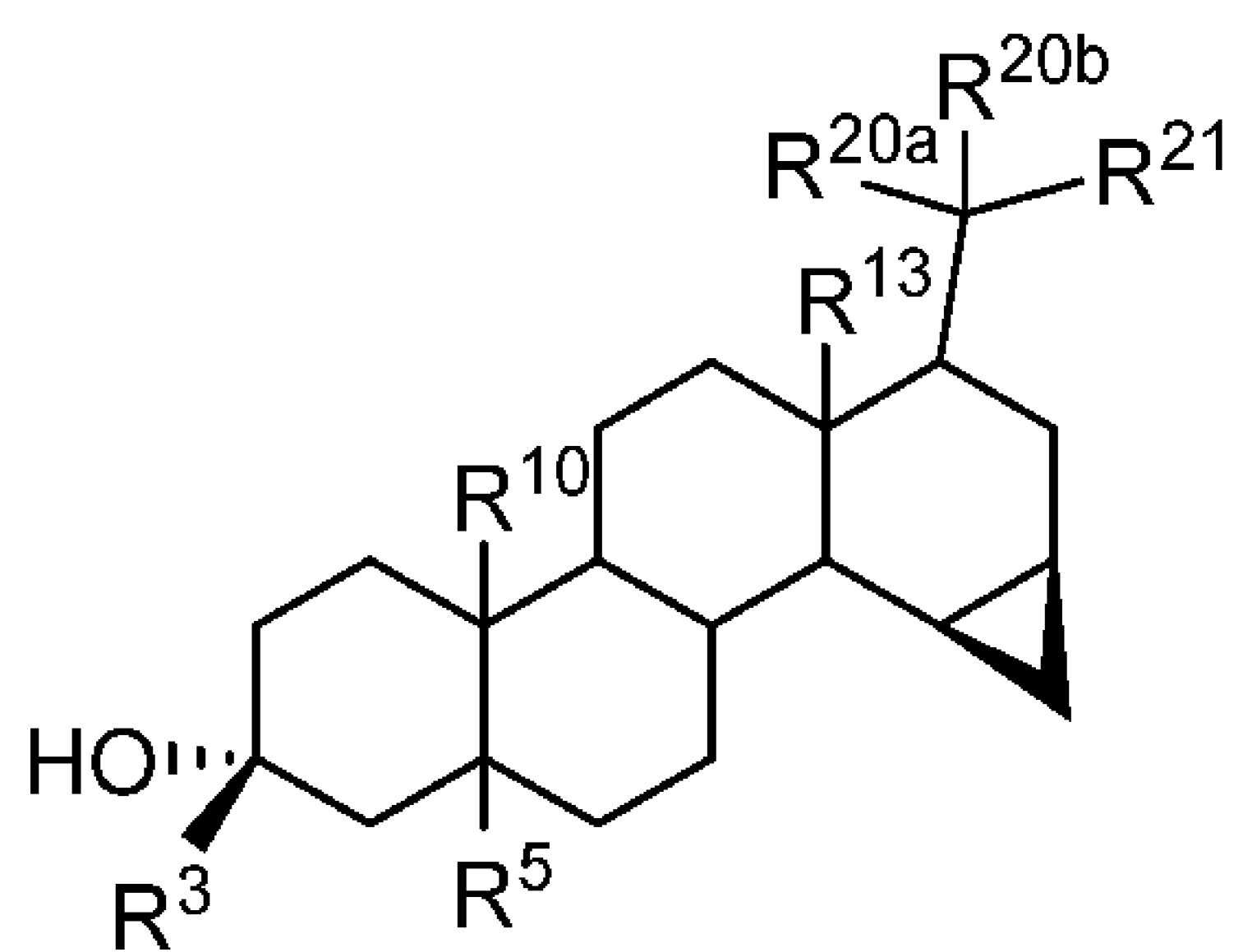


(III-A2)

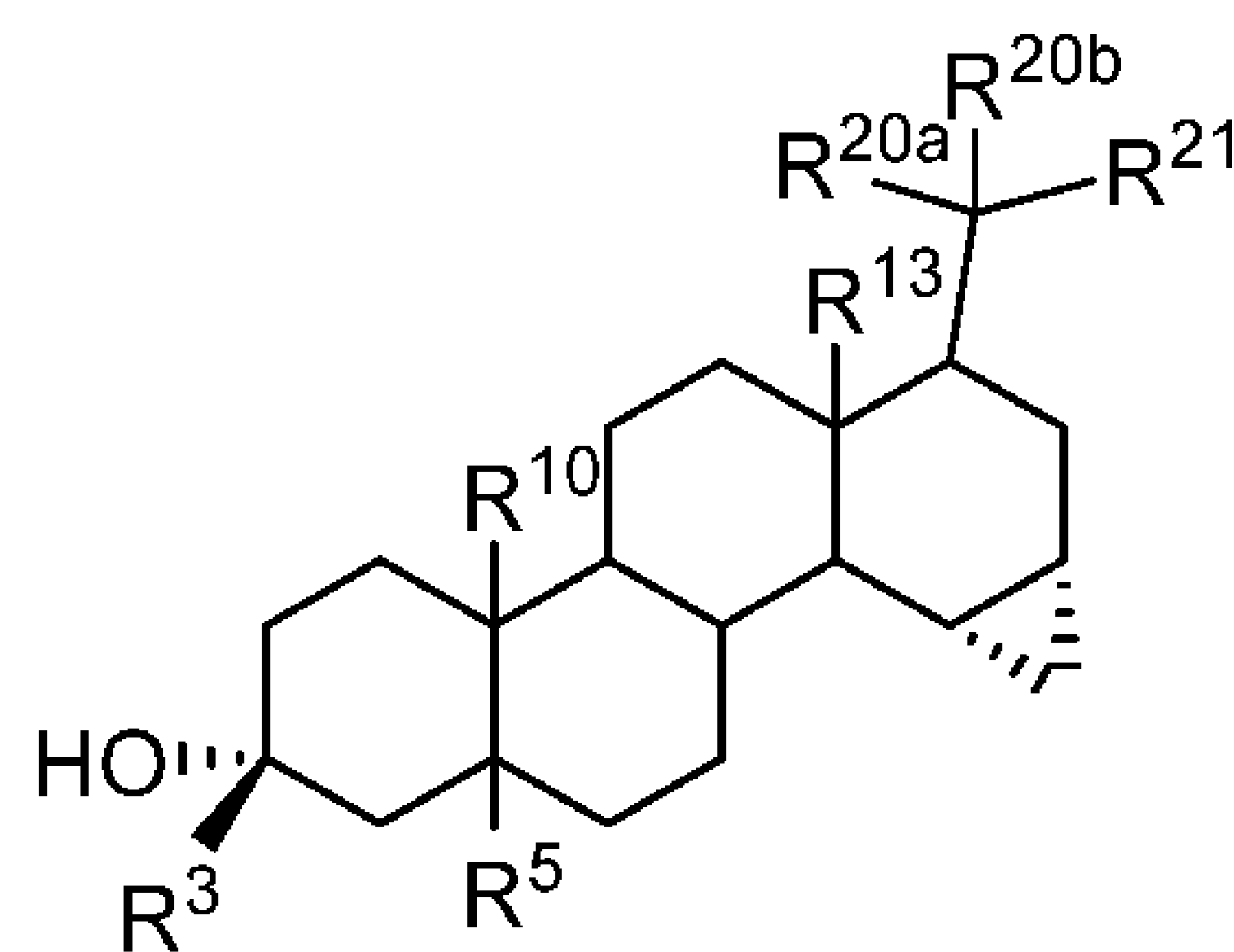
or

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), or (III-A).

[0061] Another aspect of the present invention provides a compound of Formula (III-B1) or (III-B2)



(III-B1)

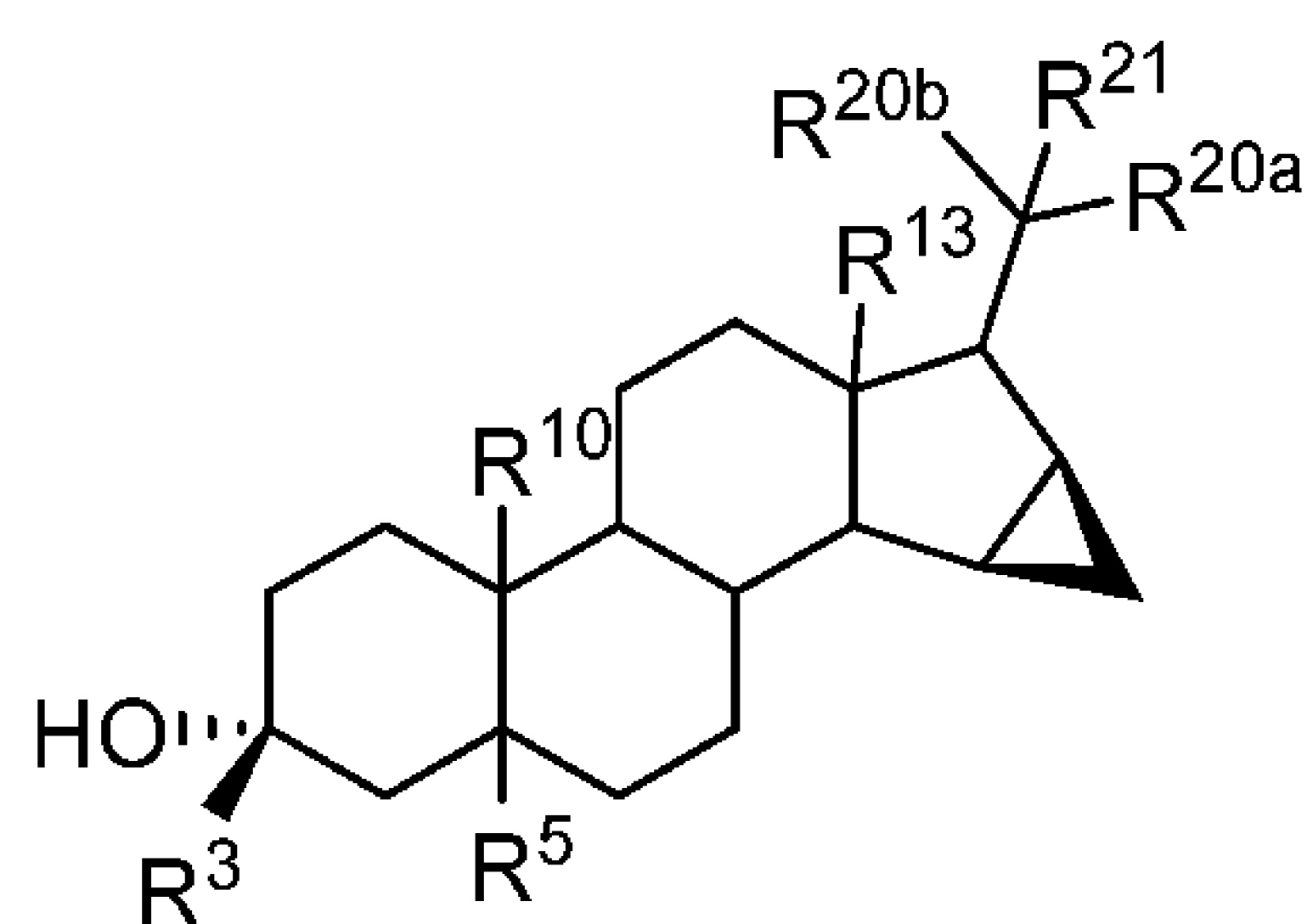


(III-B2)

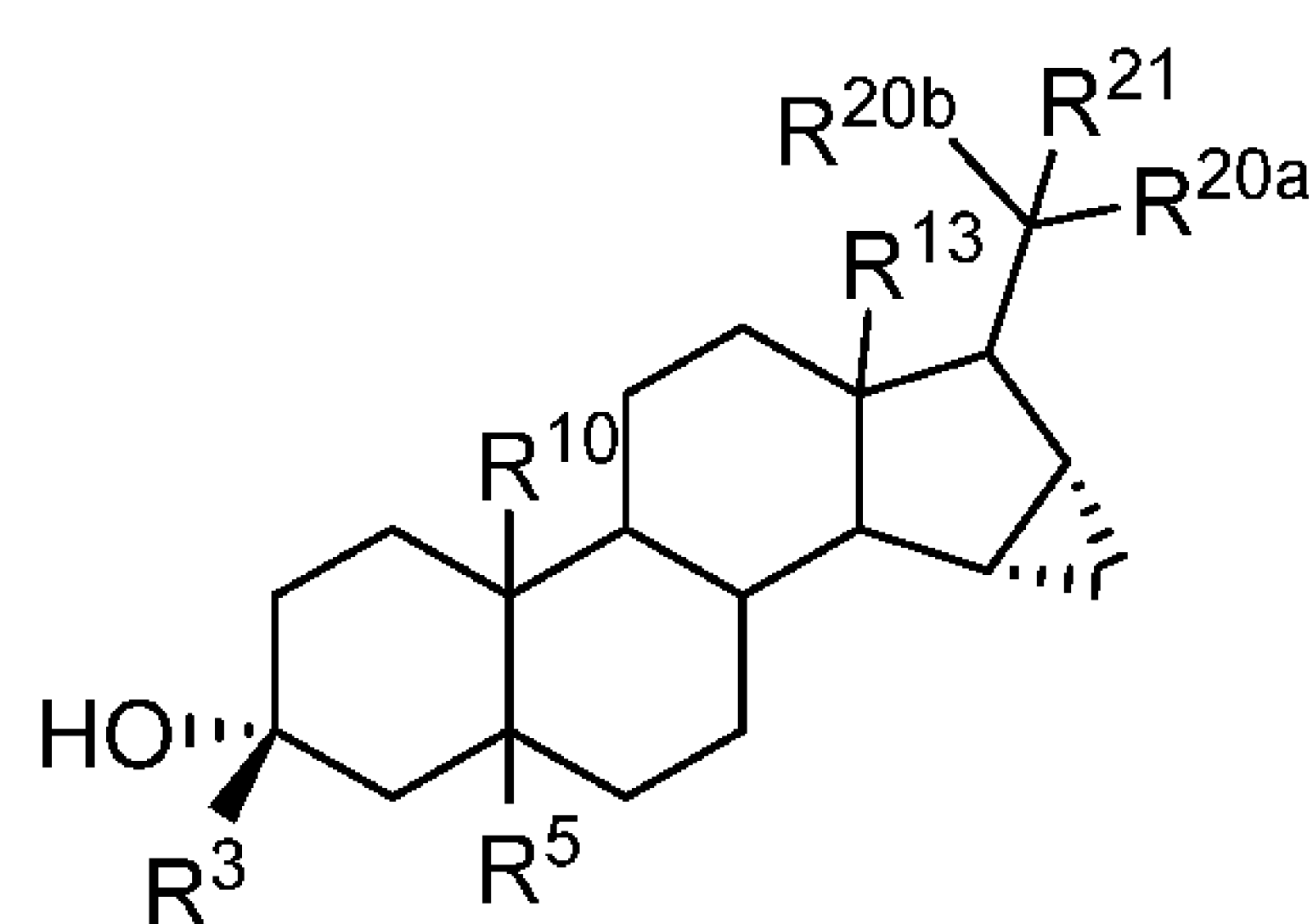
or

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), or (III-B).

[0062] Another aspect of the present invention provides a compound of Formula (III-C1) or (III-C2)



(III-C1)

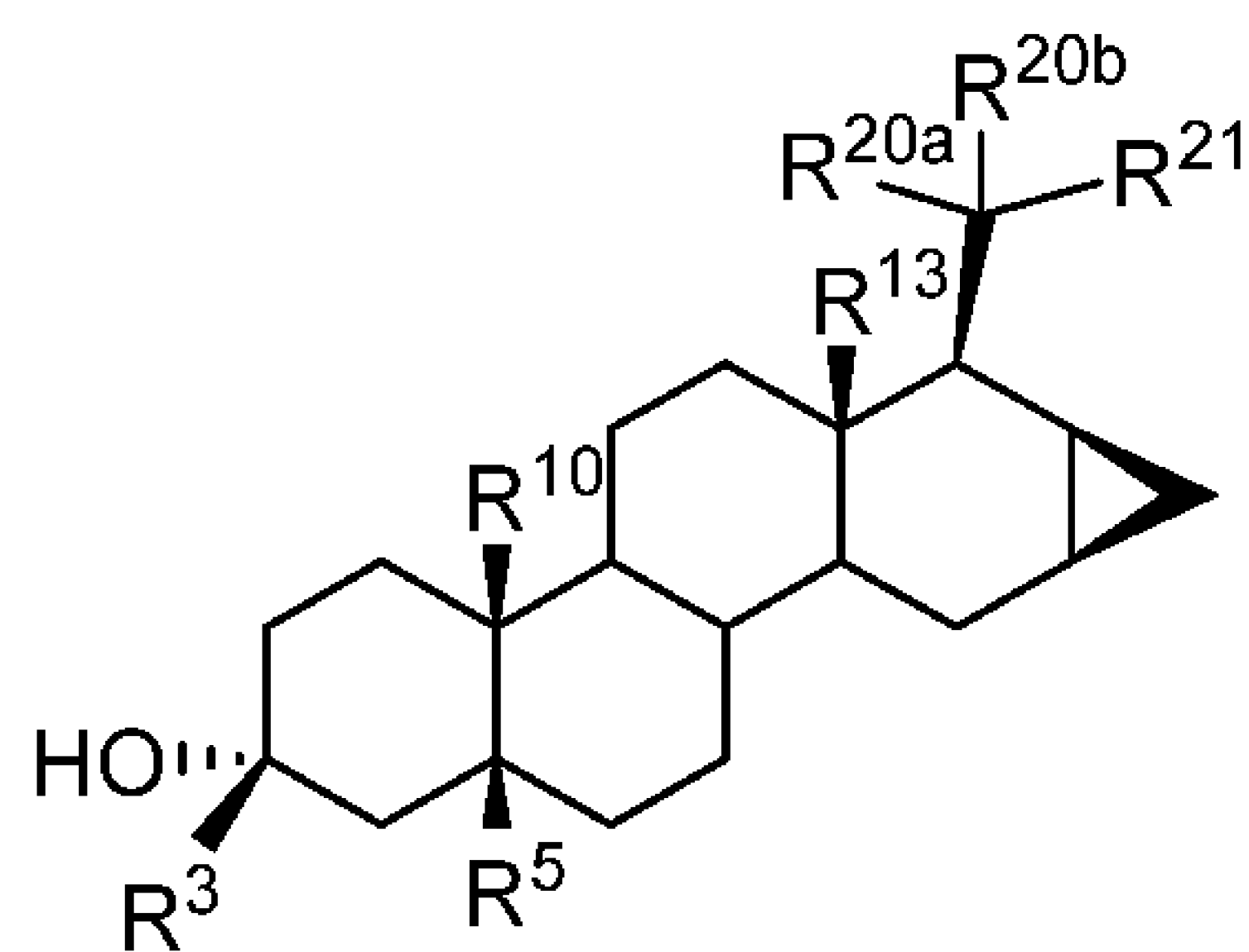


(III-C2)

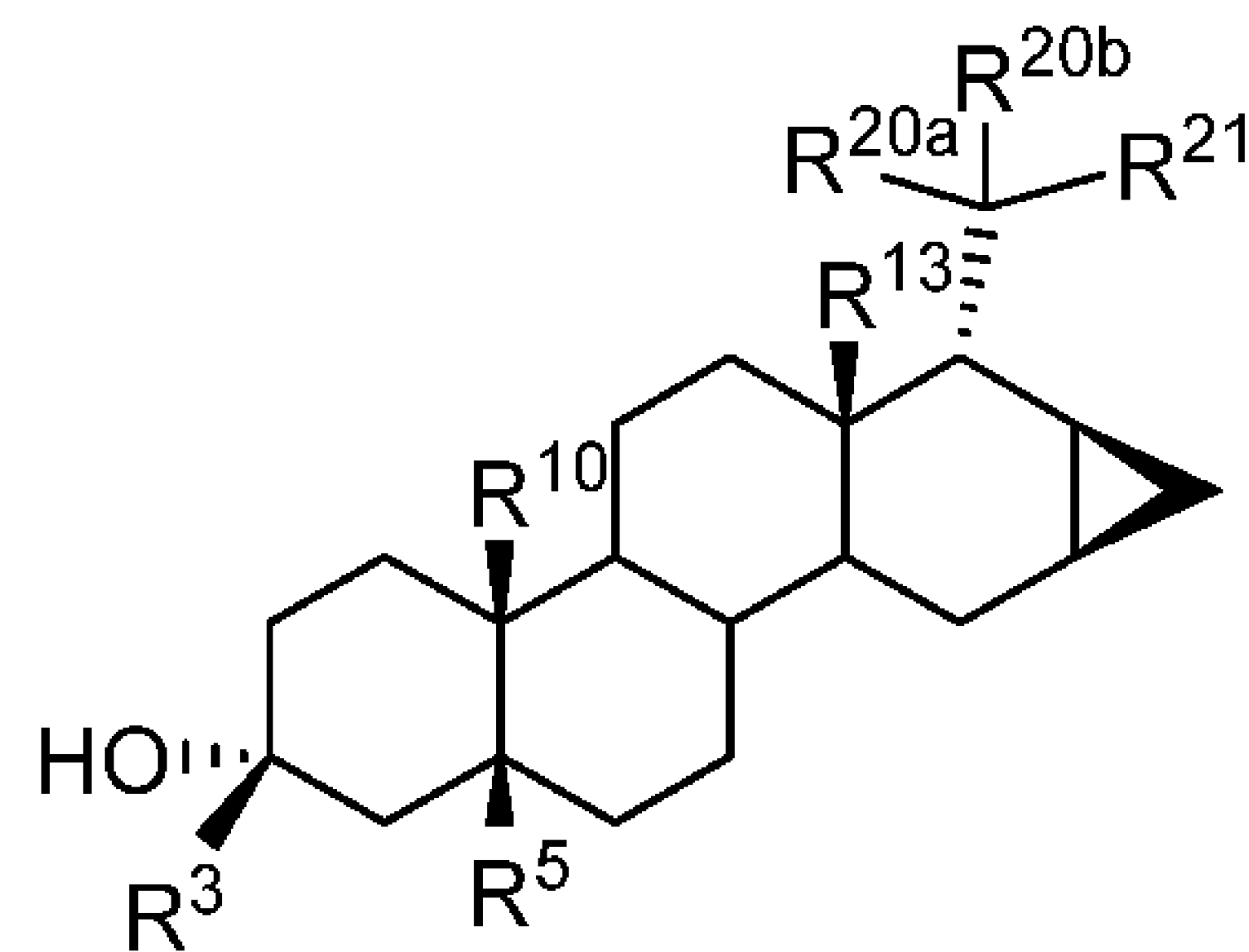
or

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), or (III-C).

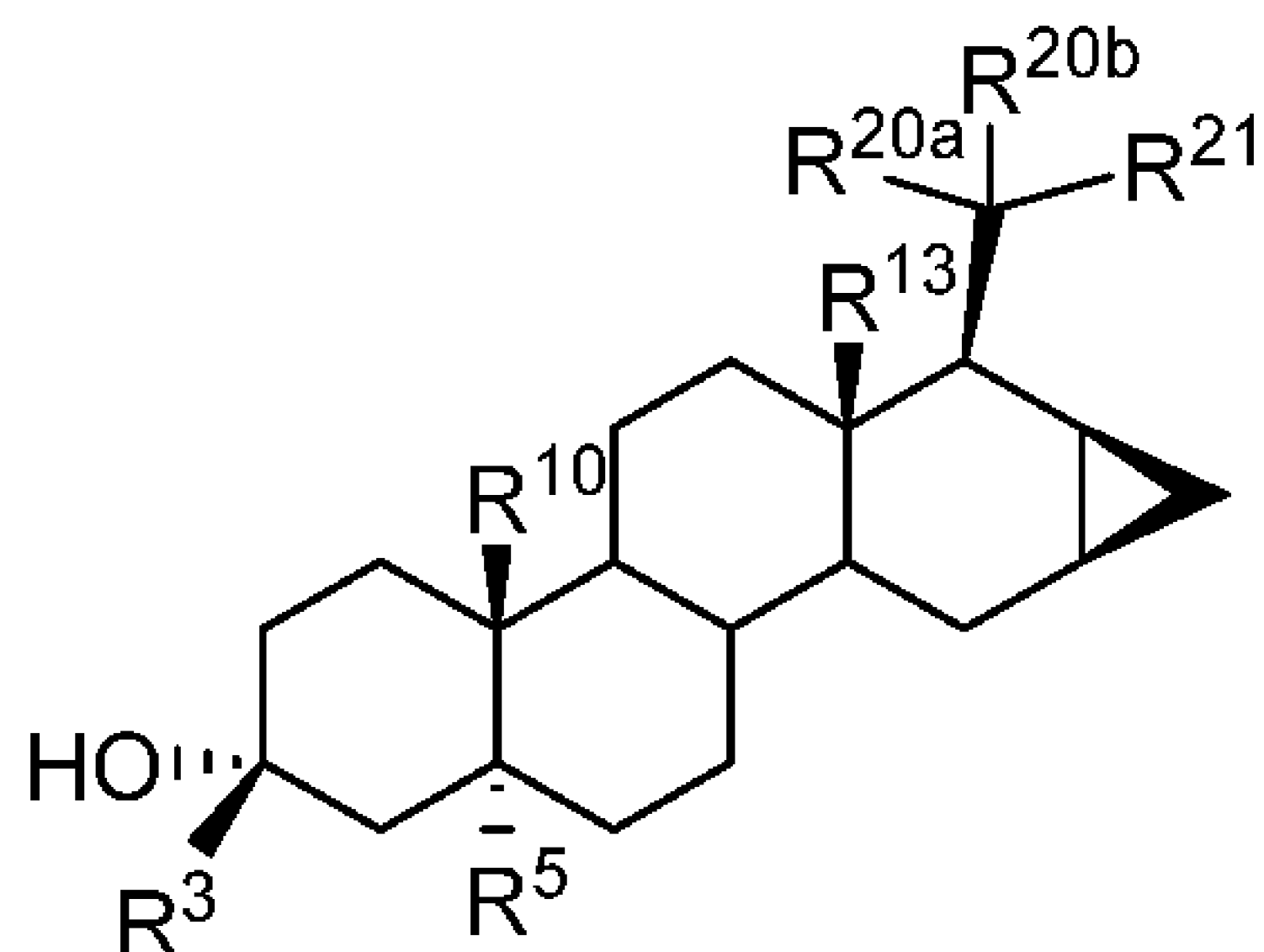
[0063] Another aspect of the present invention provides a compound of Formula (III-A1a), (III-A1b), (III-A1c), or (III-A1d)



(III-A1a),

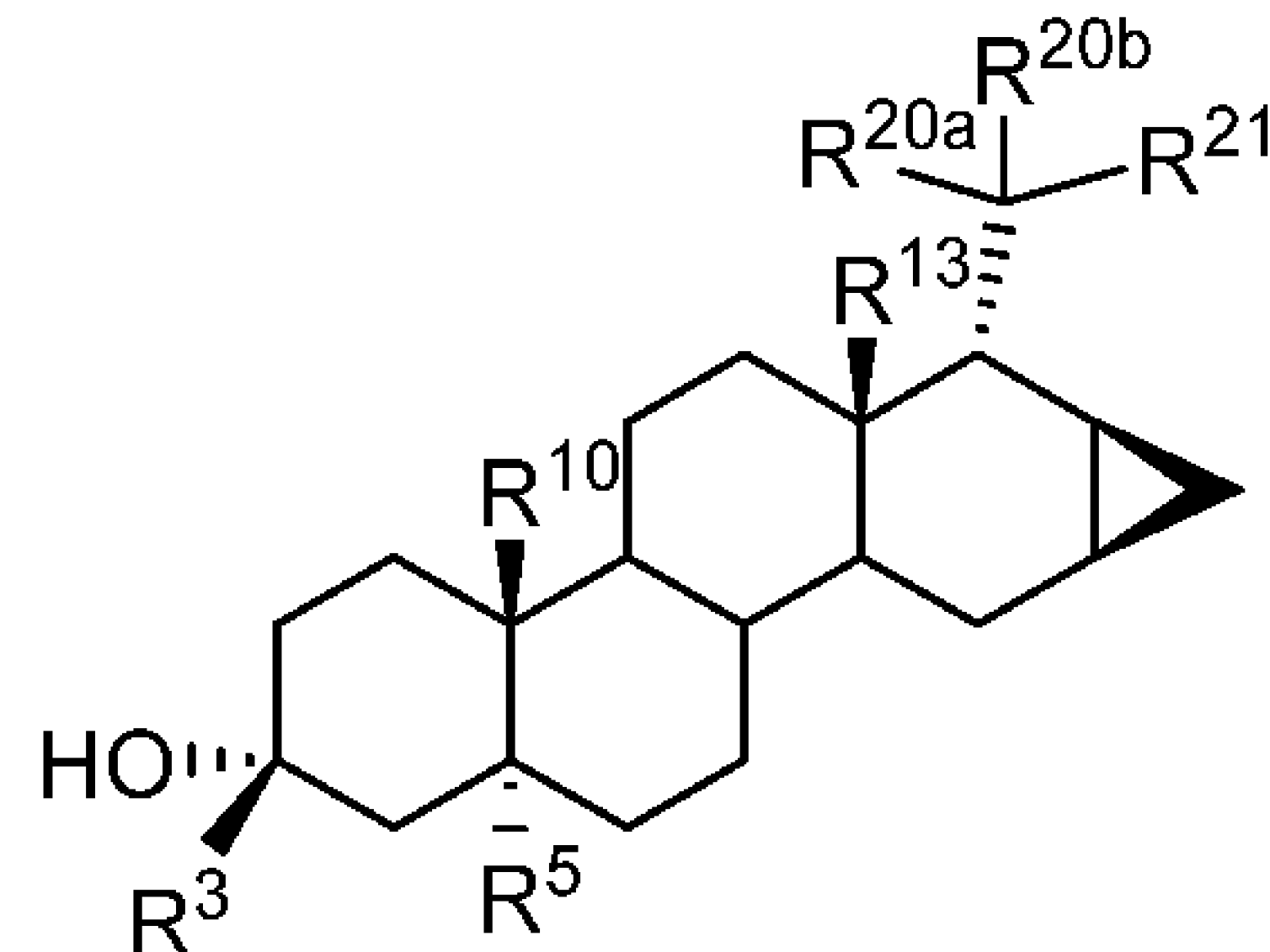


(III-A1b),



(III-A1c),

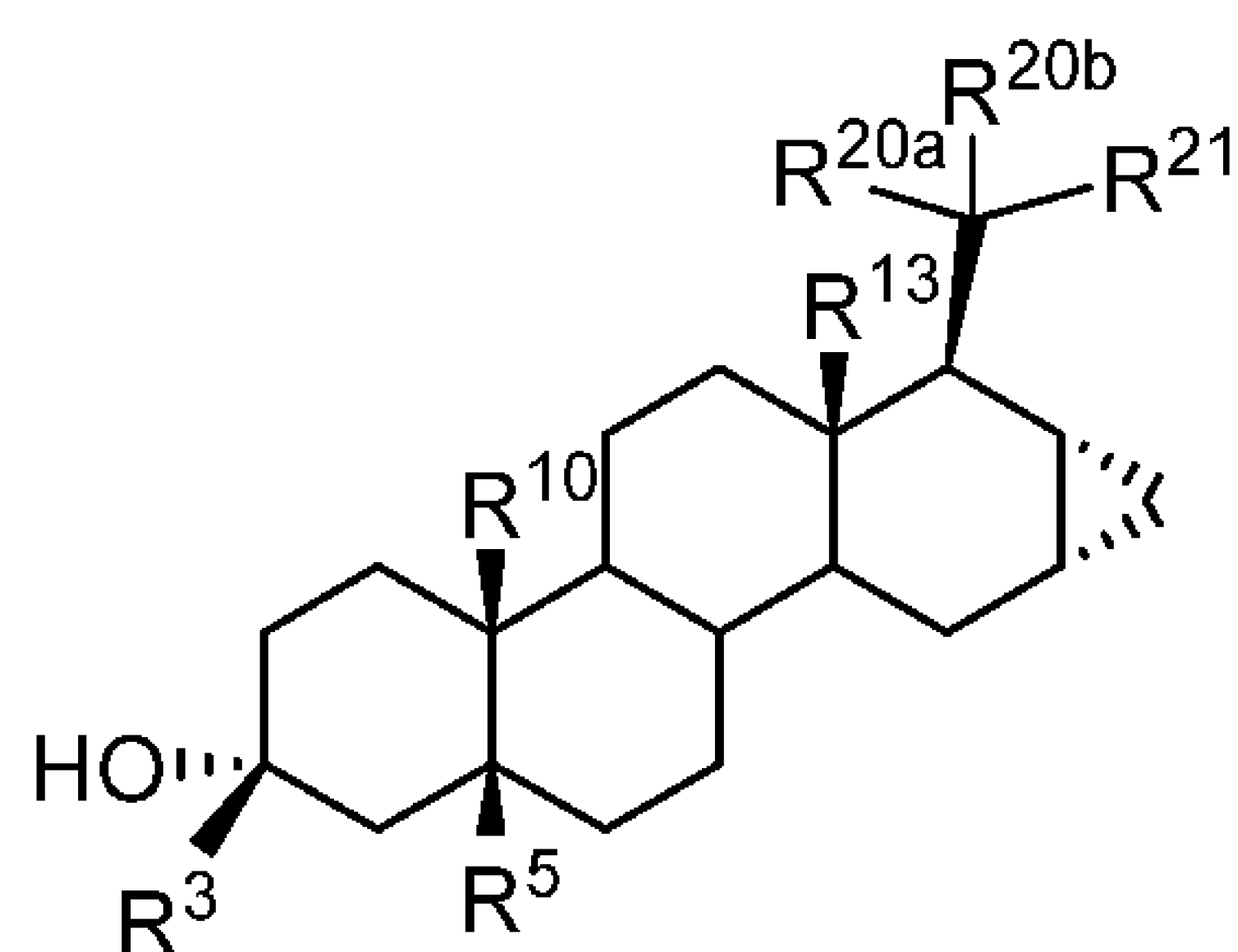
or



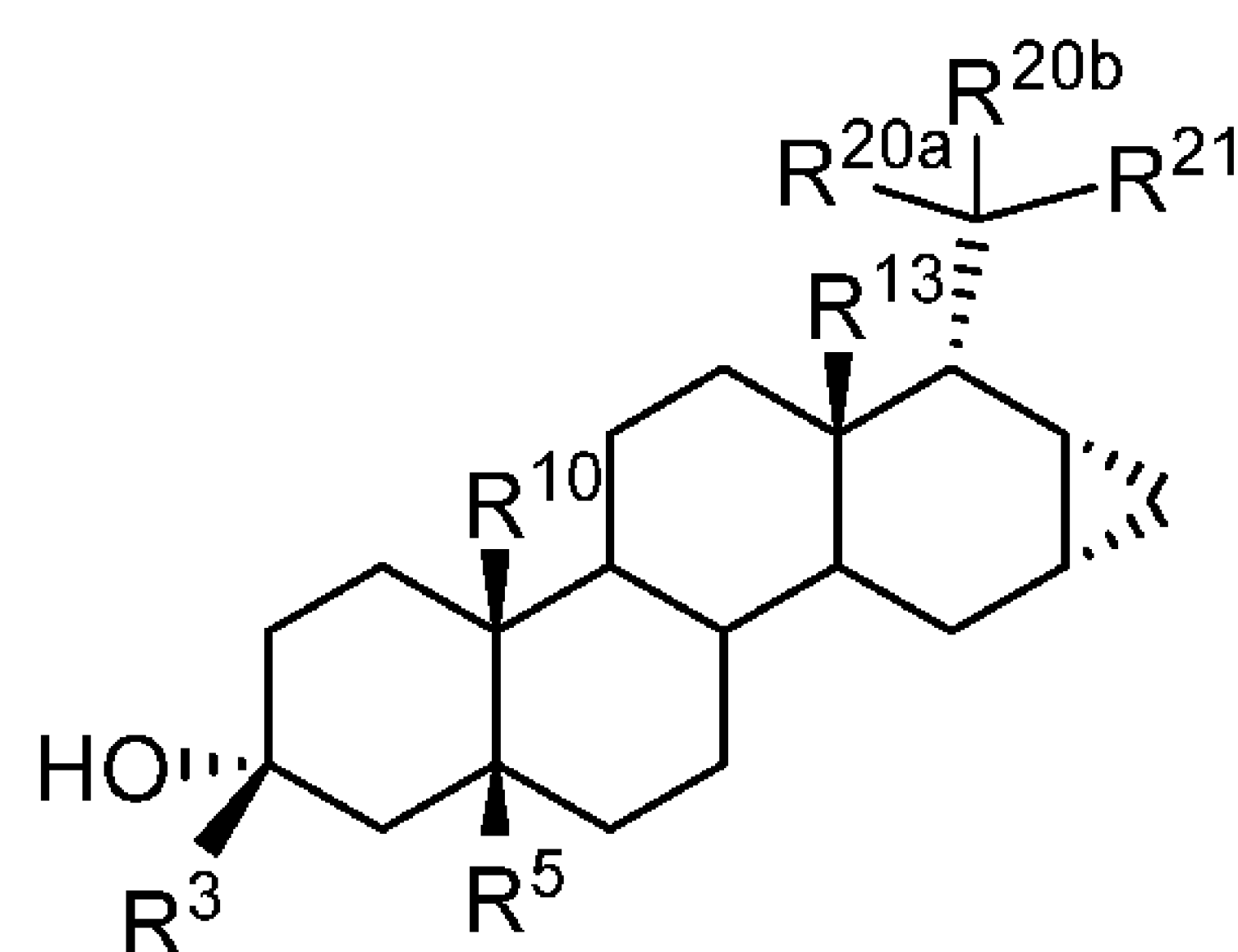
(III-A1d)

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), (III-A), or (III-A1).

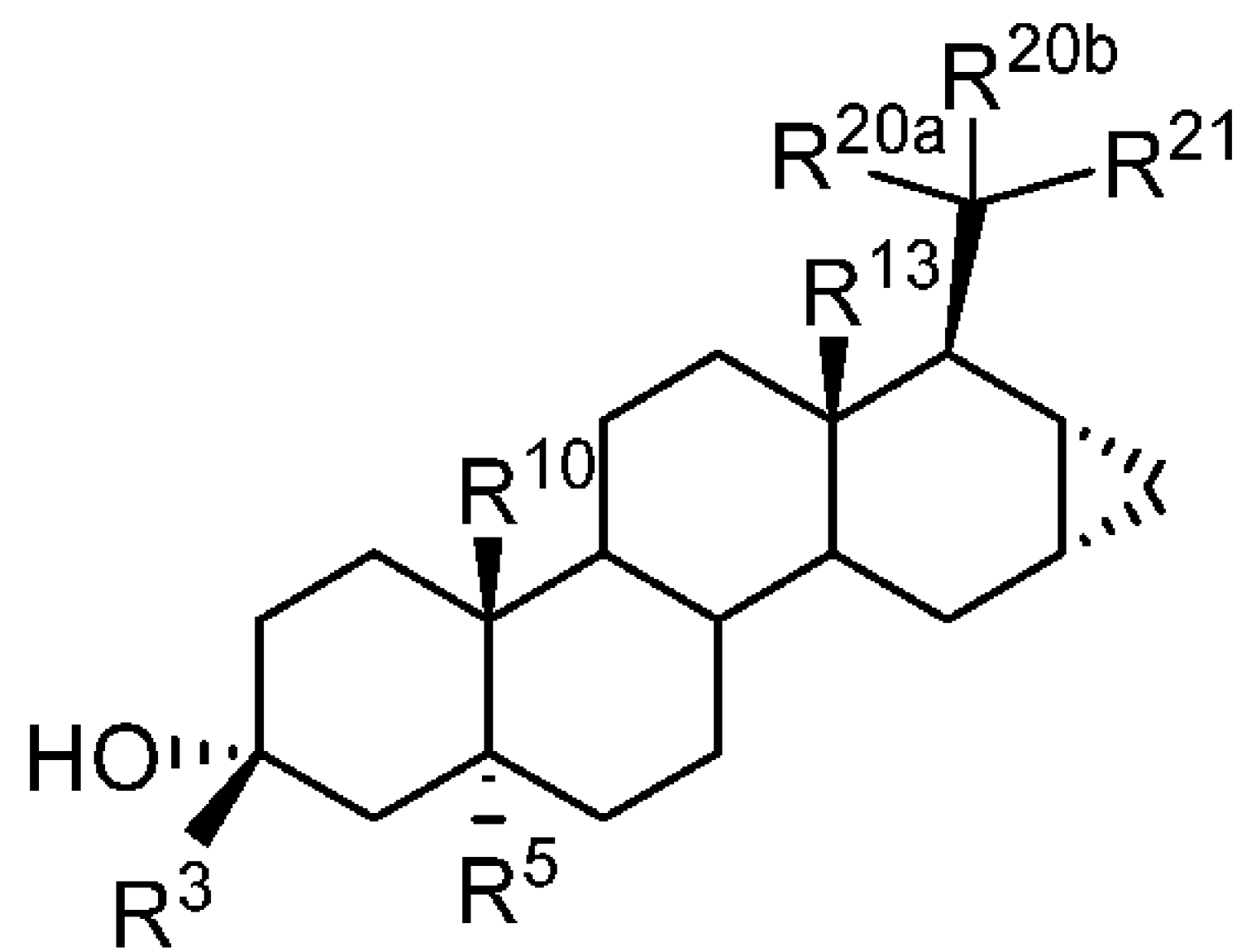
[0064] Another aspect of the present invention provides a compound of Formula (III-A2a), (III-A2b), (III-A2c), or (III-A2d)



(III-A2a),

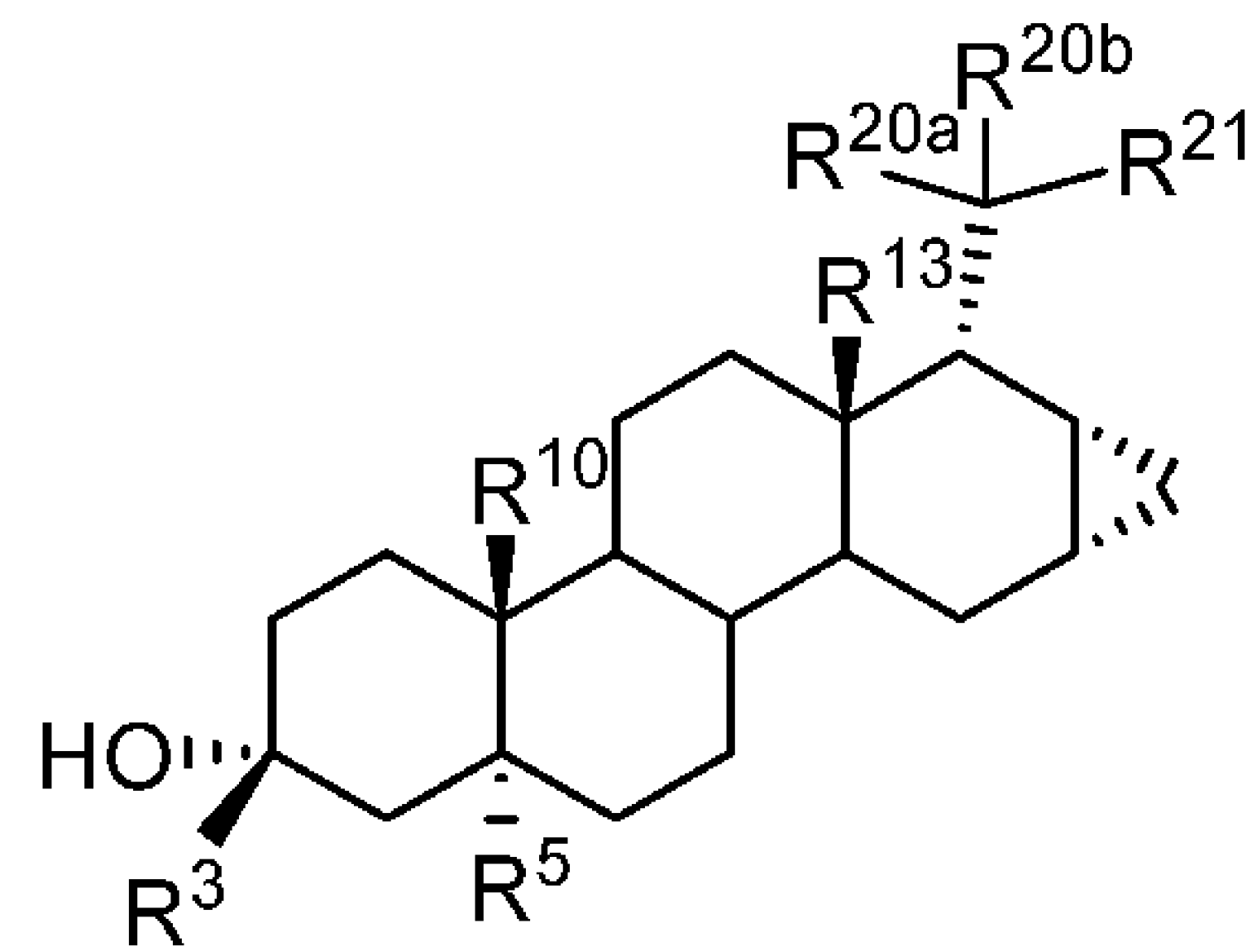


(III-A2b),



(III-A2c),

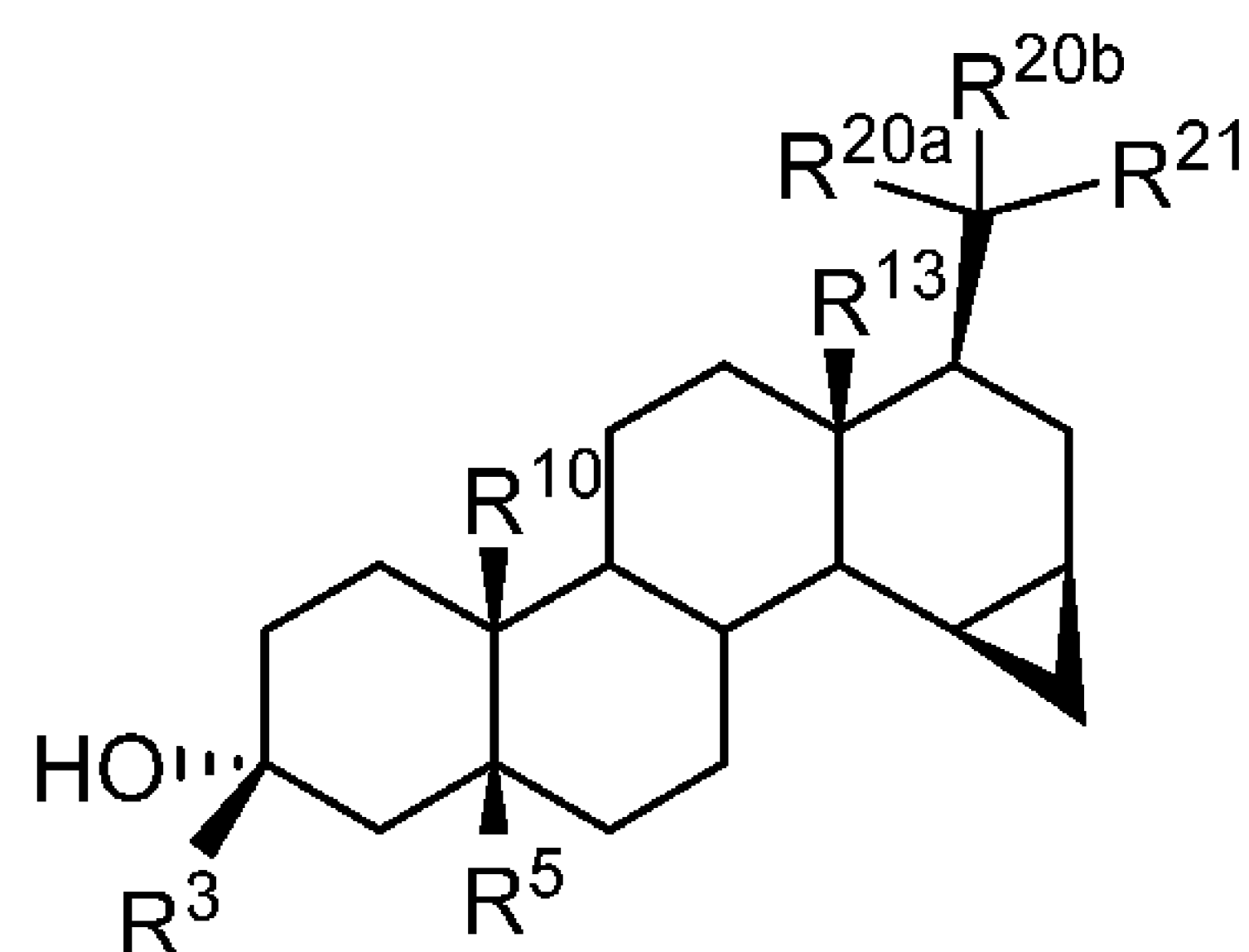
or



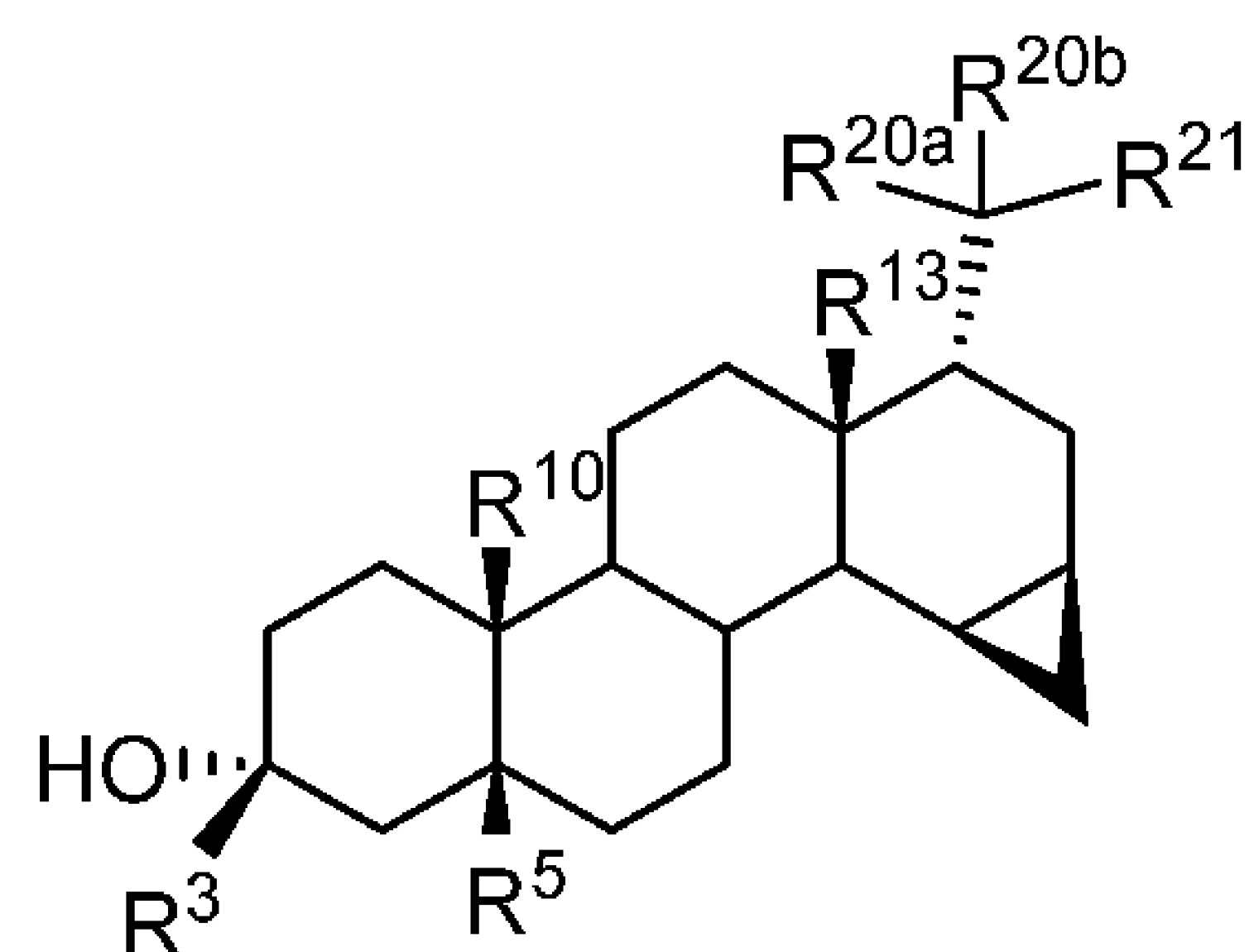
(III-A2d)

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), (III-A), or (III-A2).

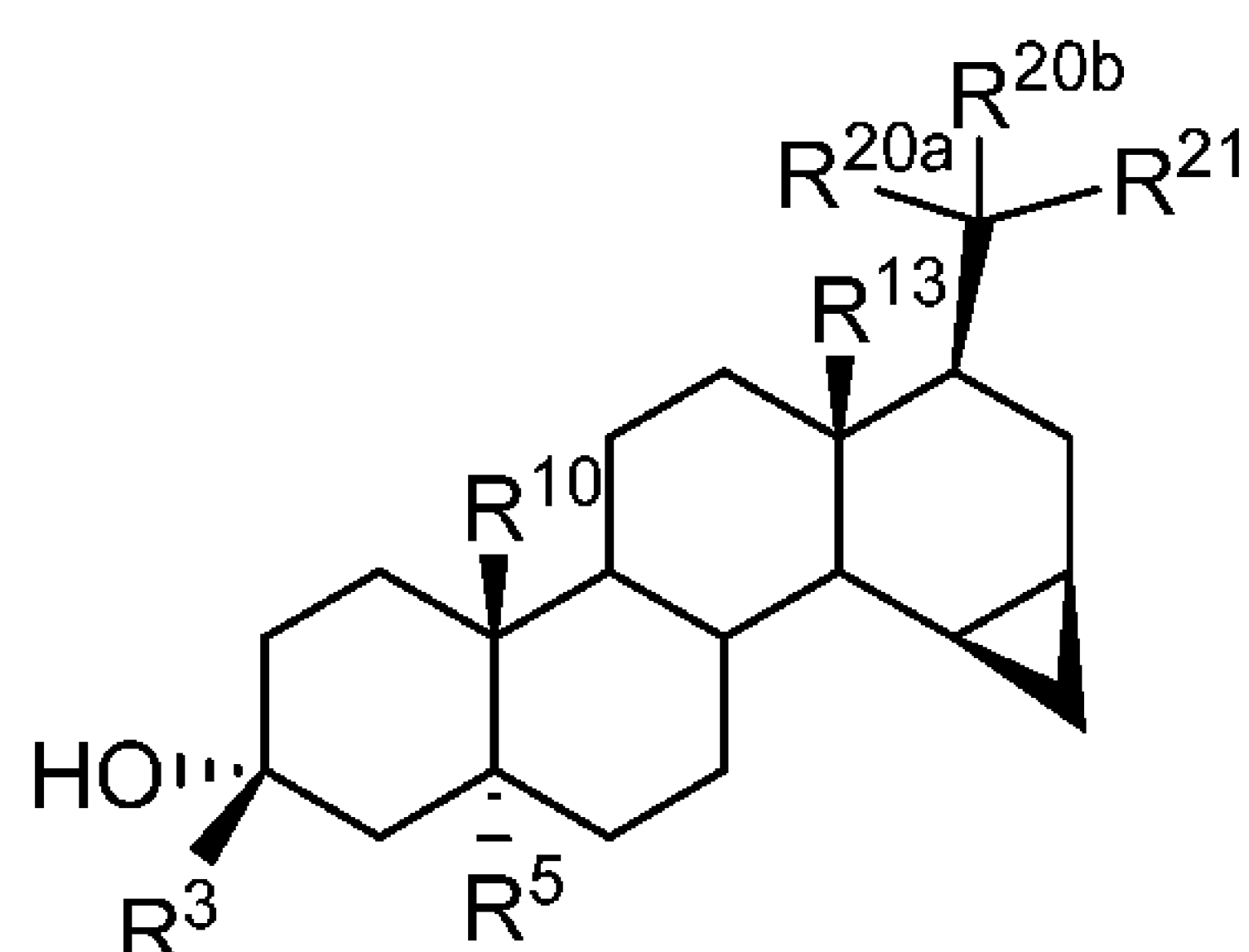
[0065] Another aspect of the present invention provides a compound of Formula (III-B1a), (III-B1b), (III-B1c), or (III-B1d)



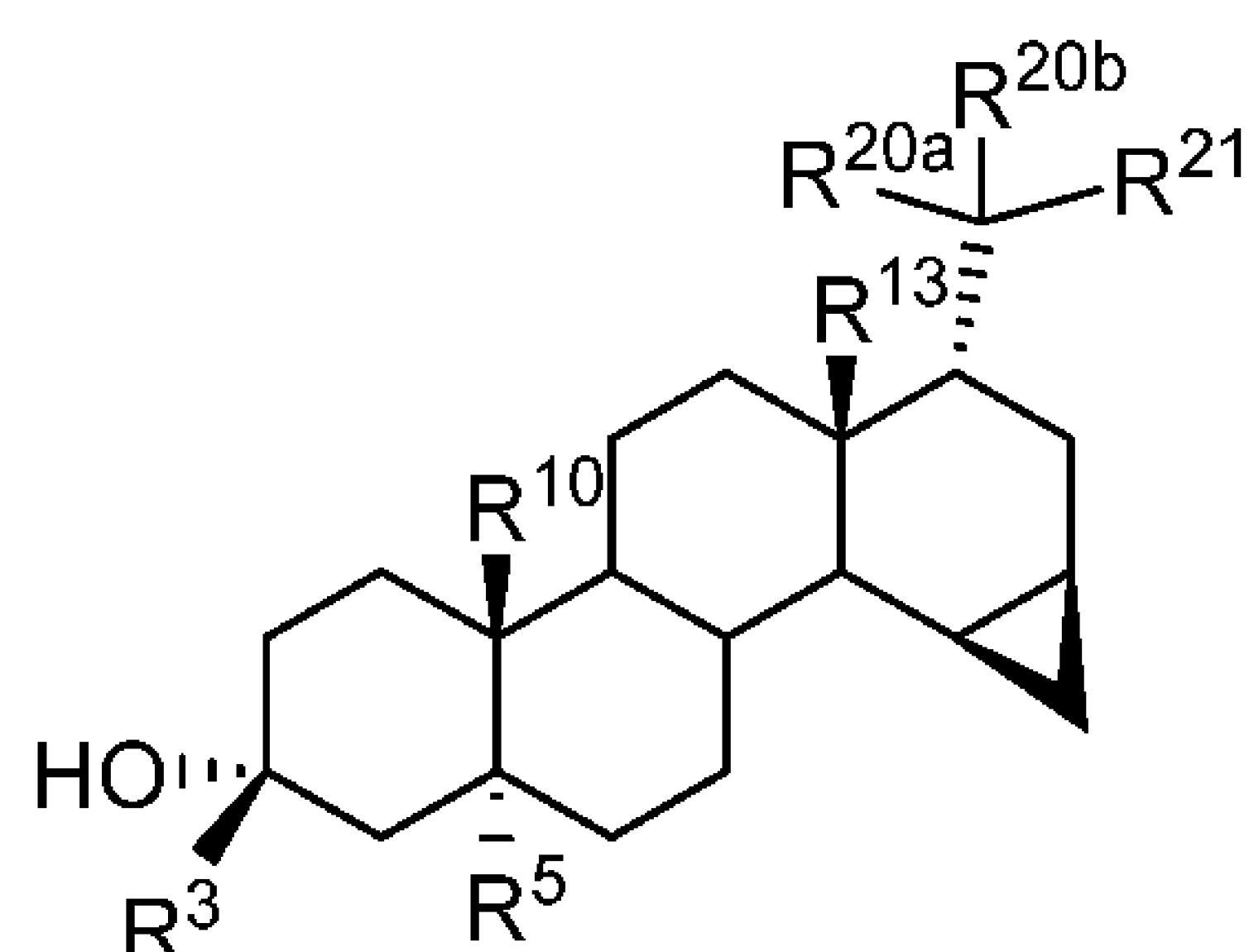
(III-B1a),



(III-B1b),



(III-B1c)

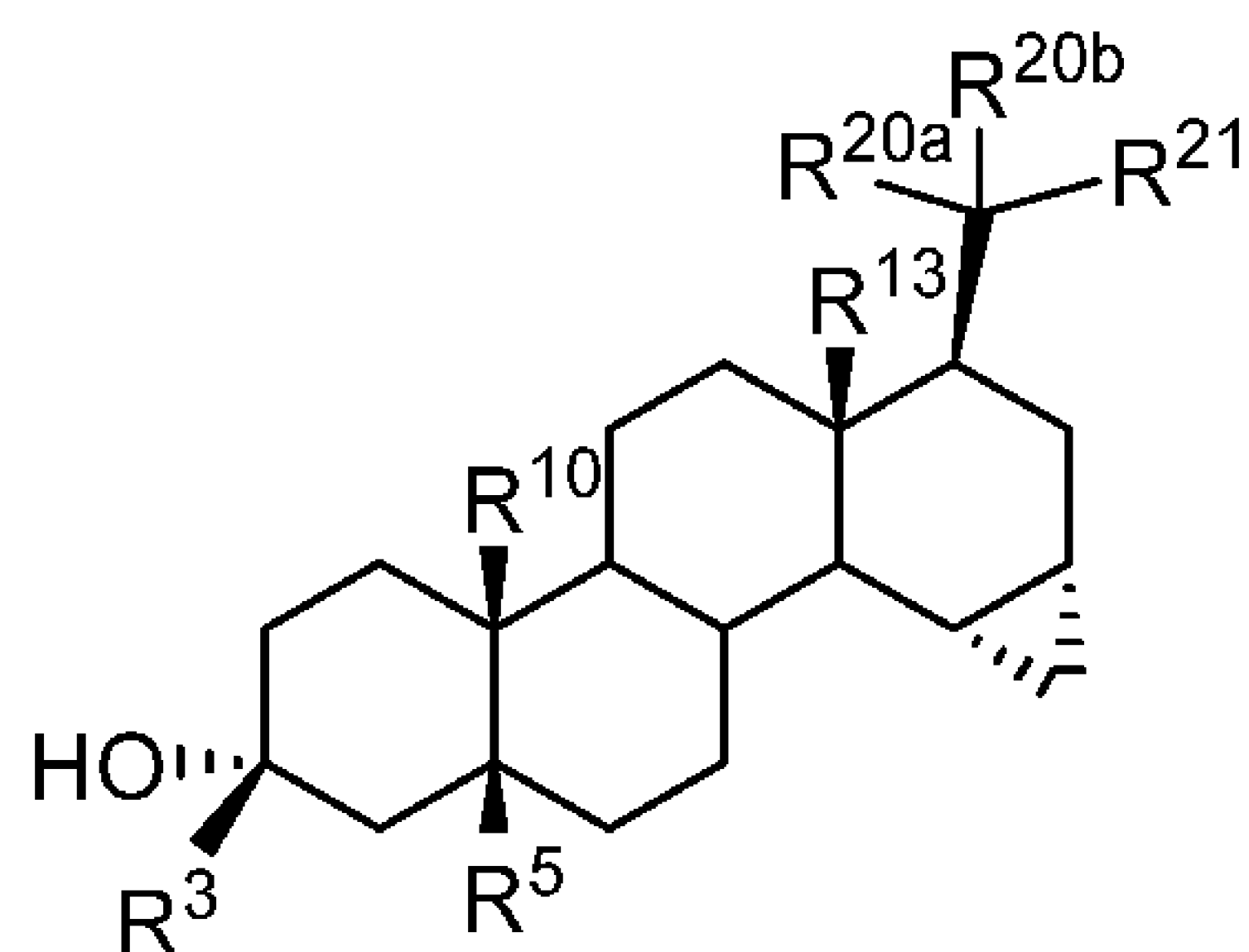


(III-B1d)

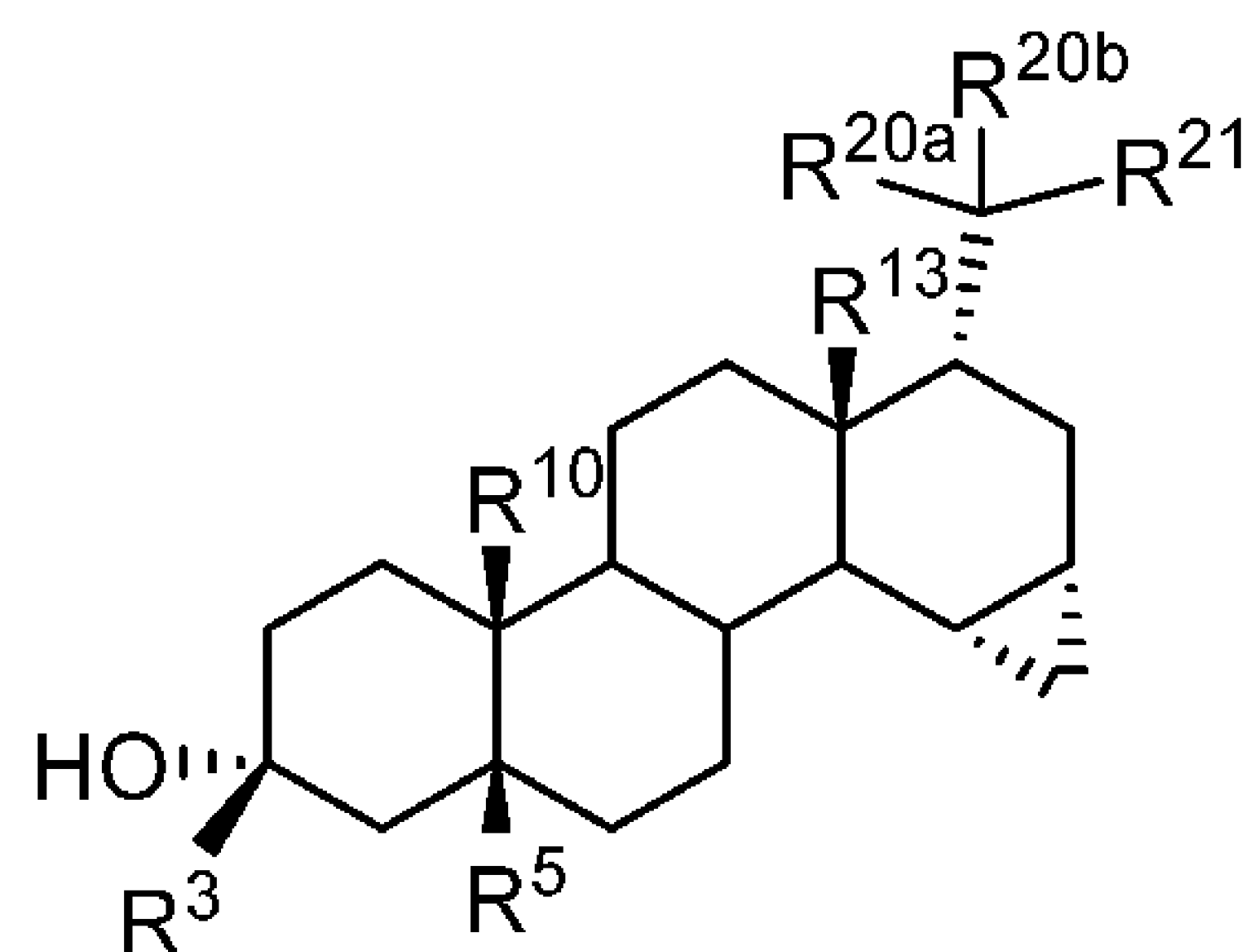
or

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), (III-B), or (III-B1).

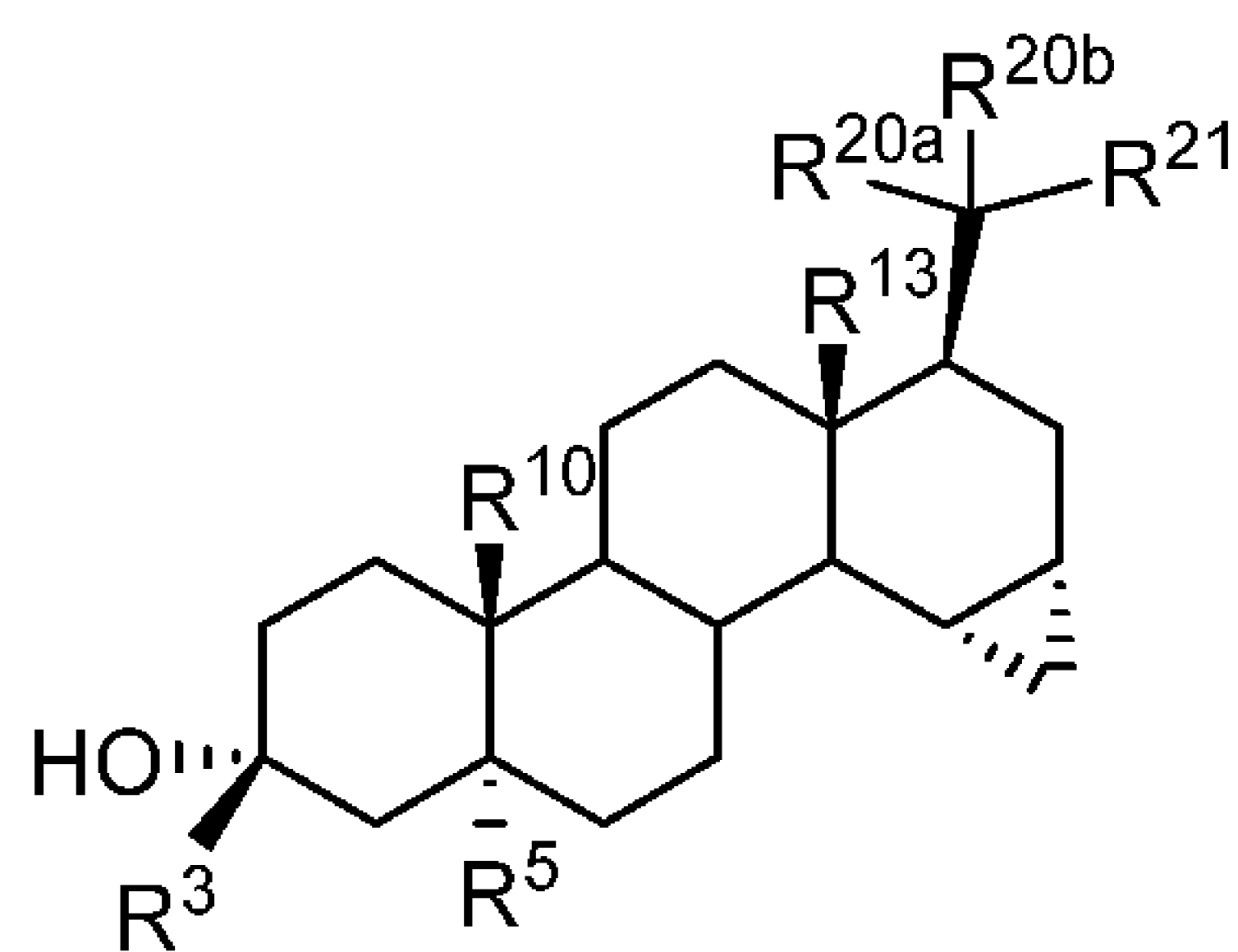
[0066] Another aspect of the present invention provides a compound of Formula (III-B2a), (III-B2b), (III-B2c), or (III-B2d)



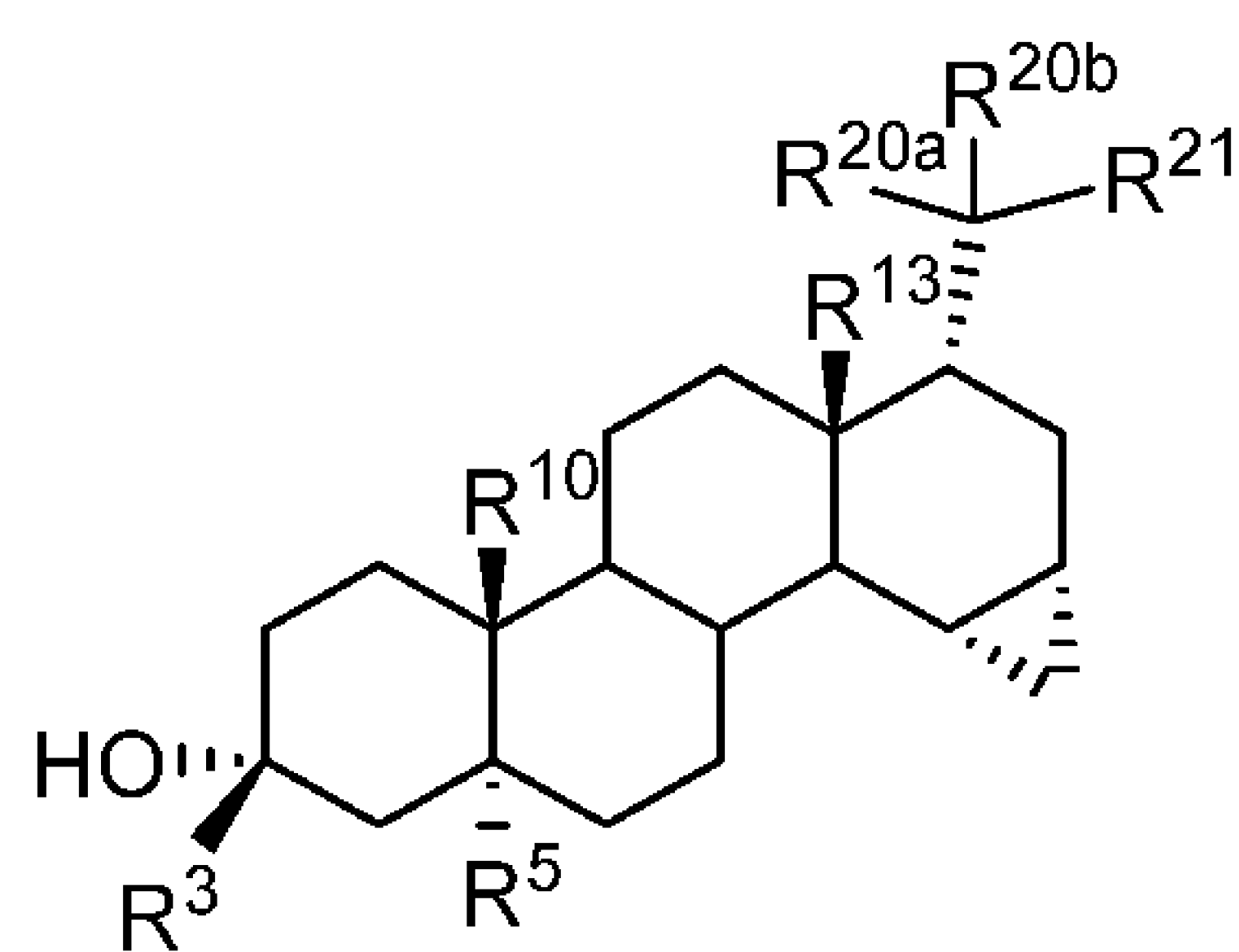
(III-B2a),



(III-B2b),



(III-B2c),

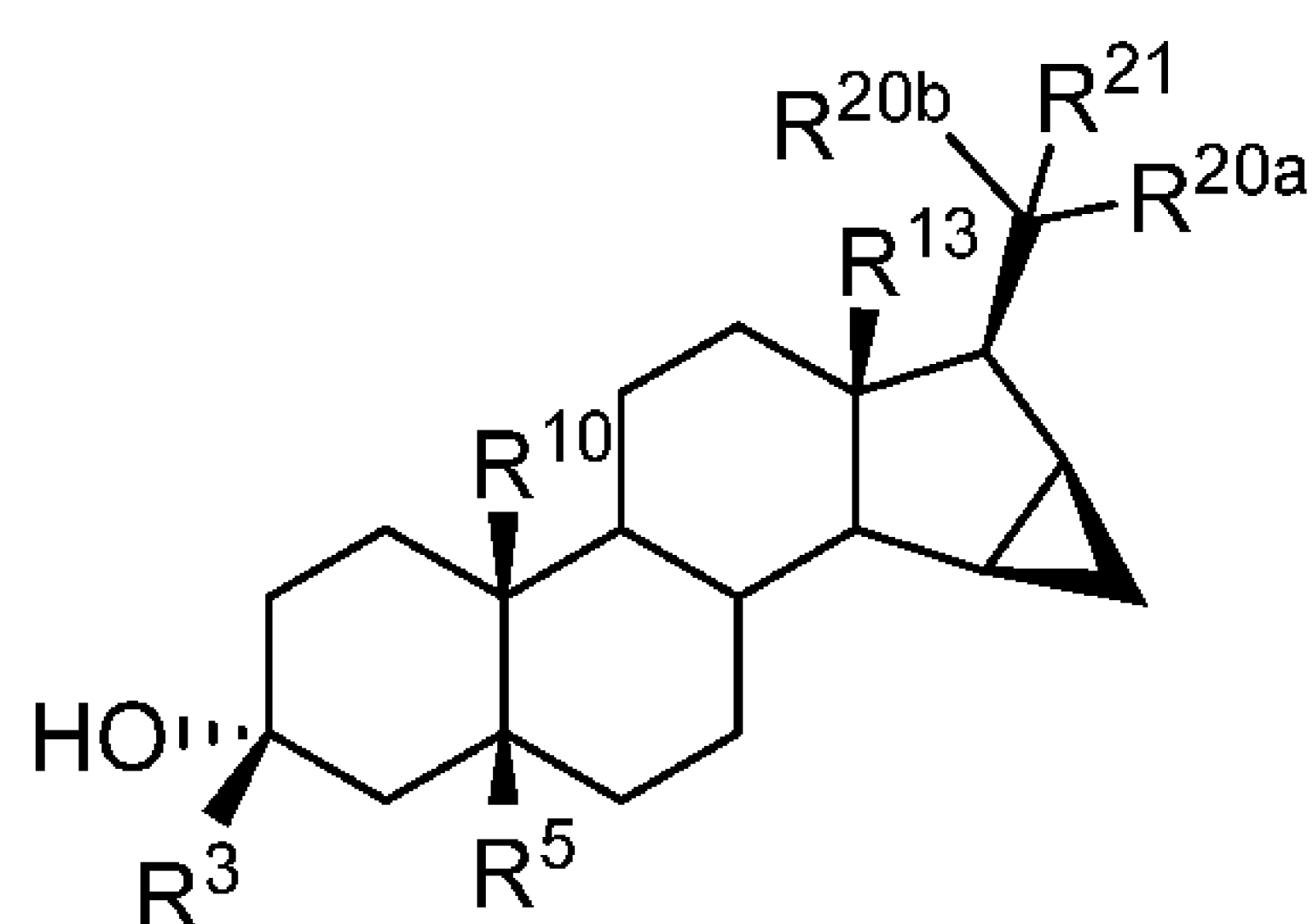


(III-B2d)

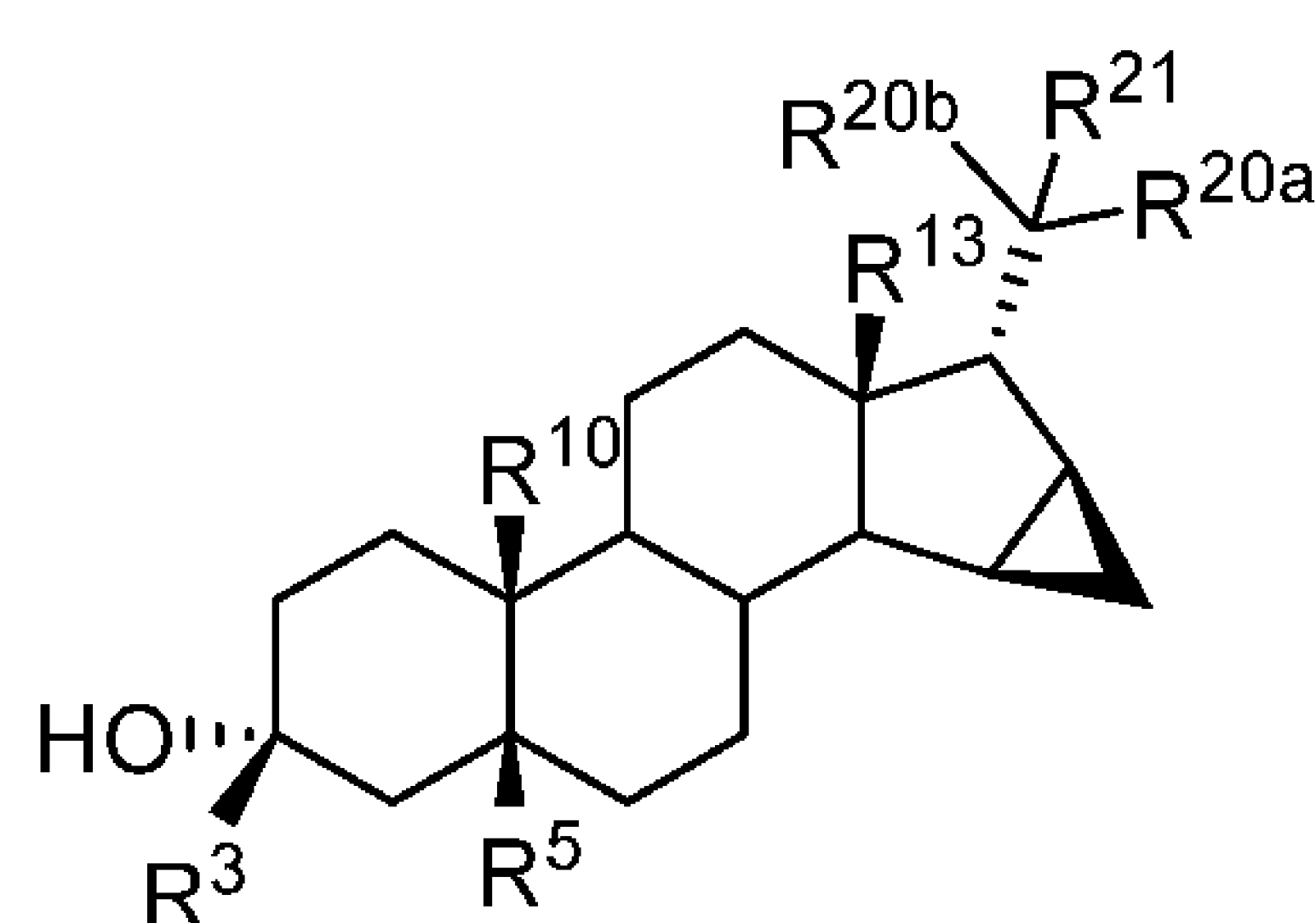
or

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), (III-B), or (III-B2).

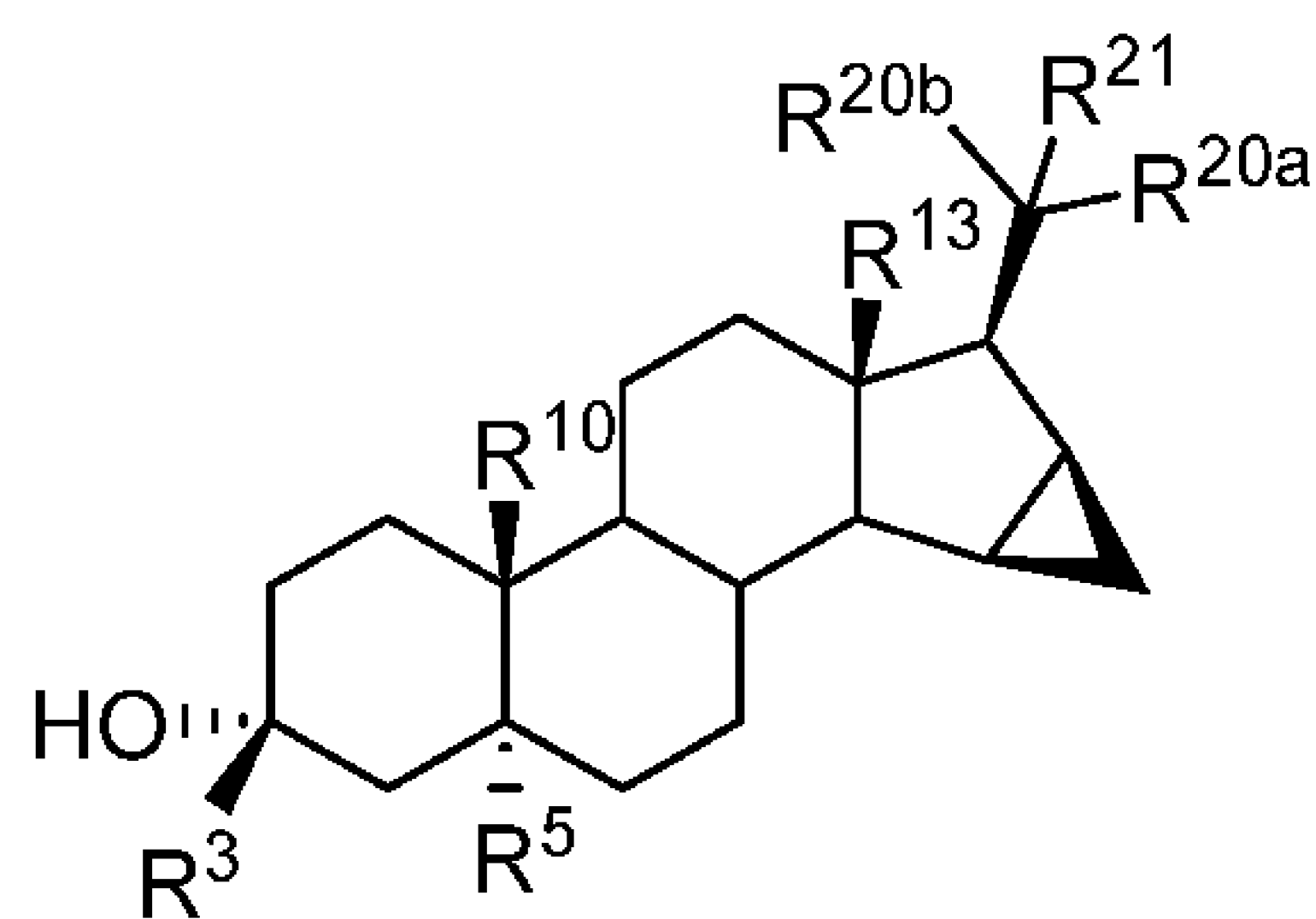
[0067] Another aspect of the present invention provides a compound of Formula (III-C1a), (III-C1b), (III-C1c), or (III-C1d)



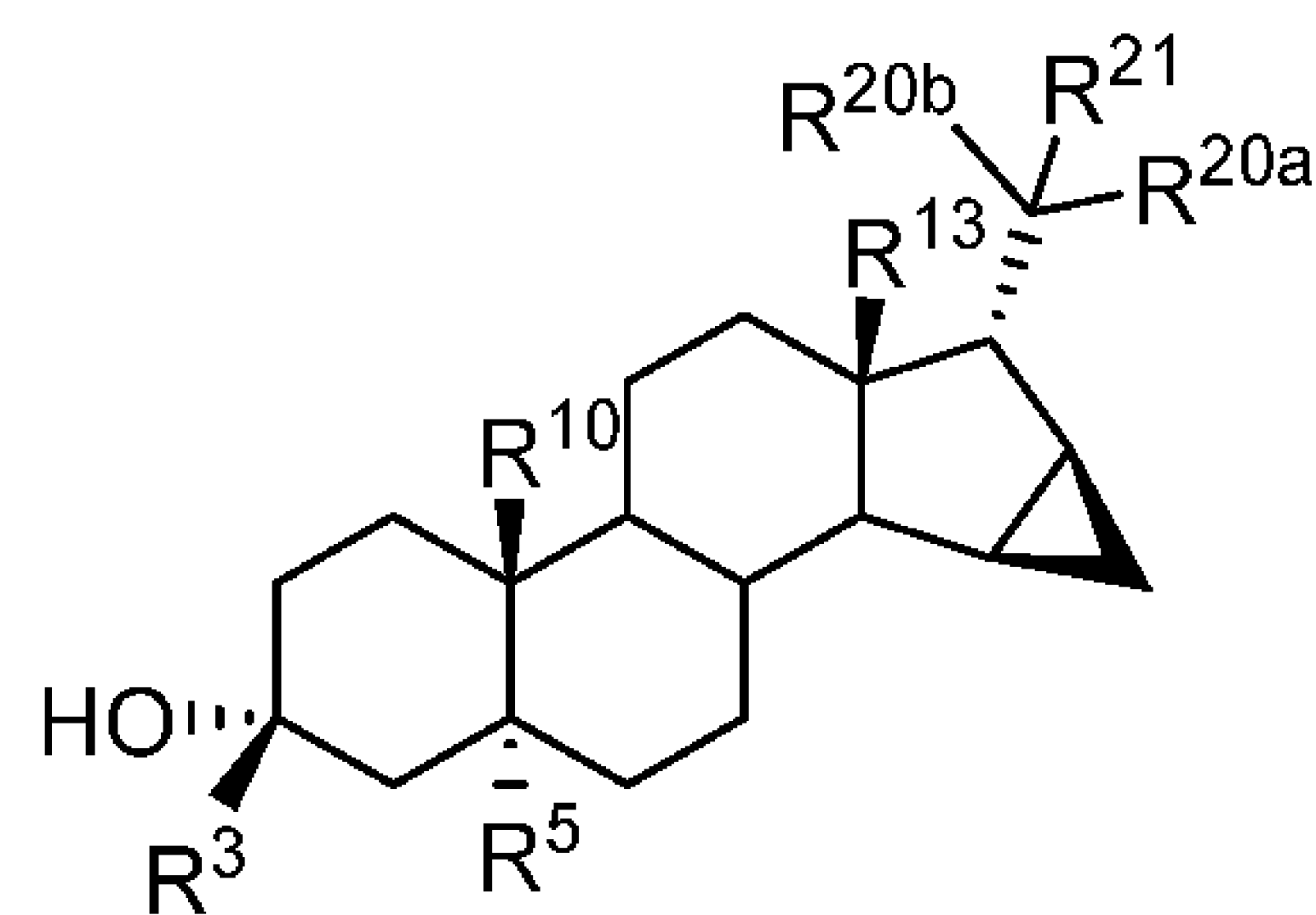
(III-C1a),



(III-C1b),



(III-C1c),

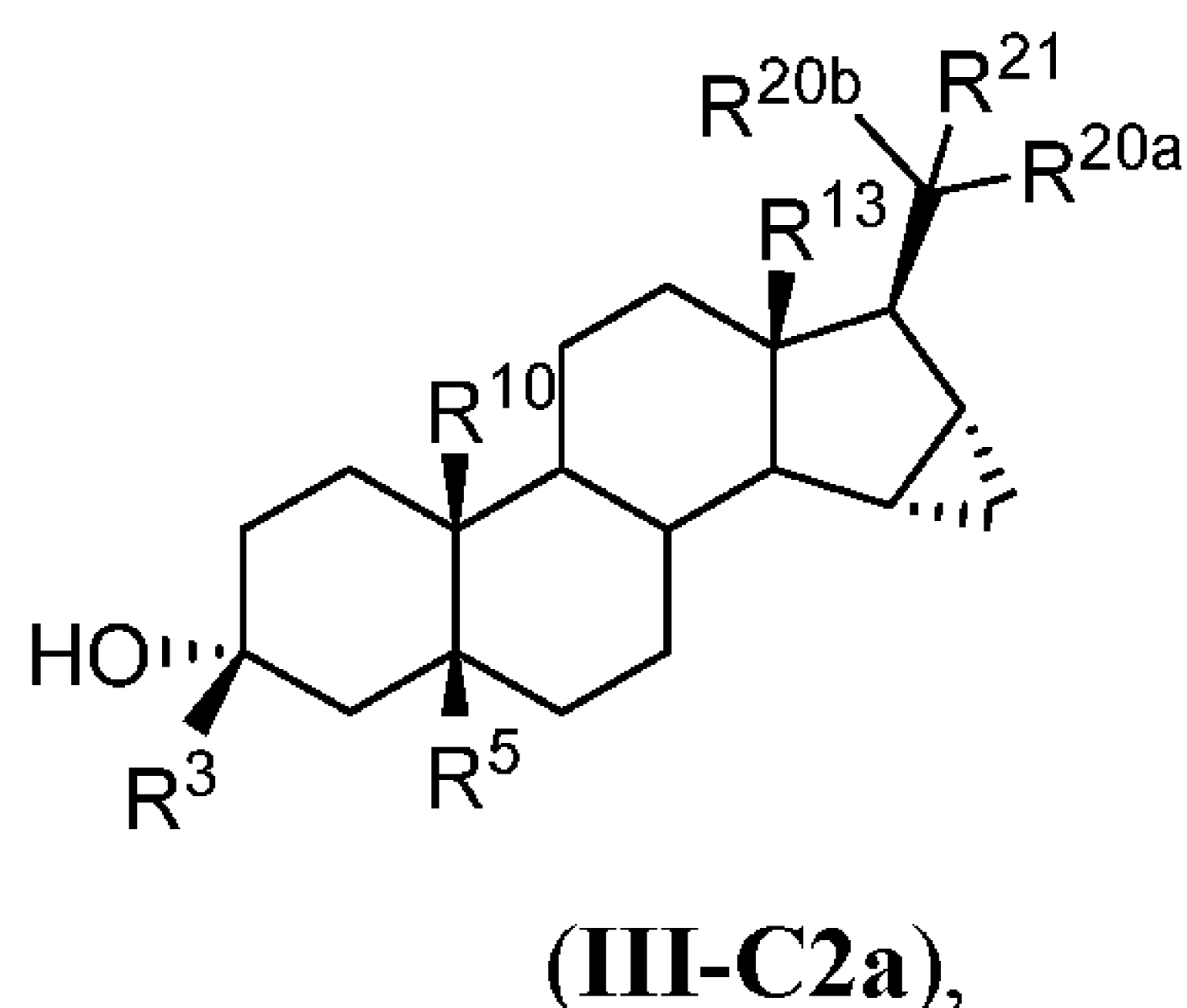
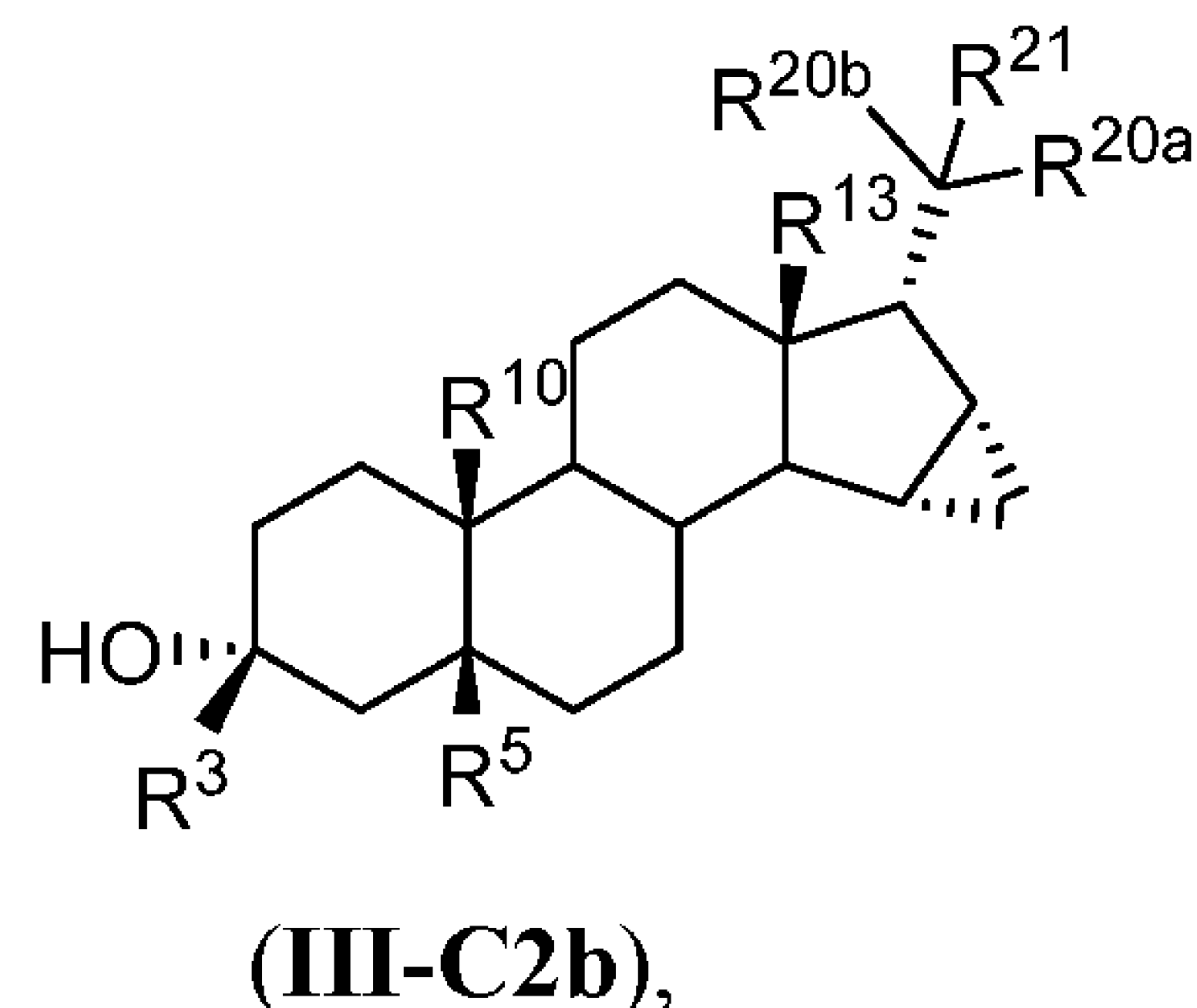
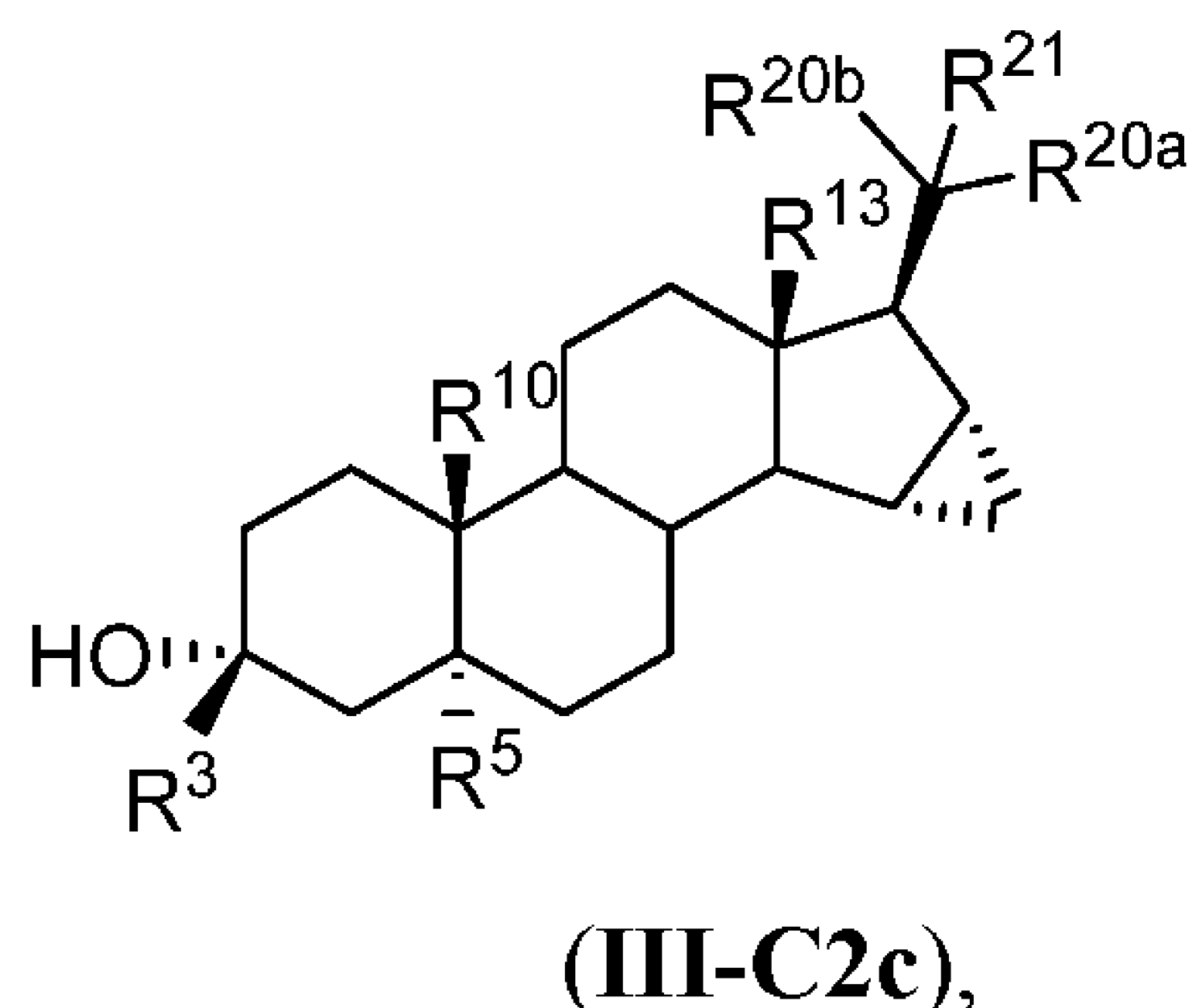


(III-C1d)

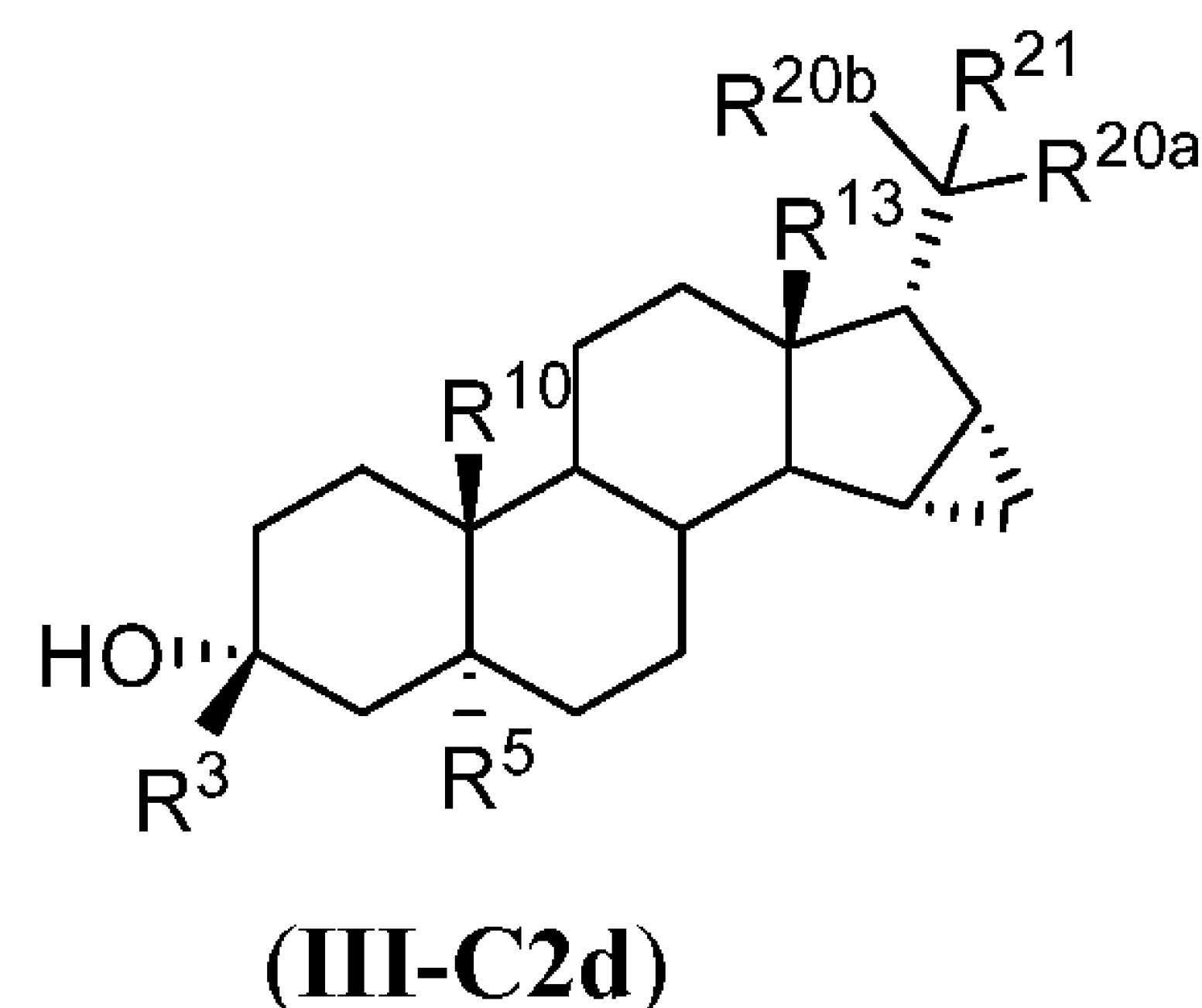
or

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), (III-C), or (III-C1).

[0068] Another aspect of the present invention provides a compound of Formula (III-C2a), (III-C2b), (III-C2c), or (III-C2d)

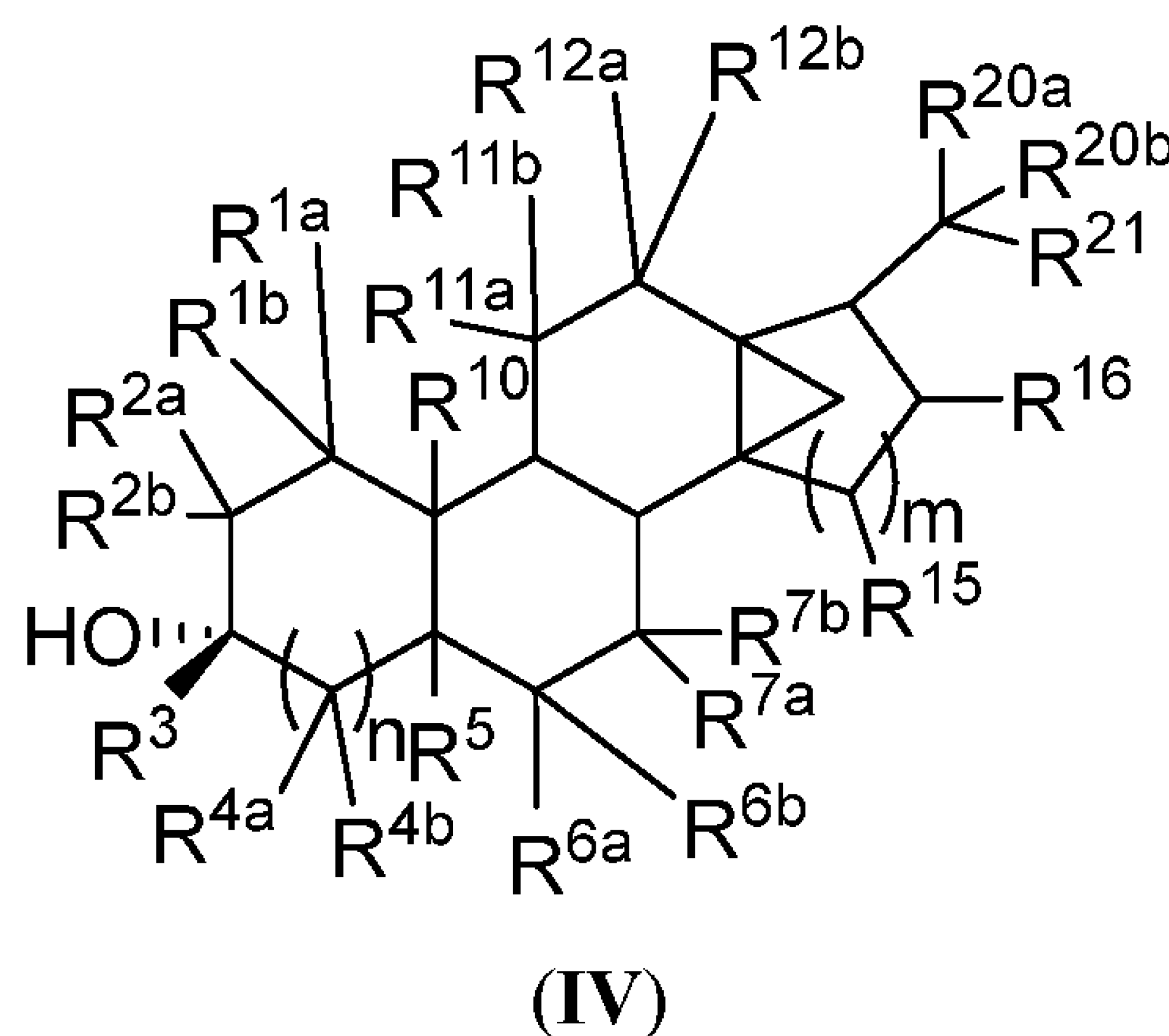


or



or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), (III-C), or (III-C2).

[0069] Another aspect of the present invention provides a compound of Formula (IV)



or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{15} , R^{16} , R^{20a} , R^{20b} , R^{21} , m , and n are as defined in any of the embodiments of the compounds of Formula (I).

[0070] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{15} , R^{16} , R^{20a} , R^{20b} , and R^{21} is $-L^A-R^{30}$, each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)-$,

$-\text{S}(\text{O})_2\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2-$, $-\text{C}(\text{O})\text{NR}'\text{NR}'-$, $-\text{NR}'\text{C}(\text{O})\text{NR}'-$, $-\text{OC}(\text{O})\text{NR}'-$, $-\text{NR}'\text{NR}'-$,
 $-\text{NR}'\text{S}(\text{O})_2\text{NR}'-$, or $-\text{S}(\text{O})_2-$; each R^{30} is independently selected from R' , halo, $-\text{CN}$, $-\text{NO}_2$,
 and $-\text{CF}_3$; each R' is independently selected from $-\text{H}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,
 and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring
 having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl,
 alkenyl, alkynyl, or 3-8-membered ring of R' is optionally substituted with 1-3 groups
 independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$,
 or R^{1a} and R^{1b} taken together form oxo, or R^{2a} and R^{2b} taken together form oxo, or R^{4a} and
 R^{4b} taken together form oxo, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken
 together form oxo, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together
 form oxo, or R^{20a} and R^{20b} taken together form oxo; R^5 is $-\text{H}$ or C_{1-3} alkyl; R^{10} is $-\text{H}$, C_{1-6}
 alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; m is 1 or 2; and n is 0, 1, or 2.

[0071] In some embodiments, each of R^{1a} and R^{1b} is independently selected from $-\text{H}$, C_{1-6}
 alkyl optionally substituted with R' , $-\text{N}(\text{R}')_2$, and $-\text{O}-\text{R}'$, or R^{1a} and R^{1b} taken together form
 oxo. In some embodiments, each of R^{1a} and R^{1b} is independently selected from $-\text{H}$ and C_{1-6}
 alkyl optionally substituted with R' , or R^{1a} and R^{1b} taken together form oxo. In some
 embodiments, one of R^{1a} and R^{1b} is $-\text{H}$, and the other is $-\text{H}$, C_{1-6} alkyl optionally substituted
 with R' , $-\text{N}(\text{R}')_2$, or $-\text{O}-\text{R}'$. In some embodiments, one of R^{1a} and R^{1b} is $-\text{H}$, and the other is
 $-\text{H}$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, one of R^{1a} and R^{1b} is
 $-\text{H}$, and the other is methyl. And, in some embodiments, each of R^{1a} and R^{1b} is $-\text{H}$.

[0072] In some embodiments, each of R^{2a} and R^{2b} is independently selected from $-\text{H}$, C_{1-6}
 alkyl optionally substituted with R' , $-\text{N}(\text{R}')_2$, and $-\text{O}-\text{R}'$, or R^{2a} and R^{2b} taken together form
 oxo. In some embodiments, each of R^{2a} and R^{2b} is independently selected from $-\text{H}$ and C_{1-6}
 alkyl optionally substituted with R' , or R^{2a} and R^{2b} taken together form oxo. In some
 embodiments, one of R^{2a} and R^{2b} is $-\text{H}$, and the other is $-\text{H}$, C_{1-6} alkyl optionally substituted
 with R' , $-\text{N}(\text{R}')_2$, or $-\text{O}-\text{R}'$. In some embodiments, one of R^{2a} and R^{2b} is $-\text{H}$, and the other is
 $-\text{H}$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, one of R^{2a} and R^{2b} is
 $-\text{H}$, and the other is methyl. And, in some embodiments, each of R^{2a} and R^{2b} is $-\text{H}$.

[0073] In some embodiments, R^3 is $-\text{H}$, C_{1-6} alkyl optionally substituted with R' , $-\text{N}(\text{R}')_2$, or
 $-\text{O}-\text{R}'$. In some embodiments, R^3 is $-\text{H}$ or C_{1-6} alkyl optionally substituted with R' . In some
 embodiments, R^3 is $-\text{H}$, $-\text{CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-CH}_3$, or $-\text{CH}_2\text{-O-CH}_3$. And, in some
 embodiments, R^3 is $-\text{H}$ or methyl.

[0074] In some embodiments, n is 0 and both of R^{4a} and R^{4b} are absent. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is methyl. And, in some embodiments, n is 1 and each of R^{4a} and R^{4b} is $-H$.

[0075] In some embodiments, R^5 is $-H$.

[0076] In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo. In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' . In some embodiments, two of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other two of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$. In some embodiments, three of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, three of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other is $-H$ or methyl. And, in some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is $-H$.

[0077] In some embodiments, R^{10} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl. And, in some embodiments, R^{10} is $-H$, methyl, or methoxymethyl.

[0078] In some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo. In some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' . In some embodiments, two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$. In some embodiments, two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are independently

selected from $-H$ and methyl. In some embodiments, three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other is $-H$ or methyl. And, in some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is $-H$.

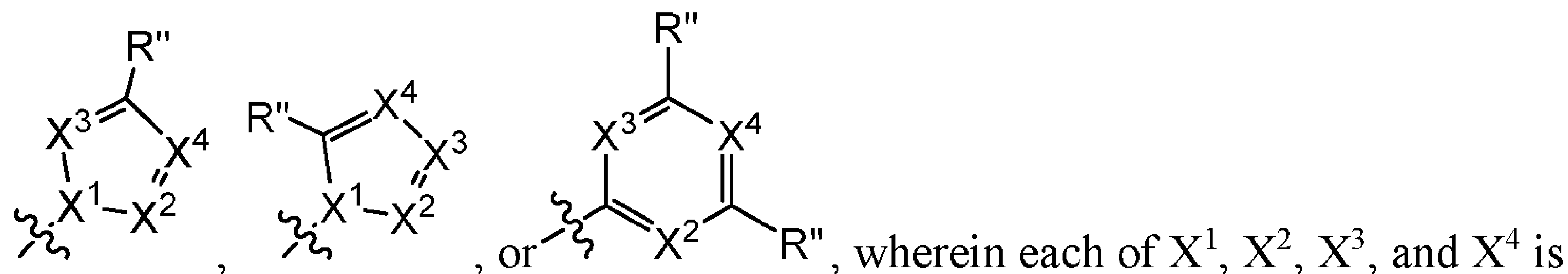
[0079] In some embodiments, m is 1 and R^{15} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, m is 1 and R^{15} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, m is 1 and R^{15} is $-H$ or C_{1-3} alkyl. In some embodiments, m is 1 and R^{15} is $-H$ or methyl. And, in some embodiments, m is 1 and R^{15} is $-H$.

[0080] In some embodiments, R^{16} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^{16} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^{16} is $-H$ or C_{1-3} alkyl. In some embodiments, R^{16} is $-H$ or methyl. And, in some embodiments, R^{16} is $-H$.

[0081] In some embodiments, each of R^{20a} and R^{20b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo. In some embodiments, each of R^{20a} and R^{20b} are independently selected from $-H$, C_{1-6} alkyl, $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo. In some embodiments, R^{20a} and R^{20b} taken together form oxo. In some embodiments, R^{20a} and R^{20b} are independently selected from $-H$, methyl, and $-OH$. In some embodiments, one of R^{20a} and R^{20b} is $-OH$, and the other is $-H$, or methyl. In some embodiments, R^{20a} and R^{20b} taken together form oxo.

[0082] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, $-NH-$, or $-CH_2-CH_2-CH_2-$; and R^{30} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, or $-NH-$; and R^{30} is a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond or $-CH_2-$; and R^{30} is a 5-6-membered partially unsaturated or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-2 groups

independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond or $-\text{CH}_2-$; and R^{30} is

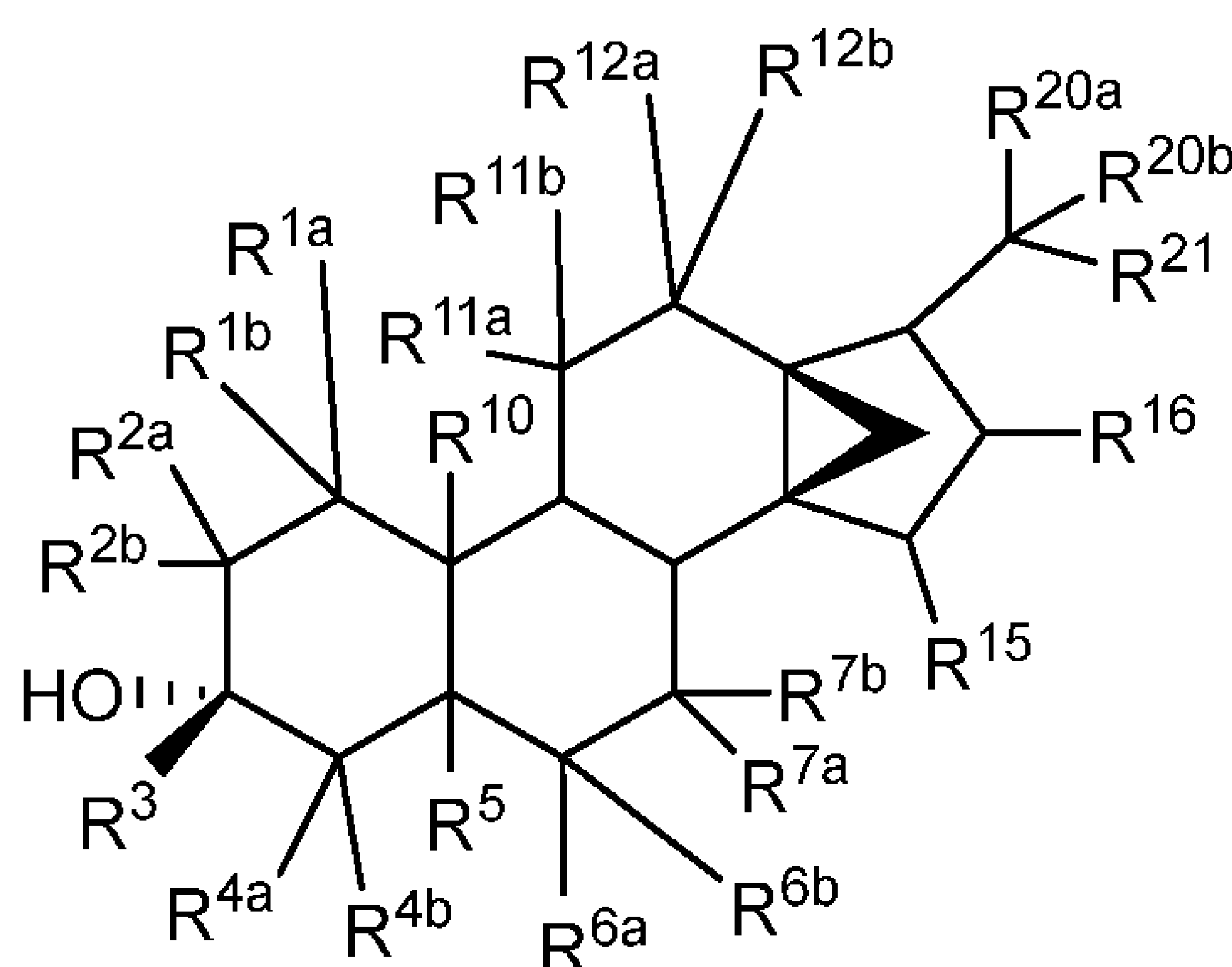


wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or a CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from

halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, R^{30} is

or , X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N or CR'' , wherein each R'' is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$, provided that no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$.

[0083] Another aspect of the present invention provides a compound of Formula (IV-A)



(IV-A)

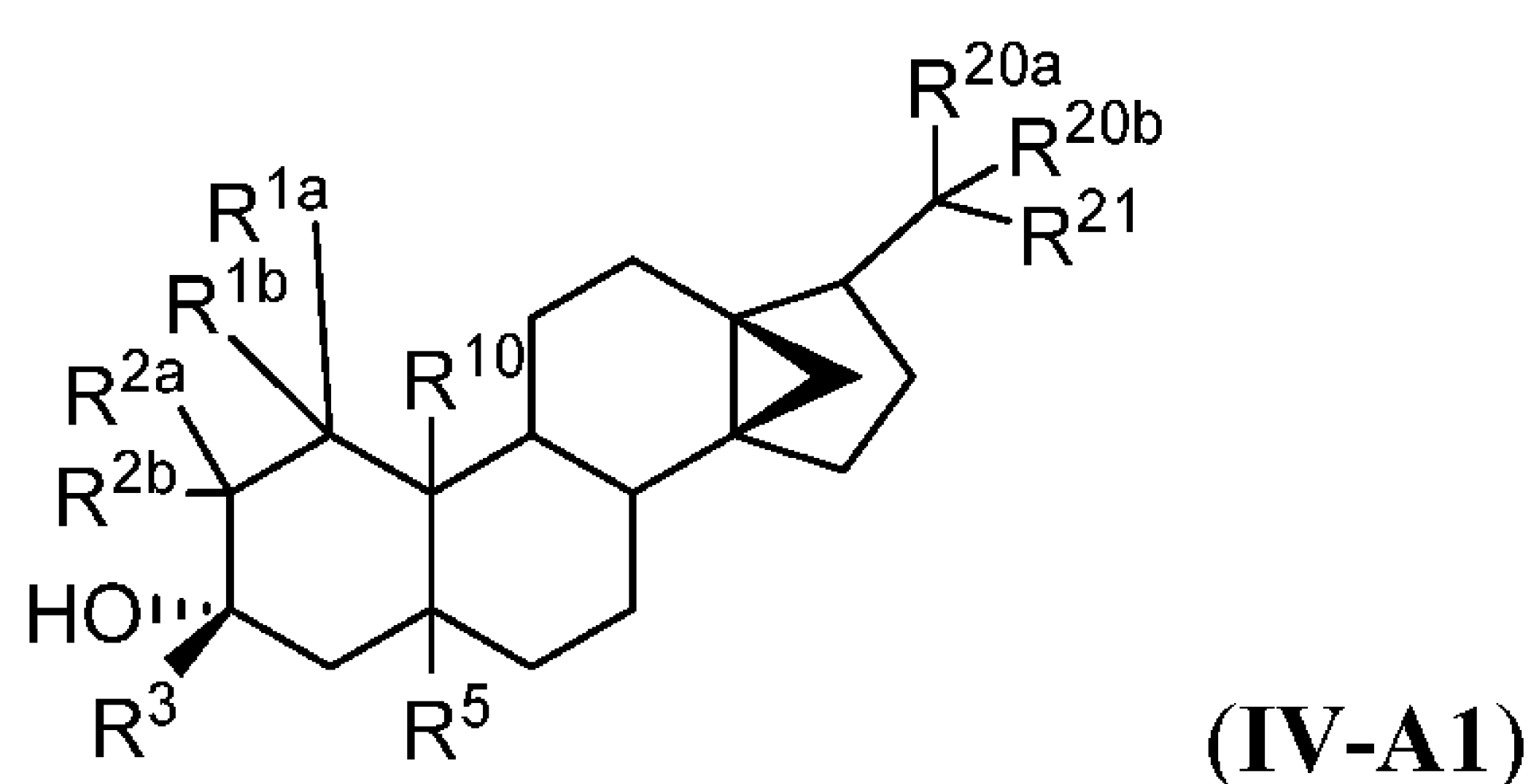
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{15} , R^{16} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I) or (IV).

[0084] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{15} , R^{16} , R^{20a} , R^{20b} , and R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; each L^{A} is independently selected

from a bond and an optionally substituted branched or straight C₁₋₆ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by –NR'–, –S–, –O–, –OC(O)–, –C(O)O–, –C(O)–, –C(O)C(O)–, –C(O)NR'–, –NR'C(O)–, –NR'C(O)O–, –S(O)–, –S(O)₂NR'–, –NR'S(O)₂–, –C(O)NR'NR'–, –NR'C(O)NR'–, –OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, or –S(O)₂–; each R³⁰ is independently selected from R', halo, –CN, –NO₂, and –CF₃; each R' is independently selected from –H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, –CH₃, –CH₂OH, and –C(CH₃)₃, or R^{20a} and R^{20b} taken together form oxo; R⁵ is –H or C₁₋₃ alkyl; and R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl.

[0085] In some embodiments, each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹⁵, and R¹⁶ is independently selected from –H and C₁₋₆ alkyl; R³ is –H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₅ alkyl-O-C₁₋₆ alkyl; R⁵ is –H or C₁₋₃ alkyl; R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; each of R¹⁵ and R¹⁶ is independently –H or C₁₋₆ alkyl; each of R^{20a} and R^{20b} is independently selected from –H, –OH, –C₁₋₅ alkyl-OH, C₁₋₆ alkyl, and –NH₂, or R^{20a} and R^{20b} taken together form oxo; R²¹ is –L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by –NR'–, –S–, –O–, –OC(O)–, –C(O)O–, –C(O)–, –C(O)C(O)–, –C(O)NR'–, –NR'C(O)–, –NR'C(O)O–, –S(O)₂NR'–, –NR'S(O)₂–, –C(O)NR'NR'–, –NR'C(O)NR'–, –OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, –S(O)–, or –S(O)₂–; R³⁰ is R', halo, –CN, –NO₂, and –CF₃; and each R' is independently selected from –H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, and –CH₃.

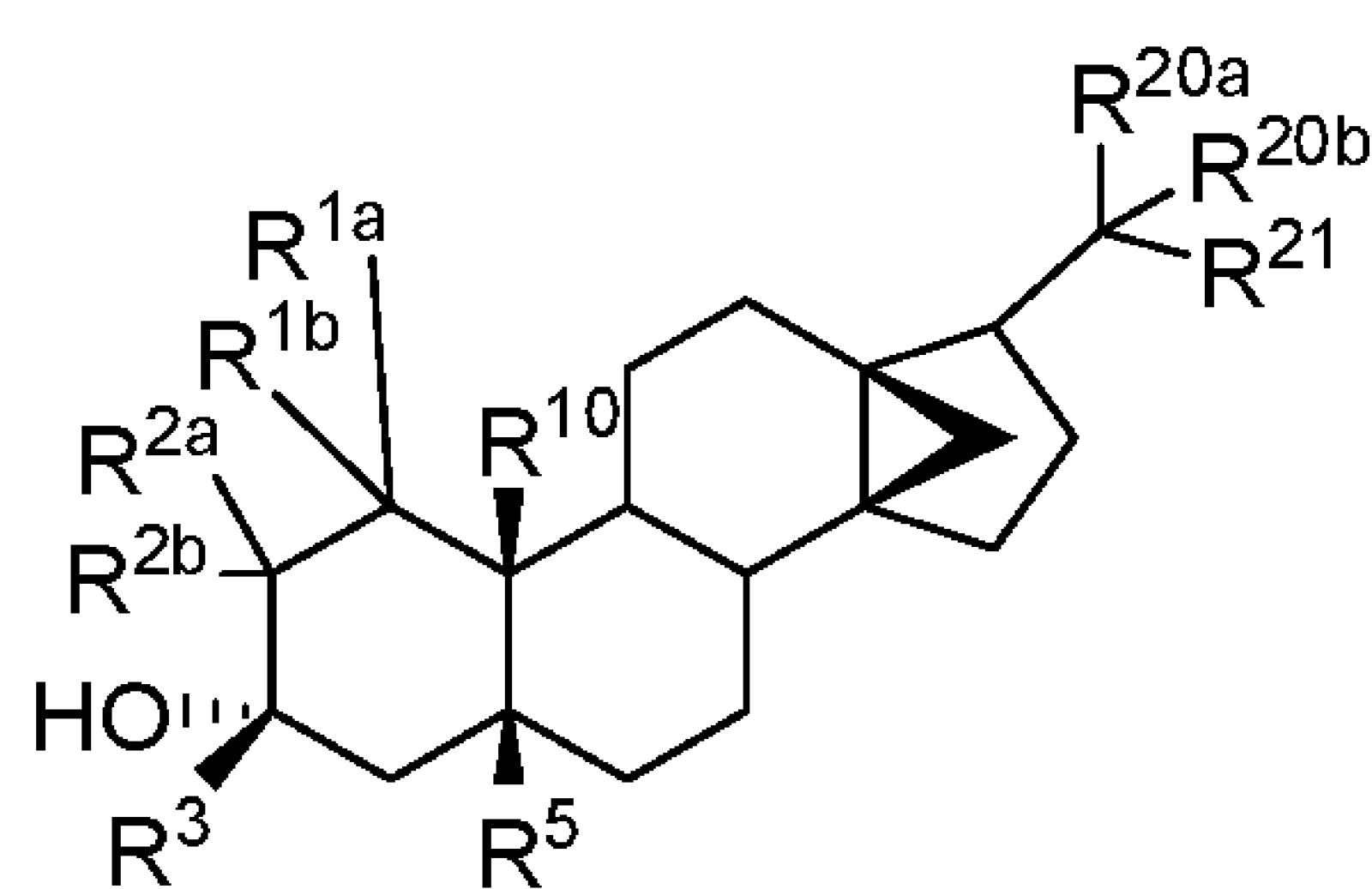
[0086] Another aspect of the present invention provides a compound of Formula (IV-A1)



or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (IV), or (IV-A).

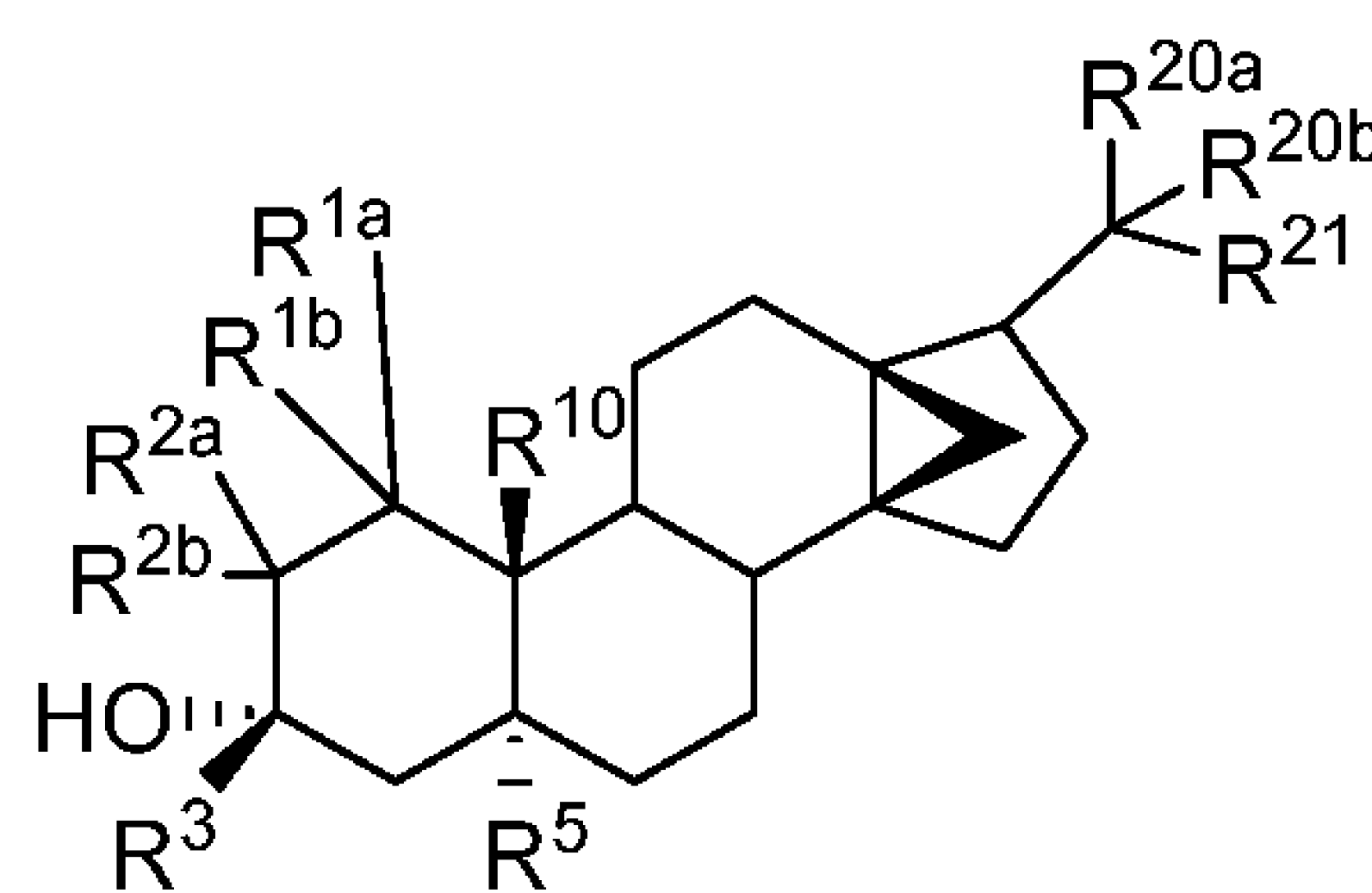
[0087] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , and R^{2b} is independently selected from $-H$ and C_{1-3} alkyl; R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-3} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-CH_2OH$, C_{1-3} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or a straight or branched C_{1-3} alkylene chain; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and R' is $-H$, C_{1-6} alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0088] Another aspect of the present invention provides a compound of Formula (IV-A1a) or (IV-A1b)



(IV-A1a)

or

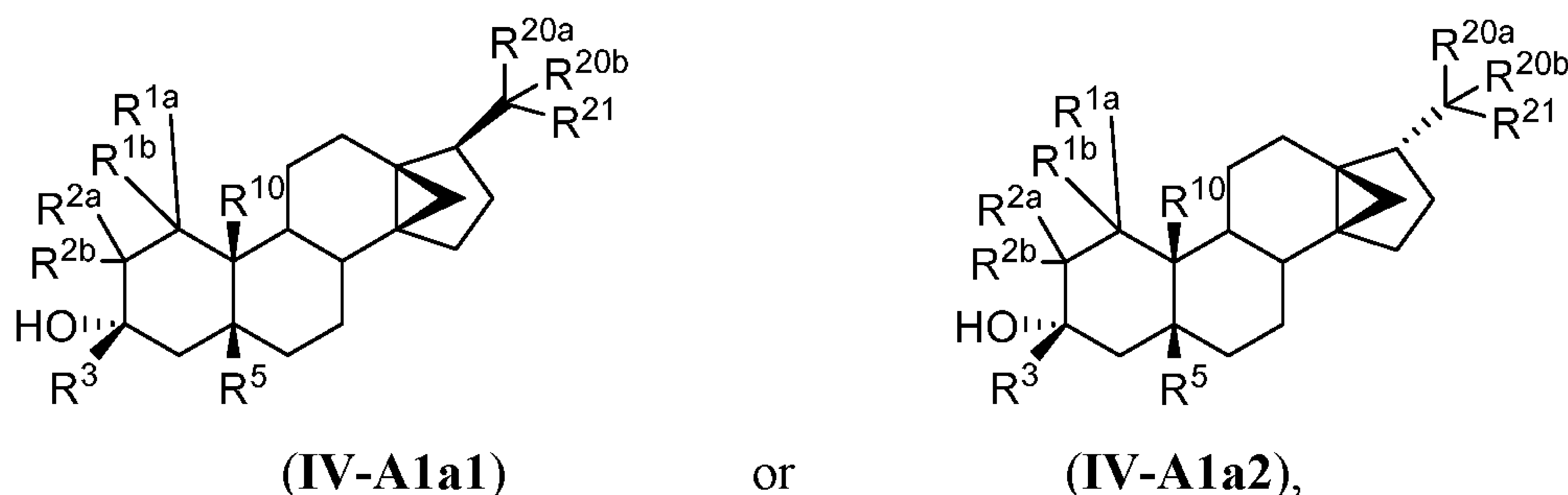


(IV-A1b),

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (IV), (IV-A), or (IV-A1).

[0089] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , and R^{2b} is selected from $-H$ and C_{1-3} alkyl; R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or C_{1-3} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-CH_2OH$, C_{1-3} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or a straight or branched C_{1-3} alkylene chain; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and R' is $-H$, C_{1-6} alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

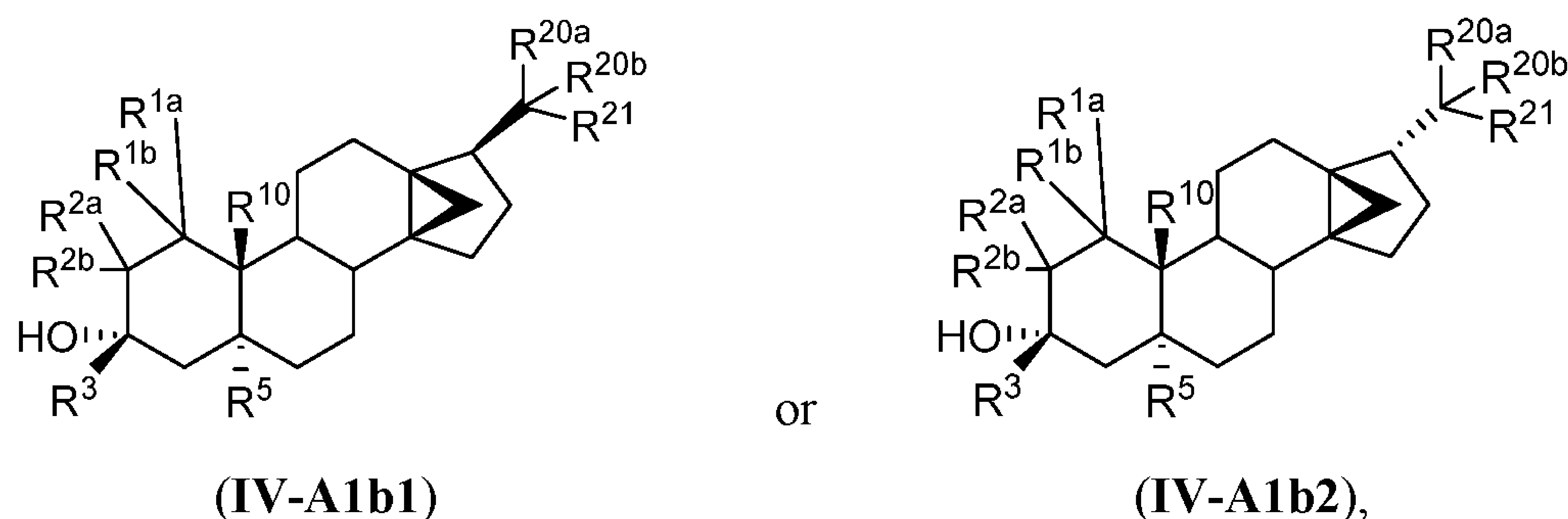
[0090] Another aspect of the present invention provides a compound of Formula (IV-A1a1) or (IV-A1a2)



or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R⁵, R¹⁰, R^{20a}, R^{20b}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (IV), (IV-A), (IV-A1), or (IV-A1a).

[0091] In some embodiments, each of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently selected from -H and C₁₋₃ alkyl; R³ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; R⁵ is -H or C₁₋₃ alkyl; R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; each of R^{20a} and R^{20b} is independently selected from -H, -OH, -CH₂OH, C₁₋₃ alkyl, and -NH₂, or R^{20a} and R^{20b} taken together form oxo; R²¹ is -L^A-R³⁰; L^A is a bond or a straight C₁₋₃ alkylene chain; R³⁰ is R', halo, -CN, -NO₂, or -CF₃; and R' is -H, C₁₋₆ alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

[0092] Another aspect of the present invention provides a compound of Formula (IV-A1b1) or (IV-A1b2)

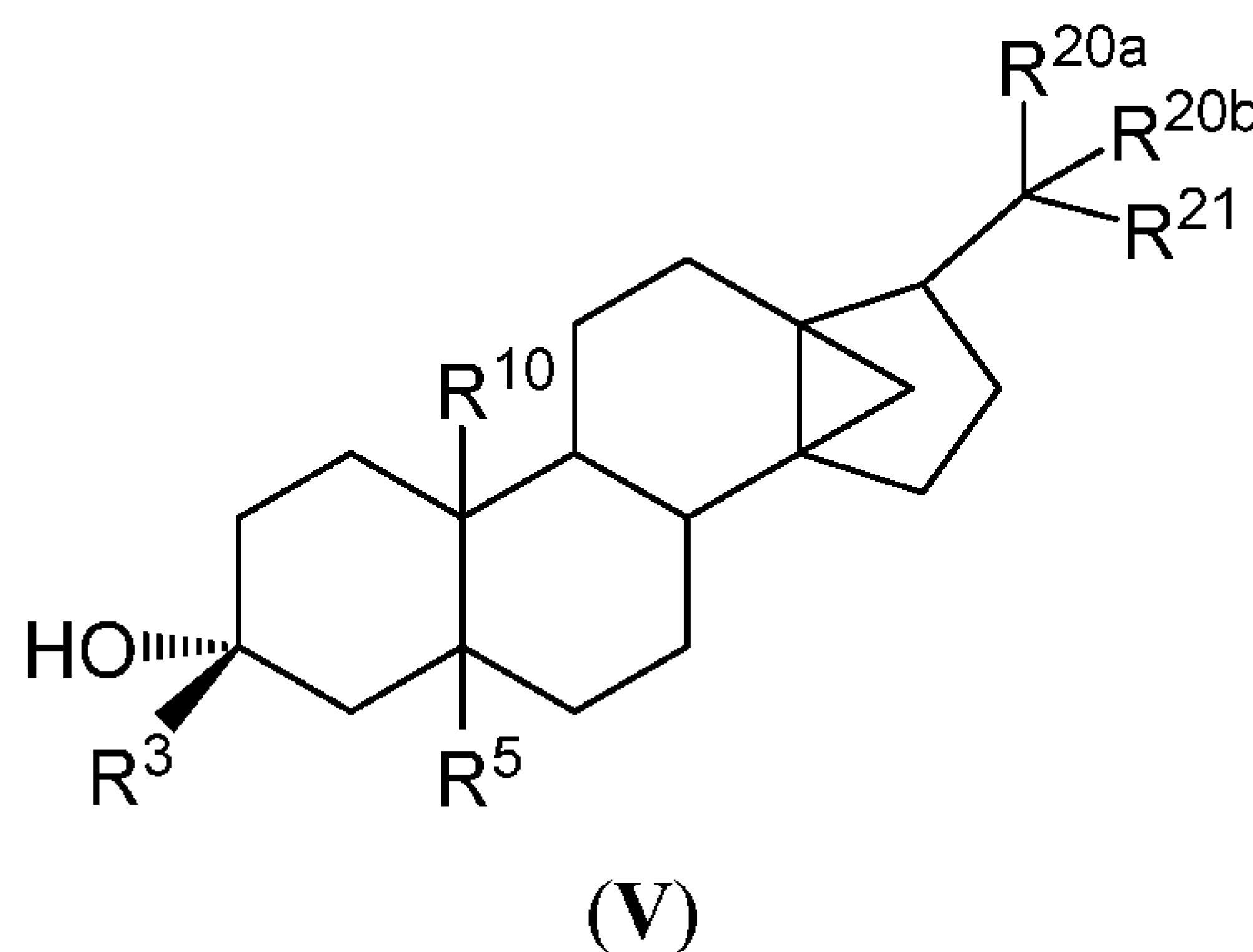


or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R⁵, R¹⁰, R^{20a}, R^{20b}, and R²¹, are as defined in any of the embodiments of the compounds of Formula (I), (IV), (IV-A), (IV-A1), or (IV-A1b).

[0093] In some embodiments, each of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently selected from -H and C₁₋₃ alkyl; R³ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; R⁵ is -H or C₁₋₃ alkyl; R¹⁰ is

–H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; each of R^{20a} and R^{20b} is independently selected from –H, –OH, –CH₂OH, C₁₋₃ alkyl, and –NH₂, or R^{20a} and R^{20b} taken together form oxo; R²¹ is –L^A-R³⁰; L^A is a bond or a straight C₁₋₃ alkylene chain; R³⁰ is R', halo, –CN, –NO₂, or –CF₃; and R' is –H, C₁₋₆ alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, and –CH₃.

[0094] Another aspect of the present invention provides a compound of Formula (V)



or a pharmaceutically acceptable salt thereof, wherein R³, R⁵, R¹⁰, R^{20a}, R^{20b}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I) or (IV).

[0095] In some embodiments, R³ is –H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; R⁵ is –H or C₁₋₆ alkyl; R¹⁰ is –H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; each of R^{20a} and R^{20b} is independently selected from –H, –OH, and C₁₋₆ alkyl, or R^{20a} and R^{20b} taken together form oxo; R²¹ is –L^A-R³⁰; L^A is a bond, a branched or straight C₁₋₆ alkylene chain, or –N(H)–; and R³⁰ is –H, halo, –OH, –CN, –NO₂, –CF₃, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, –CH₃, –CH₂OH, and –C(CH₃)₃.

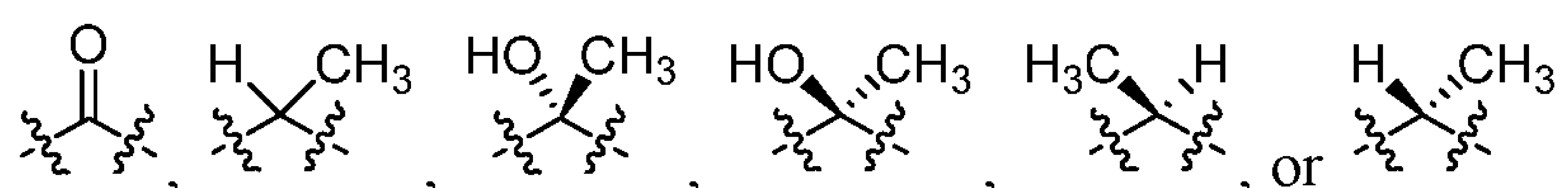
[0096] In some embodiments, R³ is C₁₋₆ alkyl or C₁₋₆ alkyl-O-C₁₋₆ alkyl. In some embodiments, R³ is methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, neopentyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R³ is –CH₃, –CH₂-CH₃, –CH₂-CH₂-CH₃, or –CH₂-O-CH₃. And, in some embodiments, R³ is –CH₃.

[0097] In some embodiments, R⁵ is –H or C₁₋₃ alkyl. In some embodiments, R⁵ is –H or methyl.

[0098] In some embodiments, R^{10} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^{10} is $-H$ or methyl.

[0099] In some embodiments, R^{13} is C_{1-6} alkyl. In some embodiments, R^{13} is methyl, ethyl, or propyl. In some embodiments, R^{13} is $-H$ or methyl. And, in some embodiments, R^{13} is methyl.

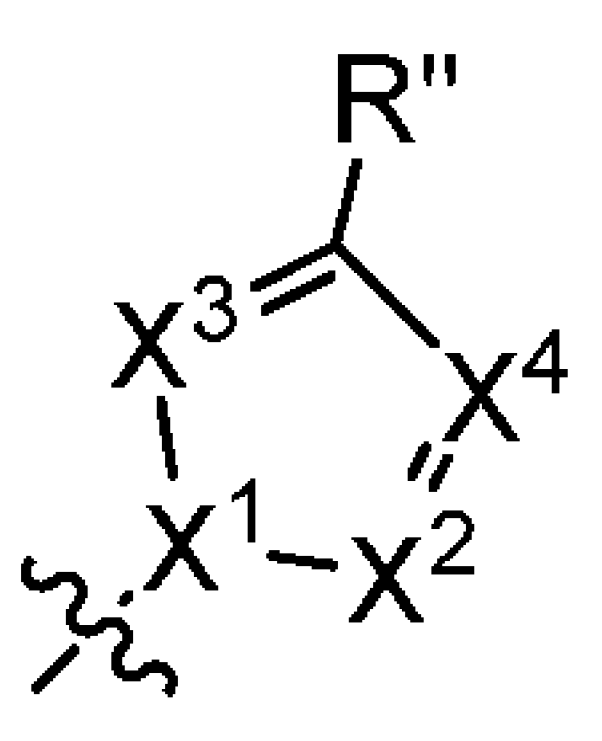
[0100] In some embodiments, R^{20a} and R^{20b} taken together form oxo. In some embodiments, one of R^{20a} and R^{20b} is $-H$, and the other of R^{20a} and R^{20b} is C_{1-6} alkyl. In some embodiments, one of R^{20a} and R^{20b} is C_{1-6} alkyl, and the other of R^{20a} and R^{20b} is $-OH$. In some embodiments, one of R^{20a} and R^{20b} is methyl, ethyl, or propyl, and the other of R^{20a} and R^{20b} is $-OH$. In some embodiments, R^{20a} , R^{20b} , and the carbon to which they are attached form

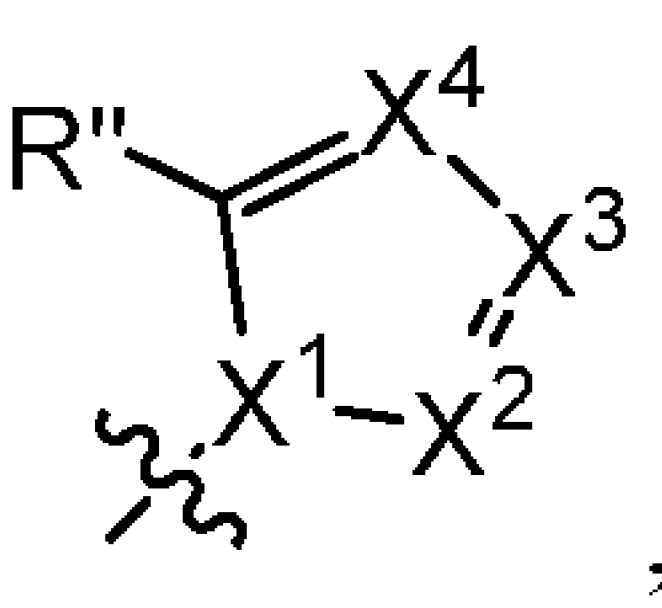


[0101] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-3} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, or $-N(H)-$; and R^{30} is $-H$ or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, or $-N(H)-$; and R^{30} is a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, or

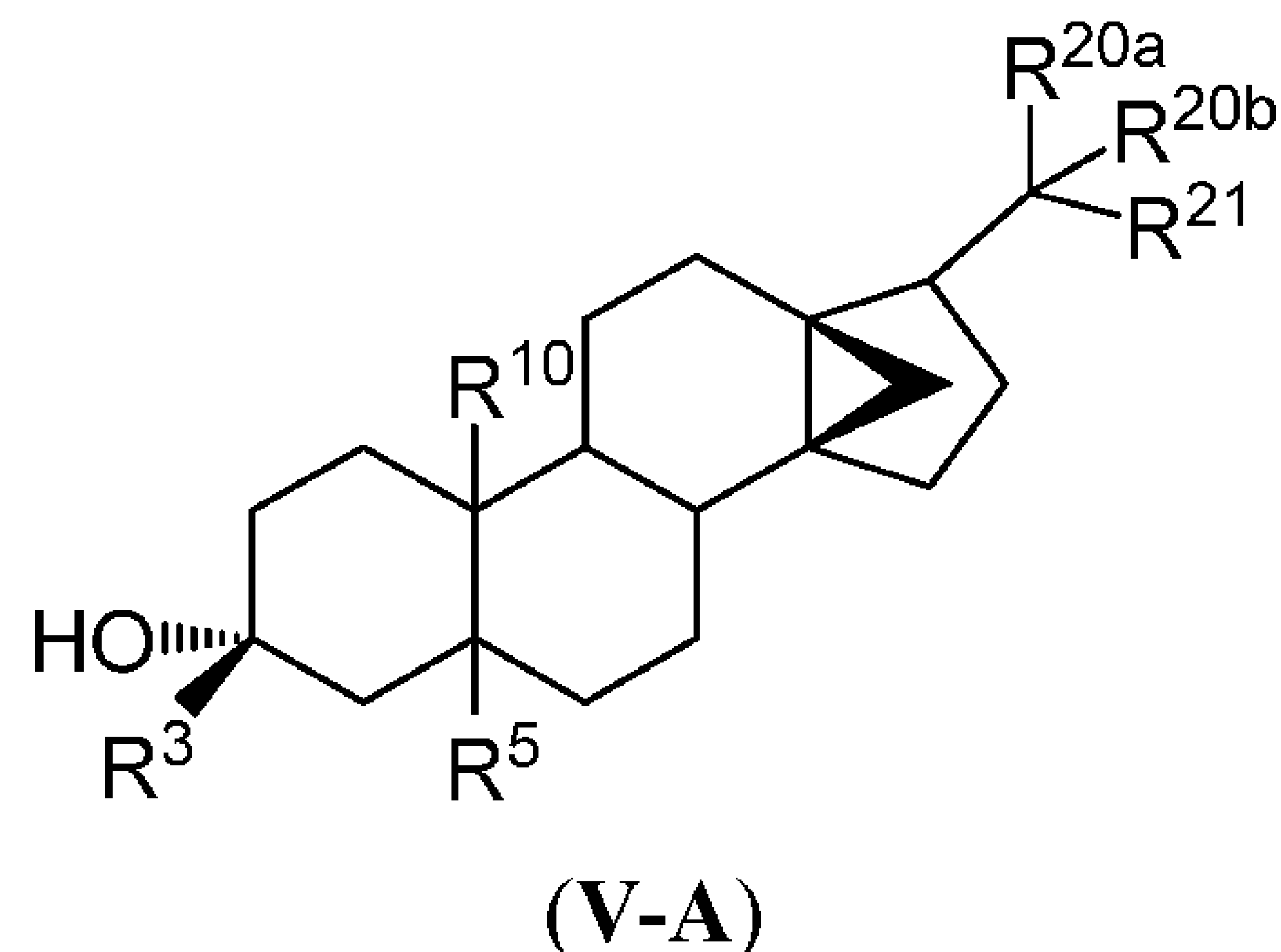
$-N(H)-$; and R^{30} is , or , wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-H$, halo,

–OH, –CN, –NO₂, –CF₃, –CH₃, –CH₂OH, and –C(CH₃)₃, provided that (i) at least one of X¹, X², X³, and X⁴ is N, and (ii) no greater than 2 instances of R" are independently selected from

halo, –OH, –CN, –NO₂, –CF₃, –CH₃, and –CH₂OH. In some embodiments, R³⁰ is 

or , X¹ is N; and each of X², X³, and X⁴ is independently selected from N or CR", wherein each R" is independently selected from –H, –OH, –CN, –NO₂, –CF₃, –CH₃, and –CH₂OH, provided that no greater than 2 instances of R" are independently selected from halo, –OH, –CN, –NO₂, –CF₃, –CH₃, and –CH₂OH.

[0102] Another aspect of the present invention provides a compound of Formula (V-A)



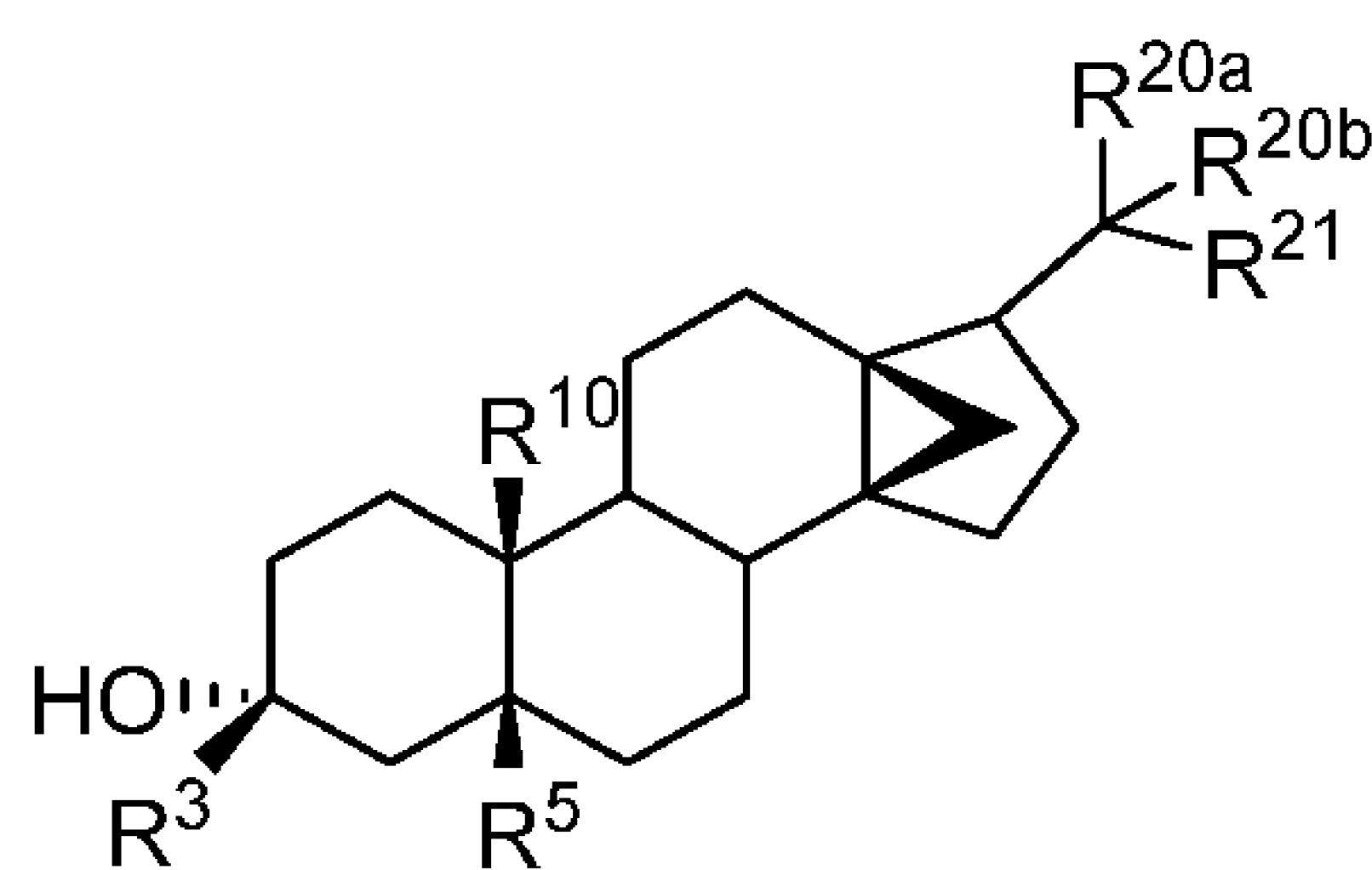
or a pharmaceutically acceptable salt thereof, wherein R³, R⁵, R¹⁰, R^{20a}, R^{20b}, and R²¹, are as defined in any of the embodiments of the compounds of Formula (I), (IV), or (V).

[0103] In some embodiments, R³ is –H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; R⁵ is –H or C₁₋₆ alkyl; R¹⁰ is –H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; each of R^{20a} and R^{20b} is independently selected from –H, –OH, and C₁₋₆ alkyl, or R^{20a} and R^{20b} taken together form oxo; R²¹ is –L^A-R³⁰; L^A is a bond, a branched or straight C₁₋₆ alkylene chain, or –N(H)–; and R³⁰ is –H, halo, –OH, –CN, –NO₂, –CF₃, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, –CH₃, –CH₂OH, and –C(CH₃)₃.

[0104] In some embodiments, R³ is –H, C₁₋₃ alkyl, C₁₋₃ alkyl-O-C₁₋₃ alkyl; R⁵ is –H or methyl; R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; each of R^{20a} and R^{20b} is independently selected from –H, –OH, and C₁₋₃ alkyl, or R^{20a} and R^{20b} taken together form oxo; R²¹ is –L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃

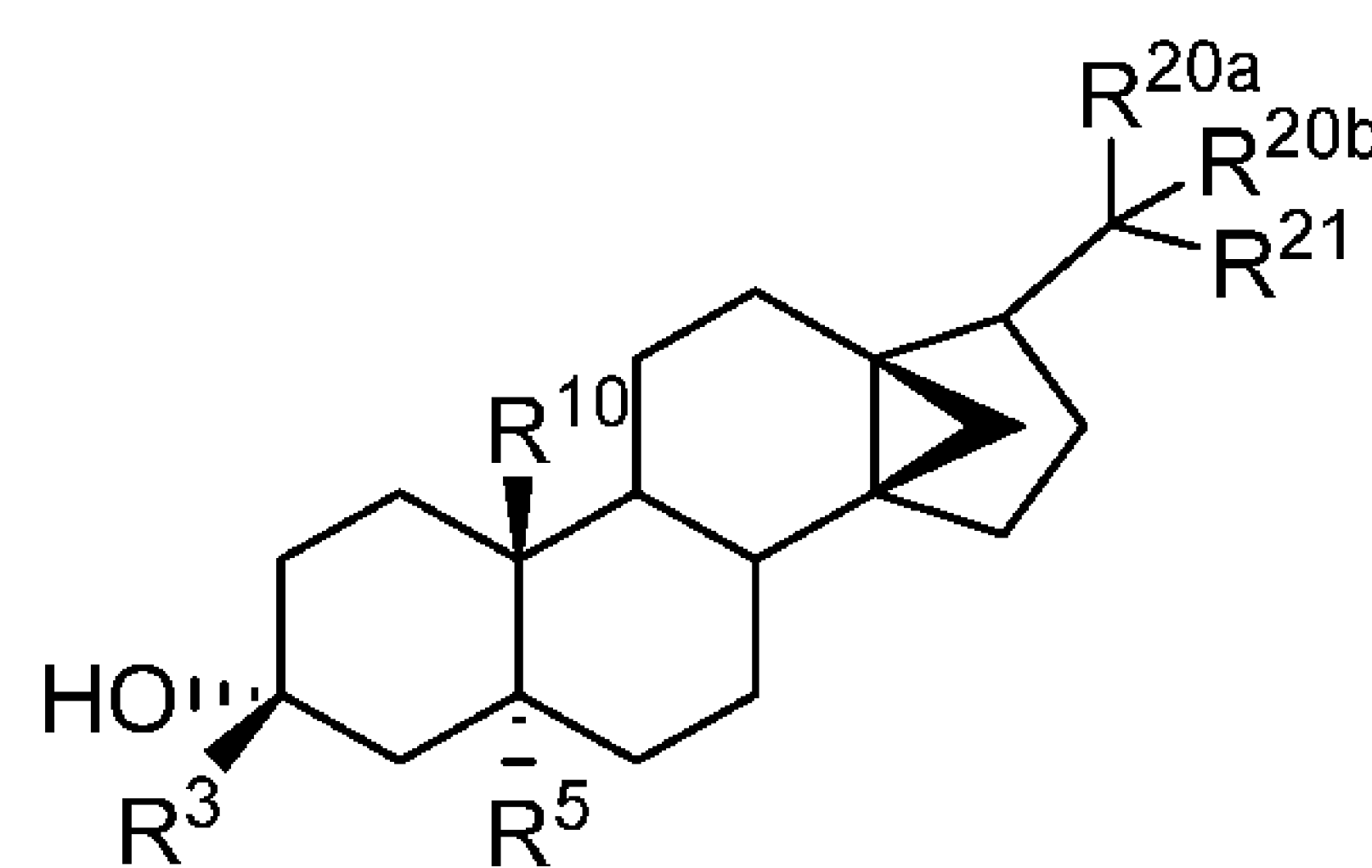
alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0105] Another aspect of the present invention provides a compound of Formula (V-A1) or (V-A2)



(V-A1)

or



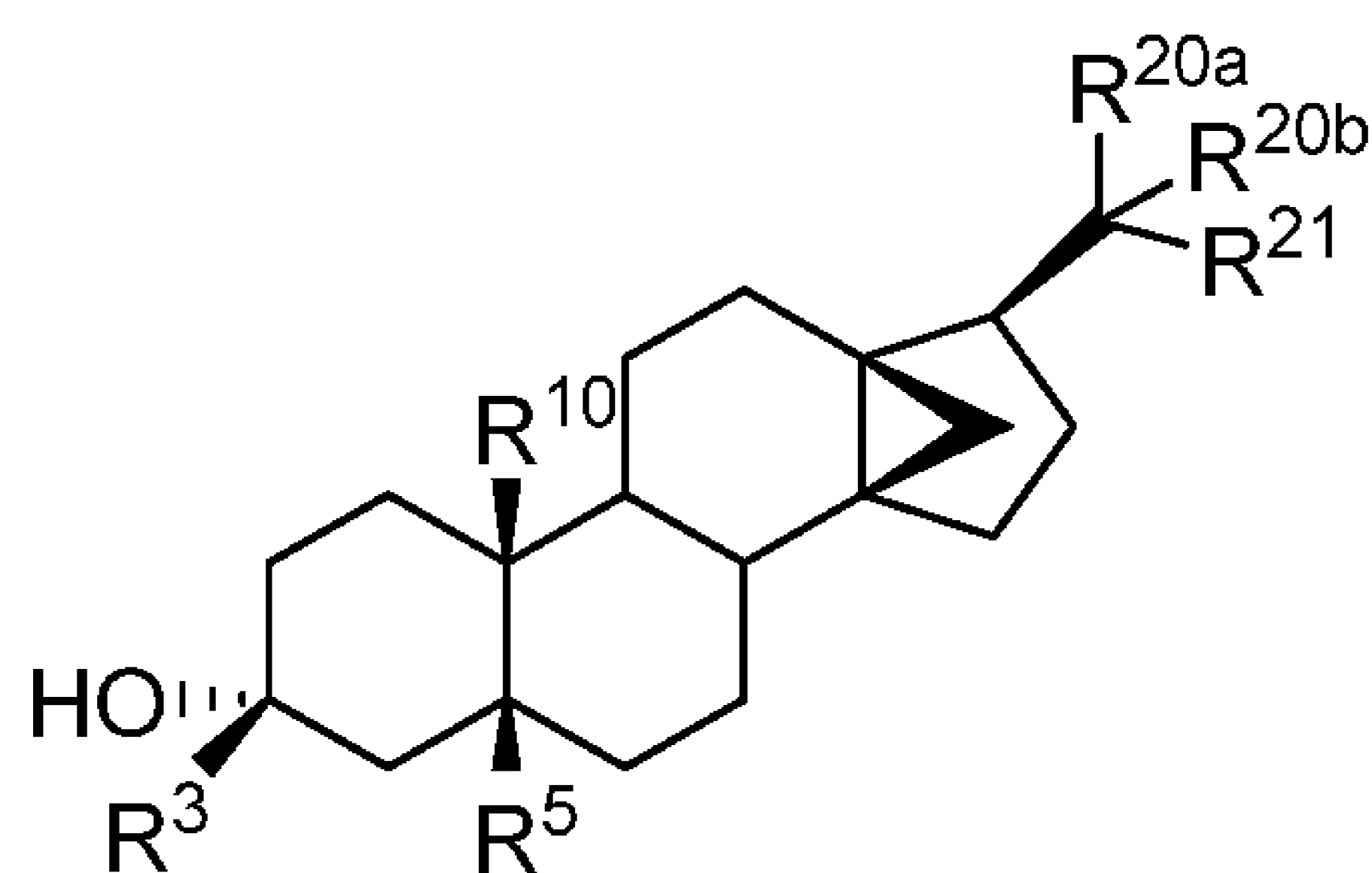
(V-A2),

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} , are as defined in any of the embodiments of the compounds of Formula (I), (IV), (V), or (V-A).

[0106] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

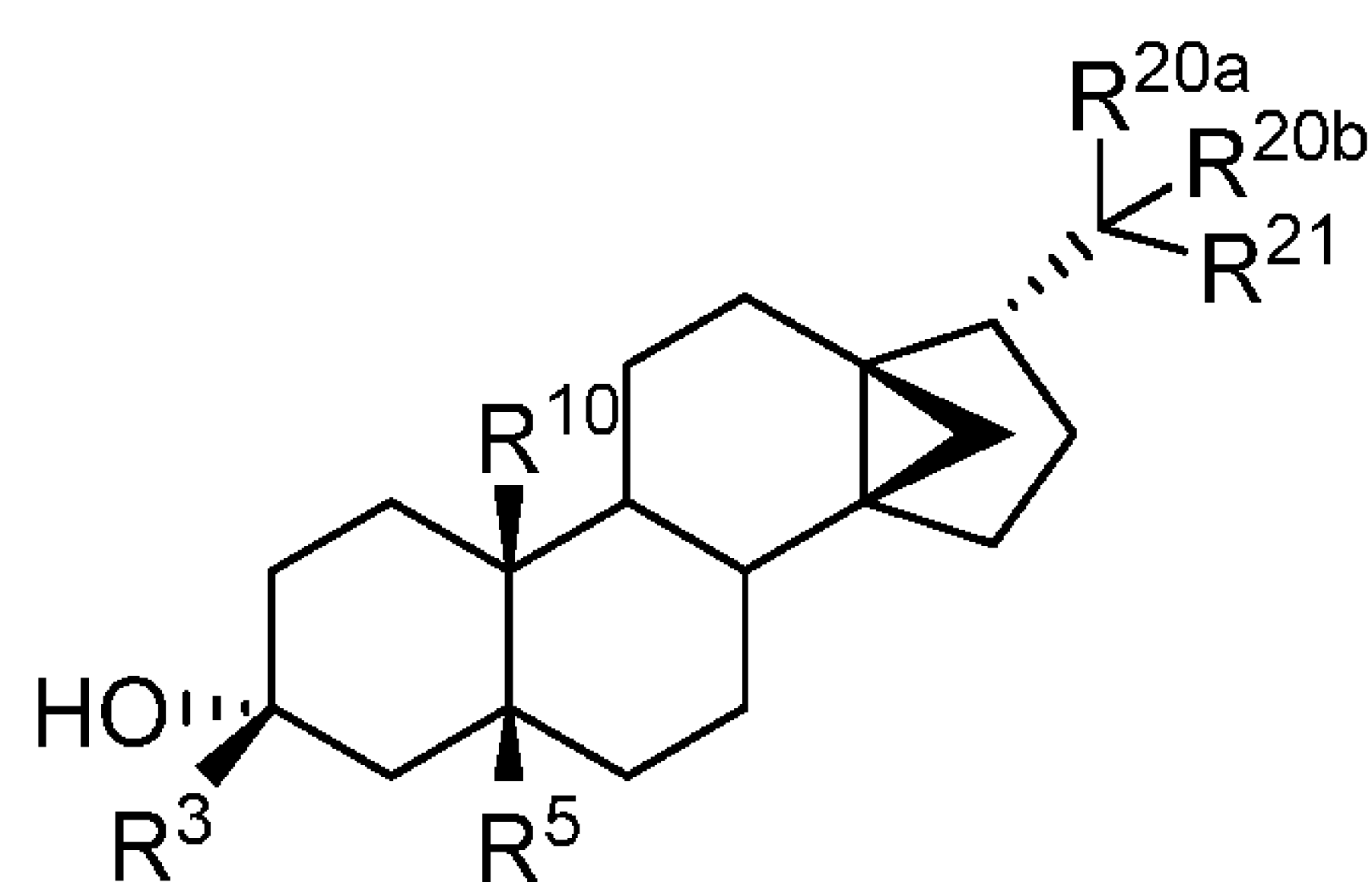
[0107] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0108] Another aspect of the present invention provides a compound of Formula (V-A1a) or (V-A1b)



(V-A1a)

or



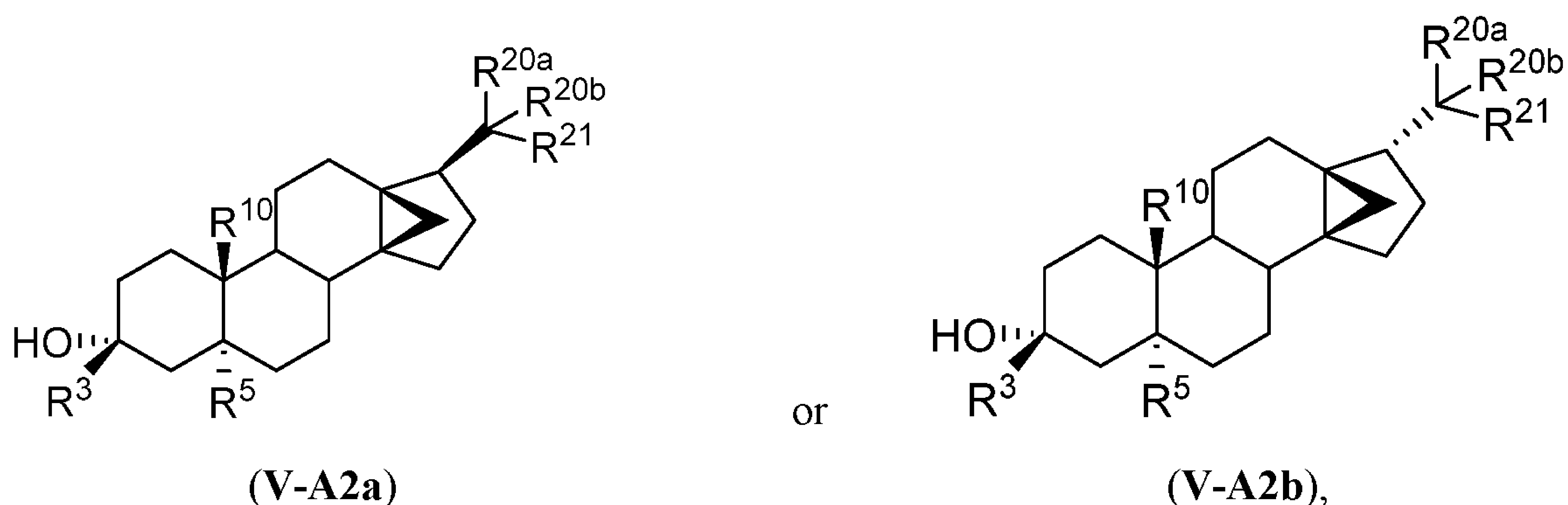
(V-A1b),

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} , are as defined in any of the embodiments of the compounds of Formula (I), (IV), (V), (V-A), or (V-A1).

[0109] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0110] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6- membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0111] Another aspect of the present invention provides a compound of Formula (V-A2a) or (V-A2b)

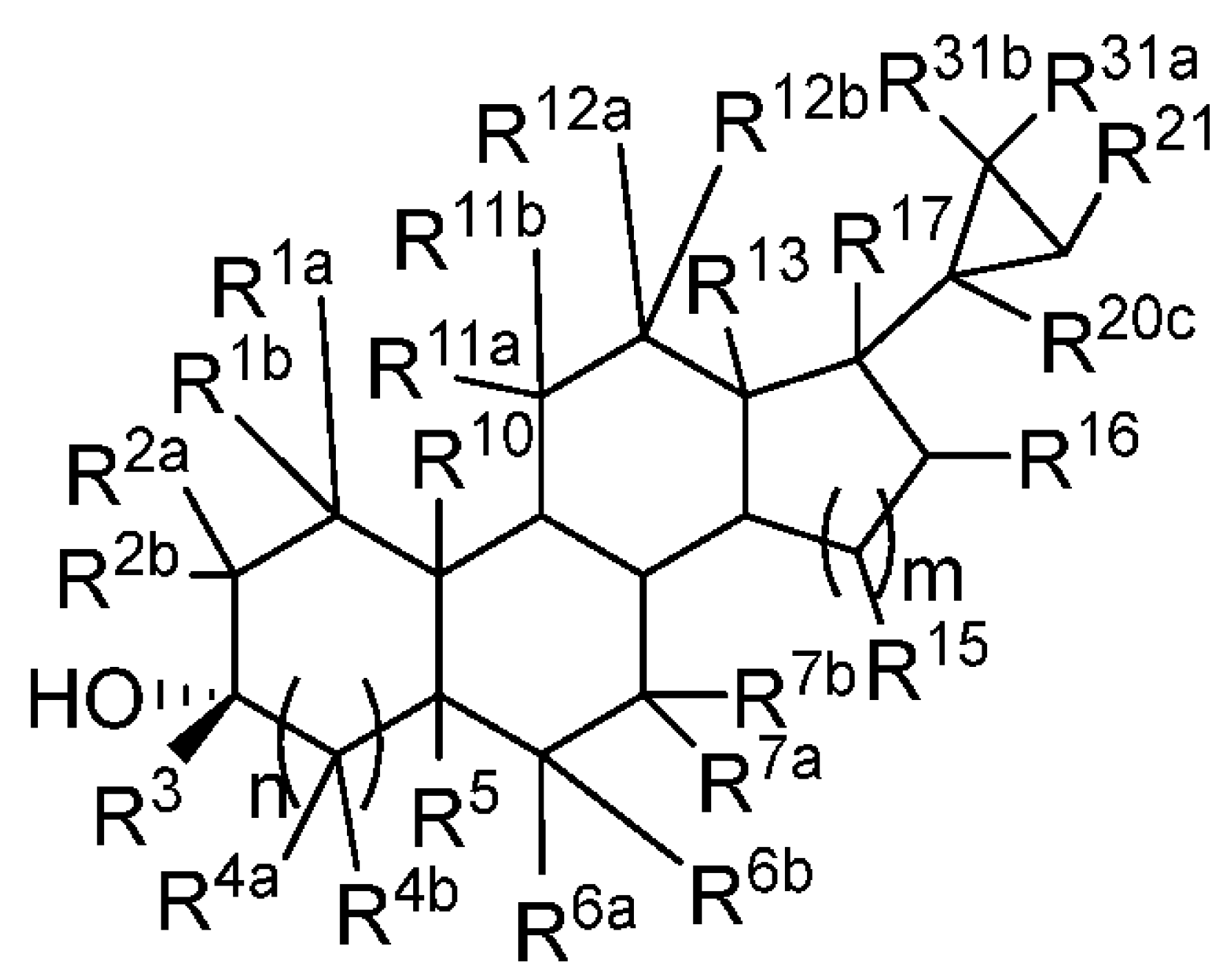


or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} , are as defined in any of the embodiments of the compounds of Formula (I), (IV), (V), (V-A), or (V-A2).

[0112] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0113] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0114] Another aspect of the present invention provides a compound of Formula (VI)



or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20c} , R^{21} , R^{31a} , R^{31b} , m , and n are as defined in any of the embodiments of the compounds of Formula (I).

[0115] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , and R^{21} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, or $-S(O)_2$ -; each R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$, or R^{1a} and R^{1b} taken together form oxo, or R^{2a} and R^{2b} taken together form oxo, or R^{4a} and R^{4b} taken together form oxo, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo; each of R^5 and R^{20c} is independently selected from $-H$ and methyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; each of R^{31a} and R^{31b} is (i) independently selected from $-H$, halo, and C_{1-6} alkyl, or (ii) when one of R^{31a} and R^{31b} is $-H$, the other of R^{31a} and R^{31b} is $-H$, halo, C_{1-6} alkyl, or $-OR^{32}$, wherein R^{32} is $-H$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S; n is 0, 1, or 2; and m is 1 or 2.

[0116] In some embodiments, each of R^{1a} and R^{1b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{1a} and R^{1b} taken together form

oxo. In some embodiments, each of R^{1a} and R^{1b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{1a} and R^{1b} taken together form oxo. In some embodiments, one of R^{1a} and R^{1b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, one of R^{1a} and R^{1b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, one of R^{1a} and R^{1b} is $-H$, and the other is methyl. And, in some embodiments, each of R^{1a} and R^{1b} is $-H$.

[0117] In some embodiments, each of R^{2a} and R^{2b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{2a} and R^{2b} taken together form oxo. In some embodiments, each of R^{2a} and R^{2b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{2a} and R^{2b} taken together form oxo. In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is methyl. And, in some embodiments, each of R^{2a} and R^{2b} is $-H$.

[0118] In some embodiments, R^3 is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^3 is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^3 is $-H$, $-CH_3$, $-CH_2-CH_2-CH_3$, or $-CH_2-O-CH_3$. In some embodiments, R^3 is $-H$ or methyl.

[0119] In some embodiments, n is 0 and both of R^{4a} and R^{4b} are absent. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is methyl. And, in some embodiments, n is 1 and each of R^{4a} and R^{4b} is $-H$.

[0120] In some embodiments, R^5 is $-H$ or methyl. In some embodiments, R^5 is $-H$.

[0121] In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo. In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted

with R'. In some embodiments, two of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are –H, and the other two of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are independently selected from –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, and –O-R'. In some embodiments, three of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are –H, and the other of R^{6a}, R^{6b}, R^{7a}, and R^{7b} is –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, or –O-R'. In some embodiments, three of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are –H, and the other is –H or methyl. And, in some embodiments, each of R^{6a}, R^{6b}, R^{7a}, and R^{7b} is –H.

[0122] In some embodiments, R¹⁰ is –H, C₁₋₆ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl. In some embodiments, R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl. In some embodiments, R¹⁰ is –H, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl. And, in some embodiments, R¹⁰ is –H, methyl, or methoxymethyl.

[0123] In some embodiments, each of R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, and –O-R', or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo. In some embodiments, each of R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from –H and C₁₋₆ alkyl optionally substituted with R'. In some embodiments, two of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are –H, and the other two of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are independently selected from –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, and –O-R'. In some embodiments, two of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are –H, and the other two of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are independently selected from –H and methyl. In some embodiments, three of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are –H, and the other of R^{11a}, R^{11b}, R^{12a}, and R^{12b} is –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, or –O-R'. In some embodiments, three of R^{11a}, R^{11b}, R^{12a}, and R^{12b} are –H, and the other is –H or methyl. And, in some embodiments, each of R^{11a}, R^{11b}, R^{12a}, and R^{12b} is –H.

[0124] In some embodiments, R¹³ is –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, or –O-R'. In some embodiments, R¹³ is –H or C₁₋₆ alkyl optionally substituted with R'. In some embodiments, R¹³ is –H or C₁₋₃ alkyl (e.g., methyl or ethyl). In some embodiments, R¹³ is –H. And, in some embodiments, R¹³ is –CH₃ (methyl). In some embodiments, R¹³ is –H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl. In some embodiments, R¹³ is –H, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl. In some embodiments, R¹³ is –H or C₁₋₃ alkyl. In some embodiments, R¹³ is –H, methyl, or methoxymethyl. And, in some embodiments, R¹³ is methyl.

[0125] In some embodiments, m is 1 and R¹⁵ is –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, or –O-R'. In some embodiments, m is 1 and R¹⁵ is –H or C₁₋₆ alkyl optionally

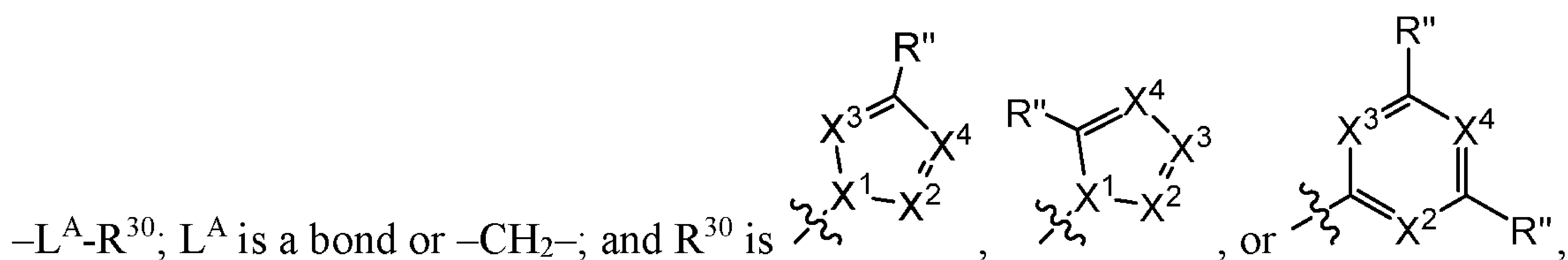
substituted with R'. In some embodiments, m is 1 and R¹⁵ is -H or C₁₋₃ alkyl (e.g., methyl or ethyl). And, in some embodiments, R¹⁵ is -H.

[0126] In some embodiments, R¹⁶ is -H, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, or -O-R'. In some embodiments, R¹⁶ is -H or C₁₋₆ alkyl optionally substituted with R'. In some embodiments, R¹⁶ is -H or C₁₋₃ alkyl (e.g., methyl or ethyl). And, in some embodiments, R¹⁶ is -H.

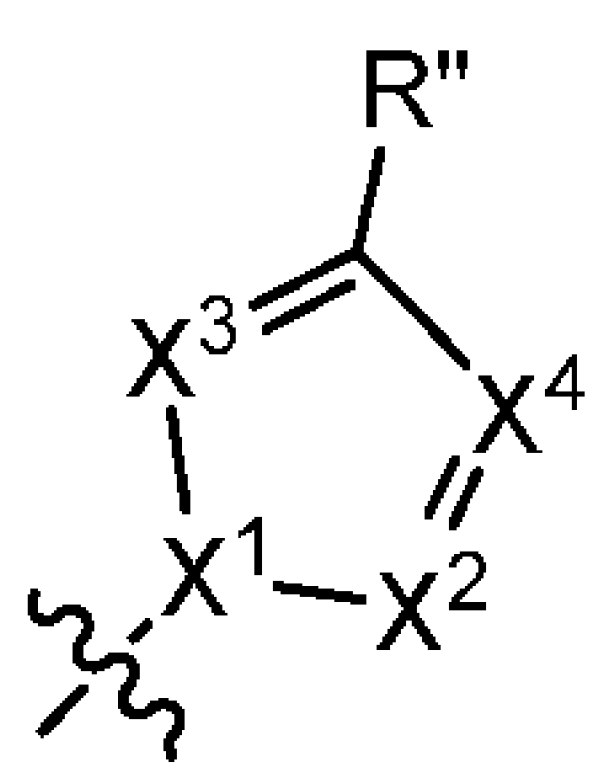
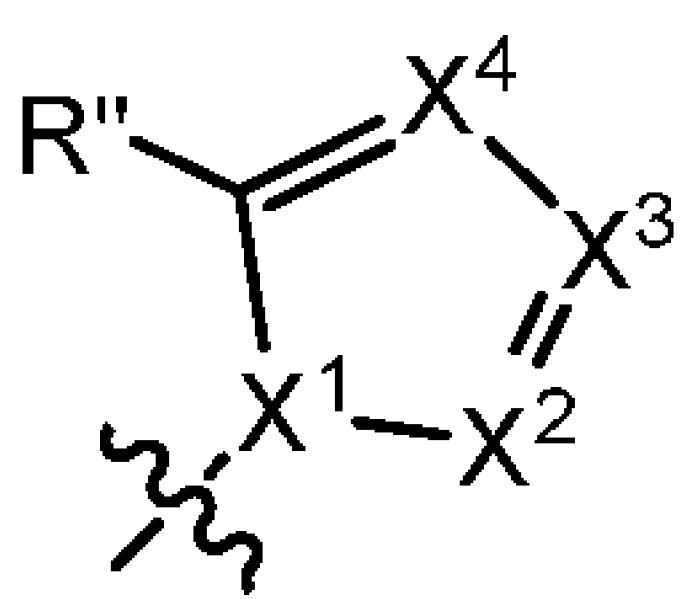
[0127] In some embodiments, R¹⁷ is -H, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, or -O-R'. In some embodiments, R¹⁷ is -H or C₁₋₆ alkyl optionally substituted with R'. In some embodiments, R¹⁷ is -H or C₁₋₃ alkyl (e.g., methyl or ethyl). And, in some embodiments, R¹⁷ is -H.

[0128] In some embodiments, R^{20c} is -H.

[0129] In some embodiments, R²¹ is -L^A-R³⁰; L^A is a bond, -CH₂-, -CH₂-CH₂-CH₂-, or -CH₂-CH₂-; and R³⁰ is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8-membered ring is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃. In some embodiments, R²¹ is -L^A-R³⁰; L^A is a bond or -CH₂-; and R³⁰ is a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃. In some embodiments, R²¹ is -L^A-R³⁰; L^A is a bond or -CH₂-; and R³⁰ is a 5-6-membered partially unsaturated or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-2 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃. In some embodiments, R²¹ is

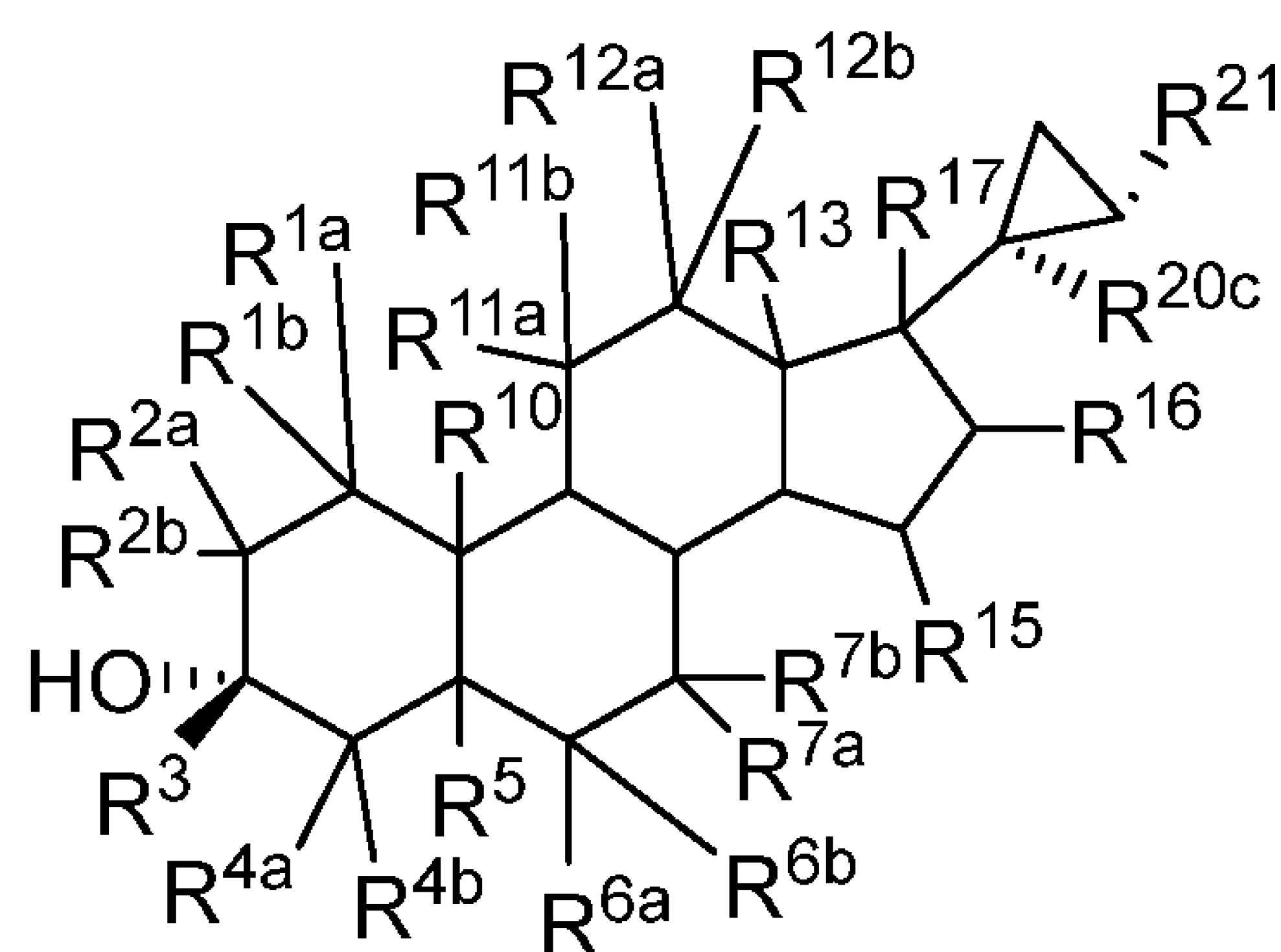


wherein each of X¹, X², X³, and X⁴ is independently N or CR'', wherein each R'' is independently selected from -H, halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃, provided that (i) at least one of X¹, X², X³, and X⁴ is N, and (ii) no greater than 2 instances of R'' are independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, and

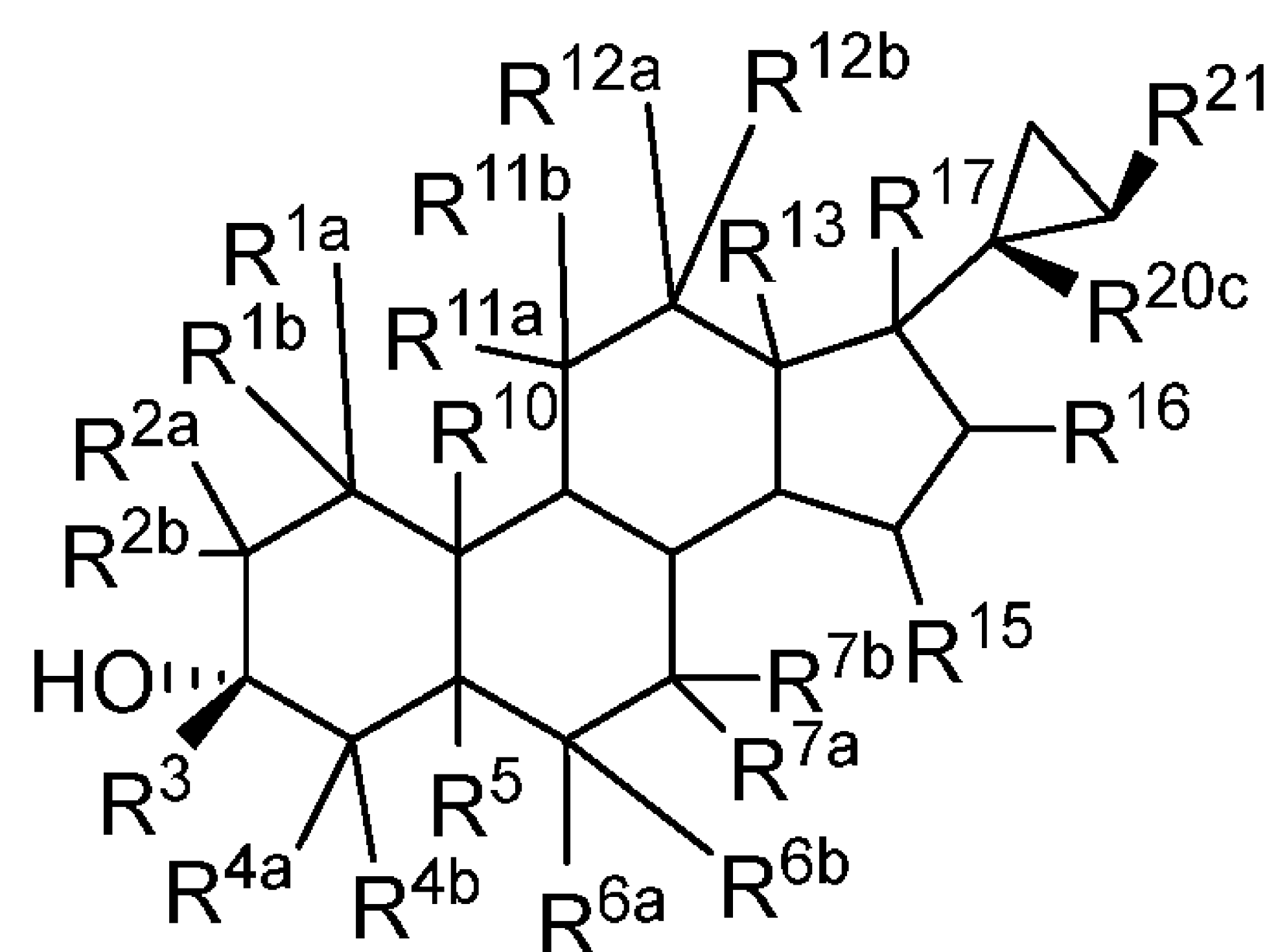
–CH₂OH. In some embodiments, R³⁰ is  or , X¹ is N; and each of X², X³, and X⁴ is independently selected from N or CR'', wherein each R'' is independently selected from –H, –OH, –CN, –NO₂, –CF₃, –CH₃, and –CH₂OH, provided no greater than 2 instances of R'' are independently selected from halo, –OH, –CN, –NO₂, –CF₃, –CH₃, and –CH₂OH.

[0130] In some embodiments, each of R^{31a} and R^{31b} is independently selected from –H, halo, C₁₋₆ alkyl, or when one of R^{31a} and R^{31b} is –H, the other is –H, halo, C₁₋₆ alkyl, or –OR³², wherein R³² is –H, C₁₋₆ alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S. In some embodiments, one of R^{31a} and R^{31b} is –H, and the other is –H, halo, C₁₋₆ alkyl, or –OR³², wherein R³² is –H, C₁₋₆ alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S. In some embodiments, each of R^{31a} and R^{31b} is independently selected from –H, halo, and C₁₋₆ alkyl. In some embodiments, one of R^{31a} and R^{31b} is –H, and the other is –OH, –O-C₁₋₆ alkyl, –O-phenyl, or –O-C₃₋₆ cycloalkyl. In some embodiments, each of R^{31a} and R^{31b} is –H.

[0131] Another aspect of the present invention provides a compound of Formula (VI-A) or (VI-B)



(VI-A)

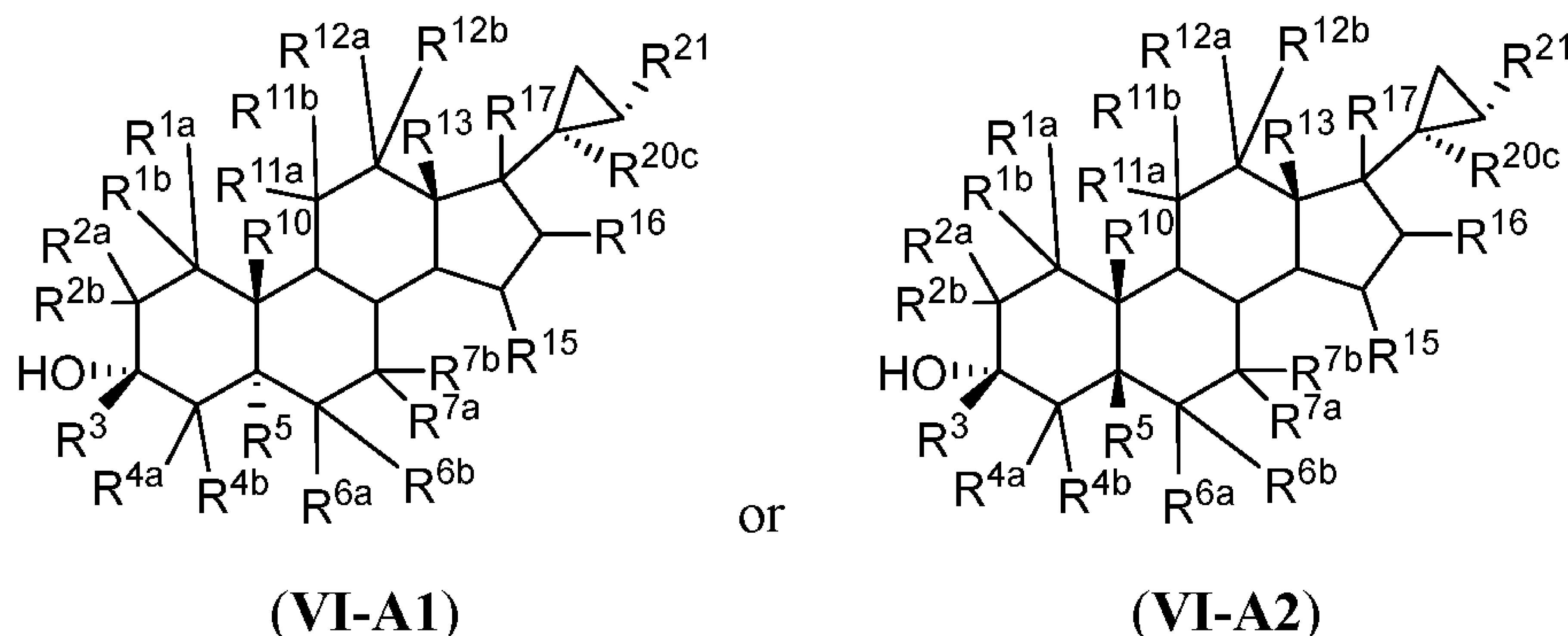


(VI-B)

or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R^{4a}, R^{4b}, R⁵, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R¹⁰, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R¹⁵, R¹⁶, R¹⁷, R^{20c}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I) or (VI).

[0132] In some embodiments, each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R¹⁵, R¹⁶, and R¹⁷ is independently selected from -H and C₁₋₆ alkyl; R³ is -H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; each of R⁵ and R^{20c} is independently selected from -H and methyl; R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; R²¹ is -L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by -NR'-, -S-, -O-, -OC(O)-, -C(O)O-, -C(O)-, -C(O)C(O)-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)O-, -S(O)₂NR'-, -NR'S(O)₂-, -C(O)NR'NR'-, -NR'C(O)NR'-, -OC(O)NR'-, -NR'NR'-, -NR'S(O)₂NR'-, -S(O)-, or -S(O)₂-; R³⁰ is R', halo, -CN, -NO₂, or -CF₃; and each R' is independently selected from -H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

[0133] Another aspect of the present invention provides a compound of Formula **(VI-A1)** or **(VI-A2)**

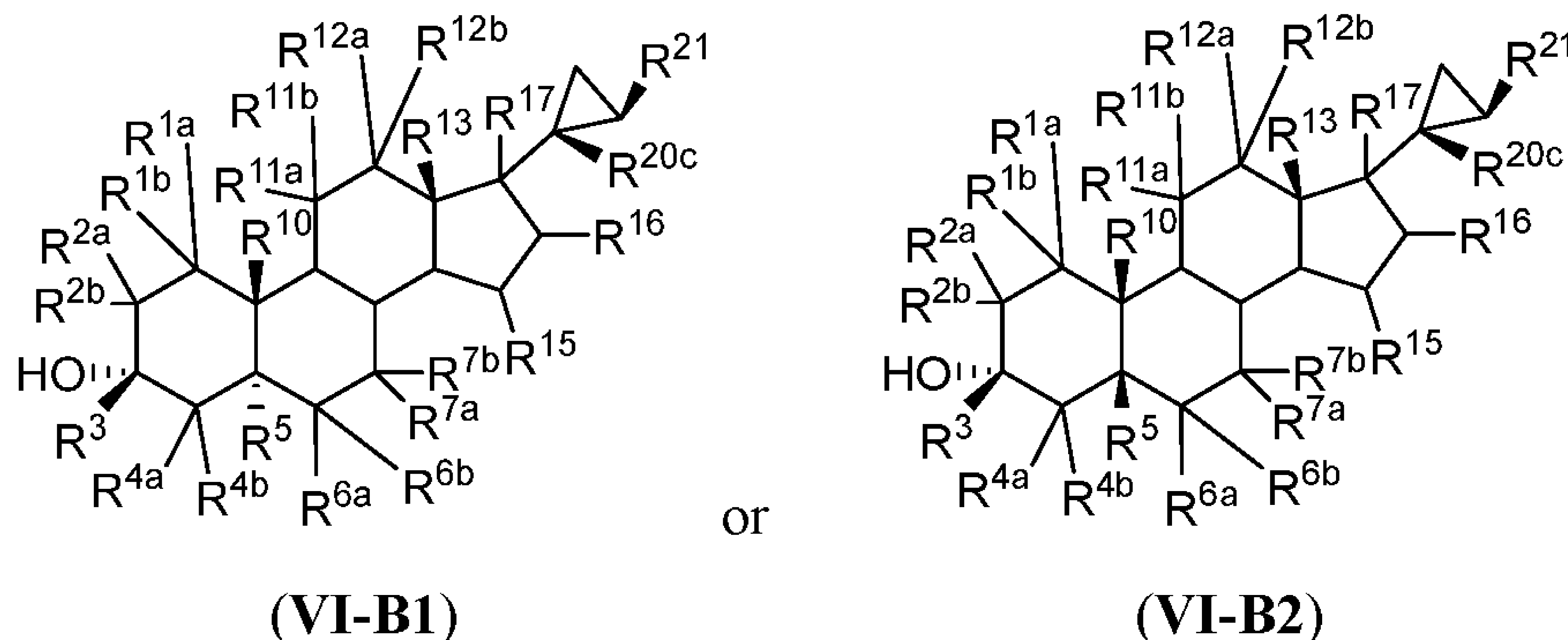


or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R^{4a}, R^{4b}, R⁵, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R¹⁰, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R¹⁵, R¹⁶, R¹⁷, R^{20c}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (VI), or (VI-A).

[0134] In some embodiments, each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R¹⁵, R¹⁶, and R¹⁷ is independently selected from -H and C₁₋₆ alkyl; R³ is -H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; each of R⁵ and R^{20c} is independently selected from -H and methyl; R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; R²¹ is -L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by -NR'-, -S-, -O-, -OC(O)-, -C(O)O-, -C(O)-, -C(O)C(O)-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)O-, -S(O)₂NR'-, -NR'S(O)₂-, -C(O)NR'NR'-, -NR'C(O)NR'-, -OC(O)NR'-,

–NR'NR'–, –NR'S(O)₂NR'–, –S(O)–, or –S(O)₂–; R³⁰ is R', halo, –CN, –NO₂, or –CF₃; and each R' is independently selected from –H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, and –CH₃.

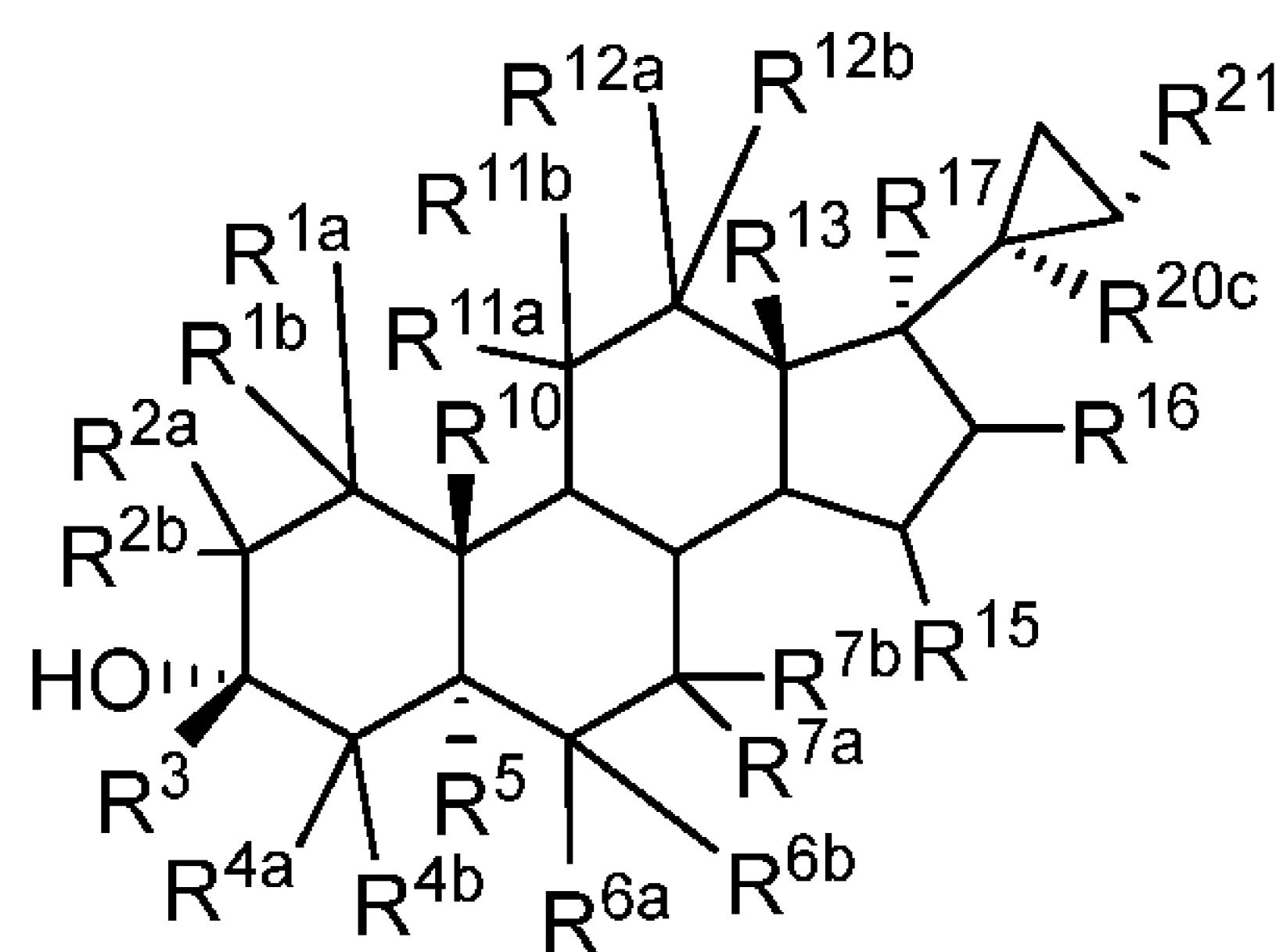
[0135] Another aspect of the present invention provides a compound of Formula **(VI-B1)** or **(VI-B2)**



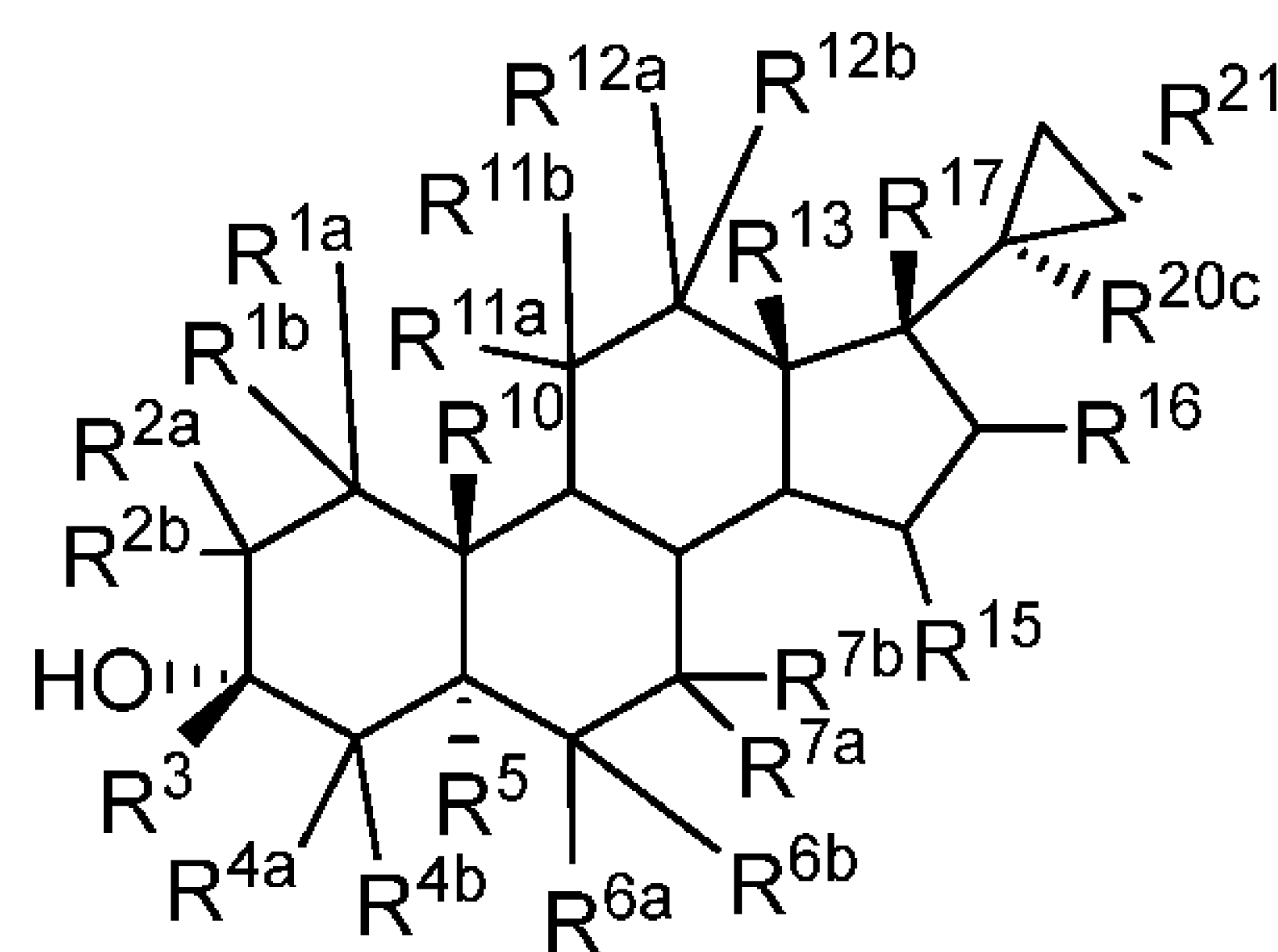
or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R^{4a}, R^{4b}, R⁵, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R¹⁰, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R¹⁵, R¹⁶, R¹⁷, R^{20c}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (VI), or (VI-B).

[0136] In some embodiments, each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R¹⁵, R¹⁶, and R¹⁷ is independently selected from -H and C₁₋₆ alkyl; R³ is -H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; each of R⁵ and R^{20c} is independently selected from -H and methyl; R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; R²¹ is -L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by -NR'-, -S-, -O-, -OC(O)-, -C(O)O-, -C(O)-, -C(O)C(O)-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)O-, -S(O)₂NR'-, -NR'S(O)₂-, -C(O)NR'NR'-, -NR'C(O)NR'-, -OC(O)NR'-, -NR'NR'-, -NR'S(O)₂NR'-, -S(O)-, or -S(O)₂-; R³⁰ is R', halo, -CN, -NO₂, or -CF₃; and each R' is independently selected from -H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

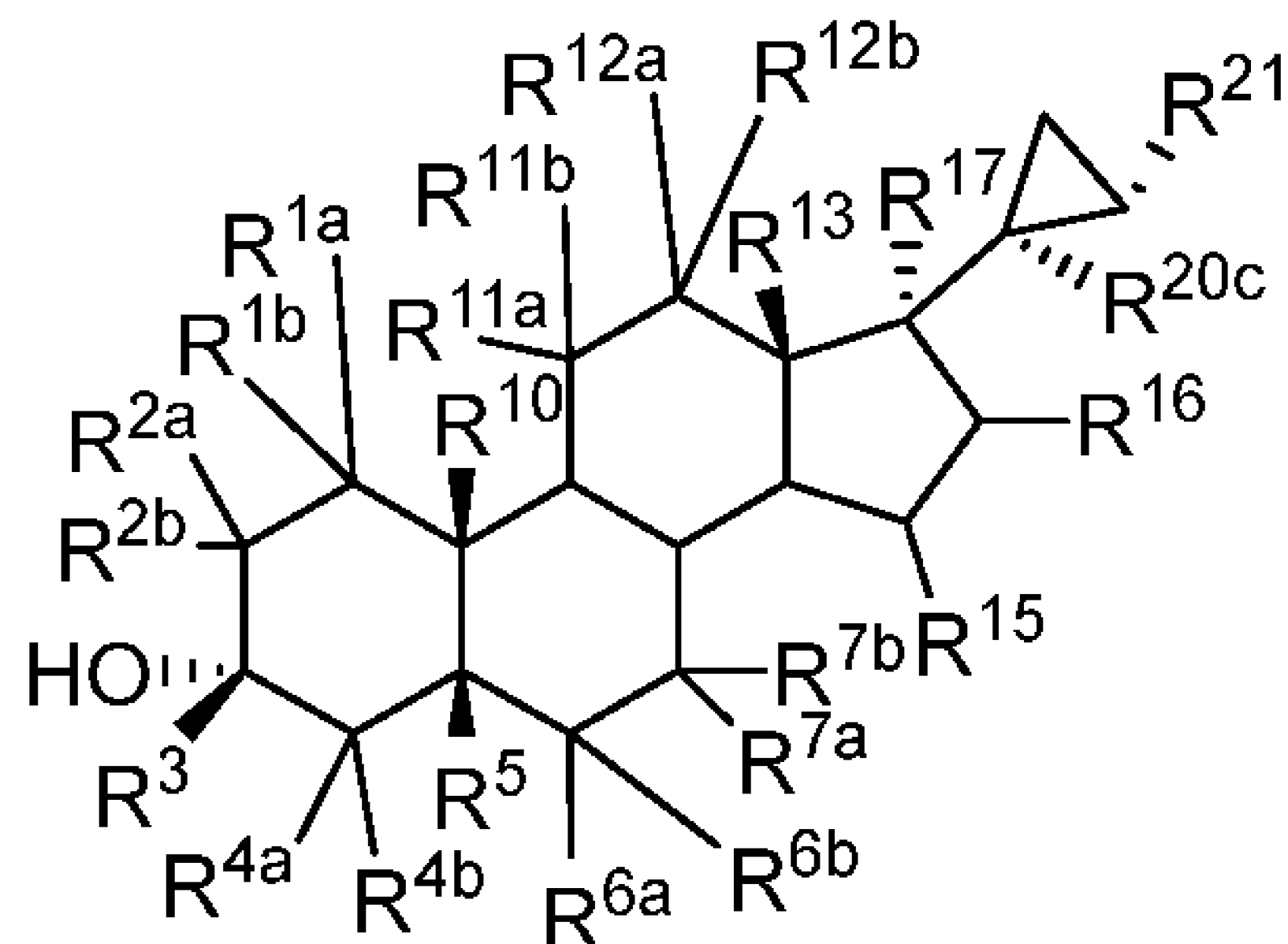
[0137] Another aspect of the present invention provides a compound of Formula (VI-A1a), (VI-A1b), (VI-A1c), or (VI-A1d)



(VI-A1a),

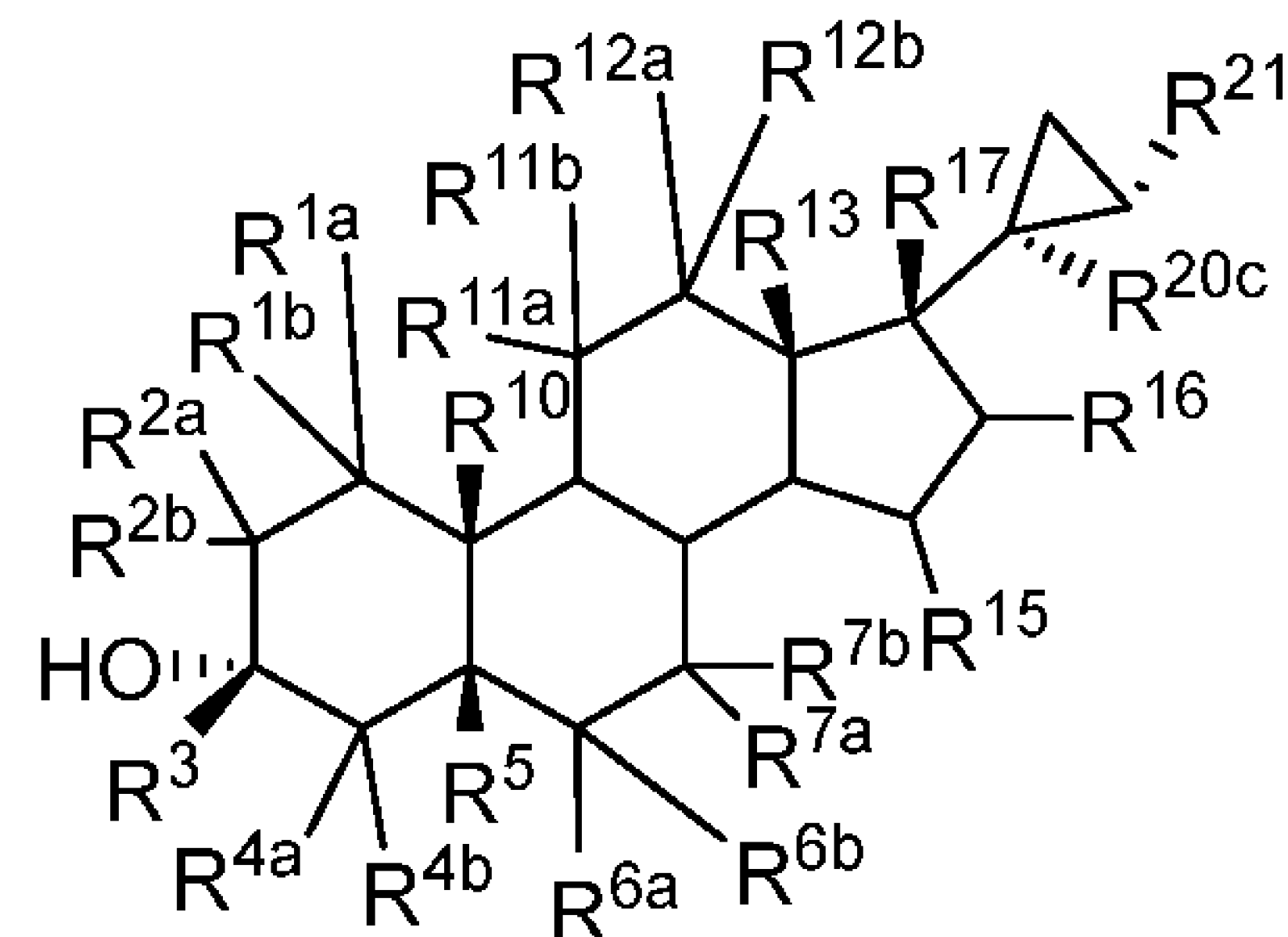


(VI-A1b),



(VI-A1c),

or

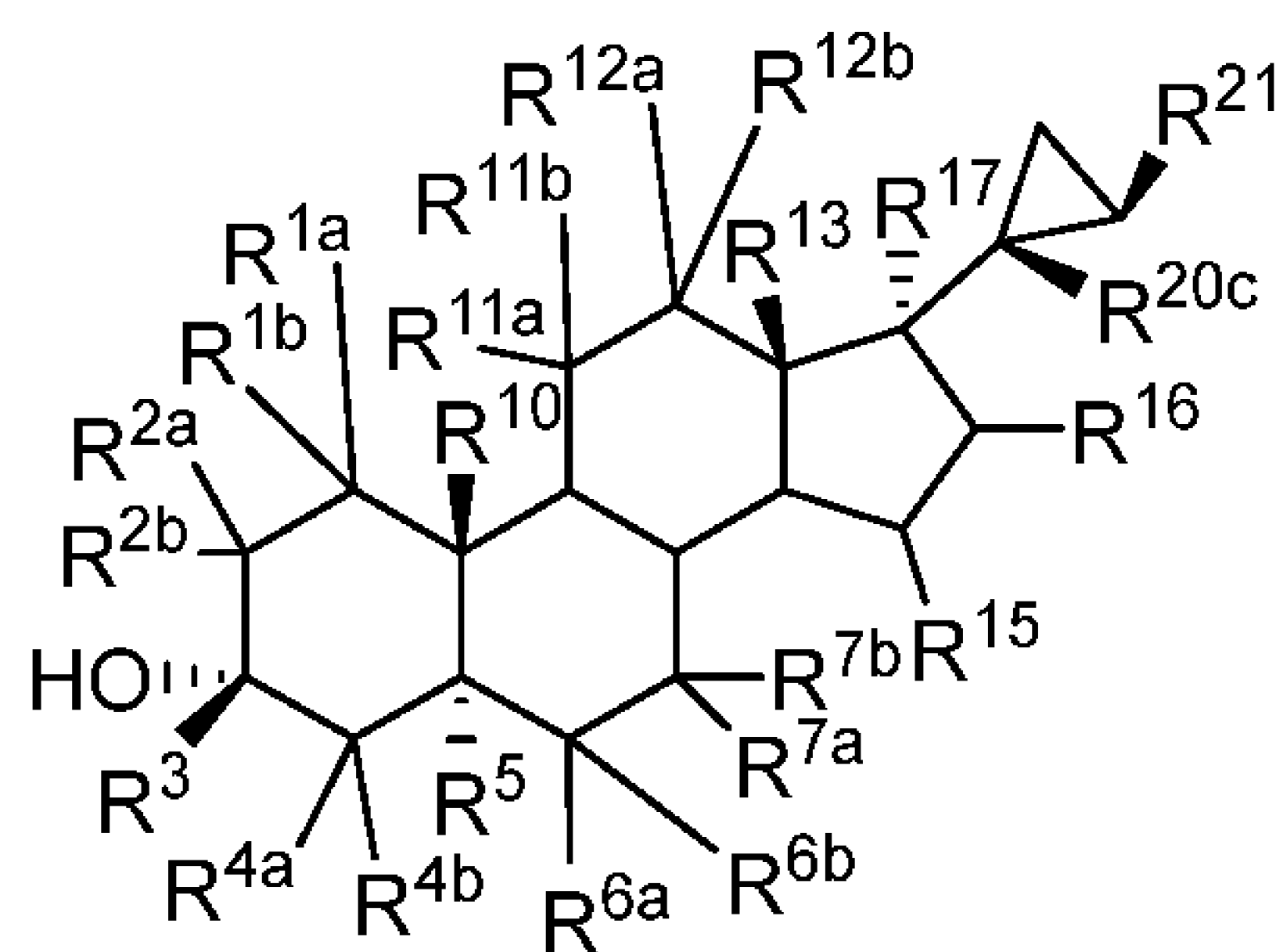


(VI-A1d),

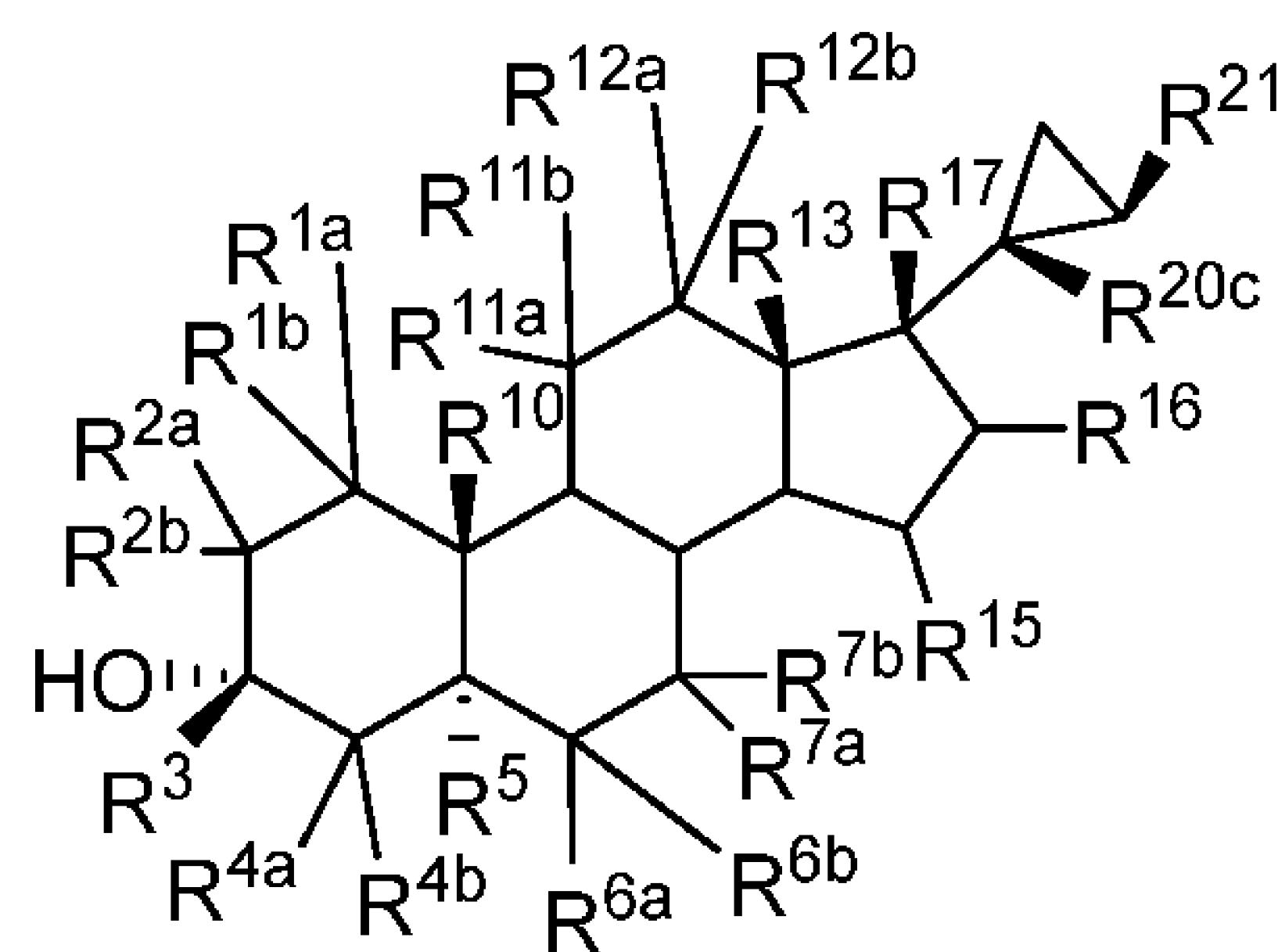
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20c} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VI-A), or (VI-A1), or (VI-A2).

[0138] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , and R^{17} is independently selected from $-H$ and C_{1-6} alkyl; R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^5 and R^{20c} is independently selected from $-H$ and methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

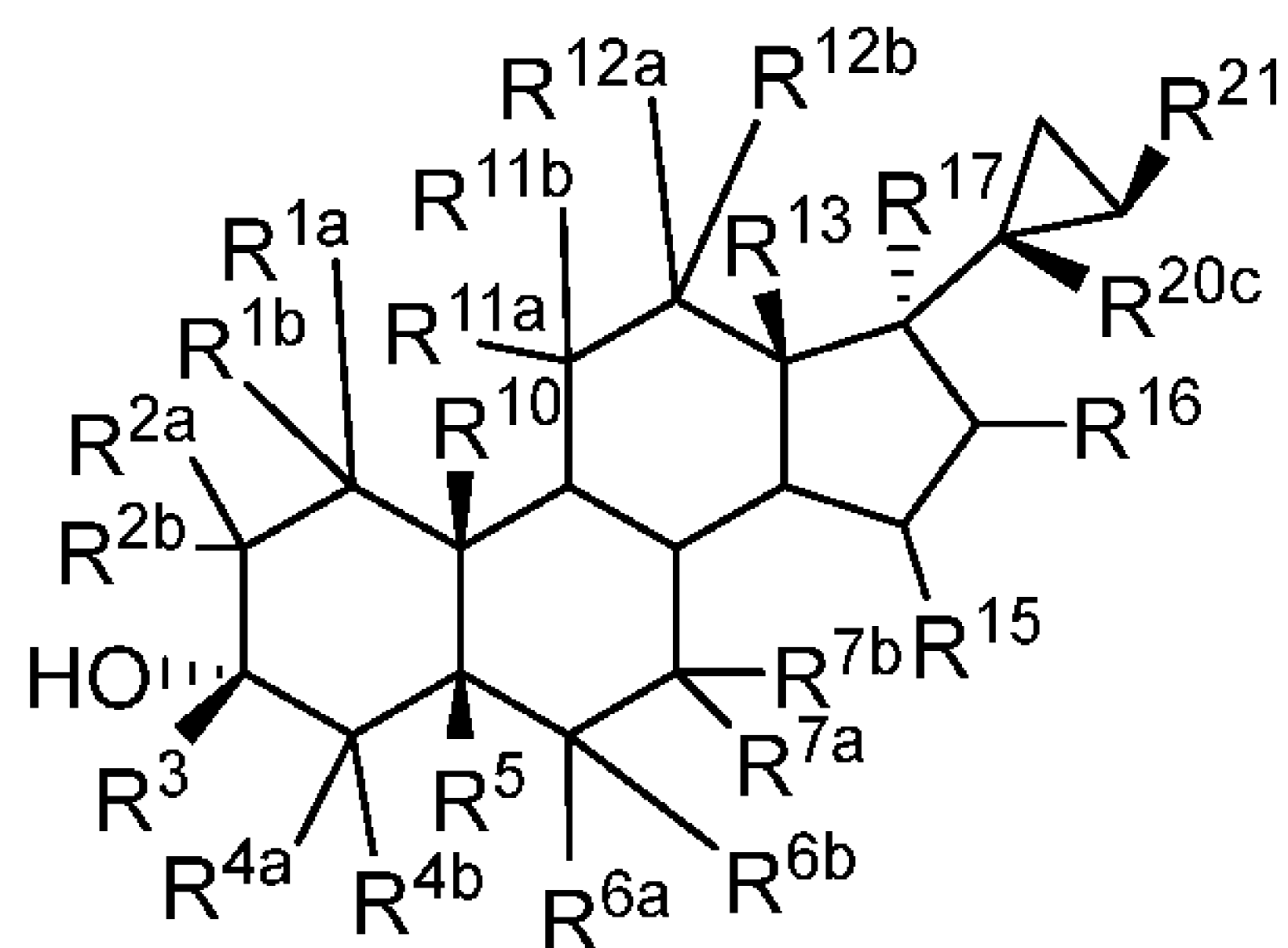
[0139] Another aspect of the present invention provides a compound of Formula (VI-B1a), (VI-B1b), (VI-B1c), or (VI-B1d)



(VI-B1a),

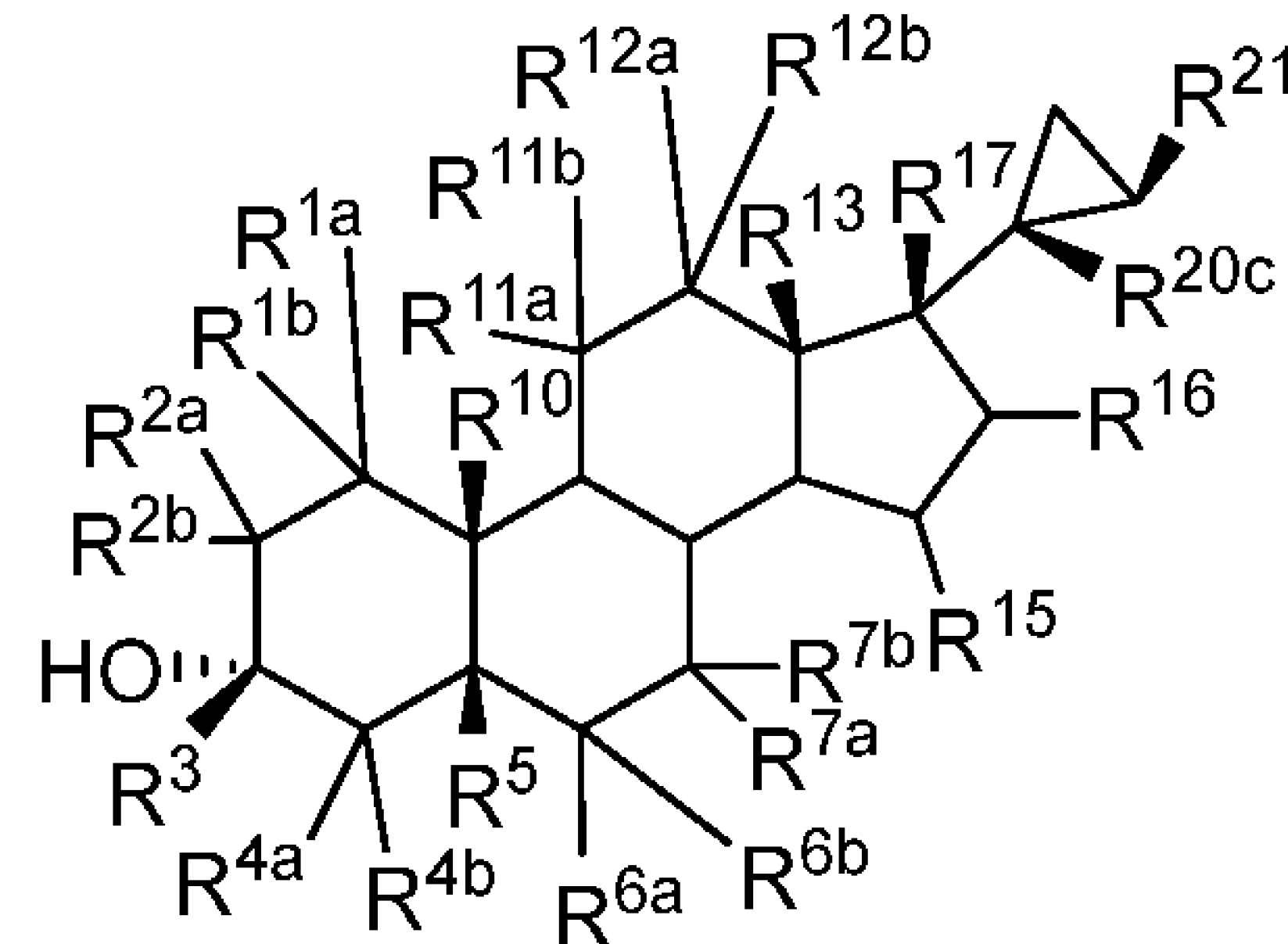


(VI-B1b),



(VI-B1c),

or

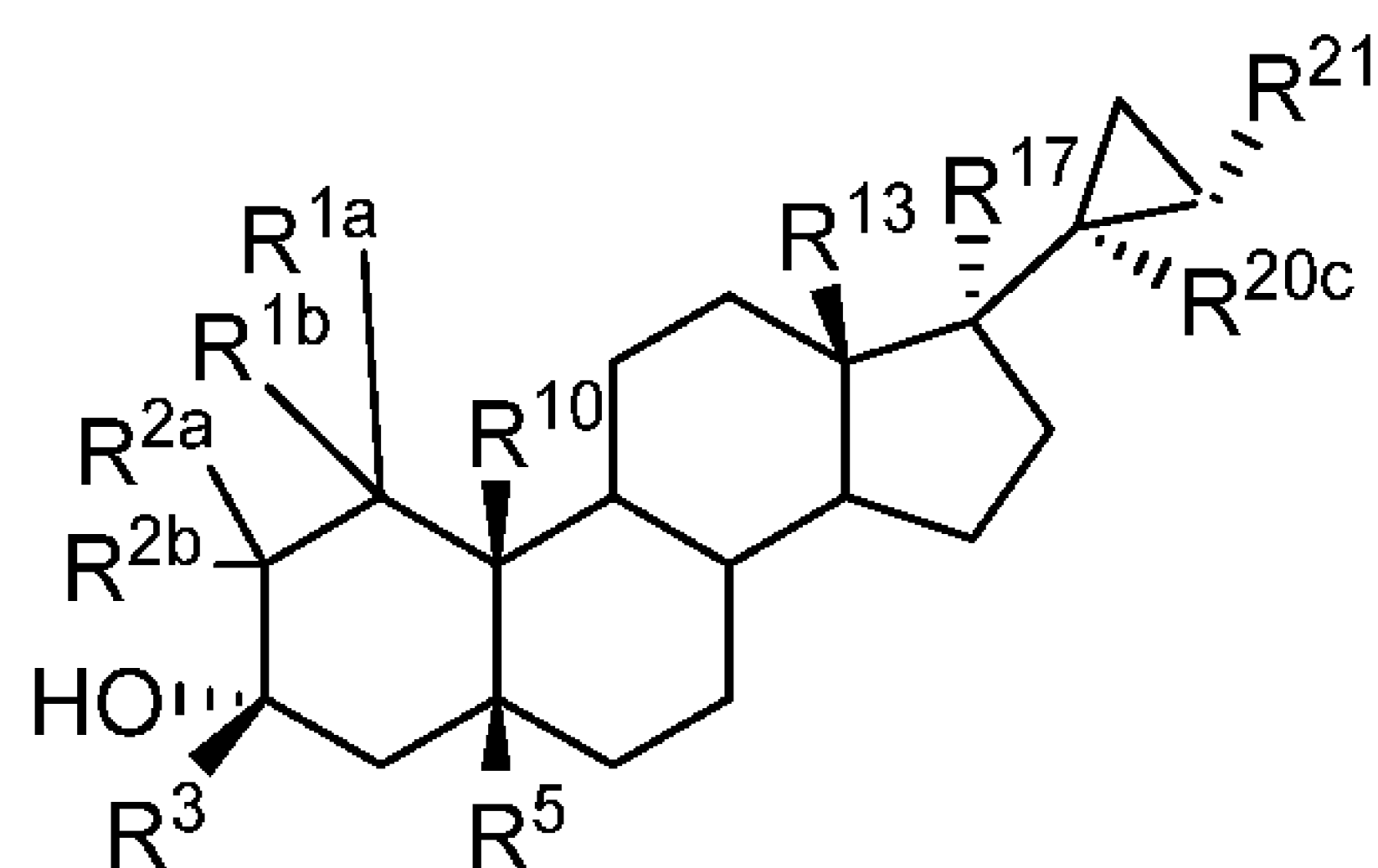


(VI-B1d),

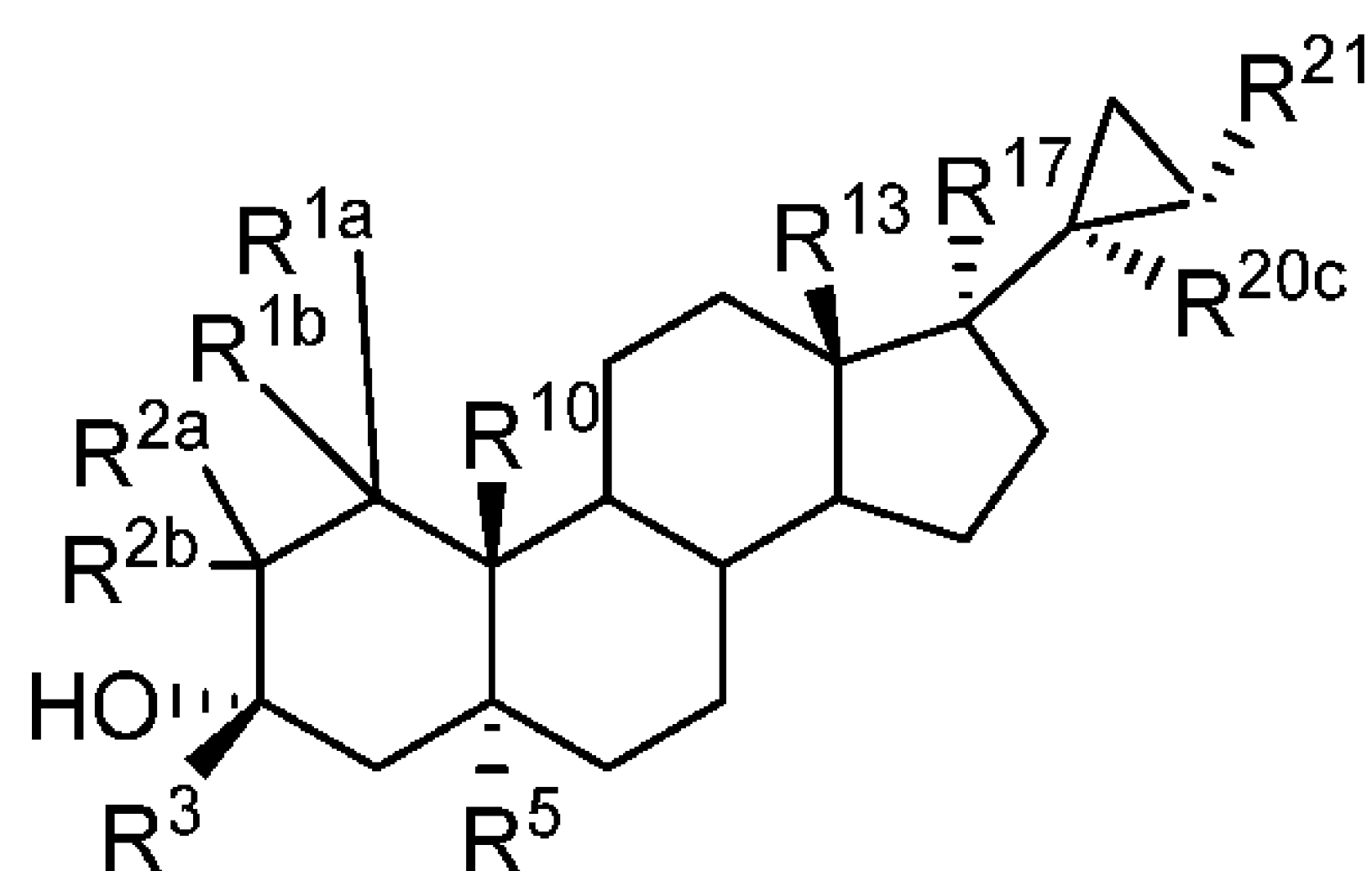
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20c} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VI-B), (VI-B1), or (VI-B2).

[0140] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , and R^{17} is independently selected from $-H$ and C_{1-6} alkyl; R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^5 and R^{20c} is independently selected from $-H$ and methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$, $-S$, $-O$, $-OC(O)$, $-C(O)O$, $-C(O)$, $-C(O)C(O)$, $-C(O)NR'$, $-NR'C(O)$, $-NR'C(O)O$, $-S(O)_2NR'$, $-NR'S(O)_2$, $-C(O)NR'NR'$, $-NR'C(O)NR'$, $-OC(O)NR'$, $-NR'NR'$, $-NR'S(O)_2NR'$, $-S(O)$, or $-S(O)_2$; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

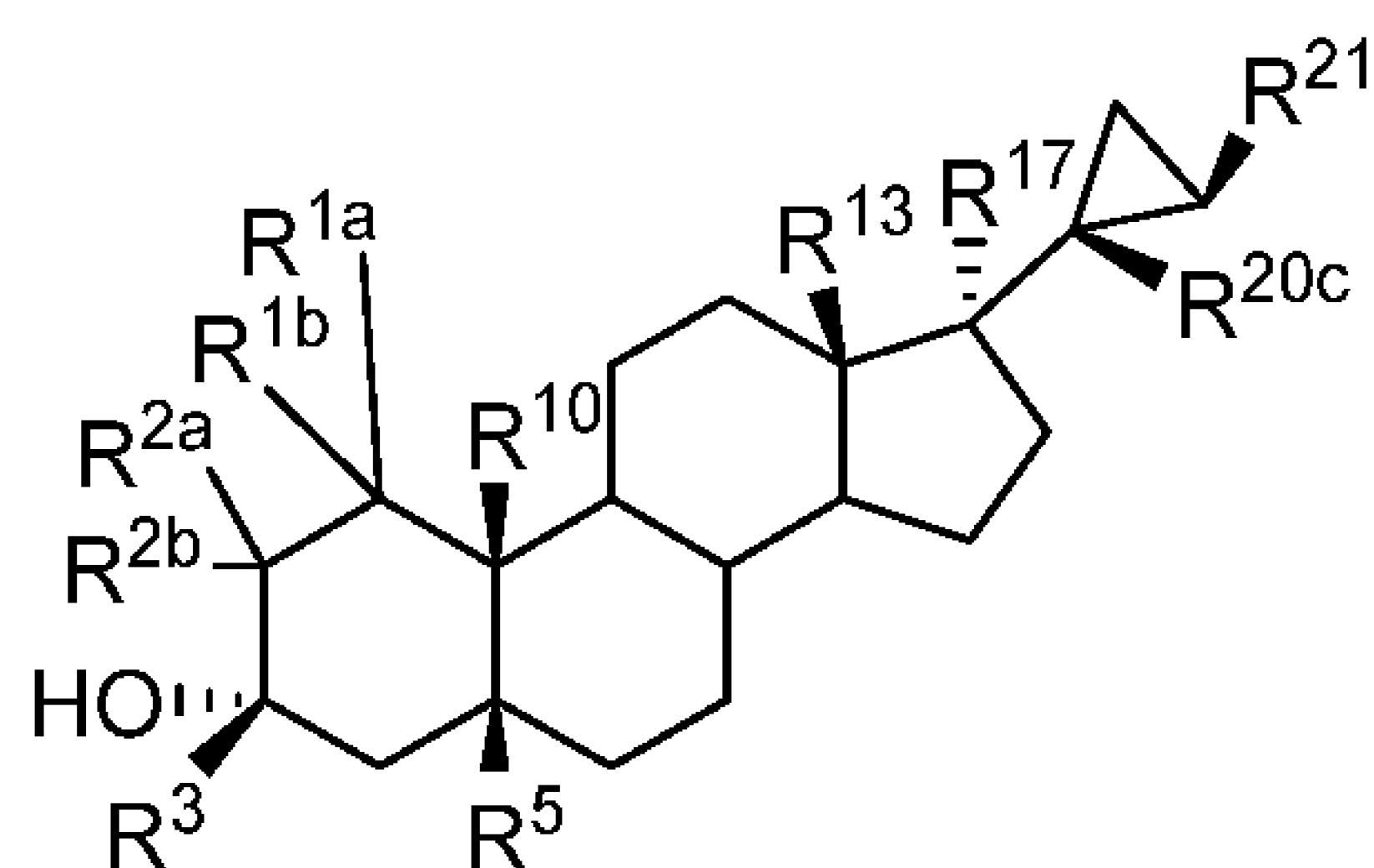
[0141] Another aspect of the present invention provides a compound of Formula (VI-A3a), (VI-A3b), (VI-B3a), or (VI-B3b)



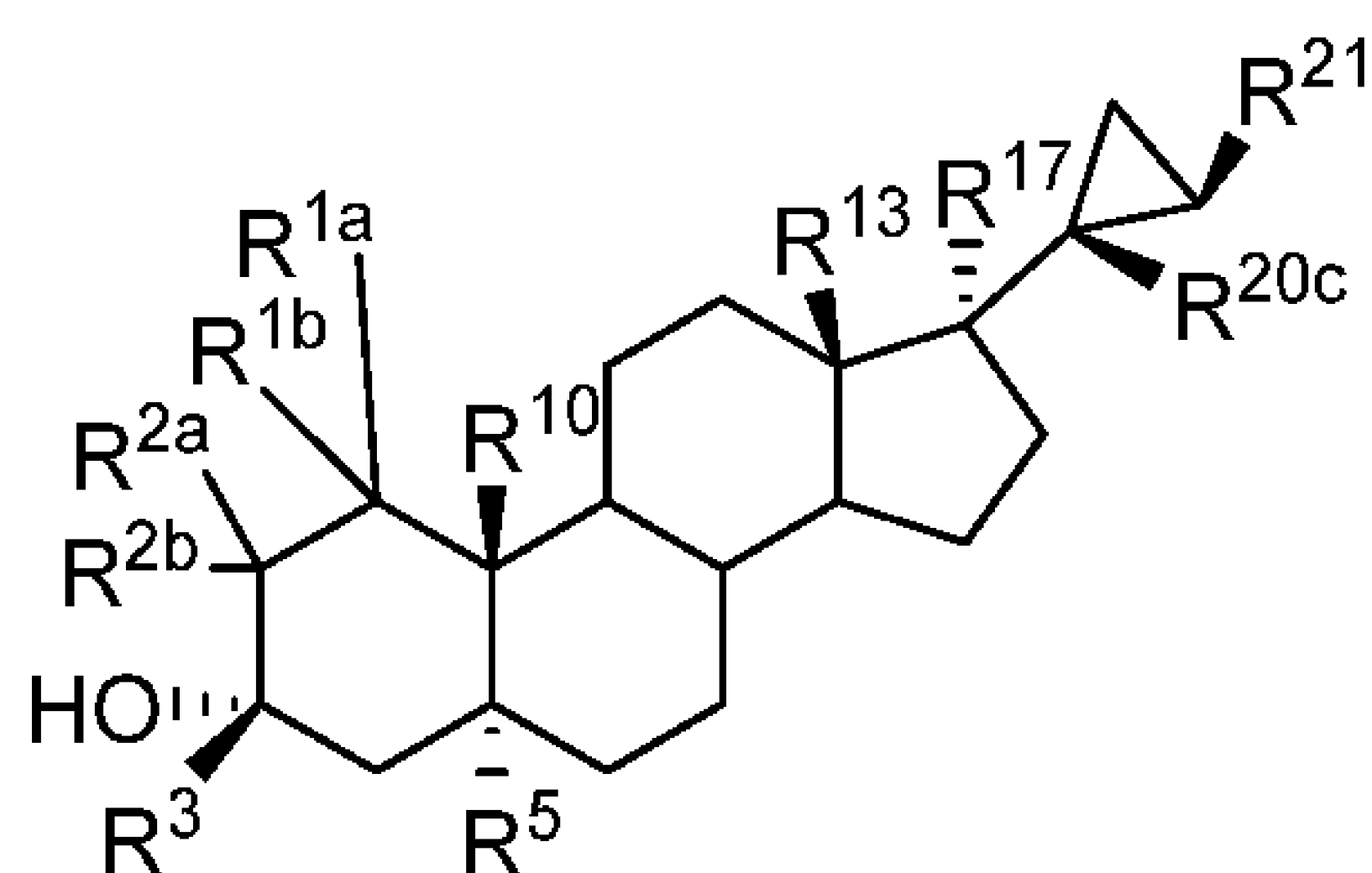
(VI-A3a),



(VI-A3b),



(VI-B3a),



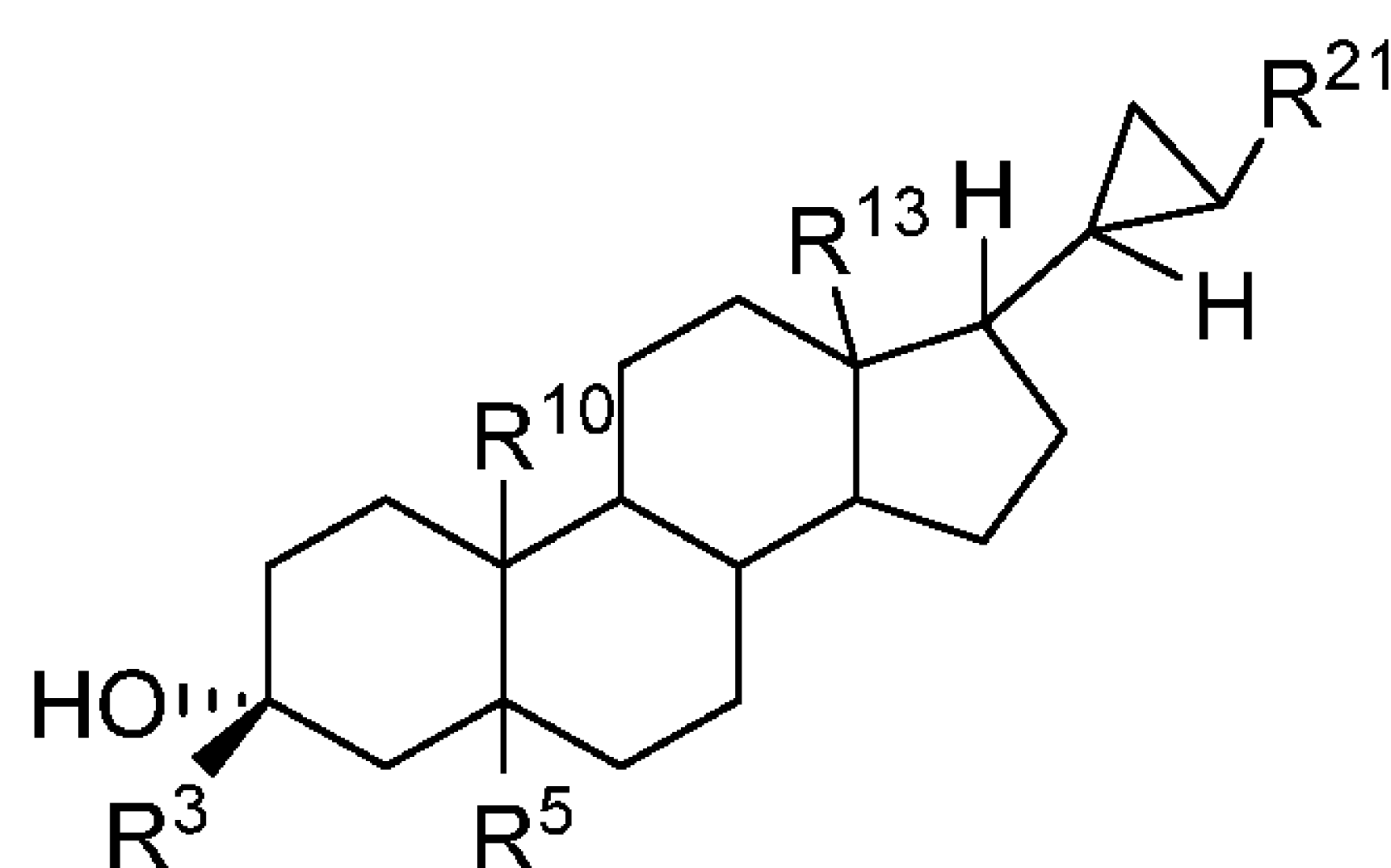
or

(VI-B3b),

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^5 , R^{10} , R^{13} , R^{17} , R^{20c} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), or (VI-B1d), as applicable.

[0142] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , and R^{2b} is independently selected from $-H$ and C_{1-3} alkyl; R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; each of R^5 , R^{13} , R^{17} , and R^{20c} is independently selected from $-H$ and methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or a straight C_{1-3} alkylene chain; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0143] Another aspect of the present invention provides a compound of Formula (VII)



(VII)

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I) or (VI).

[0144] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0145] In some embodiments, R^3 is C_{1-6} alkyl or C_{1-6} alkyl- O - C_{1-6} alkyl. In some embodiments, R^3 is methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, neopentyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^3 is $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, or $-CH_2-O-CH_3$. And, in some embodiments, R^3 is $-CH_3$.

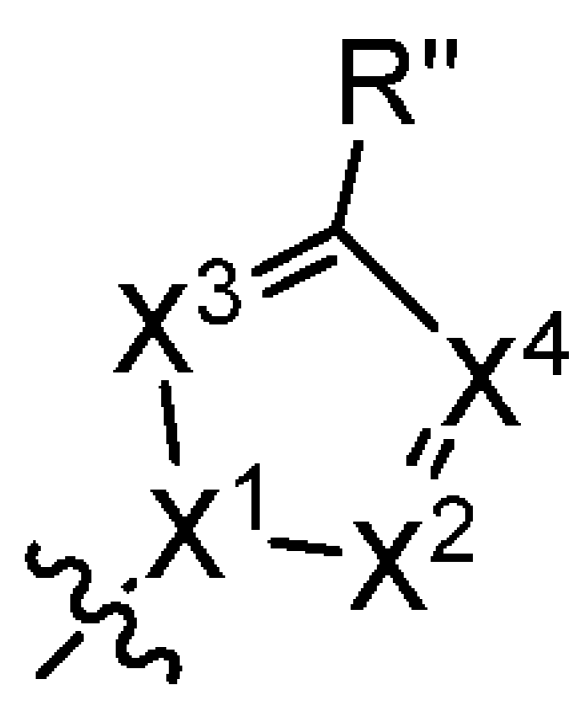
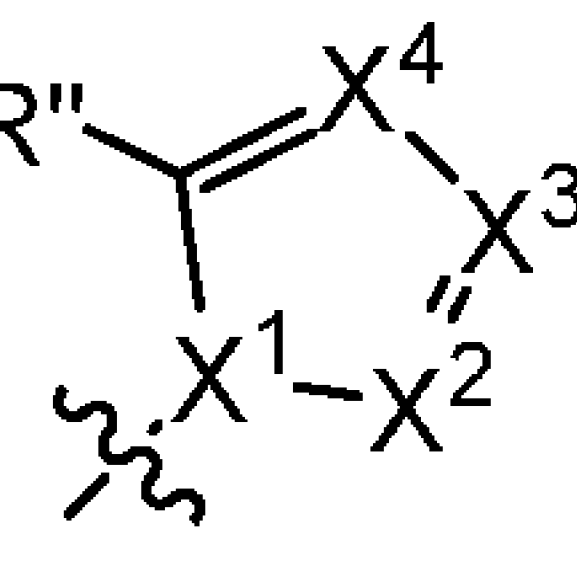
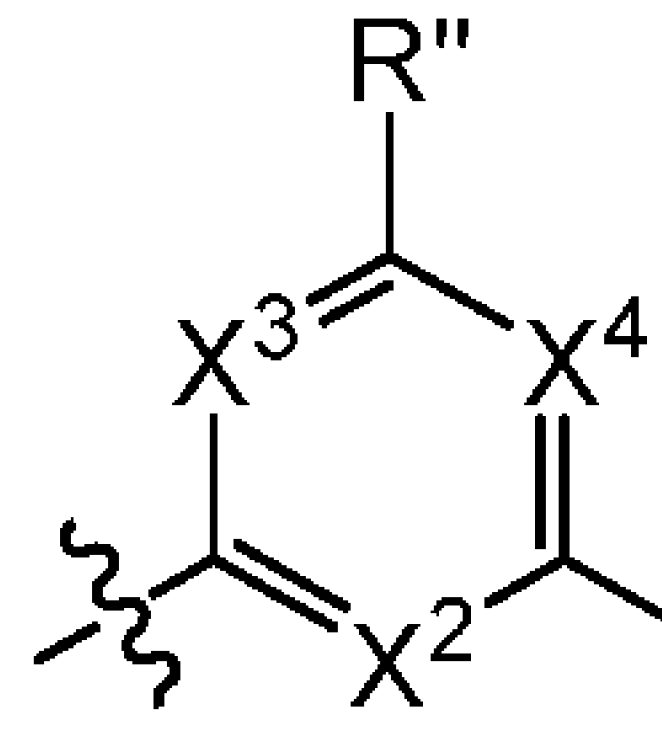
[0146] In some embodiments, R^5 is $-H$ or C_{1-3} alkyl. In some embodiments, R^5 is $-H$ or methyl.

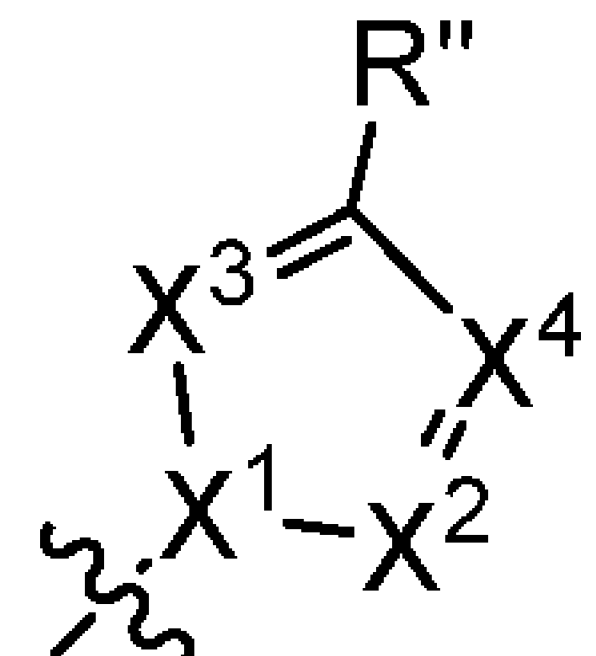
[0147] In some embodiments, R^{10} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^{10} is $-H$ or methyl.

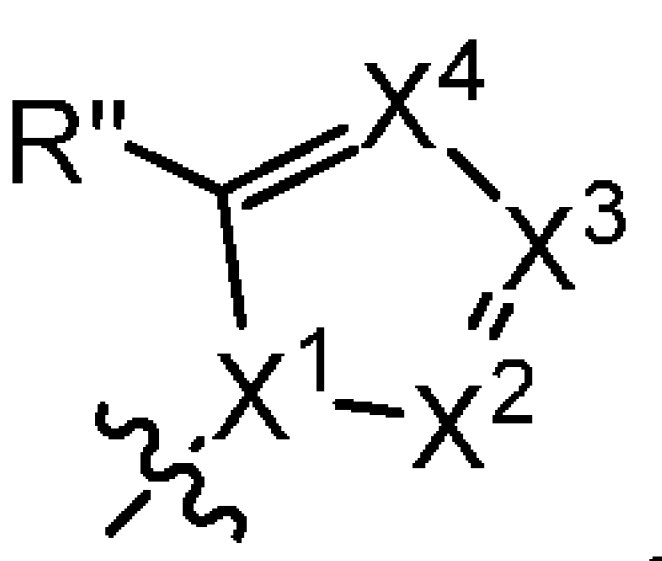
[0148] In some embodiments, R^{13} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{13} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{13} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^{13} is $-H$ or methyl. And, in some embodiments, R^{13} is methyl.

[0149] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-3} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, or $-N(H)-$; and R^{30} is $-H$ or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond,

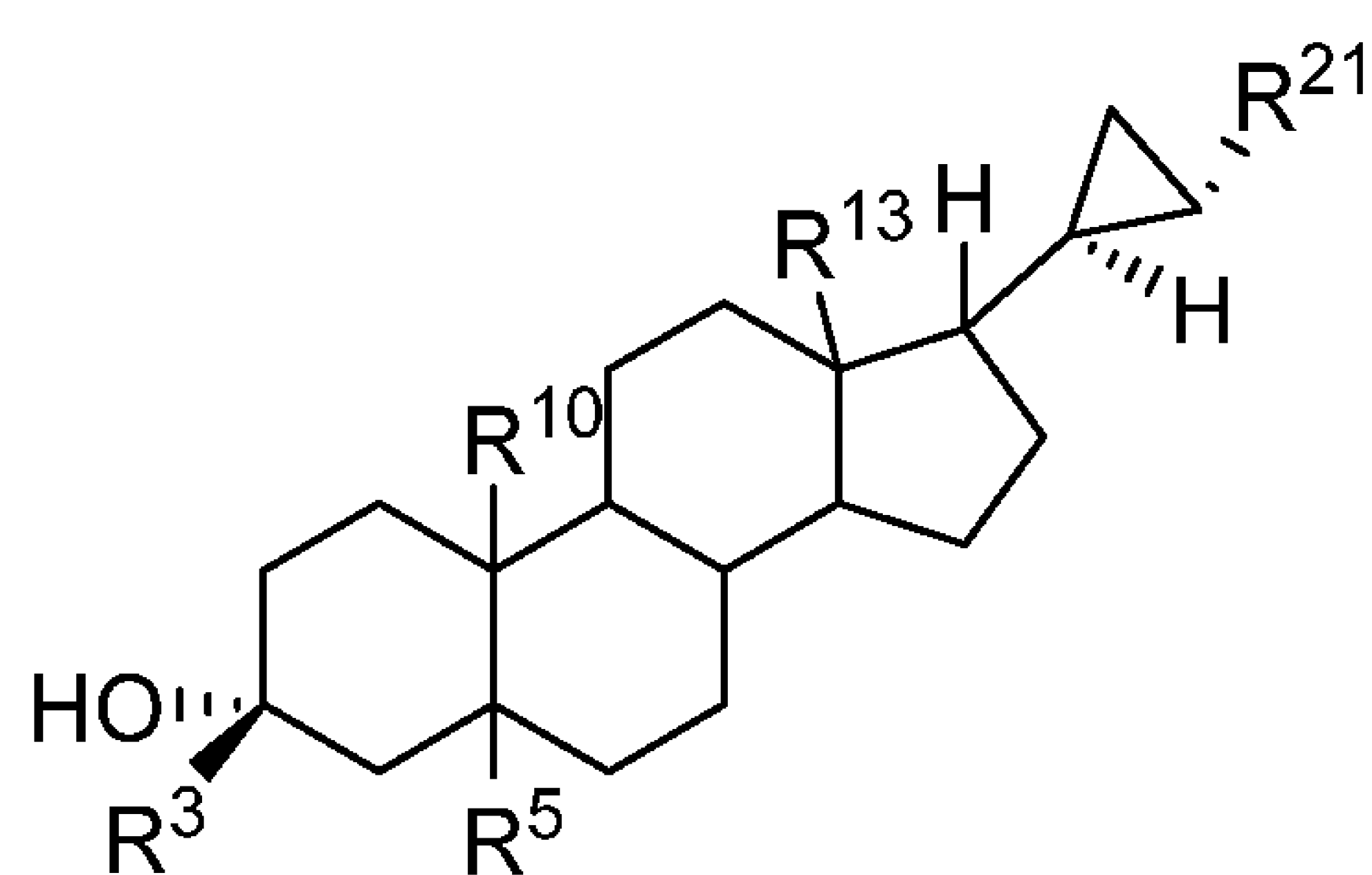
$-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, or $-\text{N}(\text{H})-$; and R^{30} is a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, $-\text{CH}_2-$, or

$-\text{N}(\text{H})-$; and R^{30} is , , or , wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from

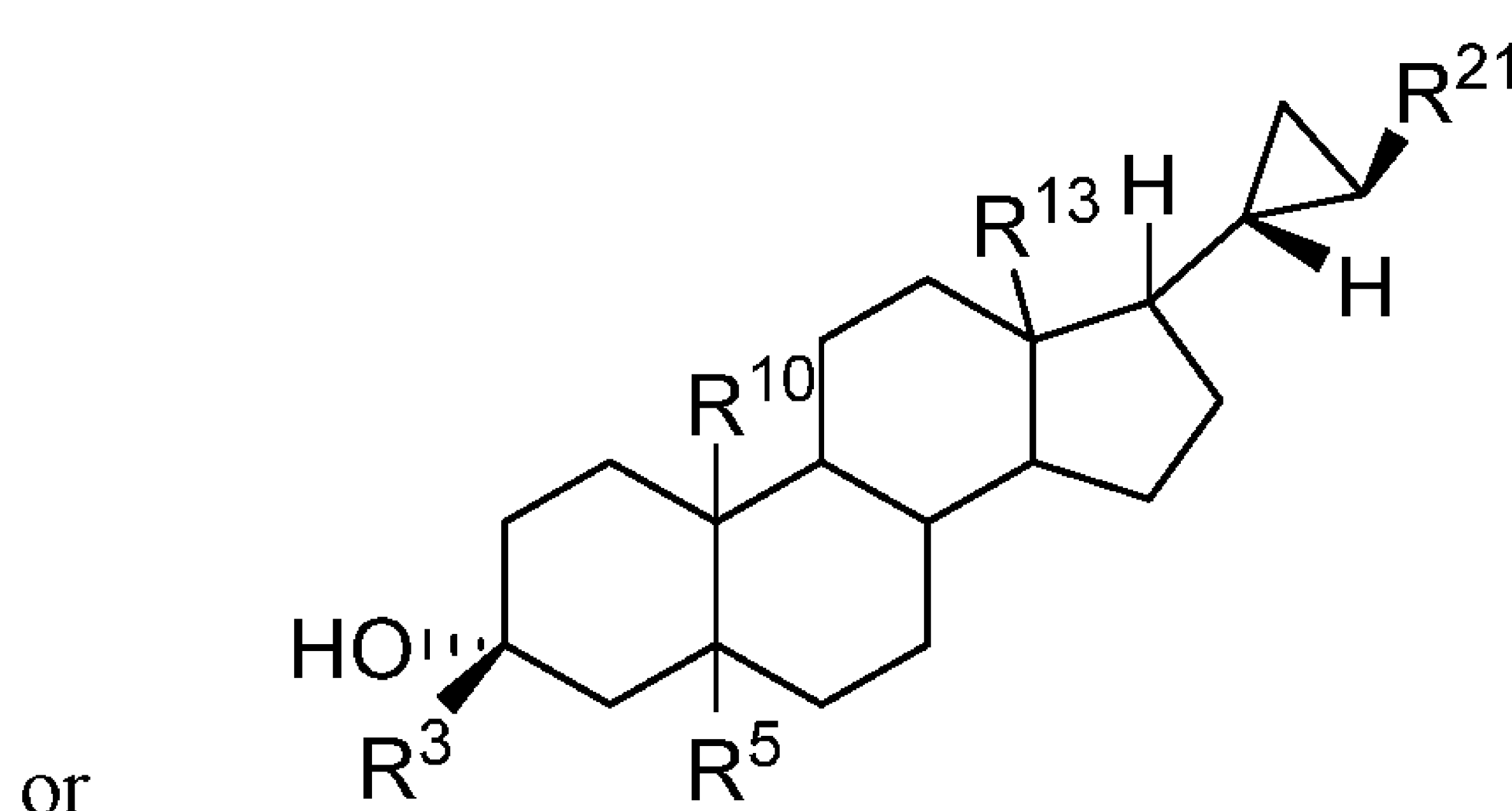
halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, R^{30} is 

or , X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N or CR'' , wherein each R'' is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$, provided that no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$.

[0150] Another aspect of the present invention provides a compound of Formula (VII-A) or (VII-B)



(VII-A)



(VII-B)

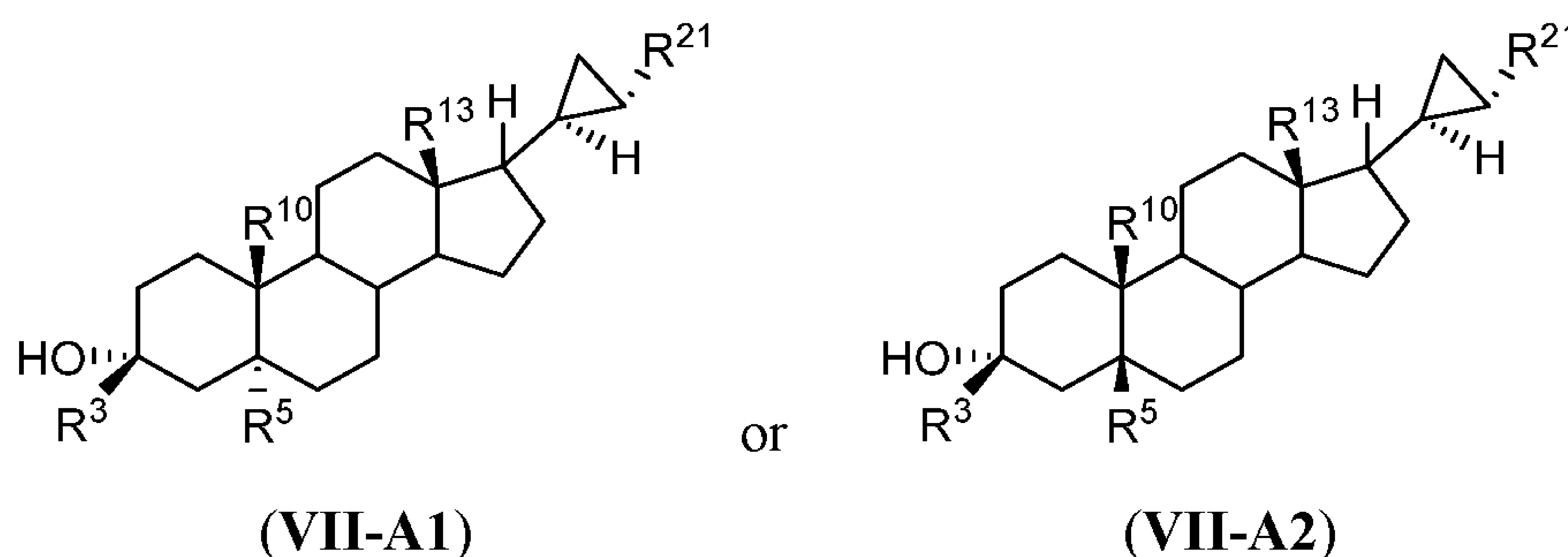
or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), or (VII).

[0151] In some embodiments, R^3 is $-\text{H}$, C_{1-6} alkyl, or C_{1-6} alkyl- $\text{O}-\text{C}_{1-6}$ alkyl; R^5 is $-\text{H}$ or C_{1-6} alkyl; each of R^{10} and R^{13} is independently selected from $-\text{H}$, C_{1-6} alkyl, and C_{1-6} alkyl- $\text{O}-\text{C}_{1-6}$

alkyl; R²¹ is -L^A-R³⁰; L^A is a bond, a branched or straight C₁₋₆ alkylene chain, or -N(H)-; and R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃.

[0152] In some embodiments, R³ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; R⁵ is -H or methyl; R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; R¹³ is -H, or C₁₋₃ alkyl; R²¹ is -L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain; and R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃.

[0153] Another aspect of the present invention provides a compound of Formula (VII-A1) or (VII-A2)



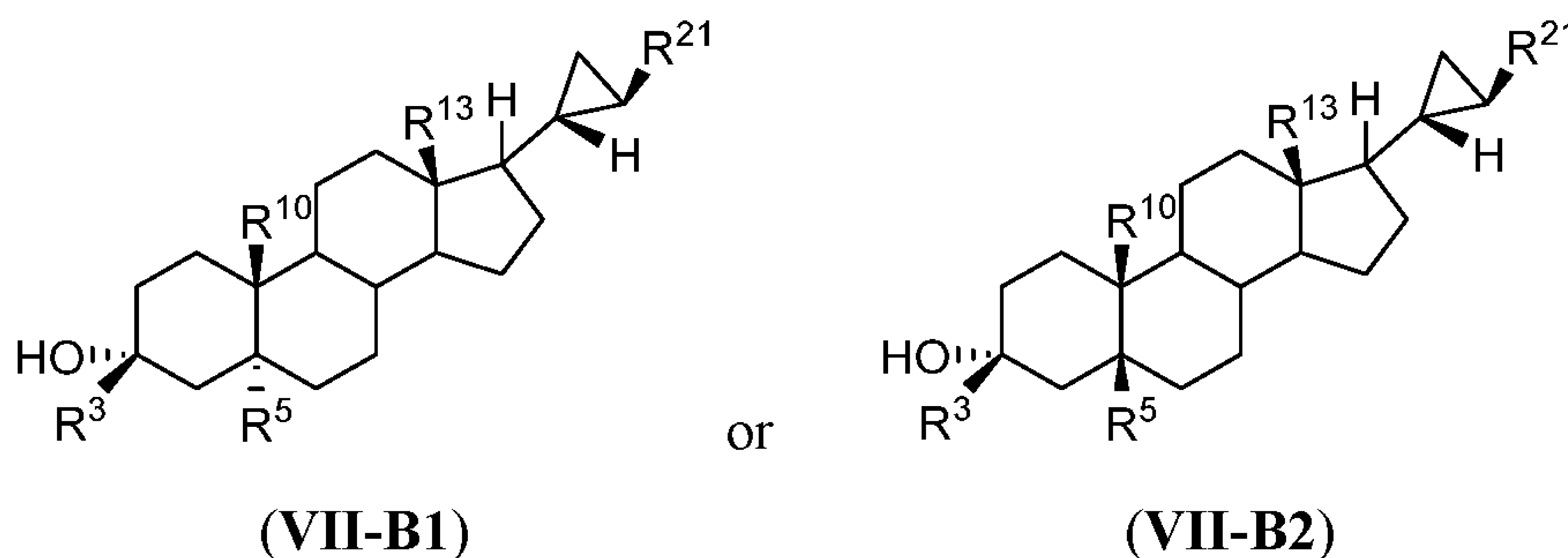
or a pharmaceutically acceptable salt thereof, wherein R³, R⁵, R¹⁰, R¹³, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VII), or (VII-A).

[0154] In some embodiments, R³ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; R⁵ is -H or C₁₋₆ alkyl; each of R¹⁰ and R¹³ is independently selected from -H, C₁₋₆ alkyl, and C₁₋₆ alkyl-O-C₁₋₆ alkyl; R²¹ is -L^A-R³⁰; L^A is a bond, a branched or straight C₁₋₆ alkylene chain, or -N(H)-; and R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃.

[0155] In some embodiments, R³ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; R⁵ is -H or methyl; R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; R¹³ is -H, or C₁₋₃ alkyl; R²¹ is -L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain; and R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 5-6-membered saturated, partially

unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0156] Another aspect of the present invention provides a compound of Formula (VII-B1) or (VII-B2)

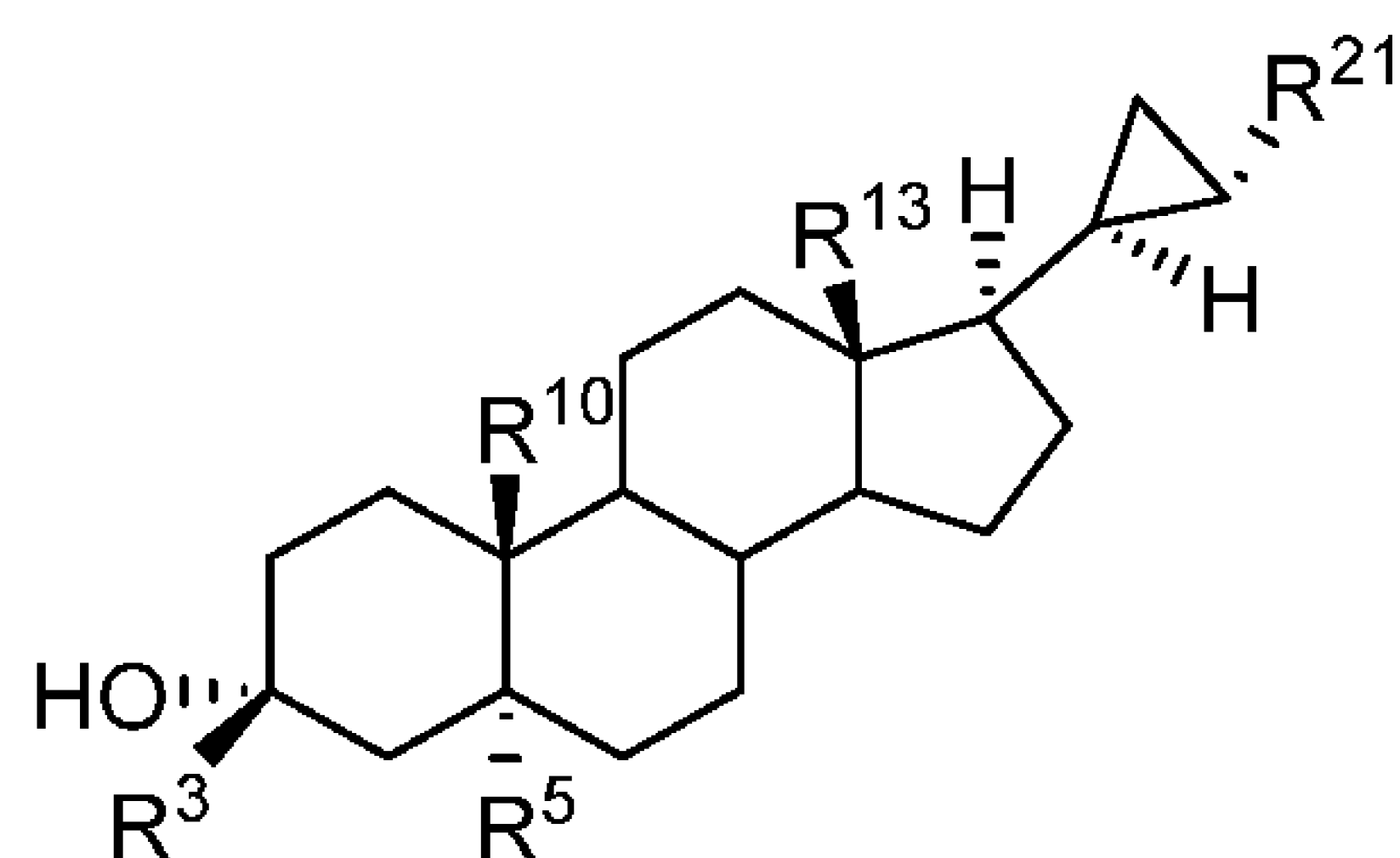


or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VII), or (VII-B).

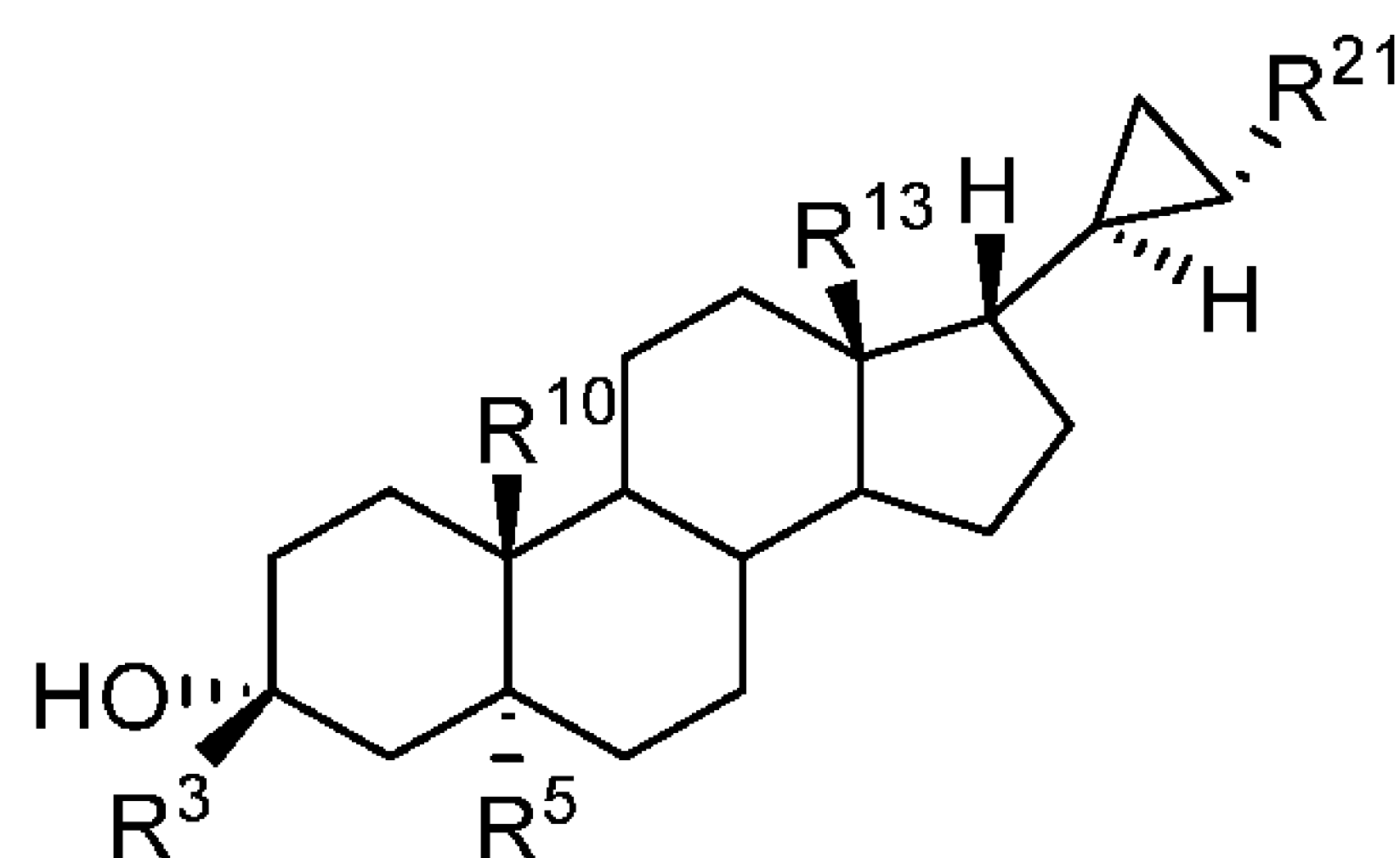
[0157] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0158] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$, or C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

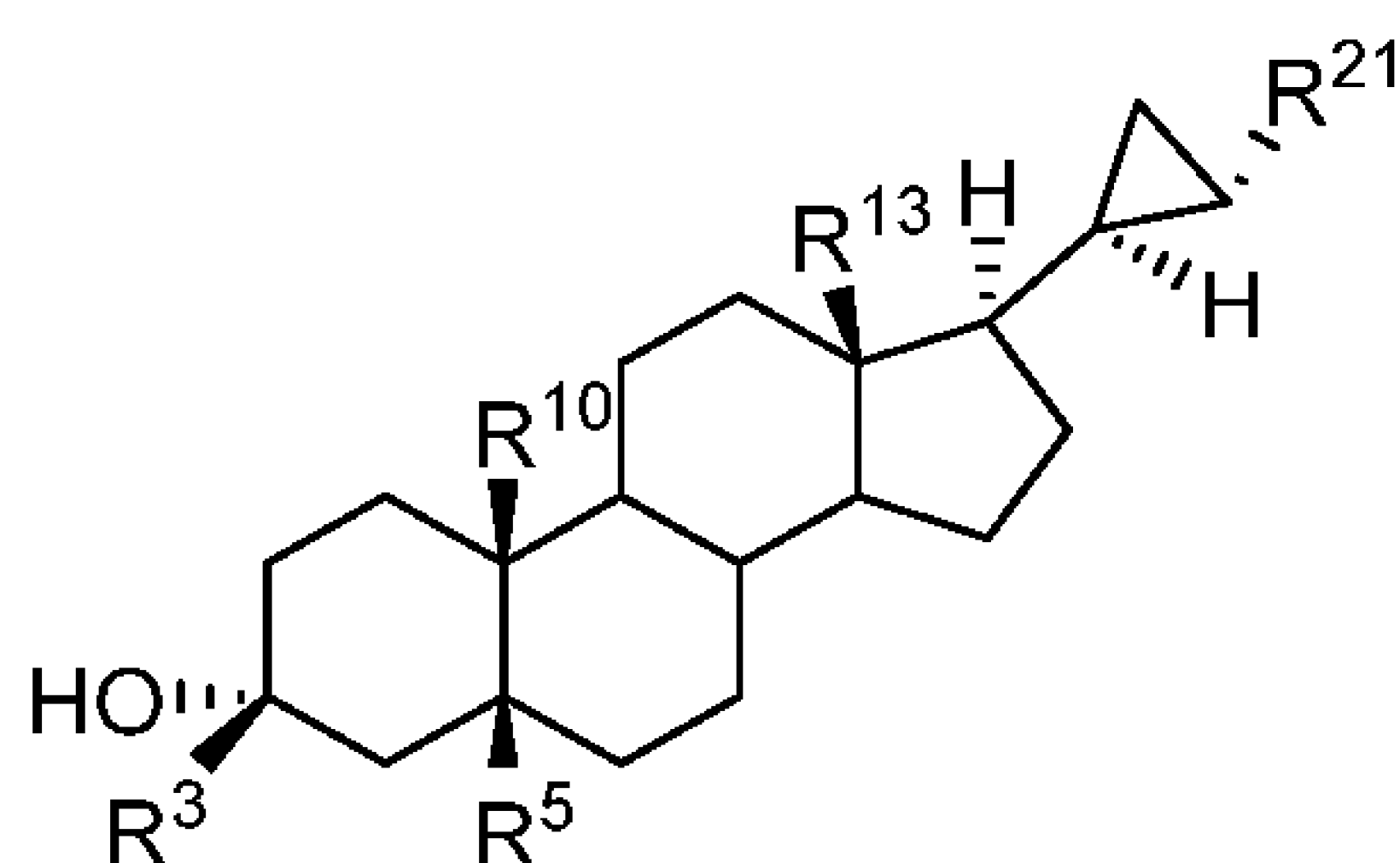
[0159] Another aspect of the present invention provides a compound of Formula (VII -A1a), (VII -A1b), (VII -A1c), or (VII -A1d)



(VII-A1a),

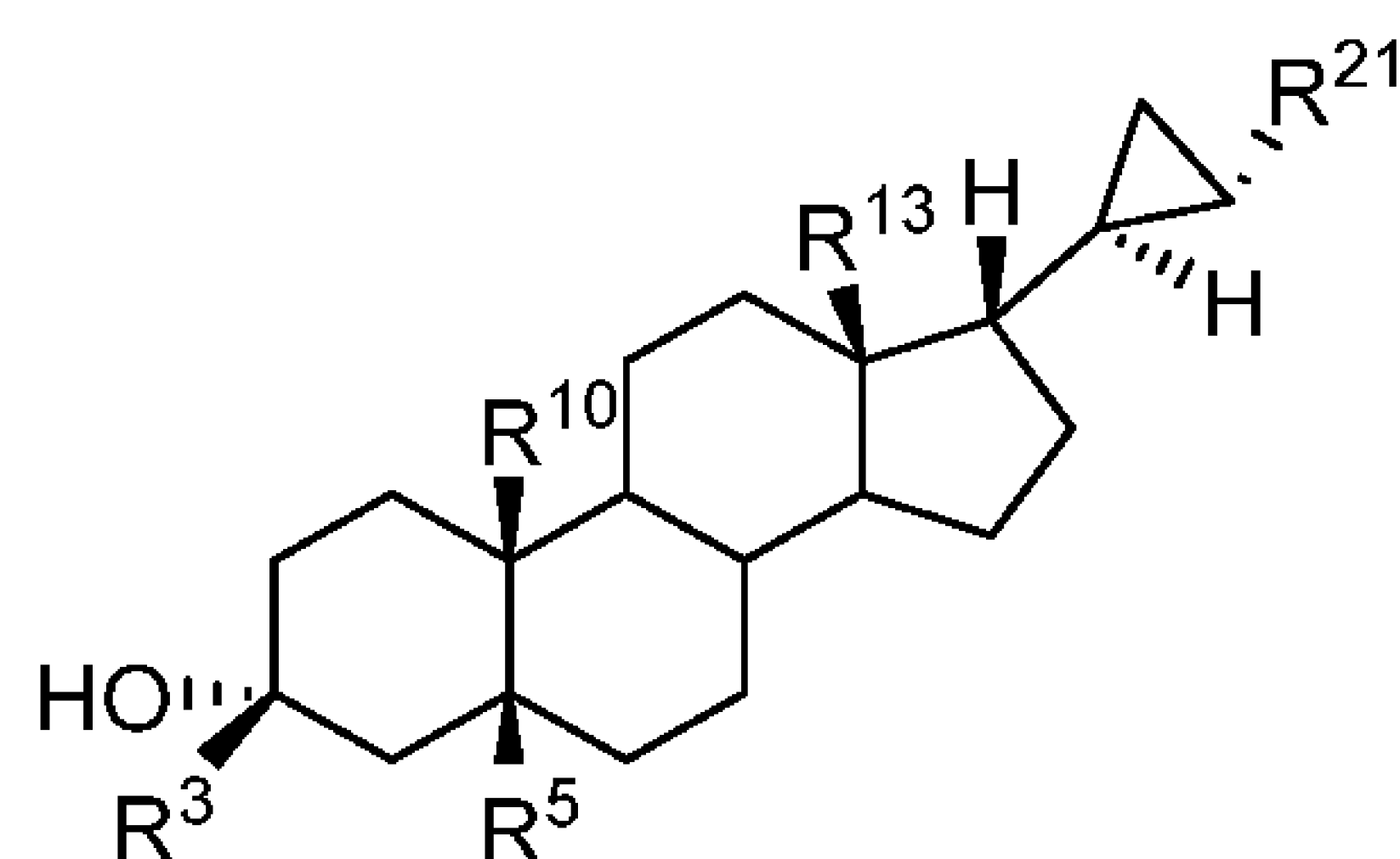


(VII-A1b),



(VII-A1c),

or



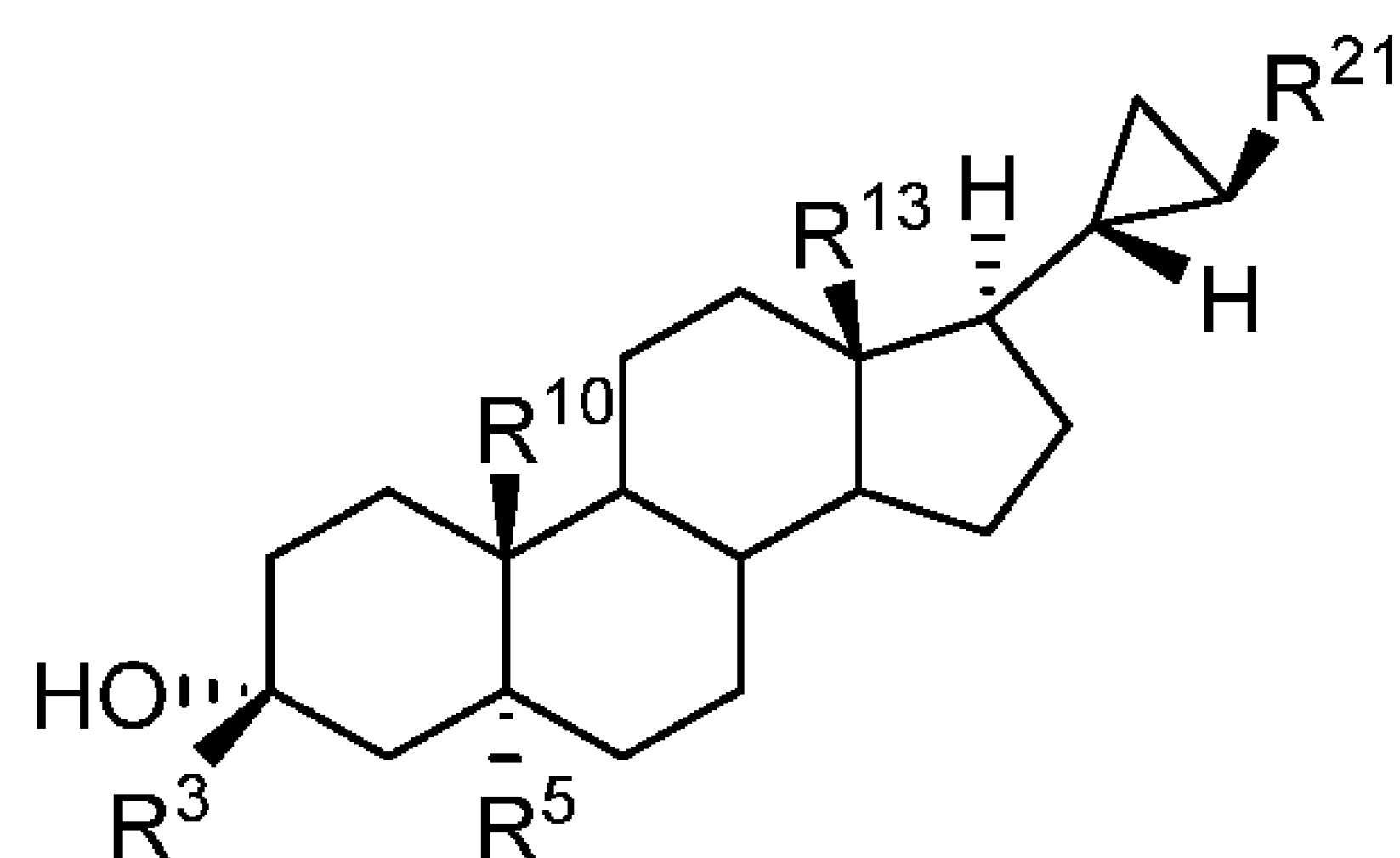
(VII-A1d),

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VII), (VII-A), (VII-A1), or (VII-A2).

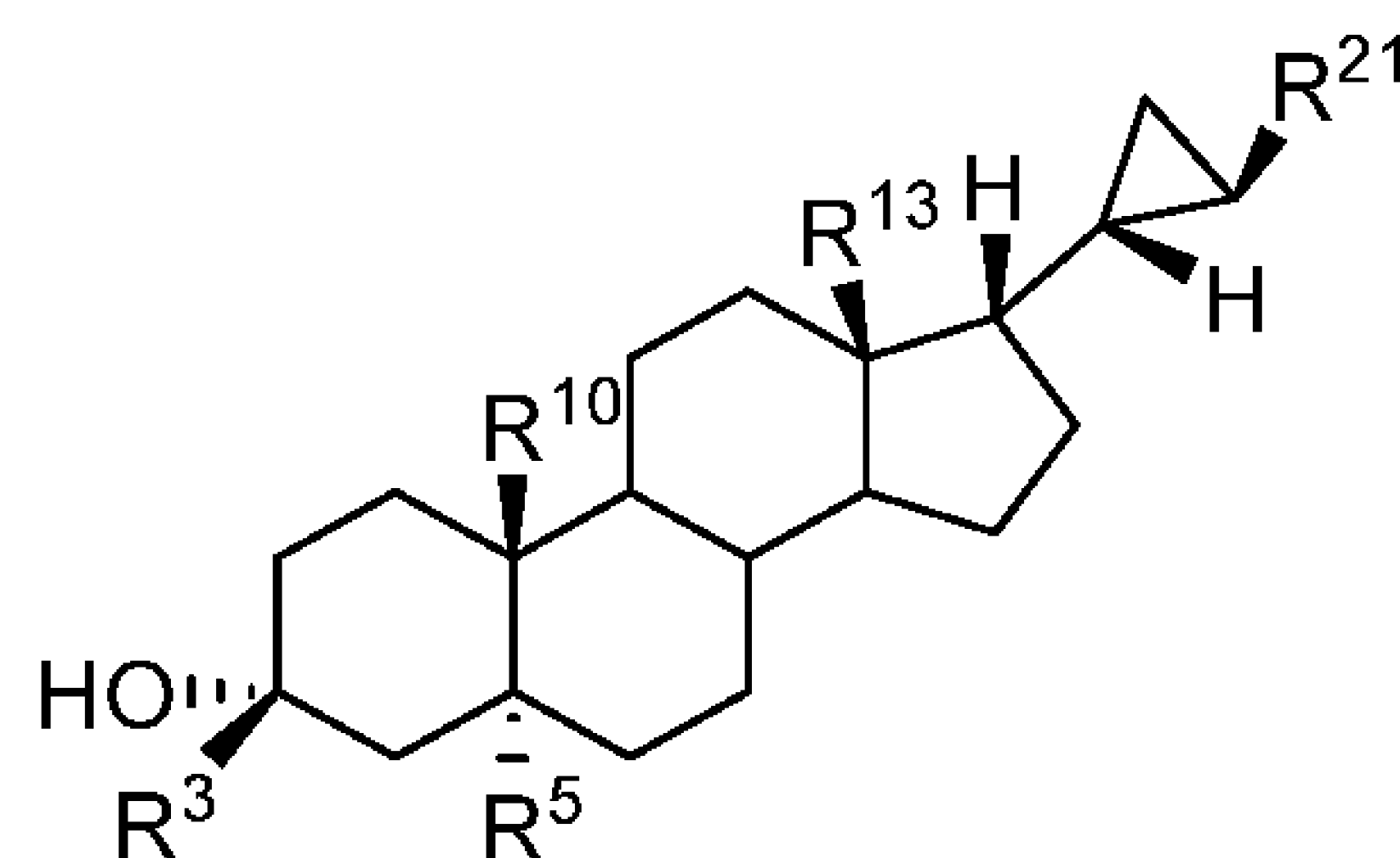
[0160] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0161] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$, or C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

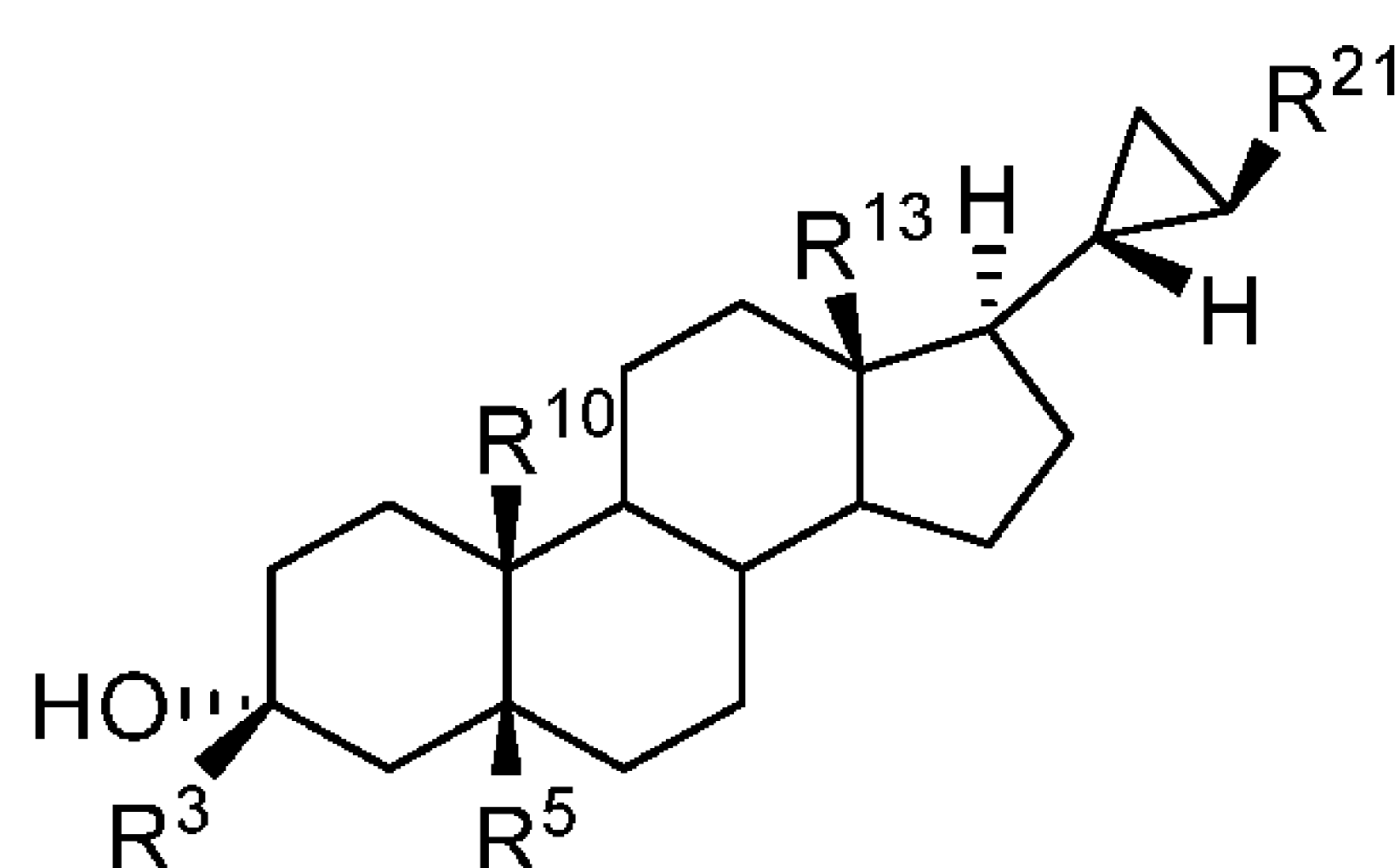
[0162] Another aspect of the present invention provides a compound of Formula (VII-B1a), (VII-B1b), (VII-B1c), or (VII-B1d)



(VII-B1a),

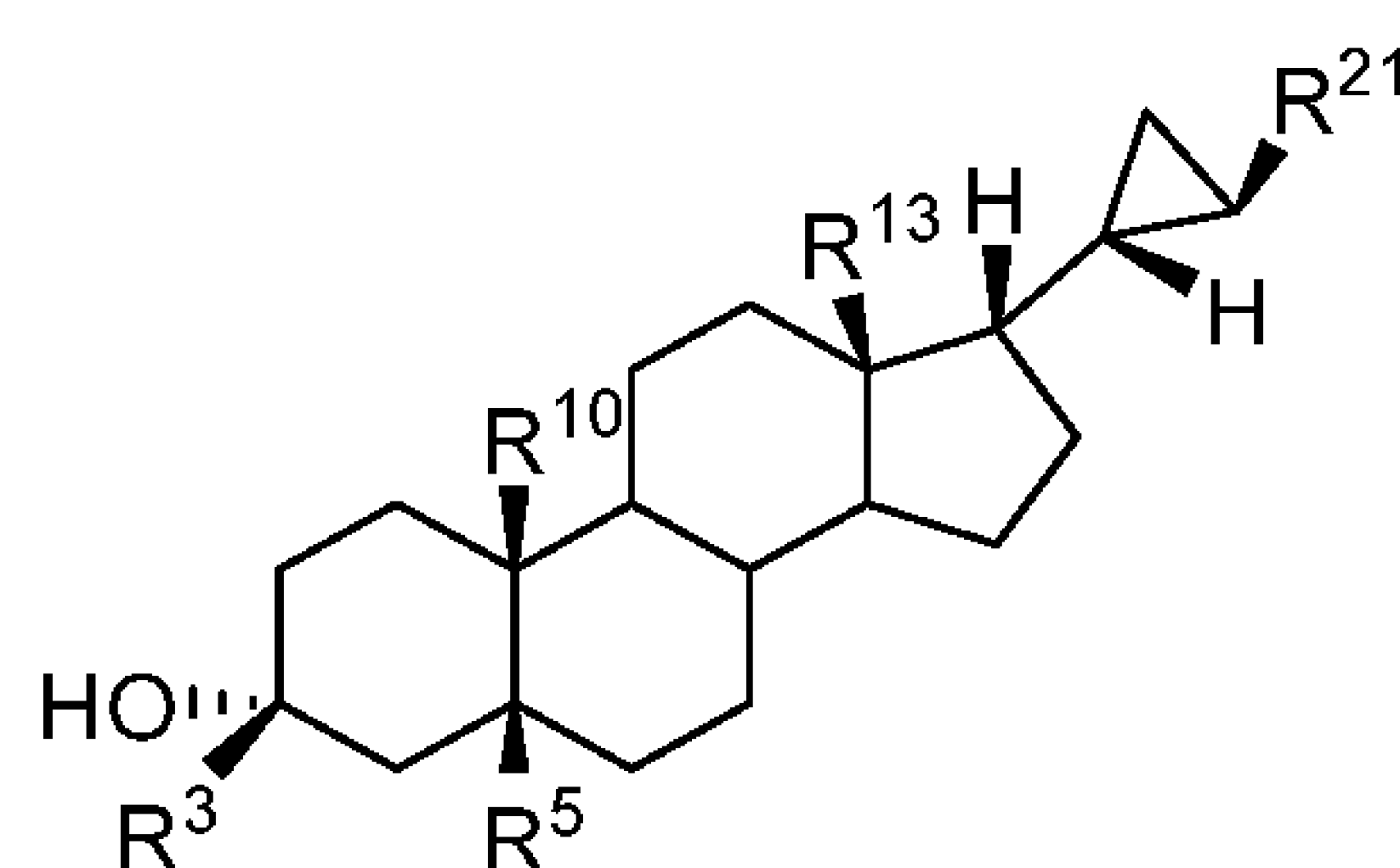


(VII-B1b),



(VII-B1c),

or



(VII-B1d),

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VII), (VII-B), (VII-B1), or (VII-B2).

[0163] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0164] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$, or C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0165] Another aspect of the present invention provides a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt of any one of compounds described herein, and a pharmaceutically acceptable carrier, vehicle, or excipient.

[0166] Another aspect of the present invention provides a method of modulating a GABA_A receptor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt of any one of compounds described herein or any pharmaceutical composition described herein.

[0167] Another aspect of the present invention provides a method of modulating a GABA_A receptor mediated CNS-related disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt of any one of the compounds described herein or any pharmaceutical composition described herein.

[0168] Another aspect of the present invention provides a method of treating a CNS-related disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt of any one of the compounds described herein or any pharmaceutical composition described herein.

In some implementations of the abovementioned methods, 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, an autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, tinnitus, or status epilepticus. In some implementations, the CNS-related disorder is a mood disorder. In some implementations, the mood disorder is depression. In some implementations, the depression is postpartum depression. In some implementations, the depression is a major depressive disorder. In some implementations, the major depressive disorder is a moderate major depressive disorder. And, in some implementations, the major depressive disorder is a severe major depressive disorder.

DETAILED DESCRIPTION

[0169] As generally described herein, the present invention provides neuroactive steroids 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).

[0170] I. DEFINITIONS

[0171] A. Chemical Definitions

[0172] 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.

[0173] 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.

[0174] "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".

[0175] 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.

[0176] 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.

[0177] The term “diastereomerically 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).

[0178] Compounds disclosed herein may be "isomerically pure" compounds. As used herein, the term "isomerically pure" refers to an isomeric form of a compound that is substantially free from other isomeric forms of the compound (e.g., substantially free from other stereoisomers (e.g., enantiomers, diastereomers, geometric (or conformational) isomers, etc.), constitutional isomers, isotopomers, etc.). For example, an "isomerically pure" compound having at least one asymmetric center of a particular configuration (i.e., R or S configuration) is substantially free from other isomeric forms of the compound having a different configuration at the at least one asymmetric center. An "isomerically pure" 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 isomer of the compound based on the total weight of all isomers of the compound that are present.

[0179] 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.

[0180] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C₁₋₆ alkyl" is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0181] 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.

[0182] "Alkyl" refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C₁₋₂₀ alkyl"). In some embodiments, an alkyl group has 1 to 12 carbon atoms ("C₁₋₁₂ alkyl"). In some embodiments, an alkyl group has 1 to 10 carbon atoms ("C₁₋₁₀ alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C₁₋₉ alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C₁₋₈ alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C₁₋₇ alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C₁₋₆ alkyl", also referred to

herein as “lower alkyl”). In some embodiments, an alkyl group has 1 to 5 carbon atoms (“C₁₋₅ alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“C₁₋₄ alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“C₁₋₃ alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“C₁₋₂ alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“C₁ alkyl”). In some embodiments, an alkyl group has 2 to 6 carbon atoms (“C₂₋₆ alkyl”). Examples of C₁₋₆ alkyl groups include methyl (C₁), ethyl (C₂), n-propyl (C₃), isopropyl (C₃), n-butyl (C₄), tert-butyl (C₄), sec-butyl (C₄), iso-butyl (C₄), n-pentyl (C₅), 3-pentanyl (C₅), amyl (C₅), neopentyl (C₅), 3-methyl-2-butanyl (C₅), tertiary amyl (C₅), and n-hexyl (C₆). Additional examples of alkyl groups include n-heptyl (C₇), n-octyl (C₈) 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 C₁₋₁₀ alkyl (e.g., –CH₃). In certain embodiments, the alkyl group is substituted C₁₋₁₀ alkyl. Common alkyl abbreviations include Me (–CH₃), Et (–CH₂CH₃), iPr (–CH(CH₃)₂), nPr (–CH₂CH₂CH₃), n-Bu (–CH₂CH₂CH₂CH₃), or i-Bu (–CH₂CH(CH₃)₂).

[0183] “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 (–CH₂–), ethylene (–CH₂CH₂–), propylene (–CH₂CH₂CH₂–), butylene (–CH₂CH₂CH₂CH₂–), pentylene (–CH₂CH₂CH₂CH₂CH₂–), hexylene (–CH₂CH₂CH₂CH₂CH₂CH₂–), 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(CH₃)–, –C(CH₃)₂–), substituted ethylene (–CH(CH₃)CH₂–, –CH₂CH(CH₃)–, –C(CH₃)₂CH₂–, –CH₂C(CH₃)₂–), substituted propylene (–CH(CH₃)CH₂CH₂–, –CH₂CH(CH₃)CH₂–, –CH₂CH₂CH(CH₃)–, –C(CH₃)₂CH₂CH₂–, –CH₂C(CH₃)₂CH₂–, –CH₂CH₂C(CH₃)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.

[0184] “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) (“C₂₋₂₀ alkenyl”). In certain embodiments, alkenyl

does not contain any triple bonds. In some embodiments, an alkenyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 9 carbon atoms (“C₂₋₉ alkenyl”). In some embodiments, an alkenyl group has 2 to 8 carbon atoms (“C₂₋₈ alkenyl”). In some embodiments, an alkenyl group has 2 to 7 carbon atoms (“C₂₋₇ alkenyl”). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C₂₋₆ alkenyl”). In some embodiments, an alkenyl group has 2 to 5 carbon atoms (“C₂₋₅ alkenyl”). In some embodiments, an alkenyl group has 2 to 4 carbon atoms (“C₂₋₄ alkenyl”). In some embodiments, an alkenyl group has 2 to 3 carbon atoms (“C₂₋₃ alkenyl”). In some embodiments, an alkenyl group has 2 carbon atoms (“C₂ 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 C₂₋₄ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Additional examples of alkenyl include heptenyl (C₇), octenyl (C₈), octatrienyl (C₈), 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., from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkenyl group is unsubstituted C₂₋₁₀ alkenyl. In certain embodiments, the alkenyl group is substituted C₂₋₁₀ alkenyl.

[0185] “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) (“C₂₋₂₀ alkynyl”). In certain embodiments, alkynyl does not contain any double bonds. In some embodiments, an alkynyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 9 carbon atoms (“C₂₋₉ alkynyl”). In some embodiments, an alkynyl group has 2 to 8 carbon atoms (“C₂₋₈ alkynyl”). In some embodiments, an alkynyl group has 2 to 7 carbon atoms (“C₂₋₇ alkynyl”). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ alkynyl”). In some embodiments, an alkynyl group has 2 to 5 carbon atoms (“C₂₋₅ alkynyl”). In some embodiments, an alkynyl group has 2 to 4 carbon atoms (“C₂₋₄ alkynyl”). In some embodiments, an alkynyl group has 2 to 3 carbon atoms (“C₂₋₃ alkynyl”). In some embodiments, an alkynyl group has 2 carbon atoms (“C₂ alkynyl”). The one or more carbon-

carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of C₂₋₄ alkynyl groups include, without limitation, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkynyl groups as well as pentynyl (C₅), hexynyl (C₆), and the like. Additional examples of alkynyl include heptynyl (C₇), octynyl (C₈), 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., from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkynyl group is unsubstituted C₂₋₁₀ alkynyl. In certain embodiments, the alkynyl group is substituted C₂₋₁₀ alkynyl.

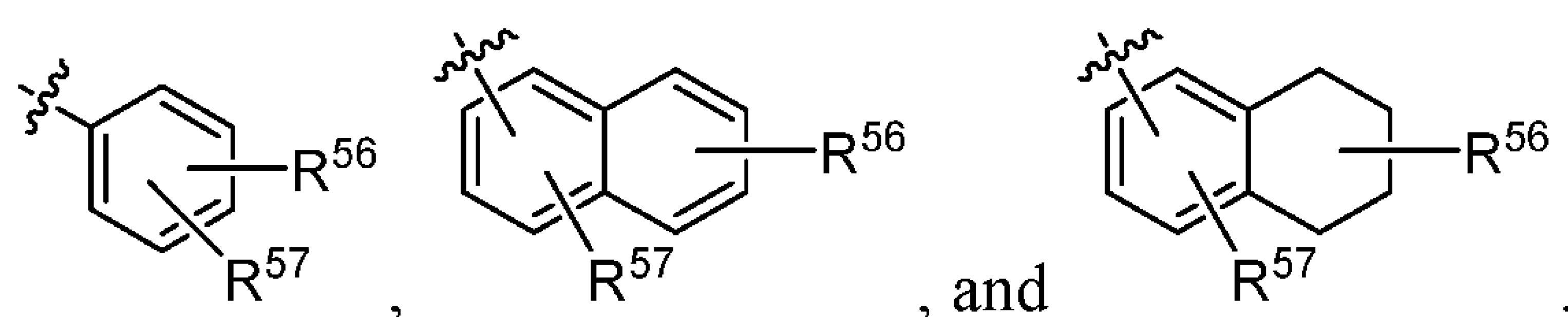
[0186] The term “heteroalkyl,” as used herein, refers to an alkyl group, as defined herein, which further comprises 1 or more (e.g., 1, 2, 3, or 4) heteroatoms (e.g., oxygen, sulfur, nitrogen, boron, silicon, phosphorus) within the parent chain, wherein the one or more heteroatoms is inserted between 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 (“heteroC₁₋₁₀ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1, 2, 3, or 4 heteroatoms (“heteroC₁₋₉ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1, 2, 3, or 4 heteroatoms (“heteroC₁₋₈ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1, 2, 3, or 4 heteroatoms (“heteroC₁₋₇ alkyl”). In some embodiments, a heteroalkyl group is a group having 1 to 6 carbon atoms and 1, 2, or 3 heteroatoms (“heteroC₁₋₆ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms (“heteroC₁₋₅ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1 or 2 heteroatoms (“heteroC₁₋₄ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom (“heteroC₁₋₃ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom (“heteroC₁₋₂ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom (“heteroC₁ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms (“heteroC₂₋₆ 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 heteroC₁₋₁₀ alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC₁₋₁₀ alkyl.

[0187] “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 no heteroatoms provided in the aromatic ring system (“C₆₋₁₄ aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; *i.e.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1-naphthyl or 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ 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 C₆₋₁₄ aryl. In certain embodiments, the aryl group is substituted C₆₋₁₄ aryl.

[0188] In certain embodiments, an aryl group substituted with one or more of groups selected from halo, C₁₋₈ alkyl, C₁₋₈ haloalkyl, cyano, hydroxy, C₁₋₈ alkoxy, and amino.

[0189] Examples of representative substituted aryls include the following:



wherein one of R⁵⁶ and R⁵⁷ may be hydrogen and at least one of R⁵⁶ and R⁵⁷ is independently selected from C₁₋₈ alkyl, C₁₋₈ haloalkyl, 4-10 membered heterocyclyl, alkanoyl, C₁₋₈ alkoxy,

heteroaryloxy, alkylamino, arylamino, heteroarylamino, $-\text{NR}^{58}\text{COR}^{59}$, $-\text{NR}^{58}\text{SOR}^{59}$, $-\text{NR}^{58}\text{SO}_2\text{R}^{59}$, $-\text{COOalkyl}$, $-\text{COOaryl}$, $-\text{CONR}^{58}\text{R}^{59}$, $-\text{CONR}^{58}\text{OR}^{59}$, $-\text{NR}^{58}\text{R}^{59}$, $-\text{SO}_2\text{NR}^{58}\text{R}^{59}$, $-\text{S-alkyl}$, $-\text{SOalkyl}$, $-\text{SO}_2\text{alkyl}$, $-\text{Saryl}$, $-\text{SOaryl}$, and $-\text{SO}_2\text{aryl}$; or R^{56} and R^{57} may be joined to form a cyclic ring (saturated or unsaturated) having 5 to 8 atoms, optionally containing one or more heteroatoms independently selected from N, O, and 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.

[0190] “Fused aryl” refers to an aryl having two of its ring carbons in common with a second aryl or heteroaryl ring or with a carbocyclyl or heterocyclyl ring.

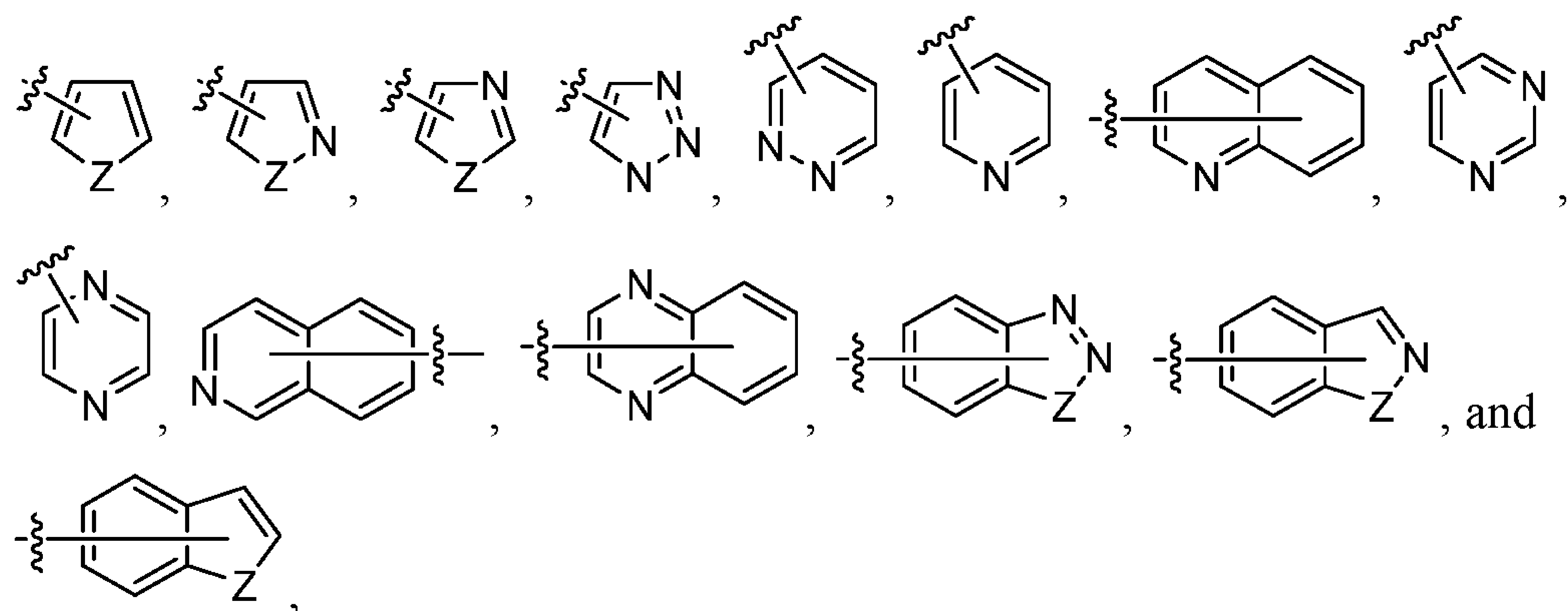
[0191] “Heteroaryl” refers to a radical of a 5-10 membered monocyclic or bicyclic $4n+2$ aromatic ring system (e.g., having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from N, O, and S (“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).

[0192] 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 N, O, and S (“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 N, O, and S (“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 N, O, and S (“5-6 membered heteroaryl”). In some embodiments, the 5-6 membered heteroaryl has 1-3 ring heteroatoms selected from N, O, and S. In some embodiments, the 5-6 membered heteroaryl has 1-2 ring heteroatoms selected from N, O, and S. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from N, O, and S. 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.

[0193] 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.

[0194] Examples of representative heteroaryls include the following:



wherein each Z is independently selected from carbonyl, N, NR⁶⁵, O, and S; and R⁶⁵ is independently hydrogen, C₁₋₈ alkyl, C₃₋₁₀ cycloalkyl, 4-10 membered heterocyclyl, C₆₋₁₀ aryl, and 5-10 membered heteroaryl.

[0195] “Carbocyclyl” or “carbocyclic” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include, without limitation, the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), 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 C₃₋₁₀ carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C₃₋₁₀ carbocyclyl.

[0196] In some embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C₃₋₈ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C₅₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ cycloalkyl”). Examples of C₅₋₆ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃₋₆ cycloalkyl groups include the aforementioned C₅₋₆ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ cycloalkyl groups include the aforementioned C₃₋₆ cycloalkyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). 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 C₃₋₁₀ cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C₃₋₁₀ cycloalkyl.

[0197] “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.

[0198] 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.

[0199] Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenlyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, 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 C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothieryl, 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.

[0200] “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.

[0201] “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 hydrocarbonyl 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.

[0202] “Acyl” refers to a radical $-C(O)R^{100}$, where R^{100} 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^{100} 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 0, 1, 2, 3, or 4. In certain embodiments, R^{100} 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 C₁₋₄ alkoxy, unsubstituted C₁₋₄ haloalkyl, unsubstituted C₁₋₄ hydroxyalkyl, or unsubstituted C₁₋₄ haloalkoxy or hydroxy.

[0203] “Alkoxy” refers to the group –OR¹⁰¹ wherein R¹⁰¹ 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.

[0204] In certain embodiments, R¹⁰¹ 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, C₆₋₁₀ aryl, aryloxy, carboxyl, cyano, C₃₋₁₀ 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-(CH₂)_t(C₆₋₁₀ aryl), –O-(CH₂)_t(5-10 membered heteroaryl), –O-(CH₂)_t(C₃₋₁₀ cycloalkyl), and –O-(CH₂)_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 C₁₋₄ alkyl, halo, unsubstituted C₁₋₄ alkoxy, unsubstituted C₁₋₄ haloalkyl, unsubstituted C₁₋₄ hydroxyalkyl, or unsubstituted C₁₋₄ haloalkoxy or hydroxy. Particular exemplary ‘substituted alkoxy’ groups are –OCF₃, –OCH₂CF₃, –OCH₂Ph, –OCH₂-cyclopropyl, –OCH₂CH₂OH, and –OCH₂CH₂NMe₂.

[0205] “Amino” refers to the radical –NH₂.

[0206] “Oxo group” refers to =O.

[0207] “Substituted amino” refers to an amino group of the formula –N(R³⁸)₂ wherein R³⁸ 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, substituted or unsubstituted heteroaryl, or an amino protecting group, wherein at least one of R³⁸ is not a hydrogen. In certain embodiments, each R³⁸ is independently selected from hydrogen, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, 4-10 membered heterocyclyl, or C₃₋₁₀ cycloalkyl; or C₁₋₈ alkyl, substituted with halo or hydroxy; C₃₋₈ alkenyl, substituted with halo

or hydroxy; C₃₋₈ alkynyl, substituted with halo or hydroxy, or -(CH₂)_t(C₆₋₁₀ aryl), -(CH₂)_t(5-10 membered heteroaryl), -(CH₂)_t(C₃₋₁₀ cycloalkyl), or -(CH₂)_t(4-10 membered heterocyclyl), wherein t is an integer between 0 and 8, each of which is substituted by unsubstituted C₁₋₄ alkyl, halo, unsubstituted C₁₋₄ alkoxy, unsubstituted C₁₋₄ haloalkyl, unsubstituted C₁₋₄ hydroxyalkyl, or unsubstituted C₁₋₄ haloalkoxy or hydroxy; or both R³⁸ groups are joined to form an alkylene group.

[0208] Exemplary “substituted amino” groups include, but are not limited to, -NR³⁹-C₁₋₈ alkyl, -NR³⁹-(CH₂)_t(C₆₋₁₀ aryl), -NR³⁹-(CH₂)_t(5-10 membered heteroaryl), -NR³⁹-(CH₂)_t(C₃₋₁₀ cycloalkyl), and -NR³⁹-(CH₂)_t(4-10 membered heterocyclyl), wherein t is an integer from 0 to 4, for instance 1 or 2; each R³⁹ independently represents H or C₁₋₈ 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 C₁₋₄ alkyl, halo, unsubstituted C₁₋₄ alkoxy, unsubstituted C₁₋₄ haloalkyl, unsubstituted C₁₋₄ hydroxyalkyl, or unsubstituted C₁₋₄ 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.

[0209] “Carboxy” refers to the radical -C(O)OH.

[0210] “Cyano” refers to the radical -CN.

[0211] “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.

[0212] “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.

[0213] “Hydroxy” refers to the radical -OH.

[0214] “Nitro” refers to the radical -NO₂.

[0215] “Oxo” refers to the group =O.

[0216] “Thioketo” refers to the group =S.

[0217] 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.

[0218] Exemplary carbon atom substituents include, but are not limited to, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_3\text{H}$, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{ON}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_3^+\text{X}^-$, $-\text{N}(\text{OR}^{\text{cc}})\text{R}^{\text{bb}}$, $-\text{SH}$, $-\text{SR}^{\text{aa}}$, $-\text{SSR}^{\text{cc}}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{H}$, $-\text{CHO}$, $-\text{C}(\text{OR}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{OR}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{OP}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OP}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{OP}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3$, $-\text{B}(\text{R}^{\text{aa}})_2$, $-\text{B}(\text{OR}^{\text{cc}})_2$, $-\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}})$, 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 $=\text{O}$, $=\text{S}$, $=\text{NN}(\text{R}^{\text{bb}})_2$, $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{OR}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{S}(=\text{O})_2\text{R}^{\text{aa}}$, $=\text{NR}^{\text{bb}}$, or $=\text{NOR}^{\text{cc}}$; 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; 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; 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; 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 $=S$; 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; 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 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.

[0219] 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., methanesulfonate, 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).

[0220] 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.

[0221] B. Other Definitions

[0222] 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.

[0223] “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.

[0224] “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, and 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.

[0225] 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.

[0226] In an alternate embodiment, the present invention provides prodrugs of compounds described herein, wherein the prodrug includes a cleavable moiety on the C3 hydroxy as depicted in Formulae depicted herein.

[0227] “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.

[0228] A “subject” to which administration is contemplated includes humans, i.e., a male or female of any age group. Exemplary human subjects include, e.g., “a pediatric subject” (e.g., infant, child, adolescent) or “adult subject” (e.g., young adult, middle-aged adult or senior adult).

[0229] 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.

[0230] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxymethyl (MOM), 2-methoxyethoxymethyl (MEM), benzyl (Bn), triisopropylsilyl (TIPS), *t*-butyldimethylsilyl (TBDMS), *t*-butylmethoxyphenylsilyl (TBMPS), methanesulfonate (mesylate), and tosylate (Ts).

[0231] In certain embodiments, the substituent present on a 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.

[0232] 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.

[0233] 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]methylaniline (SEM).

[0234] The terms, “disease”, “disorder”, and “condition” are used interchangeably herein.

[0235] 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.

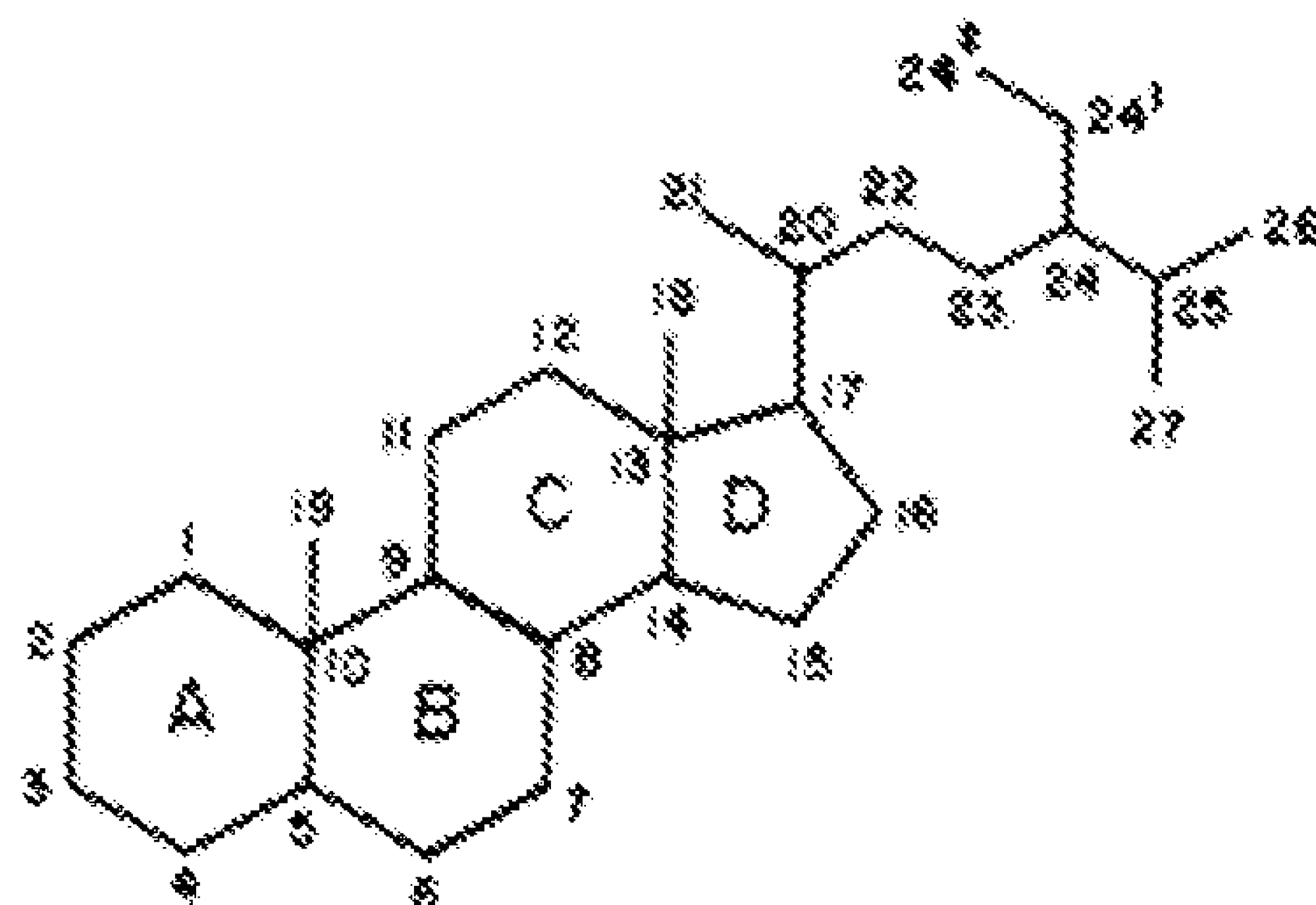
[0236] In general, the “effective amount” of a compound refers to an amount sufficient to elicit the desired biological response, e.g., to treat a CNS-related disorder, or is sufficient to induce anesthesia or sedation. As will be appreciated by those of ordinary skill in the art, the effective amount 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.

[0237] 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.

[0238] 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.

[0239] II. COMPOUNDS

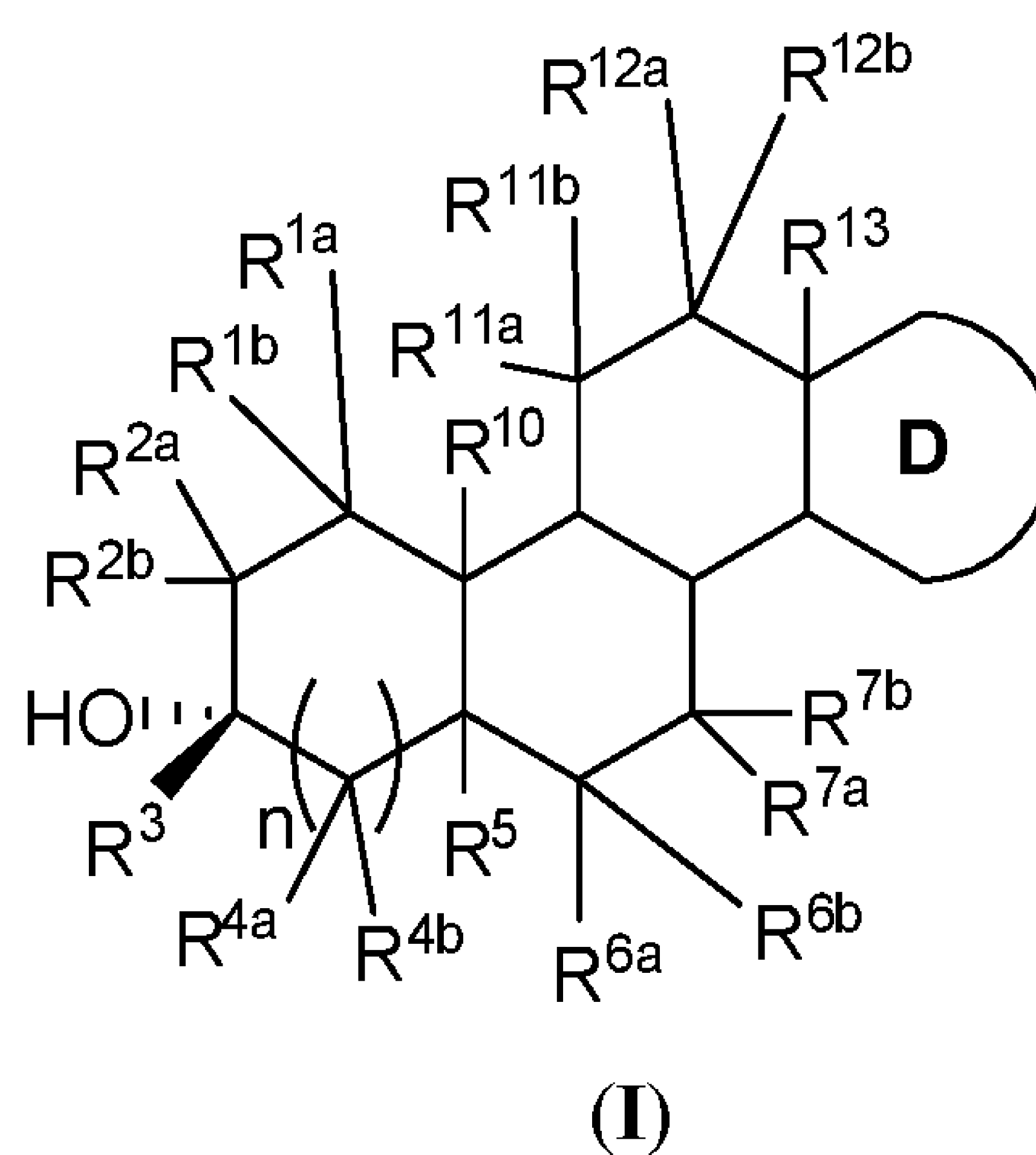
[0240] The formulas described herein may reference particular carbon atoms, such as C17, C3, C19, and the like. These references are based on the position of carbon atoms according to steroid nomenclature known and used in the industry, as shown below:



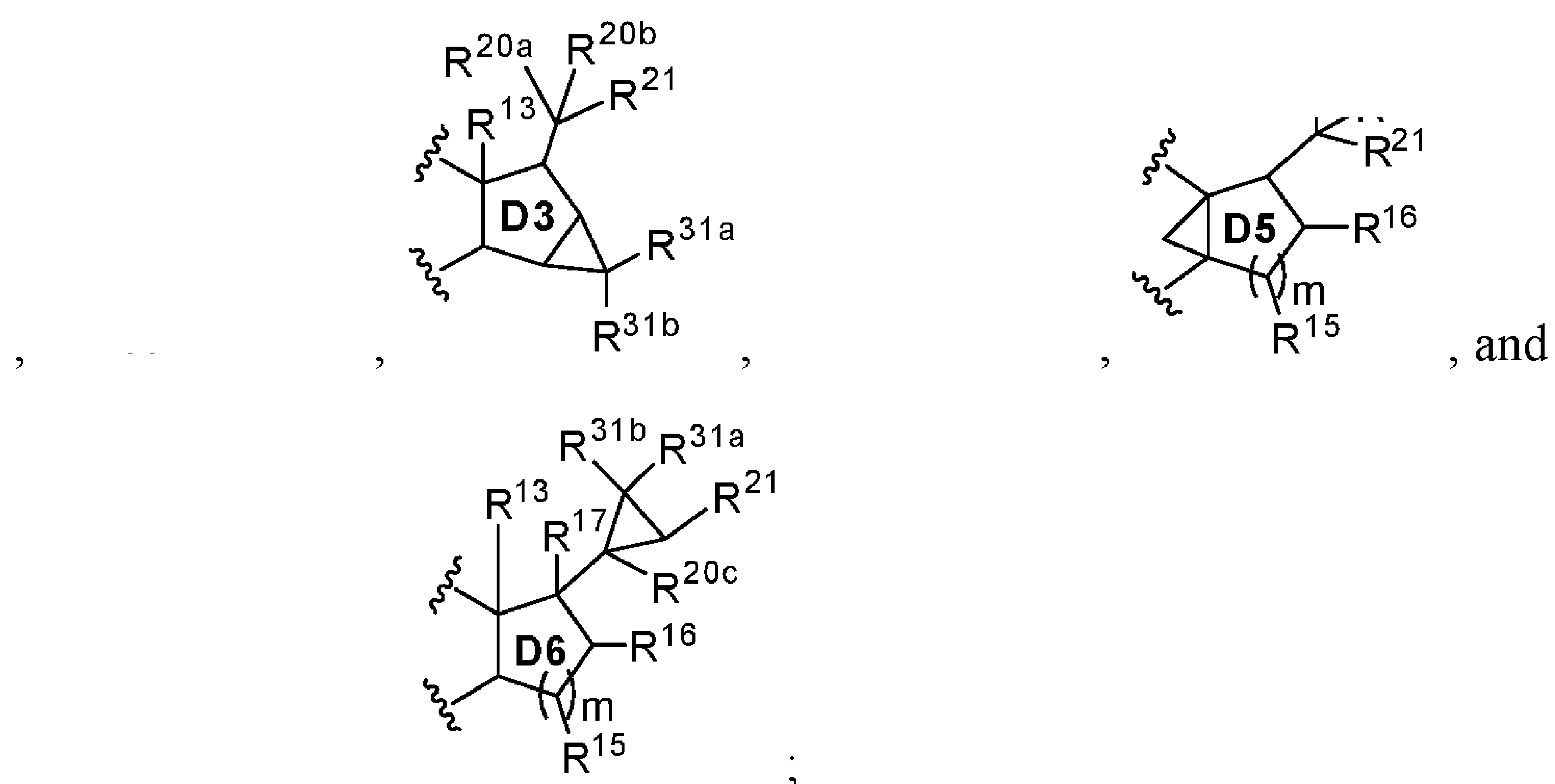
For example, C17 refers to the carbon at position 17 and C3 refers to the carbon at position 3.

[0241] A. Compounds

[0242] In one aspect, the invention includes compound of Formula (I)



or a pharmaceutically acceptable salt thereof, wherein ring D is selected from



each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20a} , R^{20b} , and R^{21} , is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl- O - C_{1-6} alkyl, and an optionally substituted 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, or R^{1a} and R^{1b} taken together form oxo, or R^{2a} and R^{2b} taken together form oxo, or R^{4a} and R^{4b} taken together form oxo, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo, or R^{20a} and R^{20b} taken together form oxo; each of R^5 and R^{20c} is independently selected from $-H$ and optionally substituted C_{1-6} alkyl; R^{10} is $-H$, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^{31a} and R^{31b} is independently selected from $-H$, halo, C_{1-6} alkyl, and $-OR^{32}$, wherein R^{32} is $-H$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, or S; m is 1 or 2; and n is 0, 1, or 2, provided that when one of R^{31a} and R^{31b} is $-OR^{32}$, the other of R^{31a} and R^{31b} is $-H$.

[0243] B. Substituents

[0244] 1. R^{1a} and R^{1b}

[0245] In some embodiments, each of R^{1a} and R^{1b} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl- O - C_{1-6} alkyl, and an optionally substituted 3-8-membered

saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, or R^{1a} and R^{1b} taken together form oxo.

[0246] In some embodiments, each of R^{1a} and R^{1b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with halo, $-CN$, $-NO_2$, R' , $-N(R')_2$, or $-O-R'$; or R^{1a} and R^{1b} taken together form oxo. In some embodiments, each of R^{1a} and R^{1b} is independently selected from $-H$; C_{1-6} alkyl (e.g., methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, or pentyl) optionally substituted with 1-3 groups independently selected from halo, $-CN$, $-OH$, $-NO_2$, C_{1-6} alkoxy (e.g., methoxy, ethoxy, or propoxy), C_{3-6} cycloalkyl, phenyl, a 5-10-membered heteroaryl having 1-3 heteroatoms independently selected from N, O, and S; $-N(H)-C_{1-6}$ alkyl; $-OH$; and $-O-C_{1-6}$ alkyl.

[0247] In some embodiments, each of R^{1a} and R^{1b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{1a} and R^{1b} taken together form oxo.

[0248] In some embodiments, one of R^{1a} and R^{1b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, one of R^{1a} and R^{1b} is $-H$, and the other is $-H$; C_{1-6} alkyl (e.g., methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, or pentyl) optionally substituted with 1-3 groups independently selected from halo, $-CN$, $-OH$, $-NO_2$, C_{1-6} alkoxy, C_{3-6} cycloalkyl, phenyl, or a 5-10-membered heteroaryl having 1-3 heteroatoms independently selected from N, O, and S; $-N(H)-C_{1-6}$ alkyl; $-OH$; or $-O-C_{1-6}$ alkyl. In some embodiments, one of R^{1a} and R^{1b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, one of R^{1a} and R^{1b} is $-H$, and the other is methyl. And, in some embodiments, each of R^{1a} and R^{1b} is $-H$.

[0249] 2. R^{2a} and R^{2b}

[0250] In some embodiments, each of R^{2a} and R^{2b} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'-$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'-$, $-NR'S(O)_2-$, $-C(O)NR'NR'-$, $-NR'C(O)NR'-$, $-OC(O)NR'-$, $-NR'NR'-$, $-NR'S(O)_2NR'-$, $-S(O)-$, or $-S(O)_2-$; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl- $O-C_{1-6}$ alkyl, and an optionally substituted 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, or R^{2a} and R^{2b} taken together form oxo.

[0251] In some embodiments, each of R^{2a} and R^{2b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl optionally substituted with halo, $-CN$, $-NO_2$, R' , $-N(R')_2$, or $-O-R'$; or R^{2a} and R^{2b} taken together form oxo. In some embodiments, each of R^{2a} and R^{2b} is independently selected from $-H$; C_{1-6} alkyl (e.g., methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, or pentyl) optionally substituted with 1-3 groups independently selected from halo, $-CN$, $-OH$, $-NO_2$, C_{1-6} alkoxy, C_{3-6} cycloalkyl, phenyl, or a 5-10-membered heteroaryl having 1-3 heteroatoms independently selected from N, O, and S; $-N(H)-C_{1-6}$ alkyl; $-OH$; and $-O-C_{1-6}$ alkyl.

[0252] In some embodiments, each of R^{2a} and R^{2b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{2a} and R^{2b} taken together form oxo.

[0253] In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is $-H$; C_{1-6} alkyl (e.g., methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, or pentyl) optionally substituted with 1-3 groups independently selected from halo, $-CN$, $-OH$, $-NO_2$, C_{1-6} alkoxy, C_{3-6} cycloalkyl, phenyl, and a 5-10-membered heteroaryl having 1-3 heteroatoms independently selected from N, O, and S; $-N(H)-C_{1-6}$ alkyl; $-OH$; or $-O-C_{1-6}$ alkyl. In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is methyl. And, in some embodiments, each of R^{2a} and R^{2b} is $-H$.

[0254] 3. R^3

[0255] In some embodiments, R^3 is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'-$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'-$, $-NR'S(O)_2-$, $-C(O)NR'NR'-$, $-NR'C(O)NR'-$, $-OC(O)NR'-$, $-NR'NR'-$, $-NR'S(O)_2NR'-$, $-S(O)-$, or $-S(O)_2-$; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl- $O-C_{1-6}$ alkyl, and an optionally substituted 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S.

[0256] In some embodiments, R^3 is $-H$ or C_{1-6} alkyl optionally substituted with halo, $-CN$, $-NO_2$, R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^3 is $-H$ or C_{1-6} alkyl optionally

substituted with R'. In some embodiments, R³ is -H; C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, or pentyl) optionally substituted with 1-3 groups independently selected from halo, -CN, -OH, -NO₂, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, phenyl, and a 5-10-membered heteroaryl having 1-3 heteroatoms independently selected from N, O, and S; -N(H)-C₁₋₆ alkyl; -OH; or -O-C₁₋₆ alkyl. In some embodiments, R³ is -H, -CH₃, -CH₂-CH₂-CH₃, or -CH₂-O-CH₃. In some embodiments, R³ is -H or methyl. And, in some embodiments, R³ is -CH₃.

[0257] In some embodiments, R³ is -H, C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, butyl, iso-butyl, tert-butyl, pentyl, hexyl, or neohexyl), or C₁₋₆ alkyl-O-C₁₋₆ alkyl (e.g., methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, or propoxypropyl). In some embodiments, R³ is methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, neopentyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R³ is -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, or -CH₂-O-CH₃. And, in some embodiments, R³ is -CH₃.

[0258] 4. R^{4a}, R^{4b}, and n

[0259] In some embodiments, n is 0 and both of R^{4a} and R^{4b} are absent.

[0260] In some embodiments, n is 1 or 2; each R^{4a} and R^{4b} is -L^A-R³⁰; each L^A is independently selected from a bond and an optionally substituted branched or straight C₁₋₆ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by -NR'-, -S-, -O-, -OC(O)-, -C(O)O-, -C(O)-, -C(O)C(O)-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)O-, -S(O)₂NR'-, -NR'S(O)₂-, -C(O)NR'NR'-, -NR'C(O)NR'-, -OC(O)NR'-, -NR'NR'-, -NR'S(O)₂NR'-, -S(O)-, or -S(O)₂-; each R³⁰ is independently selected from R', -OH, halo, -CN, -NO₂, and -CF₃; each R' is independently selected from -H, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₁₋₆ alkyl-O-C₁₋₆ alkyl, and an optionally substituted 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, or R^{4a} and R^{4b} taken together form oxo.

[0261] In some embodiments, n is 2 and each R^{4a} and R^{4b} is independently selected from -H, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, and -O-R'. In some embodiments, n is 2, and in one instance of R^{4a} and R^{4b} on the same carbon atom, each of R^{4a} and R^{4b} are independently selected from -H, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, and -O-R', and in another instance (i.e., a second instance) of R^{4a} and R^{4b} on the same carbon atom, both

of R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 2 and each R^{4a} and R^{4b} is independently selected from $-H$ and methyl. In some embodiments, n is 2 and each of R^{4a} and R^{4b} is $-H$.

[0262] In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is methyl. And, in some embodiments, n is 1 and each of R^{4a} and R^{4b} is $-H$.

[0263] 5. R^5

[0264] In some embodiments, R^5 is $-H$ or optionally substituted C_{1-6} alkyl. In some embodiments, R^5 is $-H$ or C_{1-6} alkyl (e.g., C_{1-3} alkyl (e.g., methyl)). In some embodiments, R^5 is $-H$ or methyl. For instance, R^5 is $-H$. In other examples, R^5 is methyl.

[0265] 6. R^{6a} , R^{6b} , R^{7a} , and R^{7b}

[0266] In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'-$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'-$, $-NR'S(O)_2-$, $-C(O)NR'NR'-$, $-NR'C(O)NR'-$, $-OC(O)NR'-$, $-NR'NR'-$, $-NR'S(O)_2NR'-$, $-S(O)-$, or $-S(O)_2-$; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl- O - C_{1-6} alkyl, and an optionally substituted 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo.

[0267] In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo. In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted

with R'. In some embodiments, two of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are –H, and the other two of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are independently selected from –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, and –O-R'. In some embodiments, two of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are –H, and the other two of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are independently selected from –H and methyl. In some embodiments, three of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are –H, and the other is –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, or –O-R'. In some embodiments, three of R^{6a}, R^{6b}, R^{7a}, and R^{7b} are –H, and the other is –H or methyl. In some embodiments, each of R^{6a}, R^{6b}, R^{7a}, and R^{7b} is –H.

[0268] 7. R¹⁰

[0269] In some embodiments, R¹⁰ is –H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl. In some embodiments, R¹⁰ is –H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl. In some embodiments, R¹⁰ is –H, C₁₋₆ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl. In some embodiments, R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl. In some embodiments, R¹⁰ is –H, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl. In some embodiments, R¹⁰ is –H, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R¹⁰ is –H, methyl, or methoxymethyl. And, in some embodiments, R¹⁰ is –H or methyl.

[0270] 8. R^{11a}, R^{11b}, R^{12a}, and R^{12b}

[0271] In some embodiments, each of R^{11a}, R^{11b}, R^{12a}, and R^{12b} is –L^A-R³⁰; each L^A is independently selected from a bond and an optionally substituted branched or straight C₁₋₆ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by –NR'–, –S–, –O–, –OC(O)–, –C(O)O–, –C(O)–, –C(O)C(O)–, –C(O)NR'–, –NR'C(O)–, –NR'C(O)O–, –S(O)₂NR'–, –NR'S(O)₂–, –C(O)NR'NR'–, –NR'C(O)NR'–, –OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, –S(O)–, or –S(O)₂–; each R³⁰ is independently selected from R', –OH, halo, –CN, –NO₂, and –CF₃; each R' is independently selected from –H, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₁₋₆ alkyl-O-C₁₋₆ alkyl, and an optionally substituted 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo.

[0272] In some embodiments, each of R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from –H, C₁₋₆ alkyl optionally substituted with R', –N(R')₂, and –O-R', or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo. In some embodiments, each of

R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' . In some embodiments, two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$. In some embodiments, two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are independently selected from $-H$ and methyl. In some embodiments, three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other is $-H$ or methyl. In some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is $-H$.

[0273] 9. R^{13}

[0274] In some embodiments, R^{13} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'-$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'-$, $-NR'S(O)_2-$, $-C(O)NR'NR'-$, $-NR'C(O)NR'-$, $-OC(O)NR'-$, $-NR'NR'-$, $-NR'S(O)_2NR'-$, $-S(O)-$, or $-S(O)_2-$; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl- O - C_{1-6} alkyl, and an optionally substituted 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S.

[0275] In some embodiments, R^{13} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^{13} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^{13} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl. In some embodiments, R^{13} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{13} is $-H$ or C_{1-6} alkyl. In some embodiments, R^{13} is $-H$ or C_{1-3} alkyl (e.g., methyl or ethyl). In some embodiments, R^{13} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^{13} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl. In some embodiments, R^{13} is $-H$, methyl, ethyl, propyl, or iso-propyl. In some embodiments, R^{13} is $-H$ or methyl. In some embodiments, R^{13} is $-H$, methyl, or methoxymethyl. In some embodiments, R^{13} is $-H$. And, in some embodiments, R^{13} is methyl (e.g., β -methyl).

[0276] 10. R^{15} and m

[0277] In some embodiments, m is 1 or 2 and each R^{15} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl- O - C_{1-6} alkyl, and an optionally substituted 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S.

[0278] In some embodiments, m is 2 and each R^{15} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$. In some embodiments, m is 2 and each R^{15} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' . In some embodiments, m is 2 and each R^{15} is independently selected from $-H$ and C_{1-3} alkyl (e.g., methyl or ethyl). And, in some embodiments, m is 2 and each R^{15} is $-H$.

[0279] In some embodiments, m is 1 and R^{15} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, m is 1 and R^{15} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, m is 1 and R^{15} is $-H$ or C_{1-3} alkyl (e.g., methyl or ethyl). In some embodiments, m is 1 and R^{15} is $-H$ or methyl. In some embodiments, m is 1 and R^{15} is $-H$. In some embodiments, m is 1 and R^{15} is methyl.

[0280] 11. R^{16}

[0281] In some embodiments, R^{16} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl- O - C_{1-6} alkyl, and an optionally substituted 3-8-membered saturated,

partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S.

[0282] In some embodiments, R^{16} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^{16} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^{16} is $-H$ or C_{1-3} alkyl (e.g., methyl or ethyl). In some embodiments, R^{16} is $-H$ or methyl. And, in some embodiments, R^{16} is $-H$.

[0283] 12. R^{17}

[0284] In some embodiments, R^{17} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'-$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'-$, $-NR'S(O)_2-$, $-C(O)NR'NR'-$, $-NR'C(O)NR'-$, $-OC(O)NR'-$, $-NR'NR'-$, $-NR'S(O)_2NR'-$, $-S(O)-$, or $-S(O)_2-$; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl- O - C_{1-6} alkyl, and an optionally substituted 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S.

[0285] In some embodiments, R^{17} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^{17} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^{17} is $-H$ or C_{1-3} alkyl (e.g., methyl or ethyl). And, in some embodiments, R^{17} is $-H$.

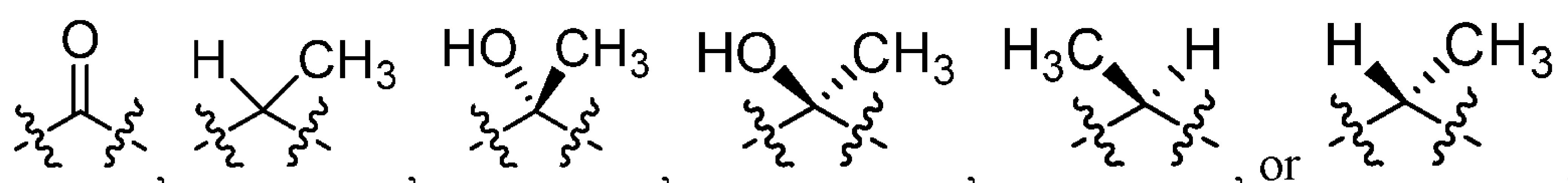
[0286] 13. R^{20a} and R^{20b}

[0287] In some embodiments, each of R^{20a} and R^{20b} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'-$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'-$, $-NR'S(O)_2-$, $-C(O)NR'NR'-$, $-NR'C(O)NR'-$, $-OC(O)NR'-$, $-NR'NR'-$, $-NR'S(O)_2NR'-$, $-S(O)-$, or $-S(O)_2-$; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl- O - C_{1-6} alkyl, and an optionally substituted 3-8-membered

saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, or R^{20a} and R^{20b} taken together form oxo.

[0288] In some embodiments, each of R^{20a} and R^{20b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo. In some embodiments, each of R^{20a} and R^{20b} is independently selected from $-H$, C_{1-6} alkyl, $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo. In some embodiments, R^{20a} and R^{20b} are each independently selected from $-H$, methyl, and $-OH$. In some embodiments, one of R^{20a} and R^{20b} is $-OH$, and the other is $-H$, or methyl. In some embodiments, R^{20a} and R^{20b} taken together form oxo.

[0289] In some embodiments, R^{20a} , R^{20b} , and the carbon atom to which they are attached form



[0290] In some embodiments, one of R^{20a} and R^{20b} is $-H$, and the other is C_{1-6} alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, or hexyl). In some embodiments, one of R^{20a} and R^{20b} is C_{1-6} alkyl, and the other is $-OH$. In some embodiments, one of R^{20a} and R^{20b} is methyl, ethyl, or propyl, and the other is $-OH$. In some embodiments, one of R^{20a} and R^{20b} is $-H$, and the other is methyl or ethyl.

[0291] 14. R^{20c}

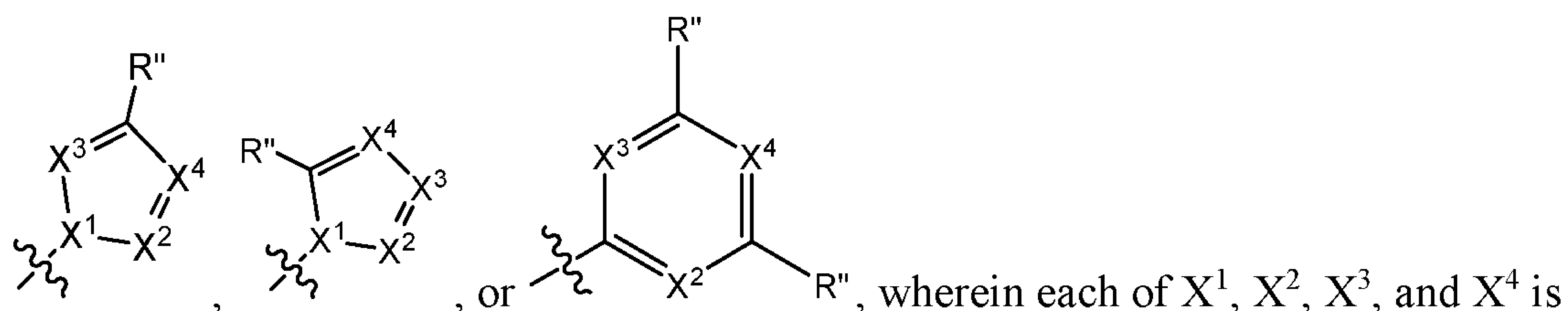
[0292] In some embodiments, R^{20c} is $-H$ or optionally substituted C_{1-6} alkyl. In some embodiments, R^{20c} is $-H$ or C_{1-6} alkyl (e.g., C_{1-3} alkyl (e.g., methyl)). In some embodiments, R^{20c} is $-H$ or methyl. For instance, R^{20c} is $-H$. In other examples, R^{20c} is methyl.

[0293] 15. R^{21}

[0294] In some embodiments, R^{21} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'-$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'-$, $-NR'S(O)_2-$, $-C(O)NR'NR'-$, $-NR'C(O)NR'-$, $-OC(O)NR'-$, $-NR'NR'-$, $-NR'S(O)_2NR'-$, $-S(O)-$, or $-S(O)_2-$; each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{1-6} alkyl- O - C_{1-6} alkyl, and an optionally substituted 3-8-membered saturated,

partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S.

[0295] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{-CH}_2-$, $-\text{CH}_2\text{-CH}_2\text{-CH}_2-$, or $-\text{NH}-$; and R^{30} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-\text{CH}_2-$, or $-\text{NH}-$; and R^{30} is a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond or $-\text{CH}_2-$; and R^{30} is a 5-6-membered partially unsaturated or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-2 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond or $-\text{CH}_2-$; and R^{30} is

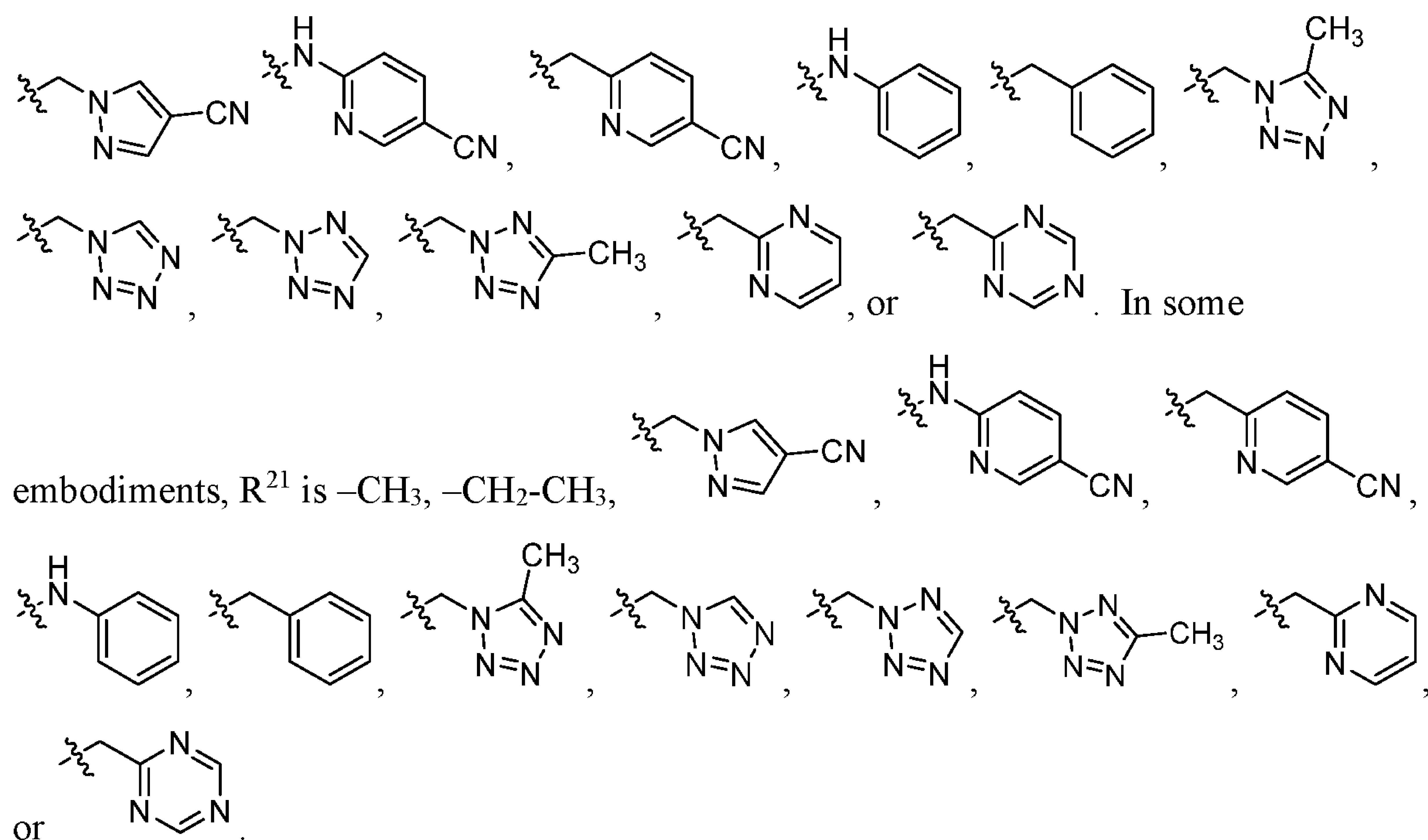


independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some

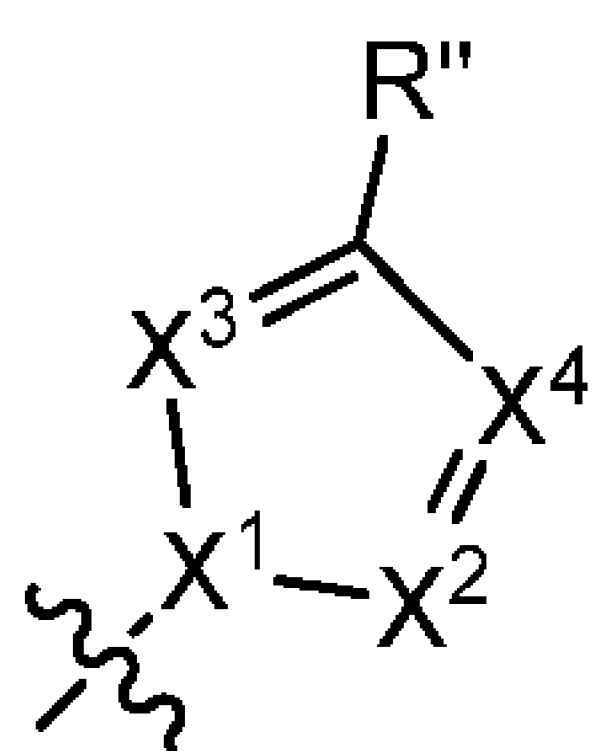
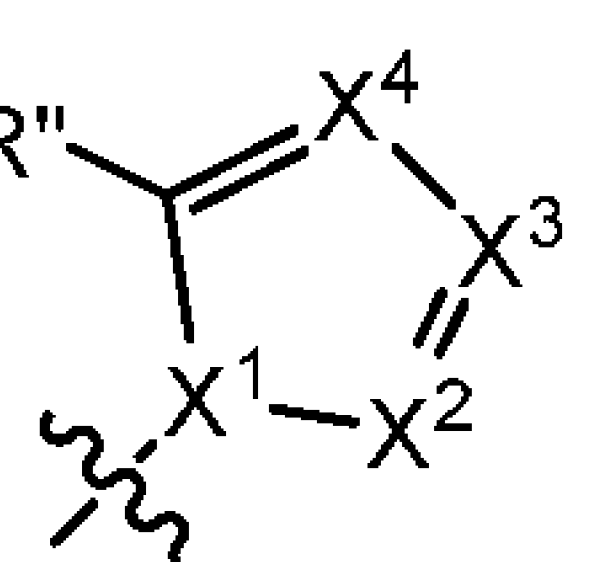
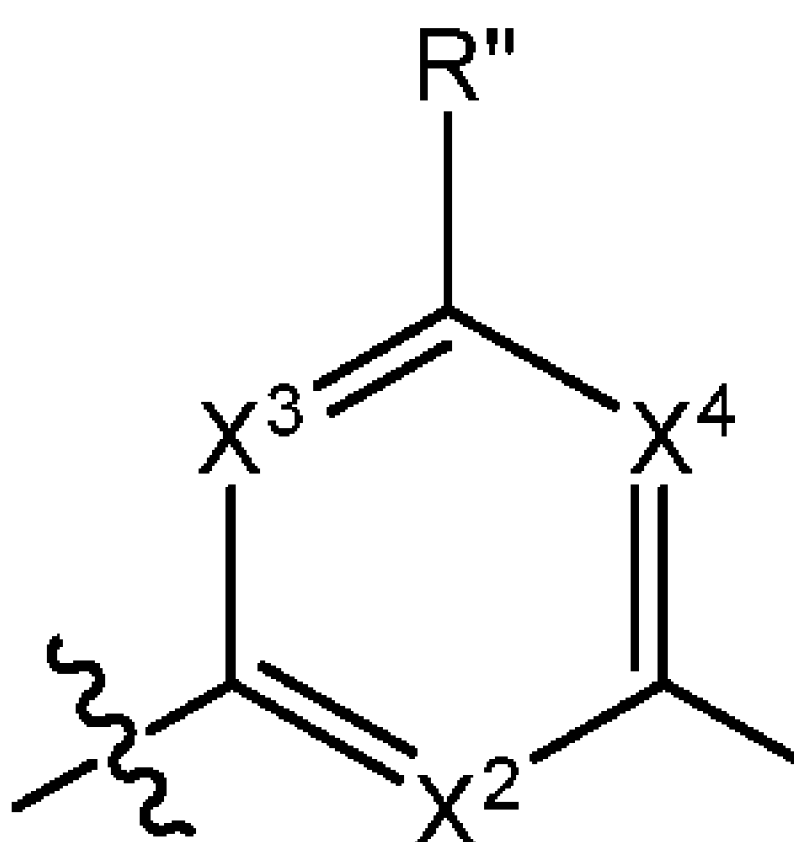
embodiments, R^{30} is or , X^1 is N; and each of X^2 , X^3 , and X^4 is

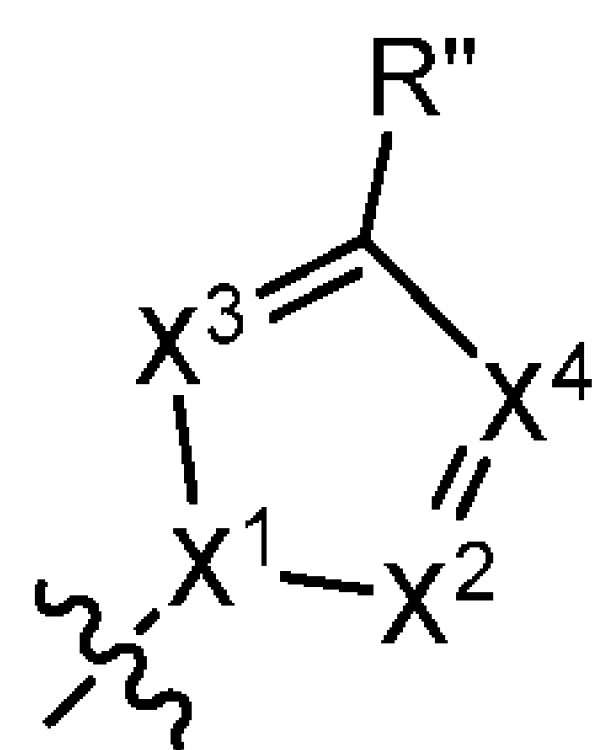
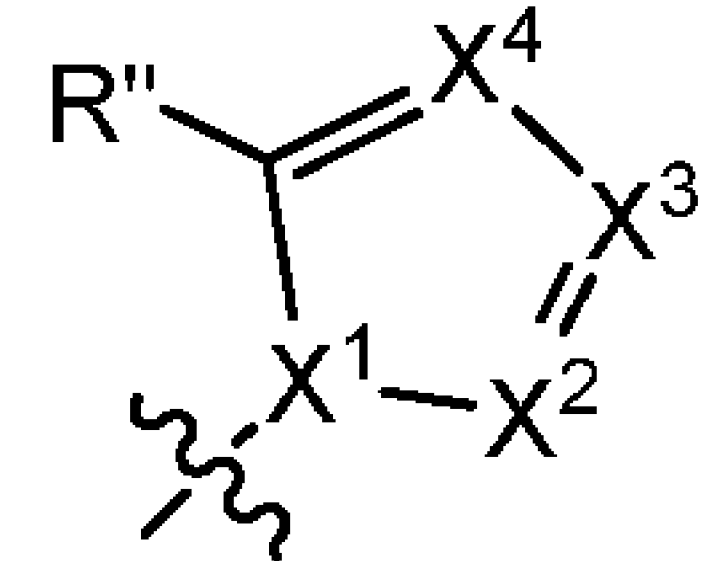
independently selected from N or CR", wherein each R" is independently selected from -H, -OH, -CN, -NO₂, -CF₃, -CH₃, and -CH₂OH, provided that no greater than 2 instances of R" are independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, and -CH₂OH.

[0296] In some embodiments, R²¹ is -CH₃, -CH₂-CH₃, -O-CH₃, -O-CH₂-CH₃,



[0297] In some embodiments, R²¹ is -L^A-R³⁰; L^A is a bond, a branched or straight C₁₋₃ alkylene chain, or -N(H)-; and R³⁰ is -H, -OH, -CN, -NO₂, -CF₃, or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6 membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃. In some embodiments, R²¹ is -L^A-R³⁰; L^A is a bond, -CH₂-, -CH₂-CH₂-, or -N(H)-; and R³⁰ is -H or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, or -C(CH₃)₃. In some embodiments, R²¹ is -L^A-R³⁰; L^A is a bond, -CH₂-, -CH₂-CH₂-, or -N(H)-; and R³⁰ is a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, or -C(CH₃)₃. In some embodiments, R²¹ is -L^A-R³⁰; L^A is a bond,

$-\text{CH}_2-$, or $-\text{N}(\text{H})-$; and R^{30} is  ,  , or  , wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$,

$-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, R^{30} is  or  , X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N and CR'' , wherein each R'' is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$, provided that no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$.

[0298] 16. R^{31a} and R^{31b}

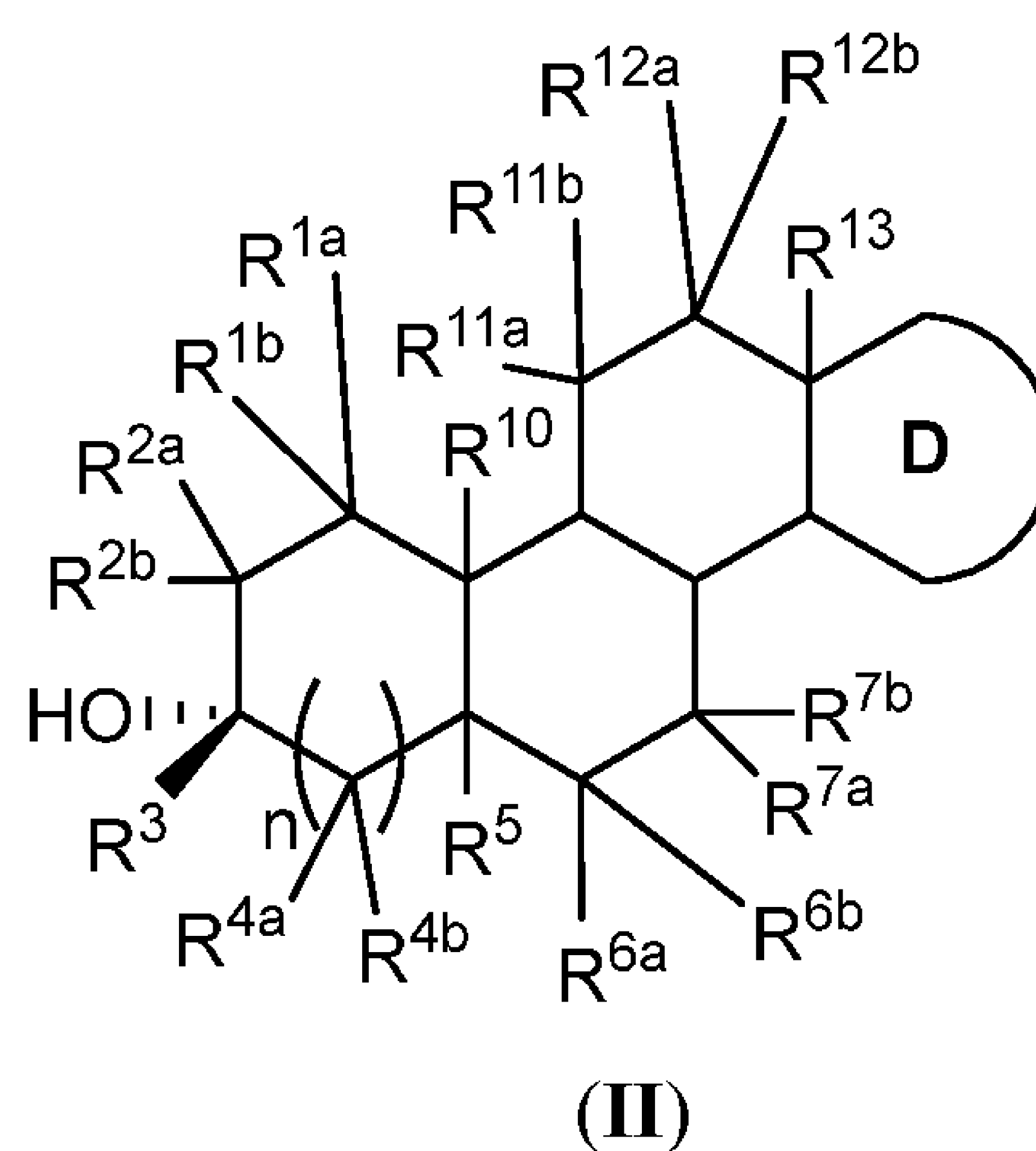
[0299] In some embodiments, each of R^{31a} and R^{31b} is independently selected from $-\text{H}$, halo, C_{1-6} alkyl, and $-\text{OR}^{32}$, wherein R^{32} is $-\text{H}$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, or S.

[0300] In some embodiments, each of R^{31a} and R^{31b} is independently selected from $-\text{H}$, halo, and C_{1-6} alkyl, or when one of R^{31a} and R^{31b} is $-\text{H}$, the other is $-\text{H}$, halo, C_{1-6} alkyl, or $-\text{OR}^{32}$, wherein R^{32} is $-\text{H}$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S. In some embodiments, one of R^{31a} and R^{31b} is $-\text{H}$, and the other is $-\text{H}$, halo, C_{1-6} alkyl, or $-\text{OR}^{32}$, wherein R^{32} is $-\text{H}$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O,

and S. In some embodiments, each of R^{31a} and R^{31b} is independently selected from $-H$, halo, and C_{1-6} alkyl. In some embodiments, one of R^{31a} and R^{31b} is $-H$, and the other is $-OH$, $-O-C_{1-6}$ alkyl, $-O$ -phenyl, or $-O-C_{3-6}$ cycloalkyl. In some embodiments, each of R^{31a} and R^{31b} is $-H$.

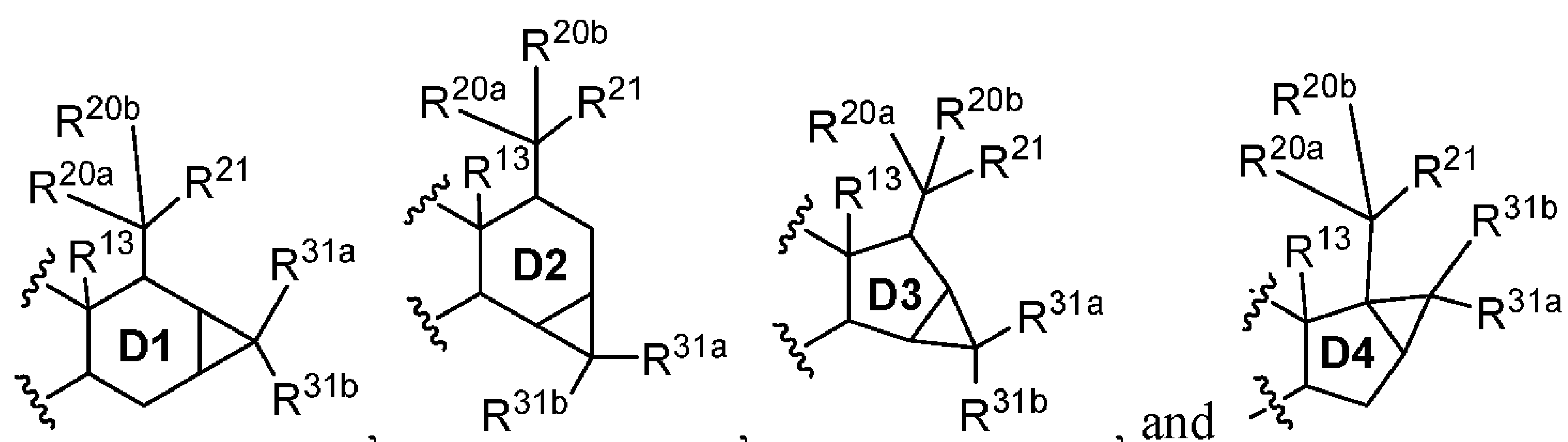
[0301] C. Other Compounds of the Present Invention

[0302] Another aspect of the present invention provides a compound of Formula (II)



or a pharmaceutically acceptable salt thereof, wherein ring D, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20a} , R^{20b} , R^{20c} , R^{21} , R^{31a} , R^{31b} , m , and n are as defined in any of the embodiments of the compound of Formula (I).

[0303] In some embodiments, ring D is a fused bicyclic ring selected from



each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{20a} , R^{20b} , and R^{21} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'$, $-NR'S(O)_2-$, $-C(O)NR'NR'$, $-S(O)-$, $-NR'C(O)NR'$, $-OC(O)NR'$, $-NR'NR'$, $-NR'S(O)_2NR'$, or $-S(O)_2-$; R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, C_{1-6} alkyl (e.g., C_{1-3} alkyl), C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently

selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃, or R^{1a} and R^{1b} taken together form oxo, or R^{2a} and R^{2b} taken together form oxo, or R^{4a} and R^{4b} taken together form oxo, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo, or R^{20a} and R^{20b} taken together form oxo; R⁵ is -H or C₁₋₆ alkyl; R¹⁰ is -H or optionally substituted C₁₋₆ alkyl; R¹³ is -H or optionally substituted C₁₋₆ alkyl; each of R^{31a} and R^{31b} is independently selected from -H, halo, C₁₋₆ alkyl, and -OR³², wherein R³² is -H, C₁₋₆ alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S; and n is 0, 1, or 2, provided that when one of R^{31a} and R^{31b} is -OR³², the other of R^{31a} and R^{31b} is -H.

[0304] In some embodiments, each of R^{1a} and R^{1b} is independently selected from -H, halo, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, and -O-R'; or R^{1a} and R^{1b} taken together form oxo. In some embodiments, each of R^{1a} and R^{1b} is independently selected from -H and C₁₋₆ alkyl optionally substituted with R', or R^{1a} and R^{1b} taken together form oxo.

[0305] In some embodiments, each of R^{1a} and R^{1b} is independently selected from -H, -OH, C₁₋₆ alkyl (e.g., C₁₋₃ alkyl), and C₁₋₆ alkoxy (e.g., C₁₋₃ alkoxy).

[0306] In some embodiments, one of R^{1a} and R^{1b} is -H, and the other is -H, halo, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, or -O-R'. In some embodiments, one of R^{1a} and R^{1b} is -H, and the other is -H, C₁₋₆ alkyl optionally substituted with R', or optionally substituted C₁₋₆ alkoxy. In some embodiments, one of R^{1a} and R^{1b} is -H, and the other is -H or C₁₋₆ alkyl optionally substituted with R'. In some embodiments, one of R^{1a} and R^{1b} is -H, and the other is -H or C₁₋₃ alkyl. In some embodiments, one of R^{1a} and R^{1b} is -H, and the other is methyl. In some embodiments, one of R^{1a} and R^{1b} is -H, and the other is halo. In some embodiments, each of R^{1a} and R^{1b} is -H. In some embodiments, each of R^{1a} and R^{1b} is halo. And, in some embodiments, each of R^{1a} and R^{1b} is C₁₋₃ alkyl.

[0307] In some embodiments, each of R^{2a} and R^{2b} is independently selected from -H, halo, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, and -O-R'; or R^{2a} and R^{2b} taken together form oxo. In some embodiments, each of R^{2a} and R^{2b} is independently selected from -H and C₁₋₆ alkyl optionally substituted with R'; or R^{2a} and R^{2b} taken together form oxo.

[0308] In some embodiments, each of R^{2a} and R^{2b} is independently selected from -H, -OH, C₁₋₆ alkyl (e.g., C₁₋₃ alkyl), and C₁₋₆ alkoxy (e.g., C₁₋₃ alkoxy).

[0309] In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is $-H$, halo, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is methyl. In some embodiments, one of R^{2a} and R^{2b} is $-H$, and the other is halo. In some embodiments, each of R^{2a} and R^{2b} is $-H$. In some embodiments, each of R^{2a} and R^{2b} is halo. And, in some embodiments, each of R^{2a} and R^{2b} is C_{1-3} alkyl.

[0310] In some embodiments, R^3 is $-H$, halo, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^3 is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^3 is $-H$, $-CH_3$, $-CH_2-CH_2-CH_3$, or $-CH_2-O-CH_3$. In some embodiments, R^3 is $-H$ or methyl. In some embodiments, R^3 is halo.

[0311] In some embodiments, n is 0 and both of R^{4a} and R^{4b} are absent.

[0312] In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$, halo, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$; or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' ; or R^{4a} and R^{4b} taken together form oxo.

[0313] In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$, $-OH$, C_{1-6} alkyl (e.g., C_{1-3} alkyl), and C_{1-6} alkoxy (e.g., C_{1-3} alkoxy).

[0314] In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is methyl. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is halo. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-OH$. And, in some embodiments, n is 1 and each of R^{4a} and R^{4b} is $-H$.

[0315] In some embodiments, R^5 is $-H$ or methyl. In some embodiments, R^5 is $-H$.

[0316] In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$, halo, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$; or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo. In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' .

[0317] In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$, $-OH$, C_{1-6} alkyl (e.g., C_{1-3} alkyl), and C_{1-6} alkoxy (e.g., C_{1-3} alkoxy).

[0318] In some embodiments, two of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other two of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$. In some embodiments, three of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, three of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other is $-H$ or methyl. And, in some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is $-H$.

[0319] In some embodiments, R^{10} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl. And, in some embodiments, R^{10} is $-H$, methyl, or methoxymethyl.

[0320] In some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$; or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo. In some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' .

[0321] In some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$, $-OH$, C_{1-6} alkyl (e.g., C_{1-3} alkyl), and C_{1-6} alkoxy (e.g., C_{1-3} alkoxy).

[0322] In some embodiments, two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$. In some embodiments, two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are independently selected from $-H$ and methyl. In some embodiments, three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other is $-H$, $-OH$, halo, or methyl. In some embodiments, three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other is $-H$ or methyl. And, in some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is $-H$.

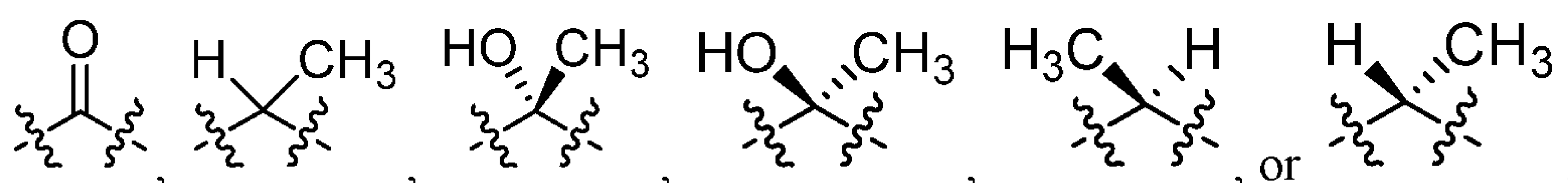
[0323] In some embodiments, R^{13} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{13} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{13} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl. In some embodiments, R^{13} is $-H$, methyl, or methoxymethyl. And, in some embodiments, R^{13} is methyl.

[0324] In some embodiments, each of R^{20a} and R^{20b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$; or R^{20a} and R^{20b} taken together form oxo. In some embodiments, each of R^{20a} and R^{20b} are independently selected from $-H$, C_{1-6} alkyl, $-N(R')_2$, and $-O-R'$; or R^{20a} and R^{20b} taken together form oxo.

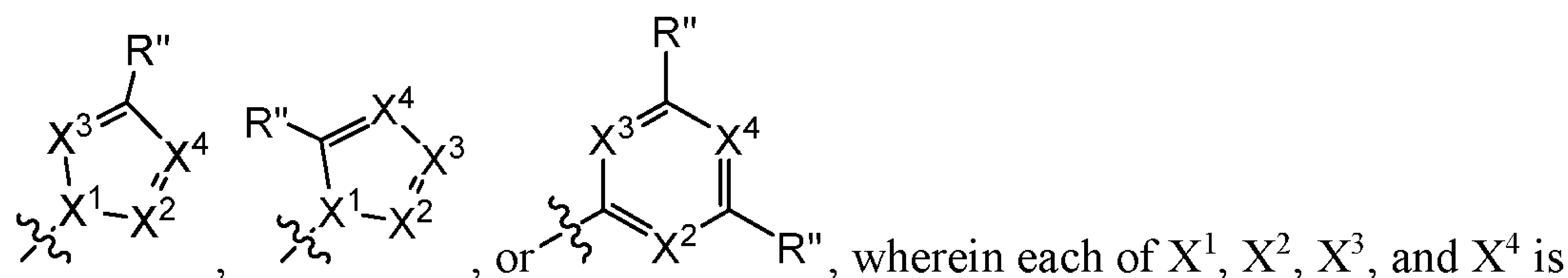
[0325] In some embodiments, each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, C_{1-6} alkyl (e.g., C_{1-3} alkyl), and C_{1-6} alkoxy (e.g., C_{1-3} alkoxy).

[0326] In some embodiments, R^{20a} and R^{20b} are independently selected from $-H$, methyl, and $-OH$. In some embodiments, one of R^{20a} and R^{20b} is $-OH$, and the other is $-H$, or methyl. And, in some embodiments, R^{20a} and R^{20b} taken together form oxo.

[0327] In some embodiments, R^{20a} , R^{20b} , and the carbon atom to which they are attached form

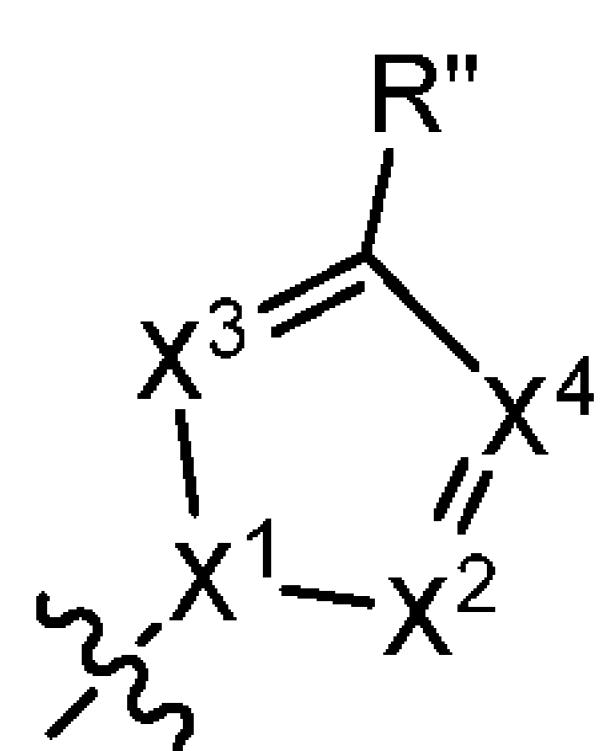
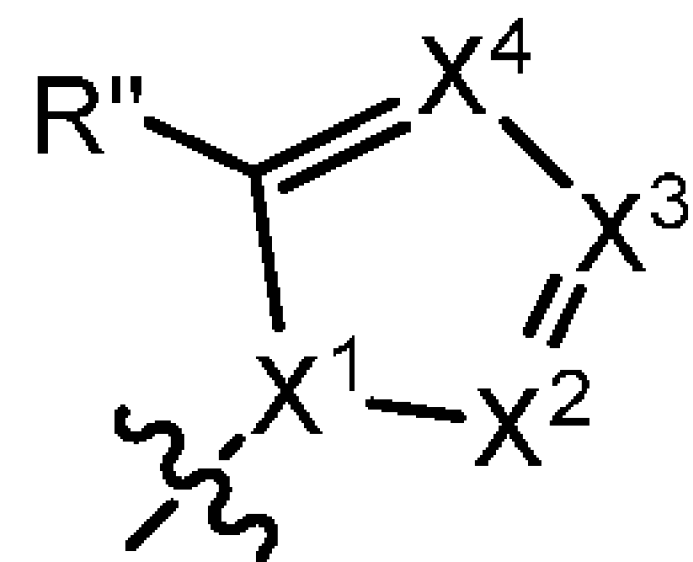


[0328] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, or $-NH-$; and R^{30} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, or $-NH-$; and R^{30} is a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond or $-CH_2-$; and R^{30} is a 5-6-membered partially unsaturated or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-2 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond or $-CH_2-$; and R^{30} is



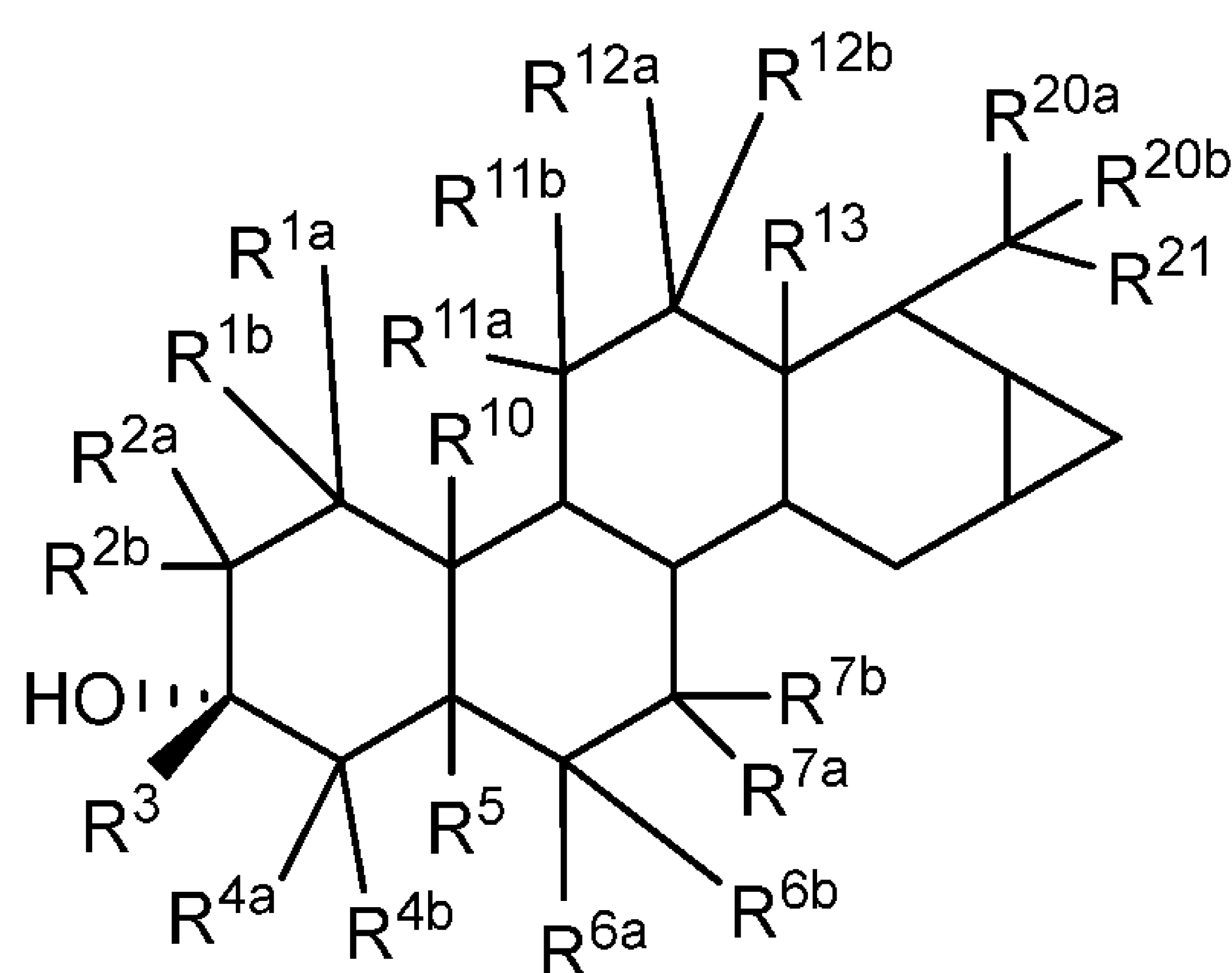
independently N or CR'' , wherein each R'' is independently selected from $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$, provided that (i) at least one of X^1 , X^2 ,

X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, and $-CH_2OH$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, or $-CH_2OH$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, and $-CH_2OH$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, or $-CH_2OH$. In some

embodiments, R^{30} is  or , X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N and CR'' , wherein each R'' is independently selected from $-H$, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, and $-CH_2OH$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, and $-CH_2OH$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, or $-CH_2OH$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, and $-CH_2OH$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, or $-CH_2OH$.

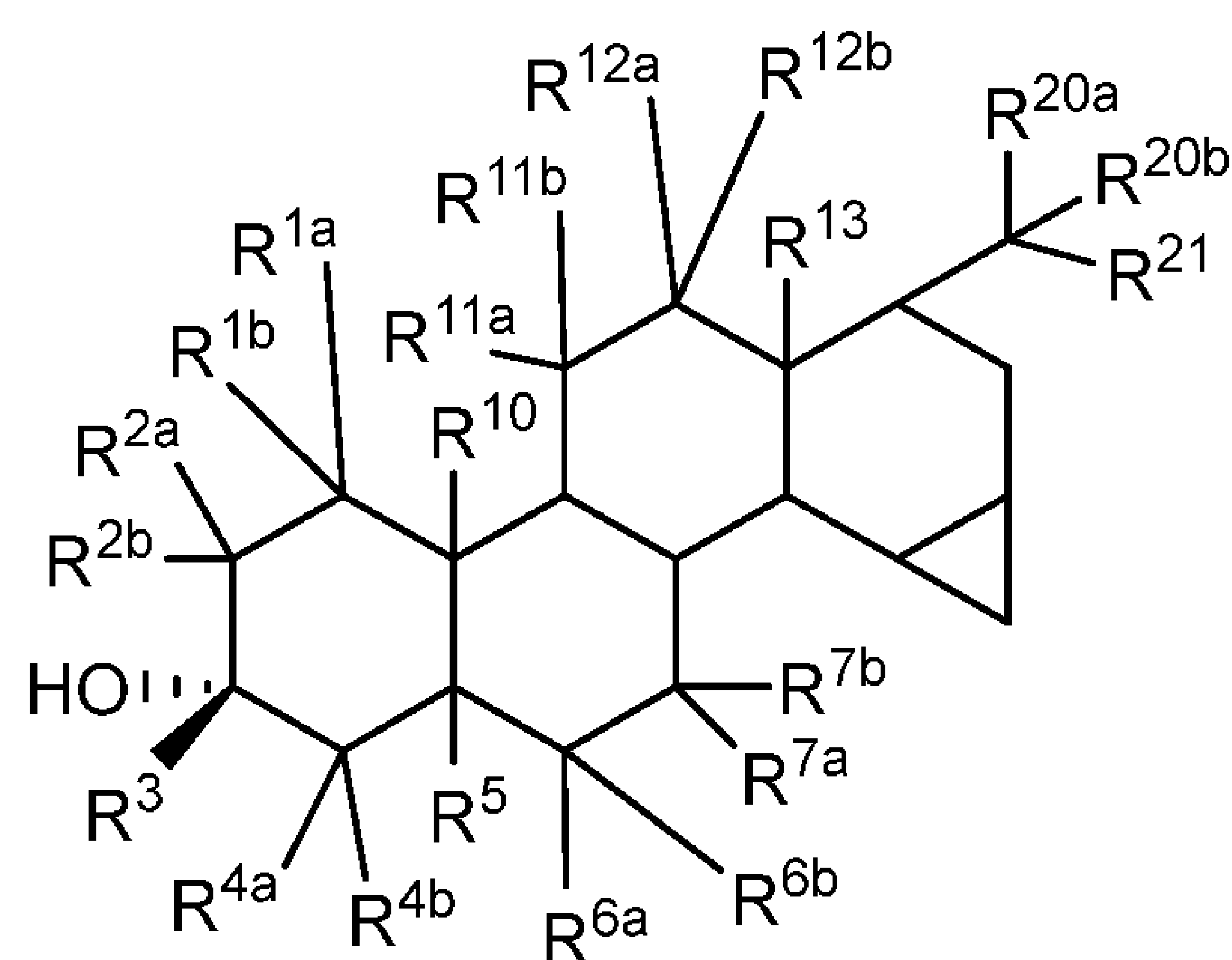
[0329] In some embodiments, each of R^{31a} and R^{31b} is independently selected from $-H$, halo, and C_{1-6} alkyl, or when one of R^{31a} and R^{31b} is $-H$, the other is $-H$, halo, C_{1-6} alkyl, or $-OR^{32}$, wherein R^{32} is $-H$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S. In some embodiments, one of R^{31a} and R^{31b} is $-H$, and the other is $-H$, halo, C_{1-6} alkyl, or $-OR^{32}$, wherein R^{32} is $-H$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S. In some embodiments, each of R^{31a} and R^{31b} is independently selected from $-H$, halo, and C_{1-6} alkyl. In some embodiments, one of R^{31a} and R^{31b} is $-H$, and the other is $-OH$, $-O-C_{1-6}$ alkyl, $-O$ -phenyl, or $-O-C_{3-6}$ cycloalkyl. And, in some embodiments, each of R^{31a} and R^{31b} is $-H$.

[0330] Another aspect of the present invention provides a compound of Formula (II-A) or (II-B)



(II-A)

or



(II-B)

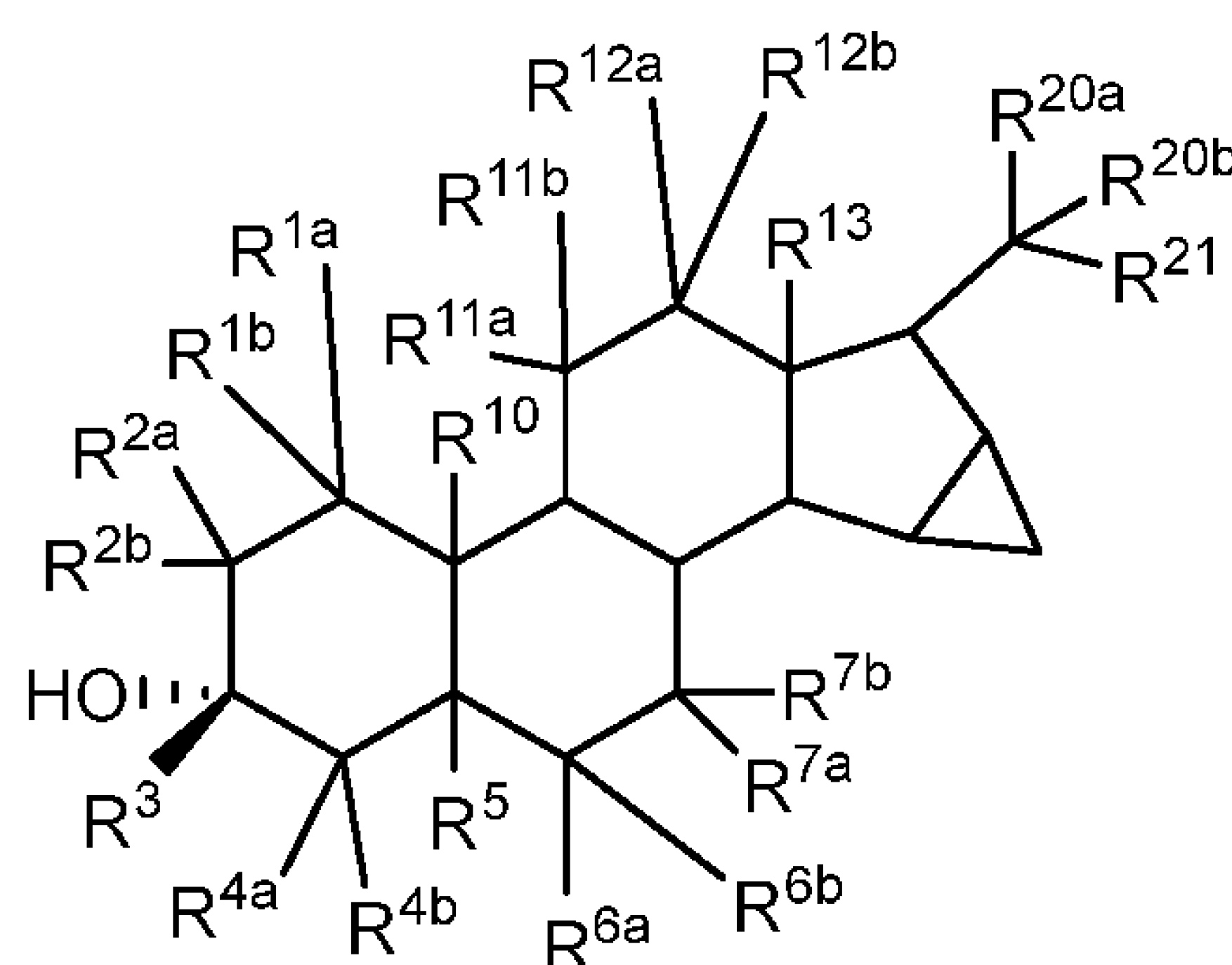
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I) or (II).

[0331] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{20a} , R^{20b} , and R^{21} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'-$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'-$, $-NR'S(O)_2-$, $-C(O)NR'NR'-$, $-NR'C(O)NR'-$, $-OC(O)NR'-$, $-NR'NR'-$, $-NR'S(O)_2NR'-$, $-S(O)-$, or $-S(O)_2-$; R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$, or R^{20a} and R^{20b} taken together form oxo; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$ or optionally substituted C_{1-3} alkyl; and R^{13} is $-H$ or optionally substituted C_{1-3} alkyl.

[0332] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl); R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-3} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-CH_2OH$, C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A

are optionally and independently replaced by $-\text{NR}'-$, $-\text{S}-$, $-\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}'-$, $-\text{NR}'\text{C}(\text{O})-$, $-\text{NR}'\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})_2\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2-$, $-\text{C}(\text{O})\text{NR}'\text{NR}'-$, $-\text{NR}'\text{C}(\text{O})\text{NR}'-$, $-\text{OC}(\text{O})\text{NR}'-$, $-\text{NR}'\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2\text{NR}'-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2-$; R^{30} is independently selected from R' , halo, $-\text{CN}$, $-\text{NO}_2$, and $-\text{CF}_3$; each R' is independently selected from $-\text{H}$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, and $-\text{CH}_3$.

[0333] Another aspect of the present invention provides a compound of Formula (II-C)



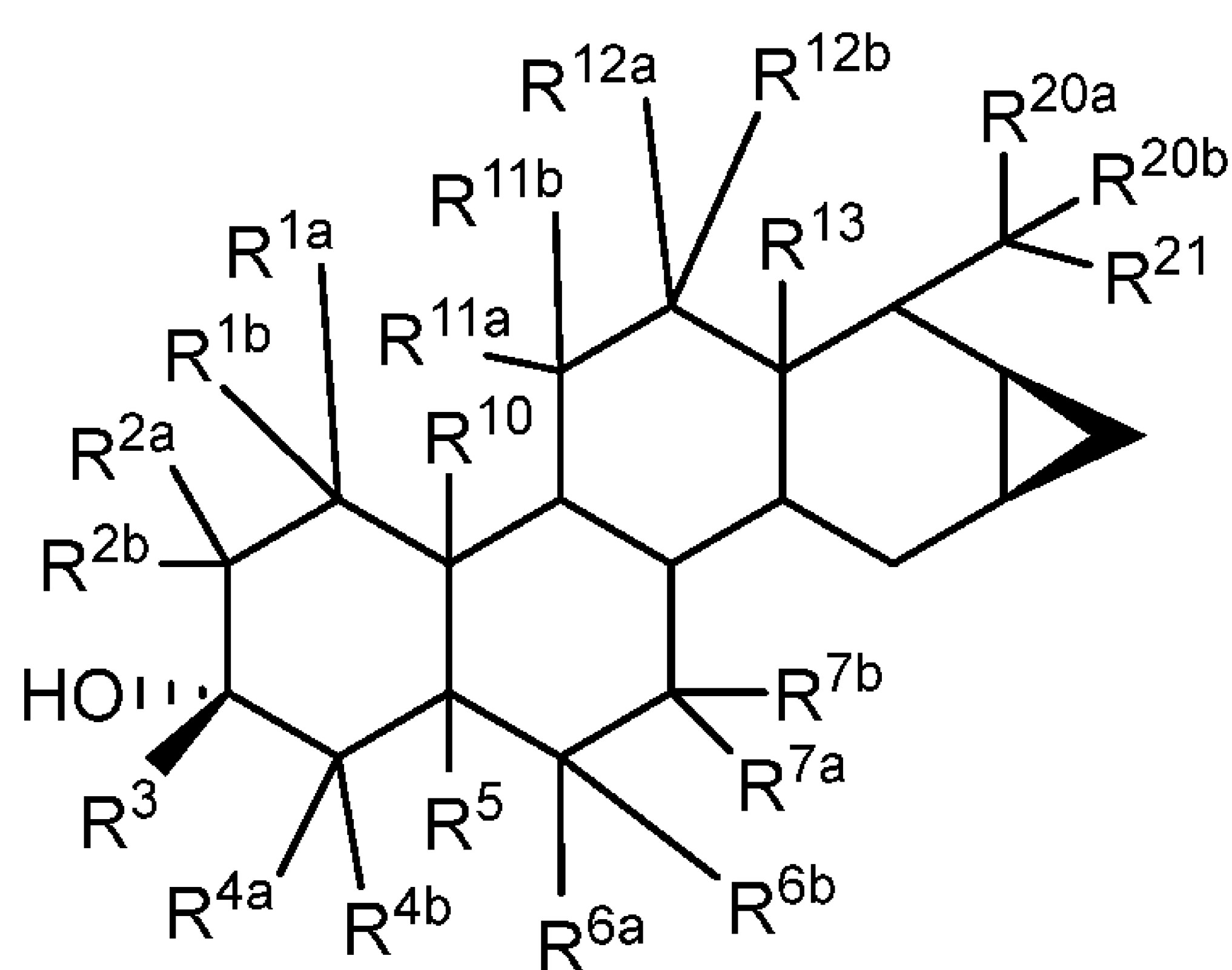
(II-C)

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I) or (II).

[0334] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{20a} , R^{20b} , and R^{21} is $-\text{L}^A-\text{R}^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-\text{NR}'-$, $-\text{S}-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}'-$, $-\text{NR}'\text{C}(\text{O})-$, $-\text{NR}'\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})_2\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2-$, $-\text{C}(\text{O})\text{NR}'\text{NR}'-$, $-\text{NR}'\text{C}(\text{O})\text{NR}'-$, $-\text{OC}(\text{O})\text{NR}'-$, $-\text{NR}'\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2\text{NR}'-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2-$; each R^{30} is independently selected from R' , halo, $-\text{CN}$, $-\text{NO}_2$, and $-\text{CF}_3$; each R' is independently selected from $-\text{H}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, or R^{20a} and R^{20b} taken together form oxo; R^5 is $-\text{H}$ or C_{1-6} alkyl; R^{10} is $-\text{H}$ or optionally substituted C_{1-3} alkyl; and R^{13} is $-\text{H}$ or optionally substituted C_{1-3} alkyl.

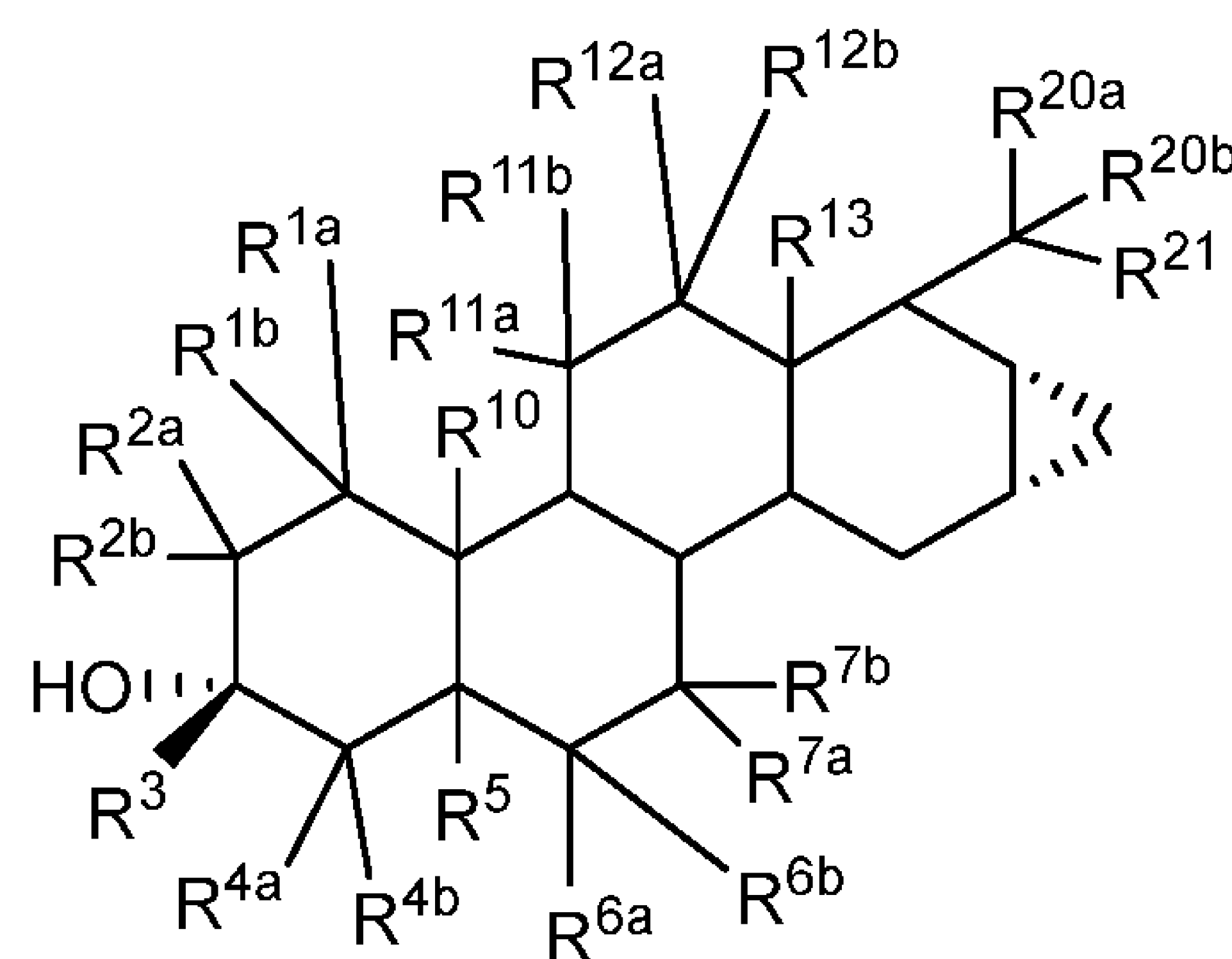
[0335] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl), R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-3} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-S(O)$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, or $-S(O)_2$ -; R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0336] Another aspect of the present invention provides a compound of Formula (II-A1) or (II-A2)



(II-A1)

or



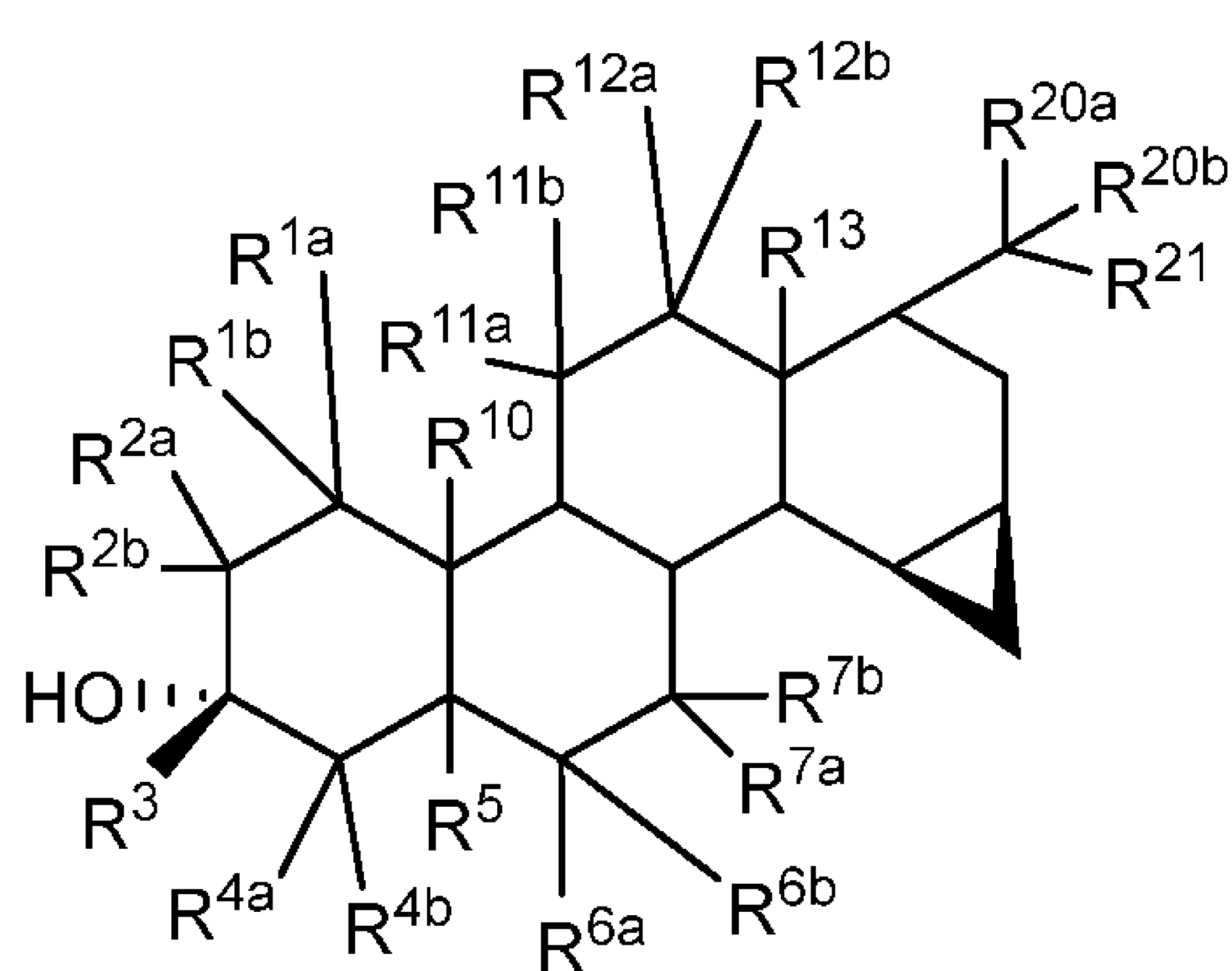
(II-A2),

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), or (II-A).

[0337] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl), R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl,

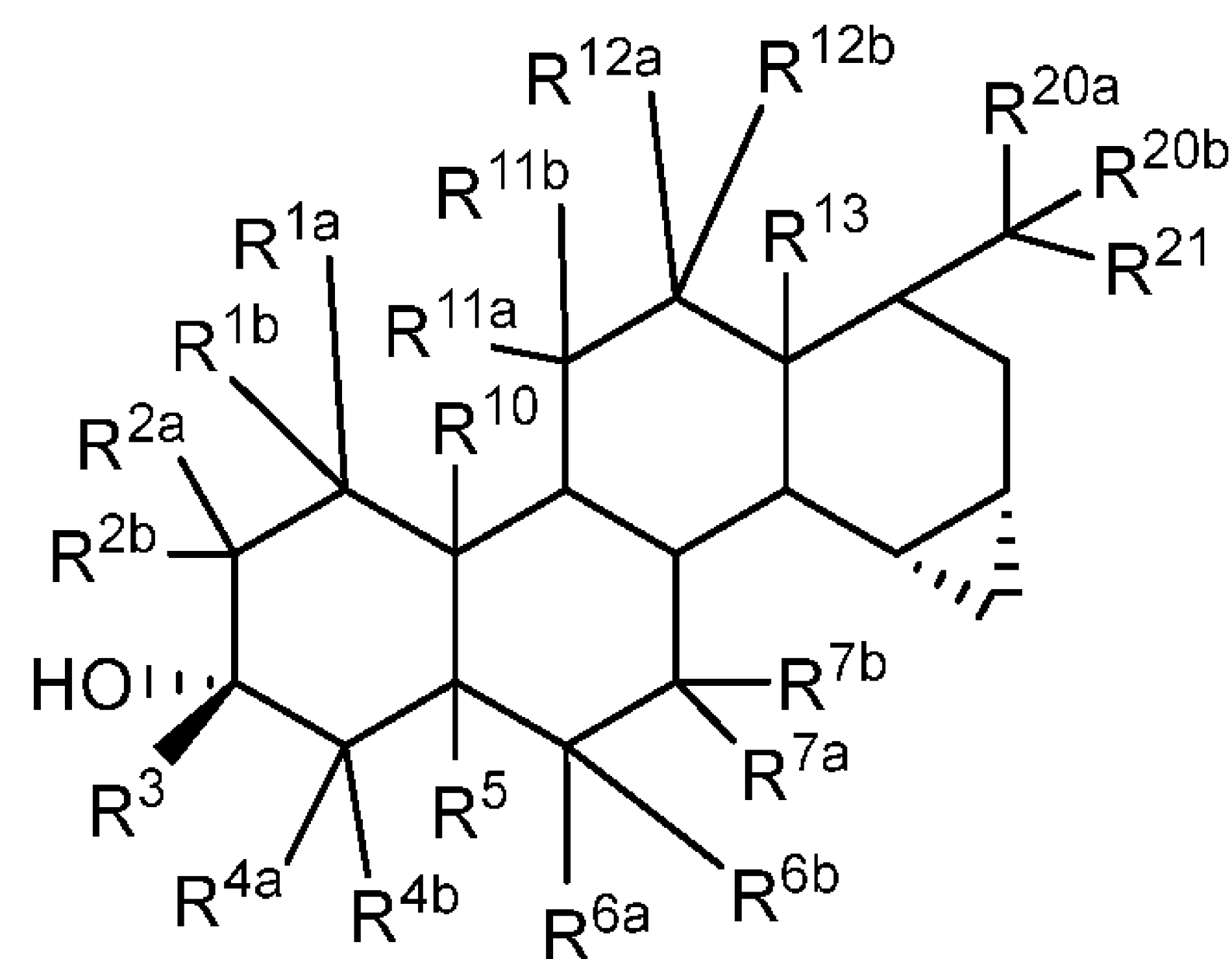
and $-\text{NH}_2$, or $\text{R}^{20\text{a}}$ and $\text{R}^{20\text{b}}$ taken together form oxo; R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^{A} are optionally and independently replaced by $-\text{NR}'$ -, $-\text{S}-$, $-\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}'$ -, $-\text{NR}'\text{C}(\text{O})-$, $-\text{NR}'\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})_2\text{NR}'$ -, $-\text{NR}'\text{S}(\text{O})_2-$, $-\text{C}(\text{O})\text{NR}'\text{NR}'$ -, $-\text{S}(\text{O})-$, $-\text{NR}'\text{C}(\text{O})\text{NR}'$ -, $-\text{OC}(\text{O})\text{NR}'$ -, $-\text{NR}'\text{NR}'$ -, $-\text{NR}'\text{S}(\text{O})_2\text{NR}'$ -, or $-\text{S}(\text{O})_2-$; R^{30} is selected from R' , halo, $-\text{CN}$, $-\text{NO}_2$, and $-\text{CF}_3$; and each R' is independently selected from $-\text{H}$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, and $-\text{CH}_3$.

[0338] Another aspect of the present invention provides a compound of Formula (II-B1) or (II-B2)



(II-B1)

or



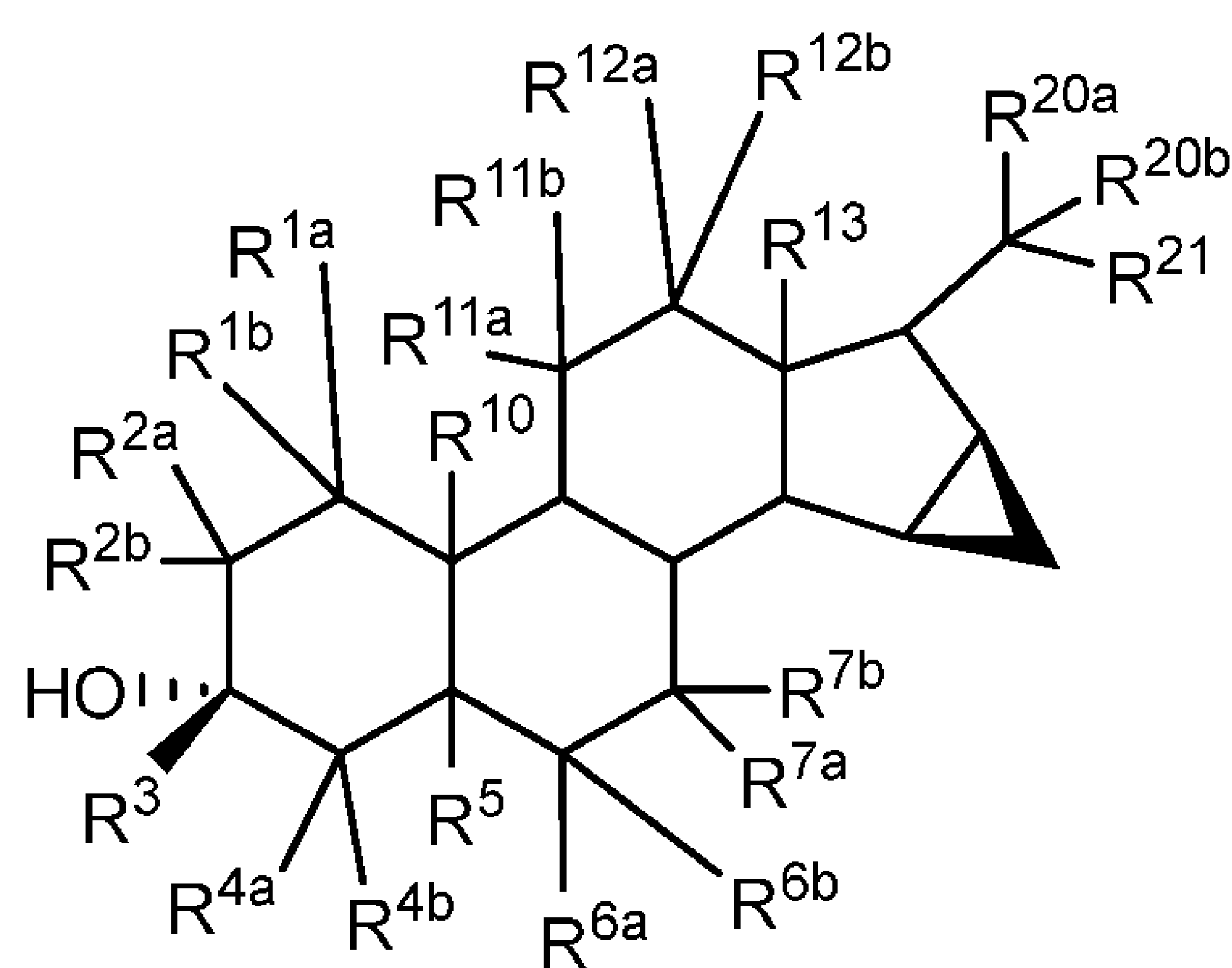
(II-B2),

or a pharmaceutically acceptable salt thereof, wherein $\text{R}^{1\text{a}}$, $\text{R}^{1\text{b}}$, $\text{R}^{2\text{a}}$, $\text{R}^{2\text{b}}$, R^3 , $\text{R}^{4\text{a}}$, $\text{R}^{4\text{b}}$, R^5 , $\text{R}^{6\text{a}}$, $\text{R}^{6\text{b}}$, $\text{R}^{7\text{a}}$, $\text{R}^{7\text{b}}$, R^{10} , $\text{R}^{11\text{a}}$, $\text{R}^{11\text{b}}$, $\text{R}^{12\text{a}}$, $\text{R}^{12\text{b}}$, R^{13} , $\text{R}^{20\text{a}}$, $\text{R}^{20\text{b}}$, and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), or (II-B).

[0339] In some embodiments, each of $\text{R}^{1\text{a}}$, $\text{R}^{1\text{b}}$, $\text{R}^{2\text{a}}$, $\text{R}^{2\text{b}}$, $\text{R}^{4\text{a}}$, $\text{R}^{4\text{b}}$, $\text{R}^{6\text{a}}$, $\text{R}^{6\text{b}}$, $\text{R}^{7\text{a}}$, $\text{R}^{7\text{b}}$, $\text{R}^{11\text{a}}$, $\text{R}^{11\text{b}}$, $\text{R}^{12\text{a}}$, and $\text{R}^{12\text{b}}$ is independently selected from $-\text{H}$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl), R^3 is $-\text{H}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-\text{H}$ or C_{1-6} alkyl; R^{10} is $-\text{H}$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-\text{H}$ or optionally substituted C_{1-3} alkyl; each of $\text{R}^{20\text{a}}$ and $\text{R}^{20\text{b}}$ is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{C}_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-\text{NH}_2$, or $\text{R}^{20\text{a}}$ and $\text{R}^{20\text{b}}$ taken together form oxo; R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^{A} are optionally and independently replaced by $-\text{NR}'$ -, $-\text{S}-$, $-\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}'$ -, $-\text{NR}'\text{C}(\text{O})-$, $-\text{NR}'\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})_2\text{NR}'$ -, $-\text{NR}'\text{S}(\text{O})_2-$, $-\text{C}(\text{O})\text{NR}'\text{NR}'$ -, $-\text{S}(\text{O})-$, $-\text{NR}'\text{C}(\text{O})\text{NR}'$ -, $-\text{OC}(\text{O})\text{NR}'$ -, $-\text{NR}'\text{NR}'$ -,

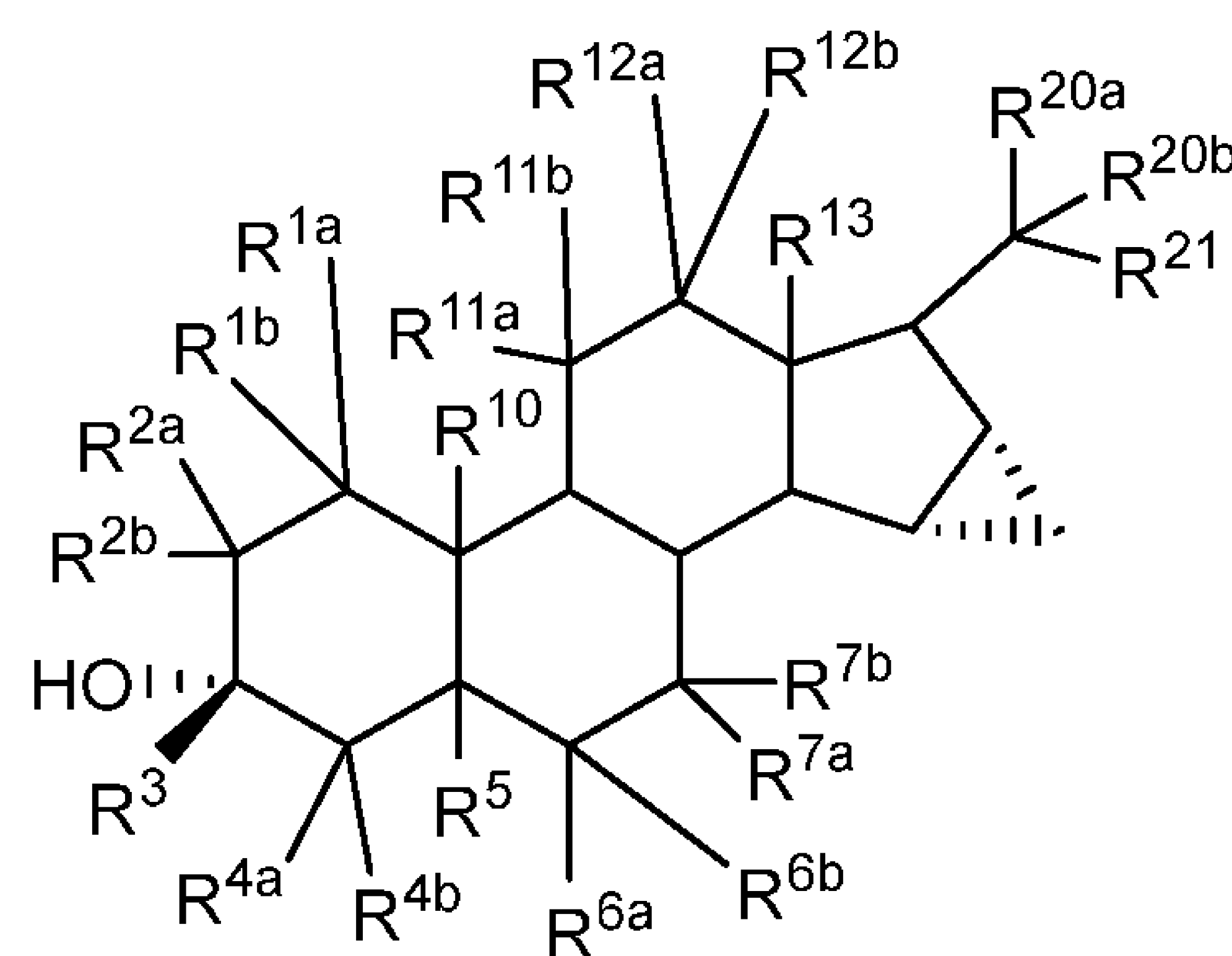
$-\text{NR}'\text{S}(\text{O})_2\text{NR}'-$, or $-\text{S}(\text{O})_2-$; R^{30} is selected from R' , halo, $-\text{CN}$, $-\text{NO}_2$, and $-\text{CF}_3$; and each R' is independently selected from $-\text{H}$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, and $-\text{CH}_3$.

[0340] Another aspect of the present invention provides a compound of Formula (II-C1) or (II-C2)



(II-C1)

or

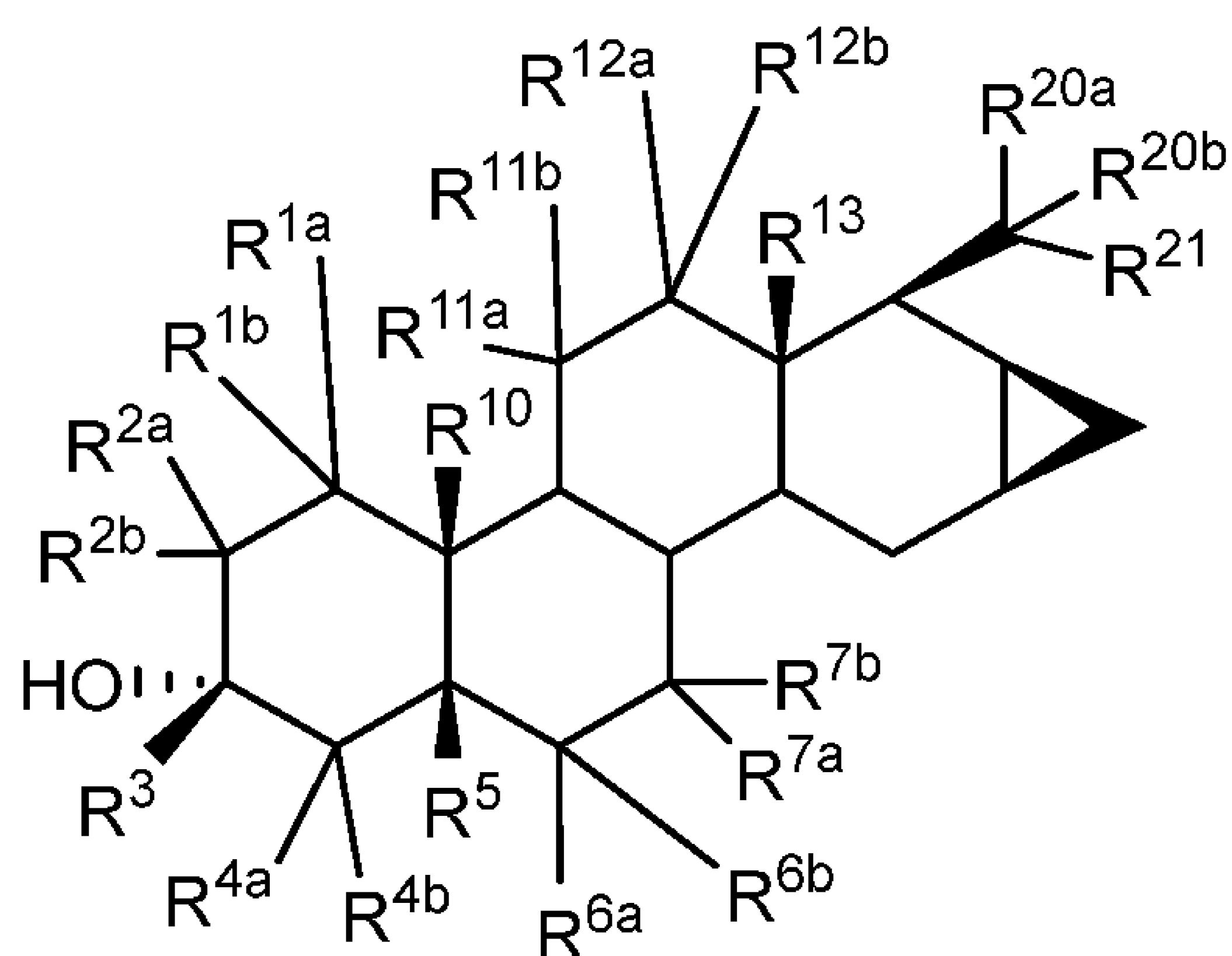


(II-C2),

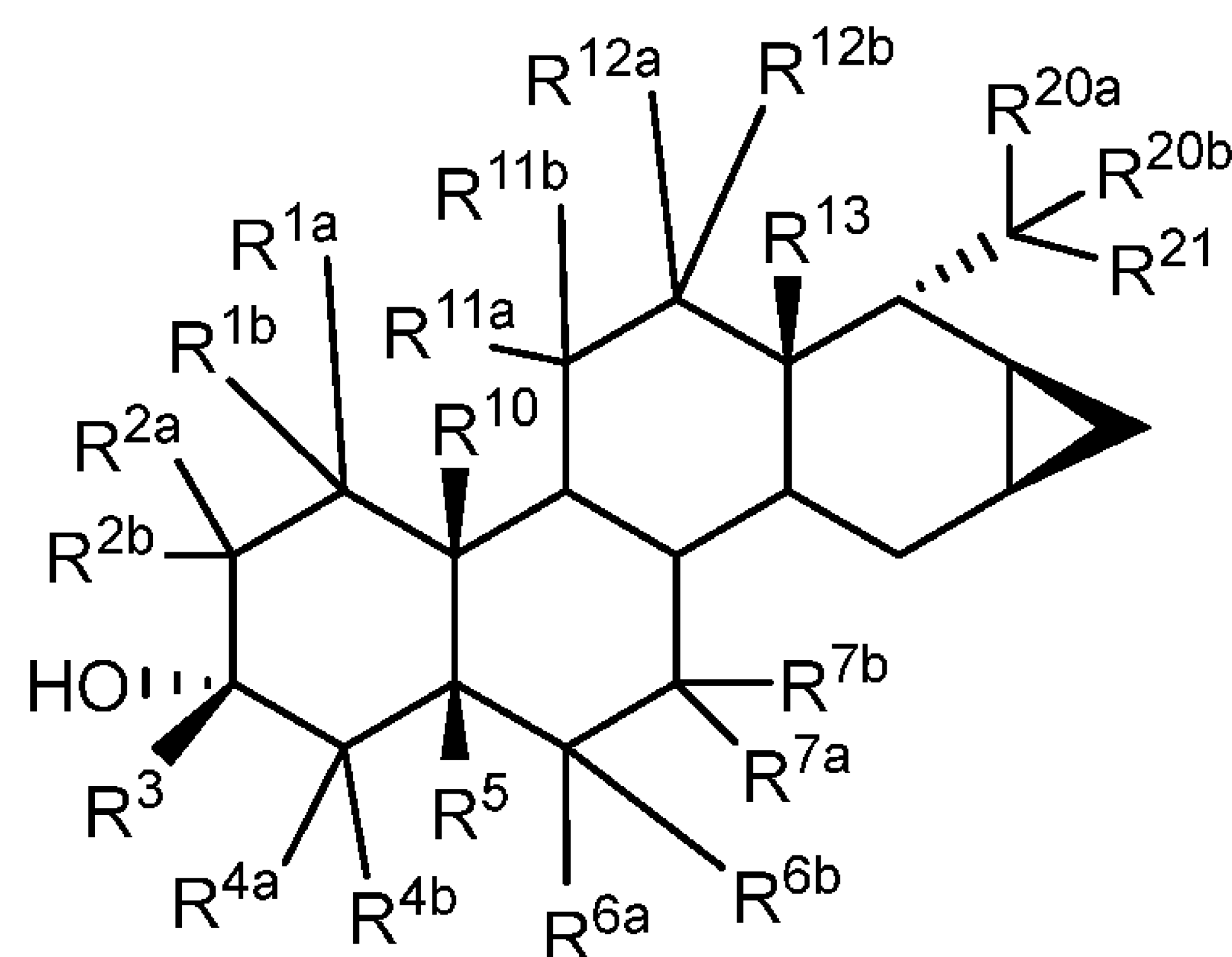
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), or (II-C).

[0341] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-\text{H}$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl), R^3 is $-\text{H}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-\text{H}$ or C_{1-6} alkyl; R^{10} is $-\text{H}$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-\text{H}$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{C}_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-\text{NH}_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-\text{L}^A-\text{R}^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-\text{NR}'-$, $-\text{S}-$, $-\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}'-$, $-\text{NR}'\text{C}(\text{O})-$, $-\text{NR}'\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})_2\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2-$, $-\text{C}(\text{O})\text{NR}'\text{NR}'-$, $-\text{S}(\text{O})-$, $-\text{NR}'\text{C}(\text{O})\text{NR}'-$, $-\text{OC}(\text{O})\text{NR}'-$, $-\text{NR}'\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2\text{NR}'-$, or $-\text{S}(\text{O})_2-$; R^{30} is selected from R' , halo, $-\text{CN}$, $-\text{NO}_2$, and $-\text{CF}_3$; and each R' is independently selected from $-\text{H}$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, and $-\text{CH}_3$.

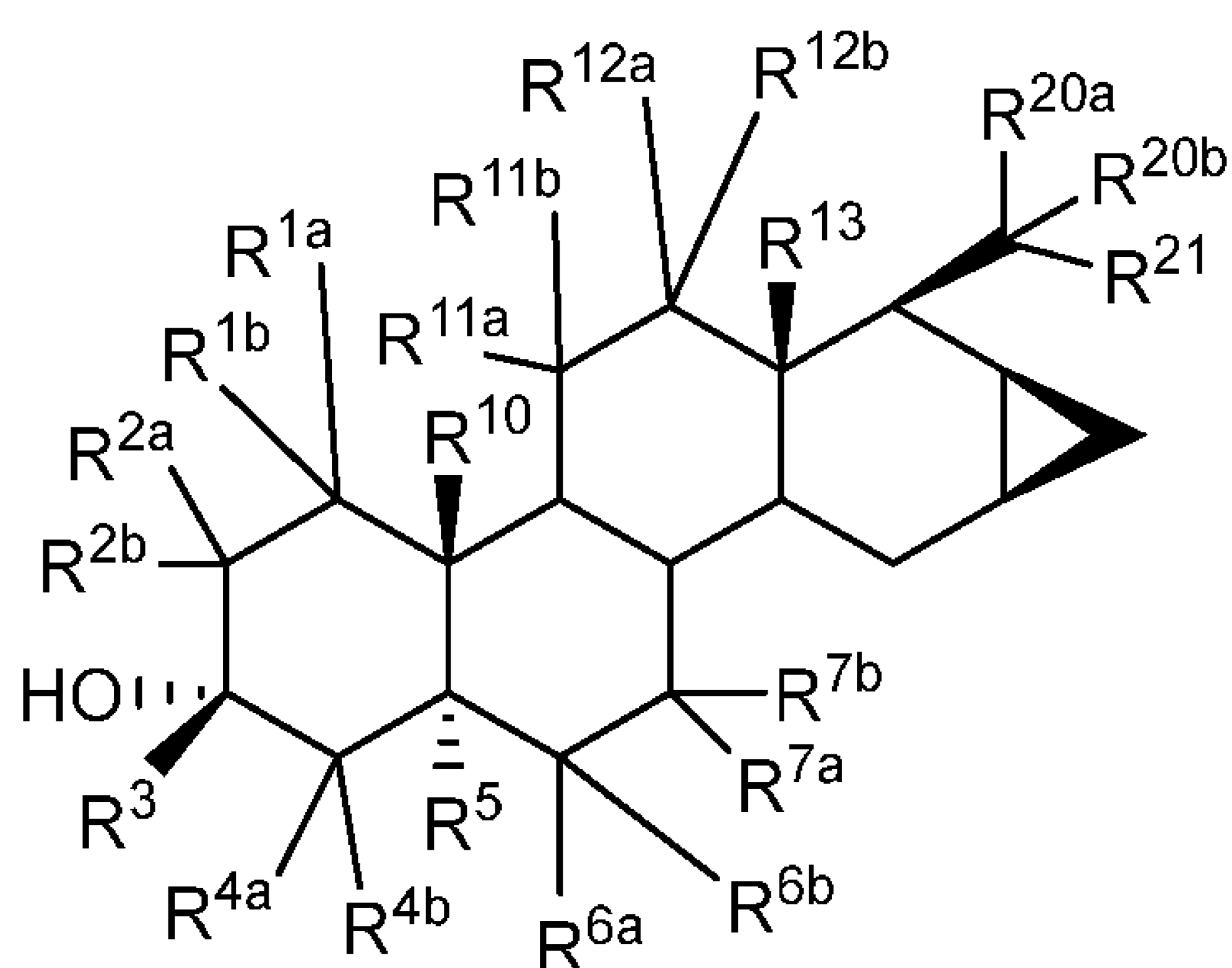
[0342] Another aspect of the present invention provides a compound of Formula (II-A1a), (II-A1b), (II-A1c) or (II-A1d)



(II-A1a),

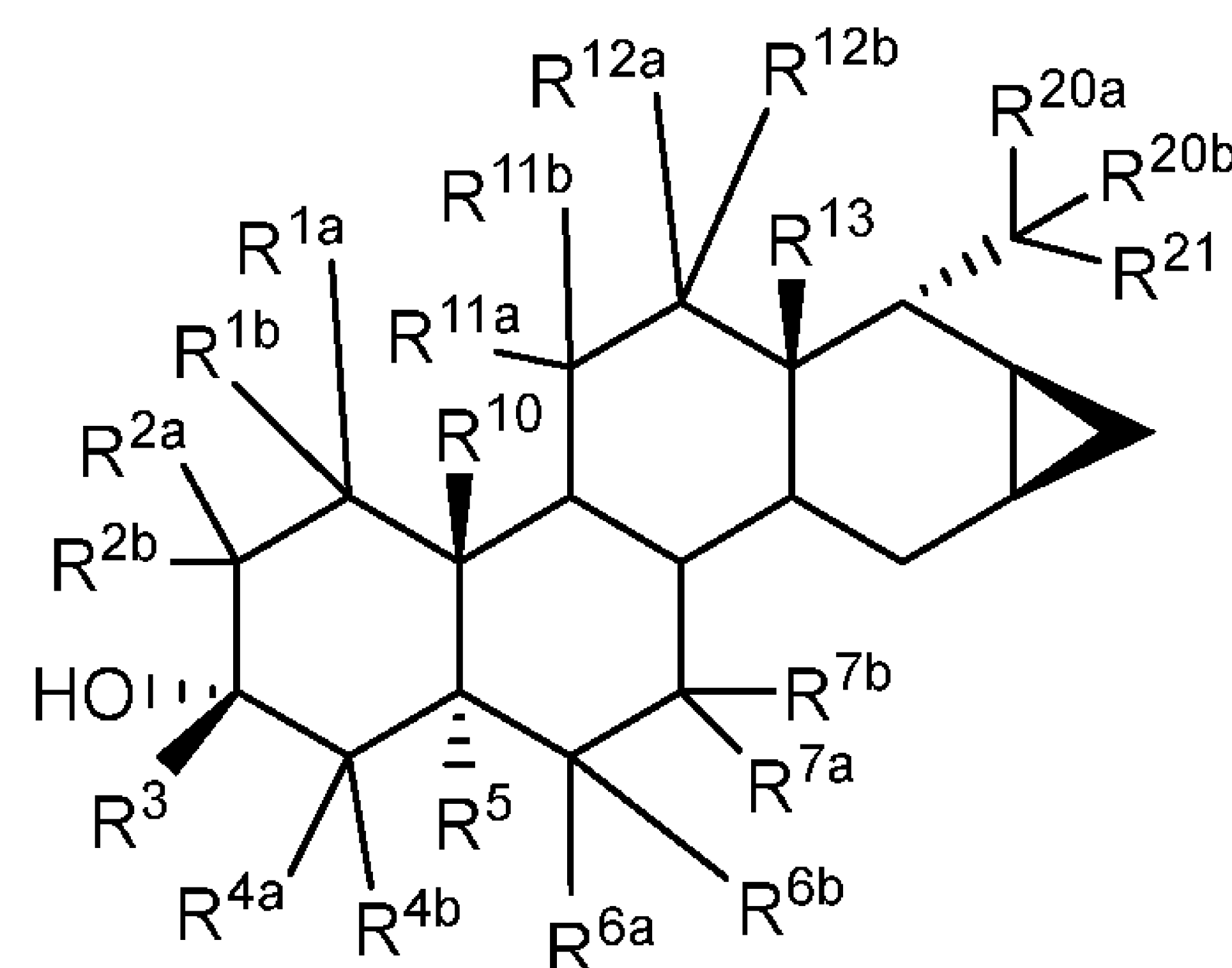


(II-A1b),



(II-A1c),

or



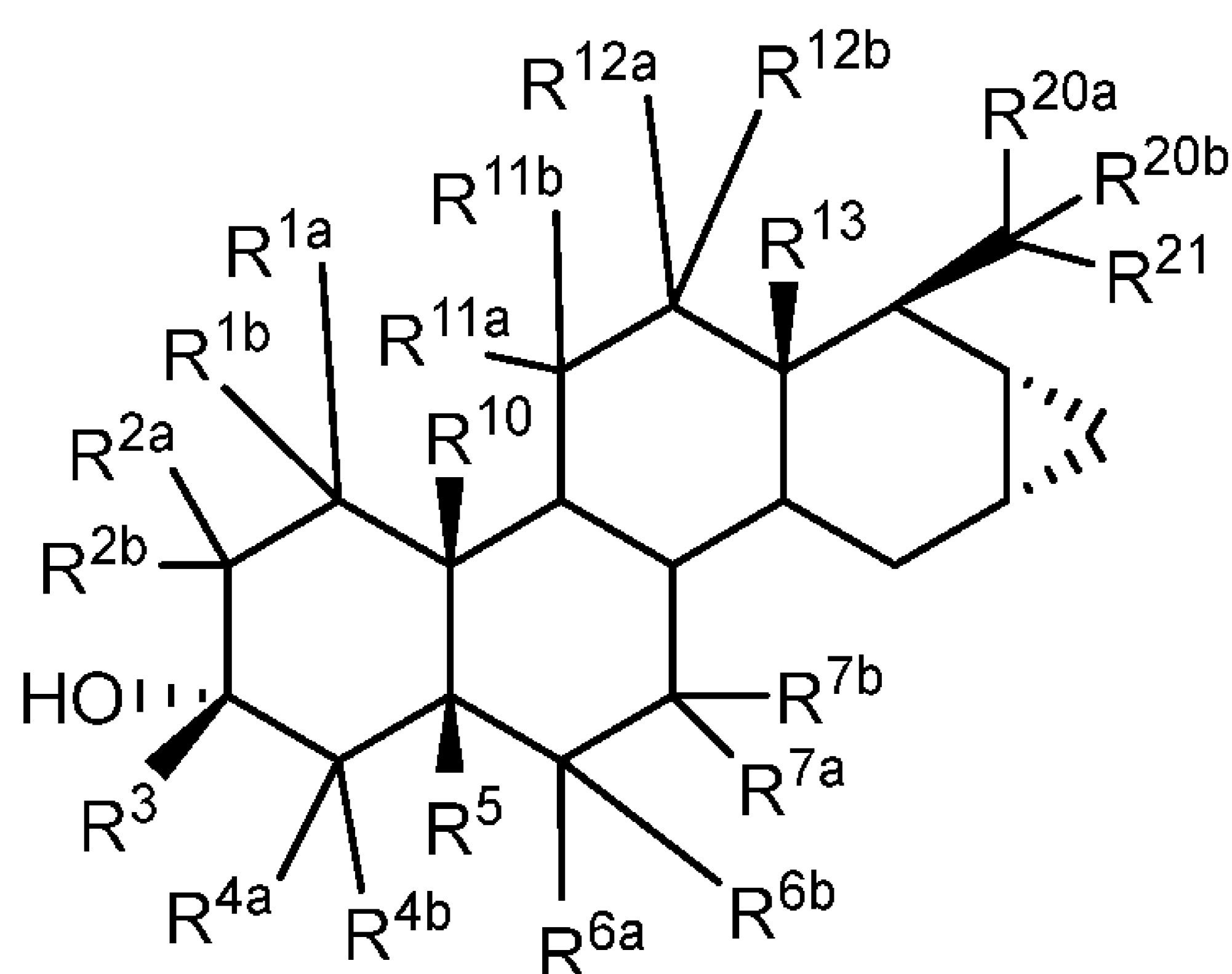
(II-A1d),

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-A), or (II-A1).

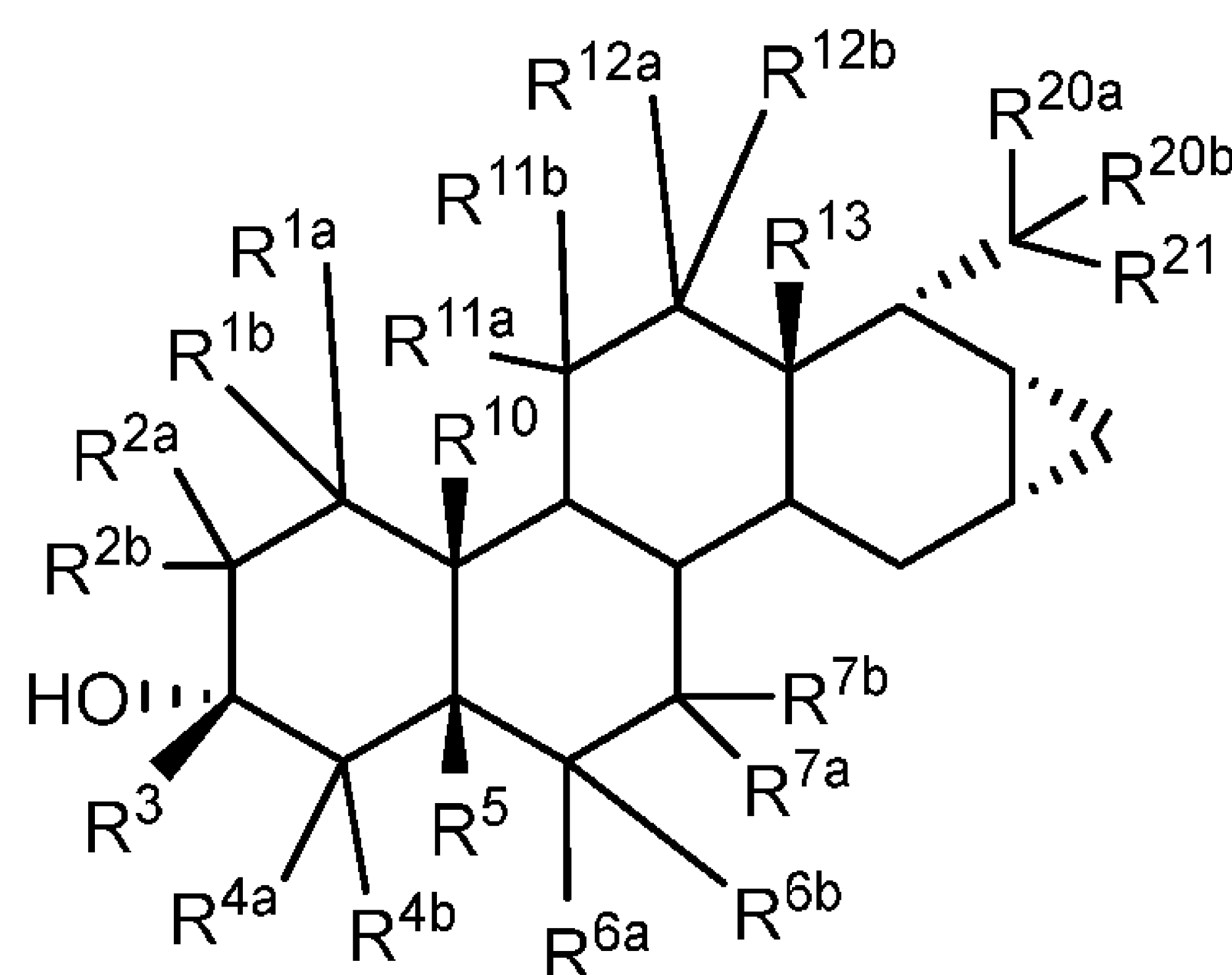
[0343] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl), R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and each R' is independently selected from $-H$,

C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, and –CH₃.

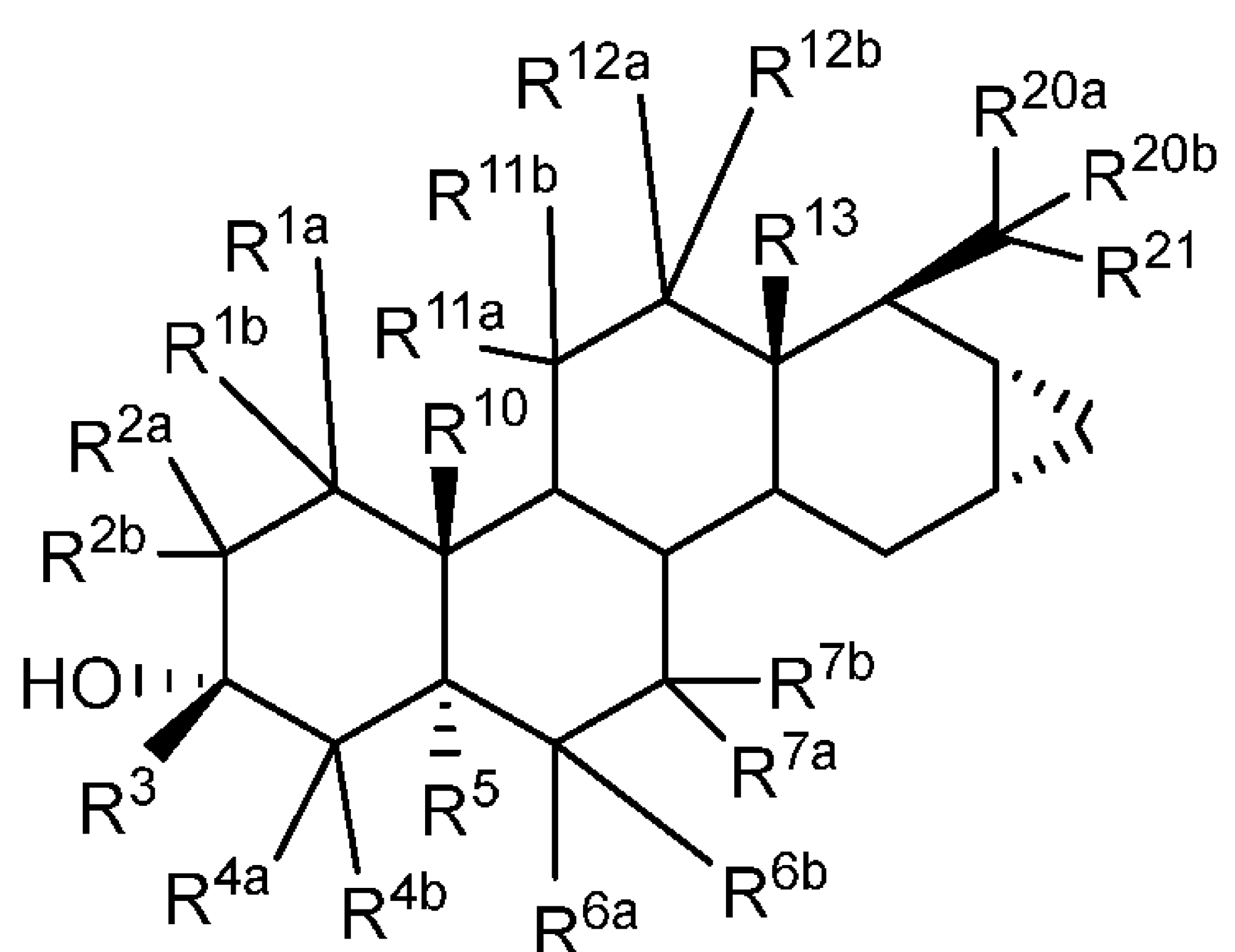
[0344] Another aspect of the present invention provides a compound of Formula (II-A2a), (II-A2b), (II-A2c) or (II-A2d)



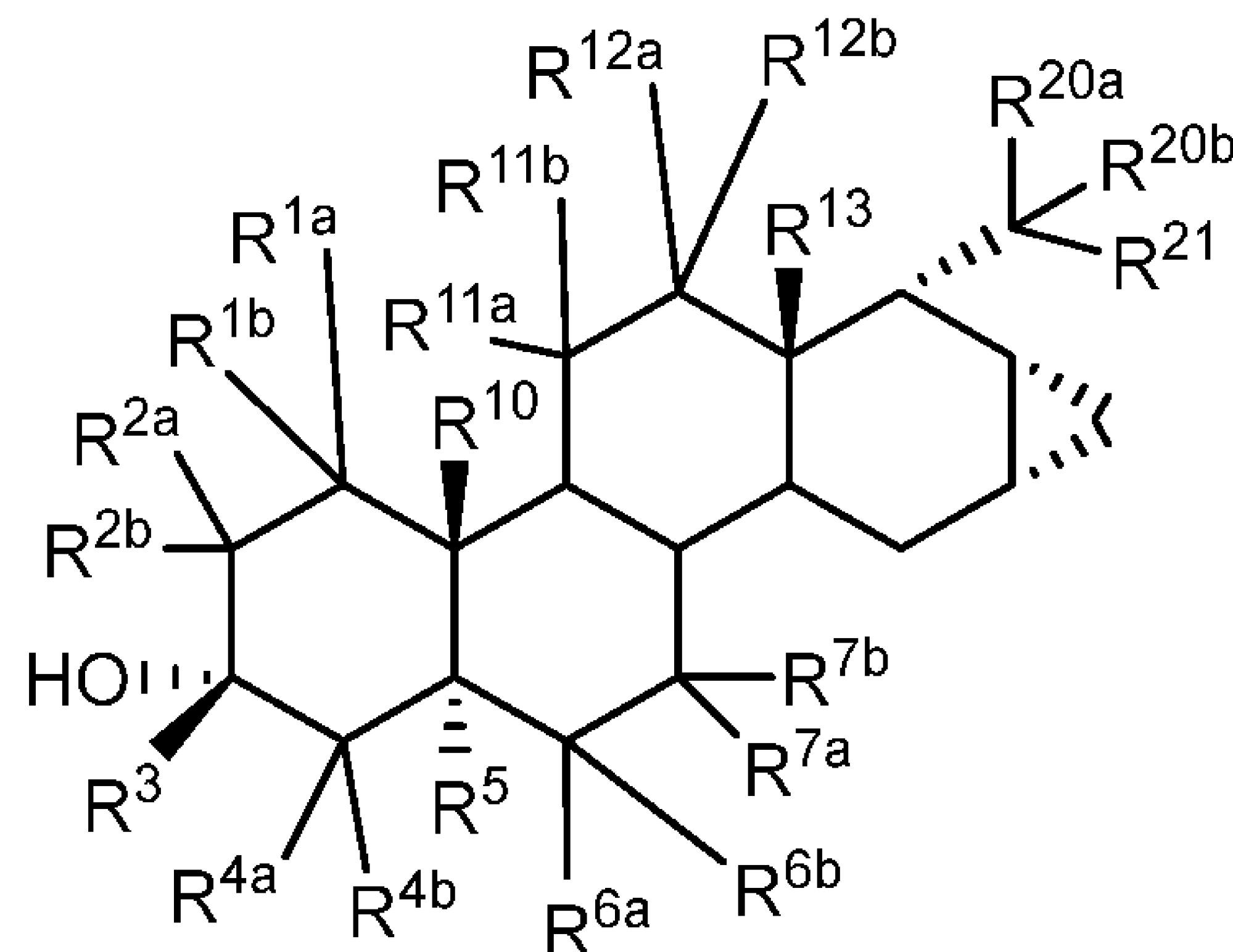
(II-A2a),



(II-A2b),



(II-A2c),



(II-A2d),

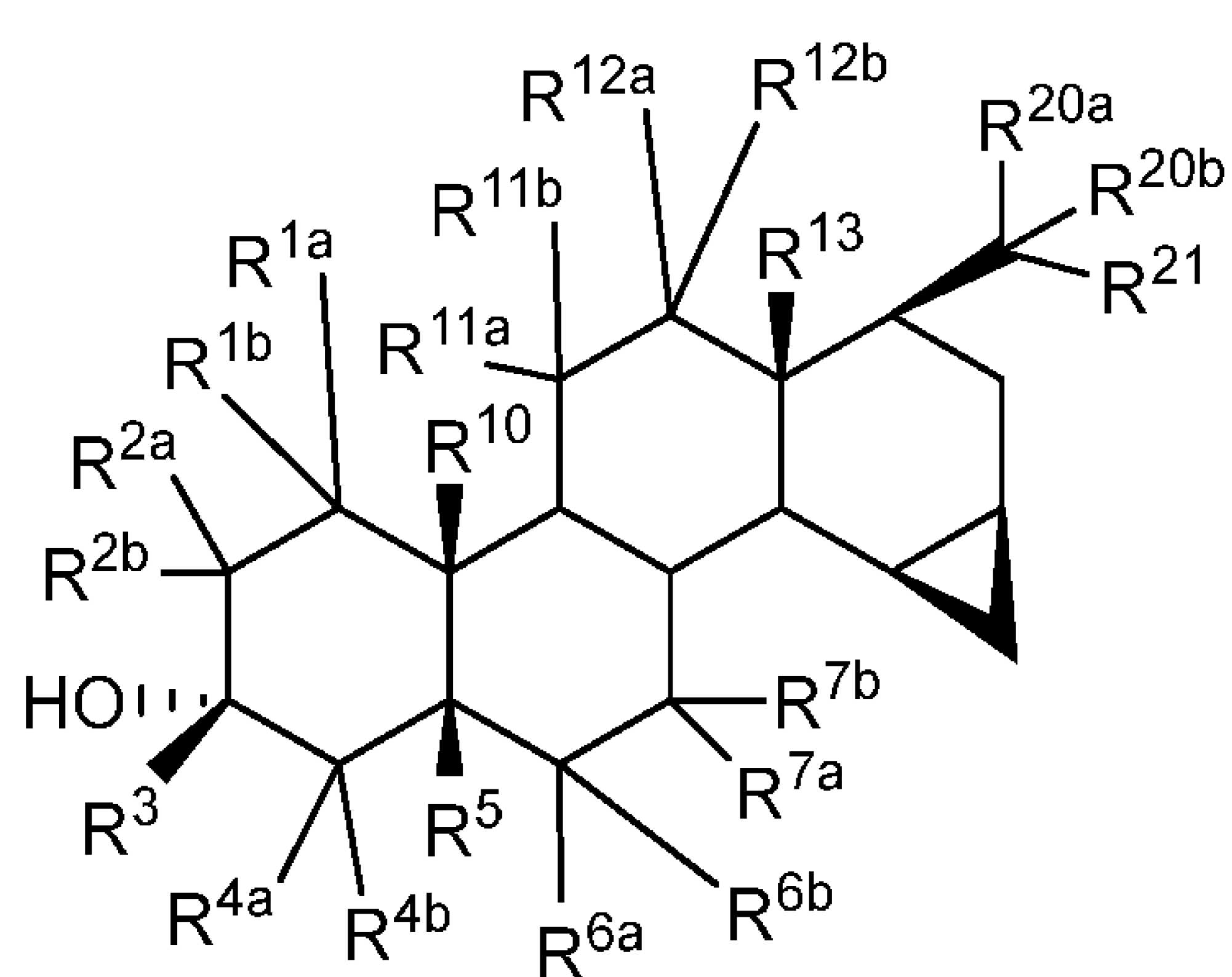
or

or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R^{4a}, R^{4a}, R⁵, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R¹⁰, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R^{20a}, R^{20b}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-A), or (II-A2).

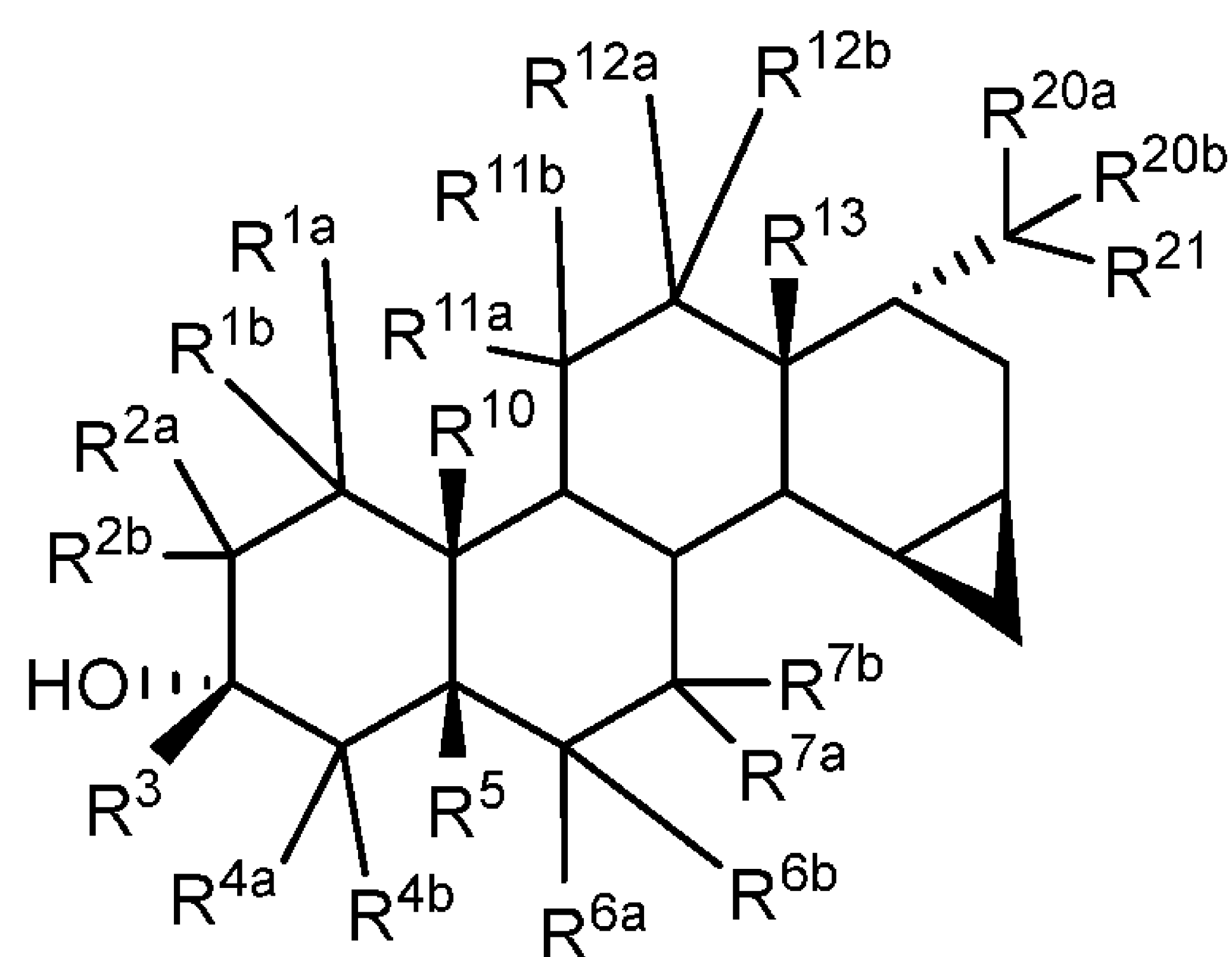
[0345] In some embodiments, each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from –H and C₁₋₆ alkyl (e.g., C₁₋₃ alkyl), R³ is –H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; R⁵ is –H or C₁₋₆ alkyl; R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; R¹³ is –H or optionally substituted C₁₋₃ alkyl; each of R^{20a} and R^{20b} is independently selected from –H, –OH, –C₁₋₅ alkyl-OH, C₁₋₆ alkyl, and –NH₂, or R^{20a} and R^{20b} taken together form oxo; R²¹ is –L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain, wherein up to two carbon atoms of L^A are optionally and

independently replaced by $-\text{NR}'-$, $-\text{S}-$, $-\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}'-$, $-\text{NR}'\text{C}(\text{O})-$, $-\text{NR}'\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})_2\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2-$, $-\text{C}(\text{O})\text{NR}'\text{NR}'-$, $-\text{NR}'\text{C}(\text{O})\text{NR}'-$, $-\text{OC}(\text{O})\text{NR}'-$, $-\text{NR}'\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2\text{NR}'-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2-$; R^{30} is selected from R' , halo, $-\text{CN}$, $-\text{NO}_2$, and $-\text{CF}_3$; and each R' is independently selected from $-\text{H}$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, and $-\text{CH}_3$.

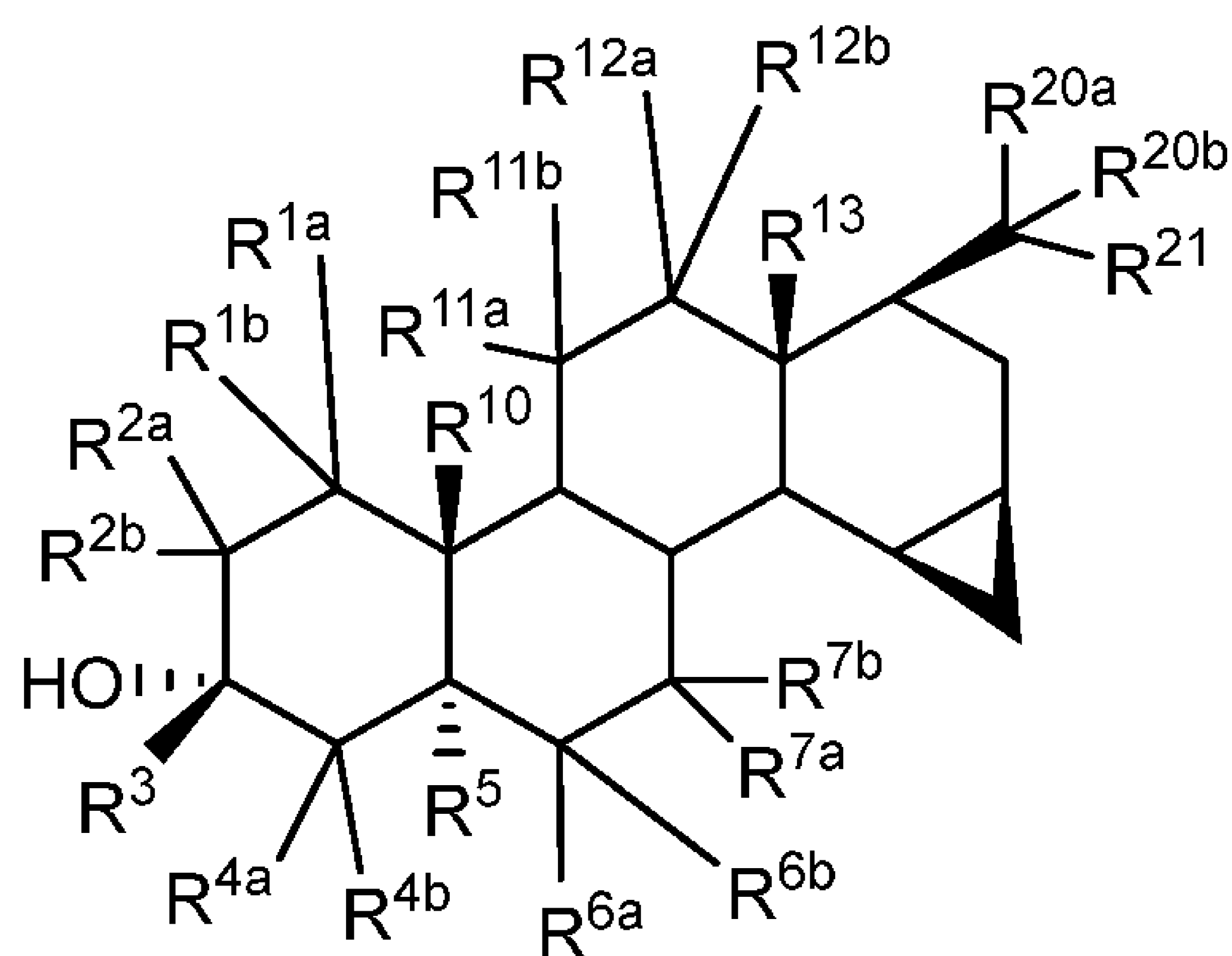
[0346] Another aspect of the present invention provides a compound of Formula (II-B1a), (II-B1b), (II-B1c) or (II-B1d)



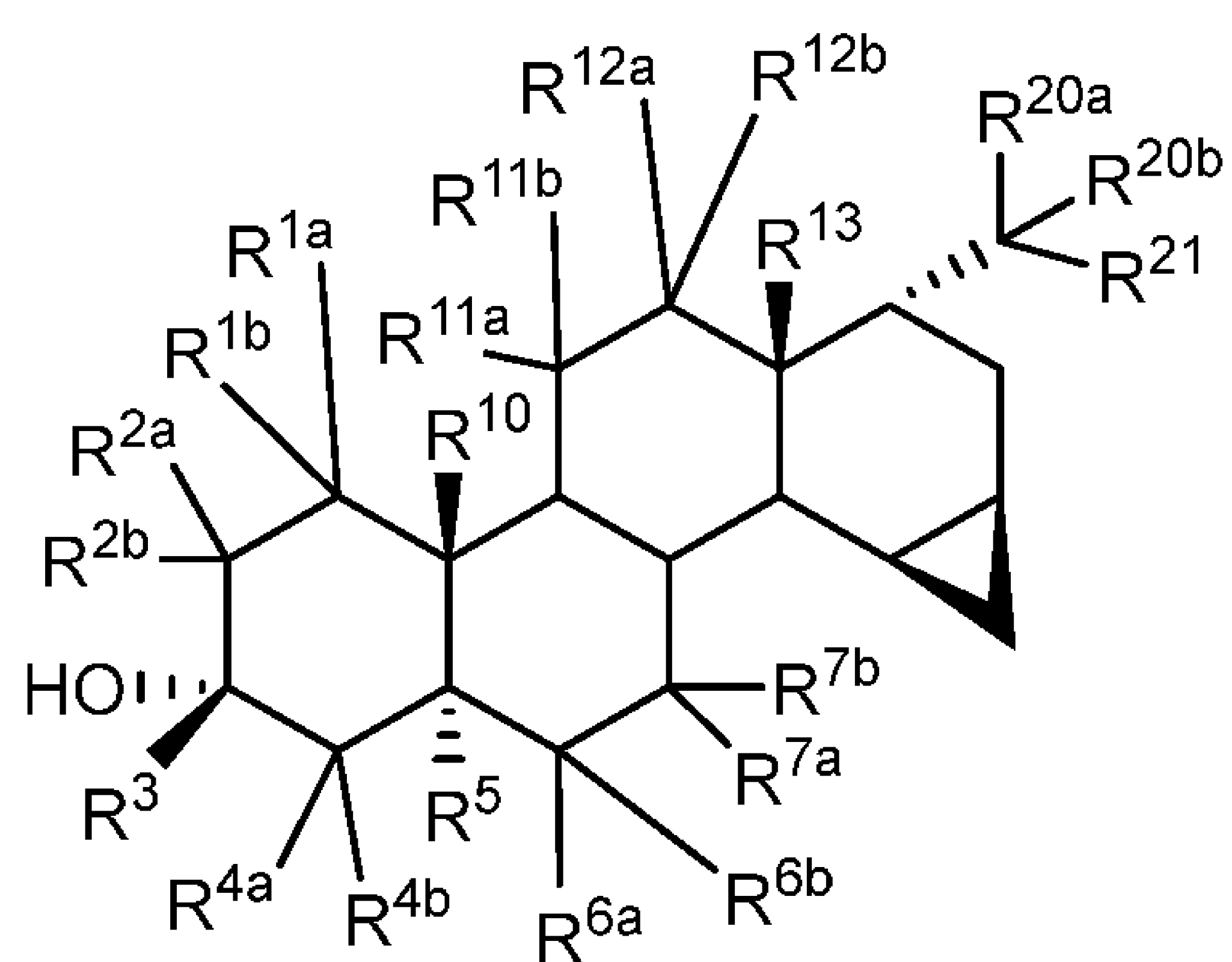
(II-B1a),



(II-B1b),



(II-B1c),



(II-B1d),

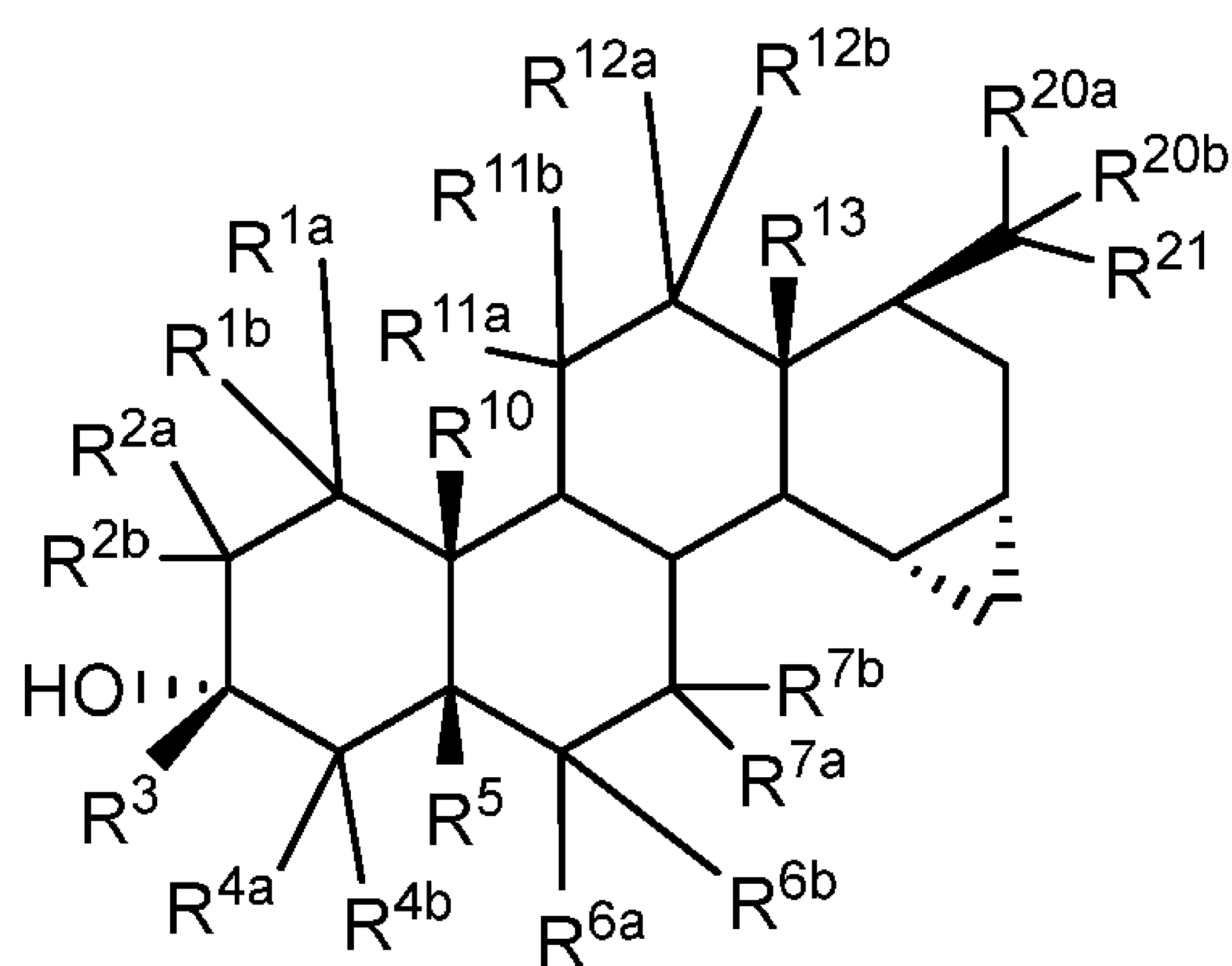
or

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-B), or (II-B1).

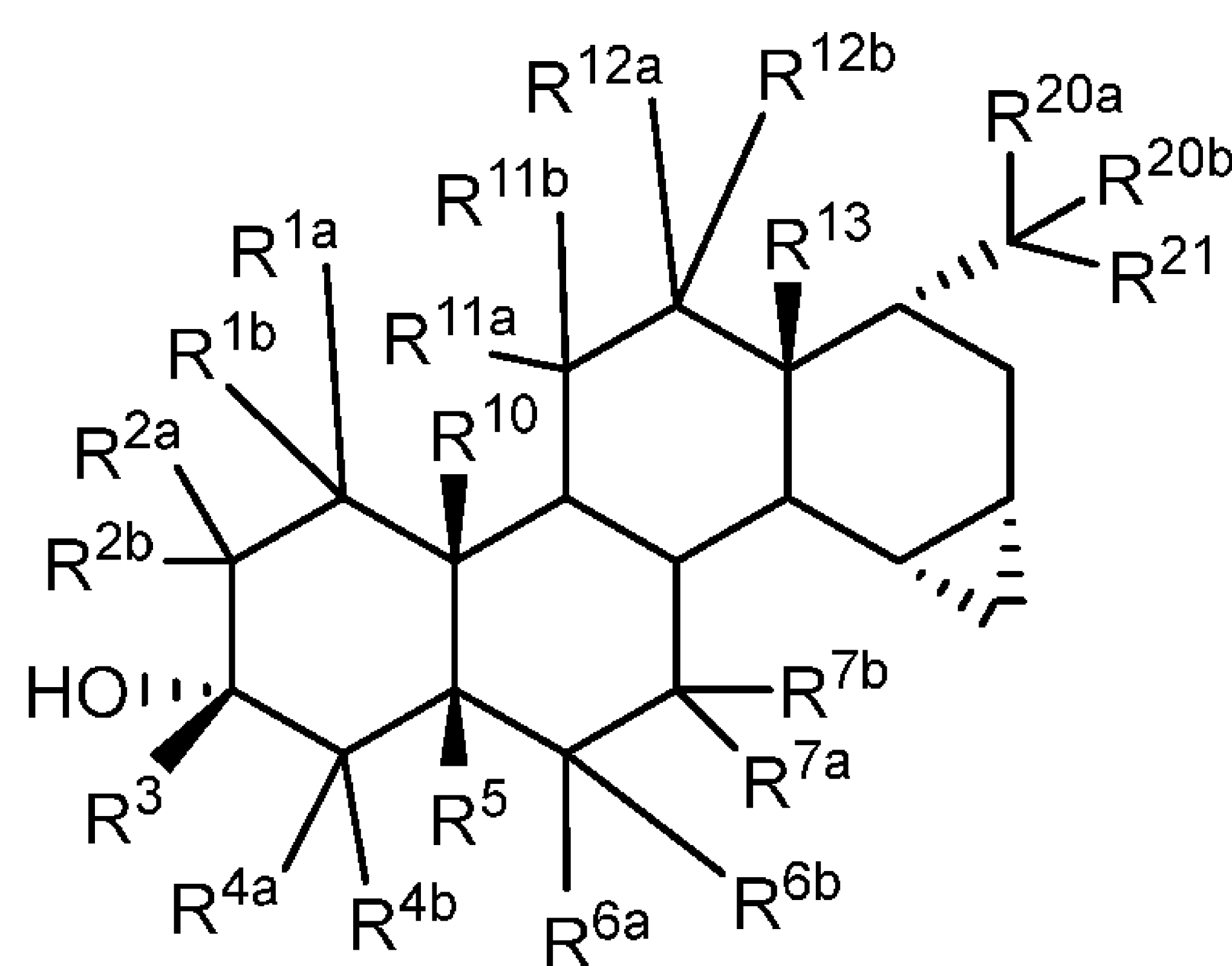
[0347] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-\text{H}$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl), R^3 is $-\text{H}$, C_{1-6} alkyl, or C_{1-6} alkyl-O- C_{1-6} alkyl; R^5 is $-\text{H}$ or C_{1-6} alkyl; R^{10} is $-\text{H}$, C_{1-3} alkyl, or C_{1-6}

alkyl-O-C₁₋₃ alkyl; R¹³ is -H or optionally substituted C₁₋₃ alkyl; each of R^{20a} and R^{20b} is independently selected from -H, -OH, -C₁₋₅ alkyl-OH, C₁₋₆ alkyl, and -NH₂, or R^{20a} and R^{20b} taken together form oxo; R²¹ is -L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by -NR'-, -S-, -O-, -OC(O)-, -C(O)O-, -C(O)-, -C(O)C(O)-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)O-, -S(O)₂NR'-, -NR'S(O)₂-, -C(O)NR'NR'-, -NR'C(O)NR'-, -OC(O)NR'-, -NR'NR'-, -NR'S(O)₂NR'-, -S(O)-, or -S(O)₂-; R³⁰ is selected from R', halo, -CN, -NO₂, and -CF₃; and each R' is independently selected from -H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

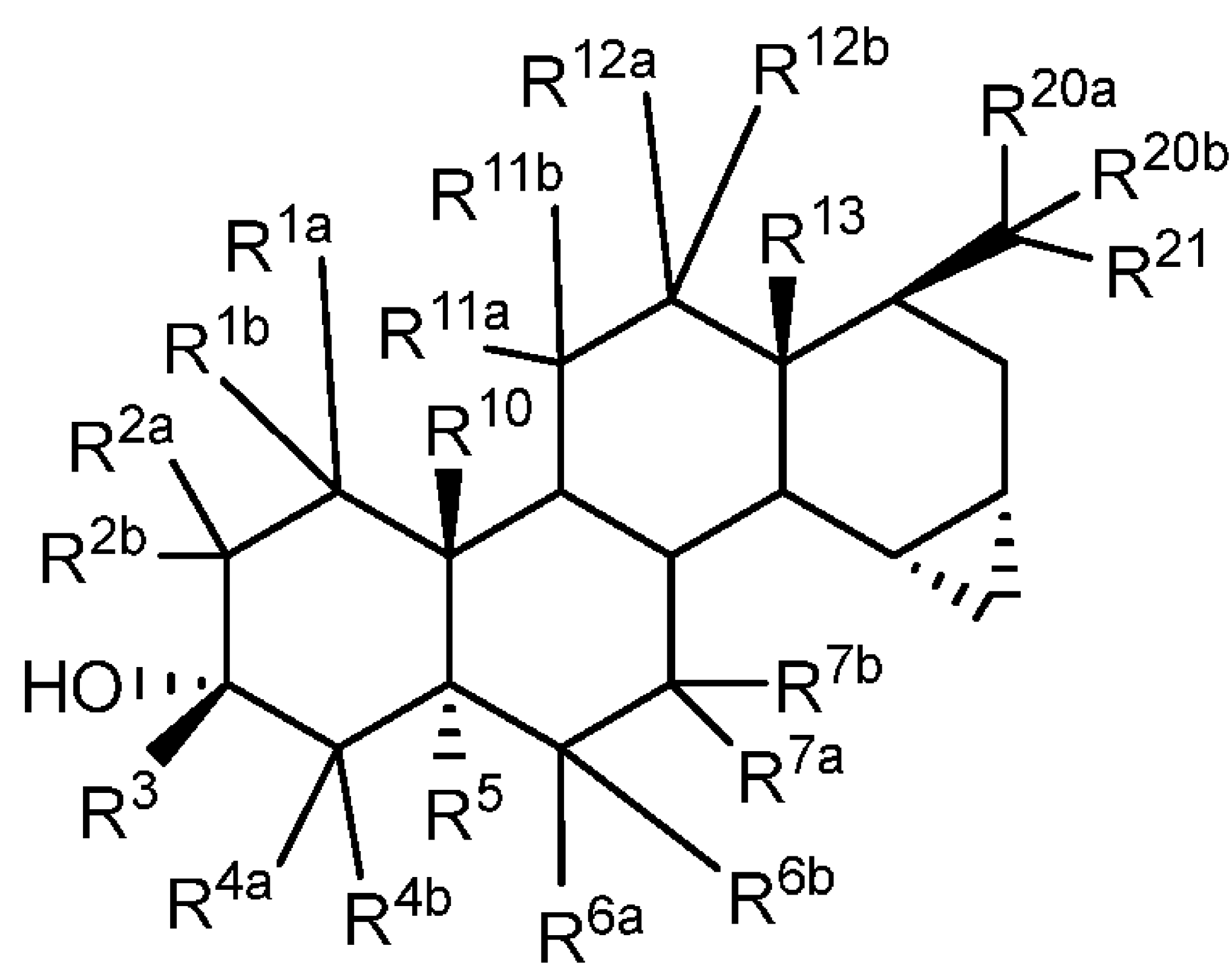
[0348] Another aspect of the present invention provides a compound of Formula (II-B2a), (II-B2b), (II-B2c) or (II-B2d)



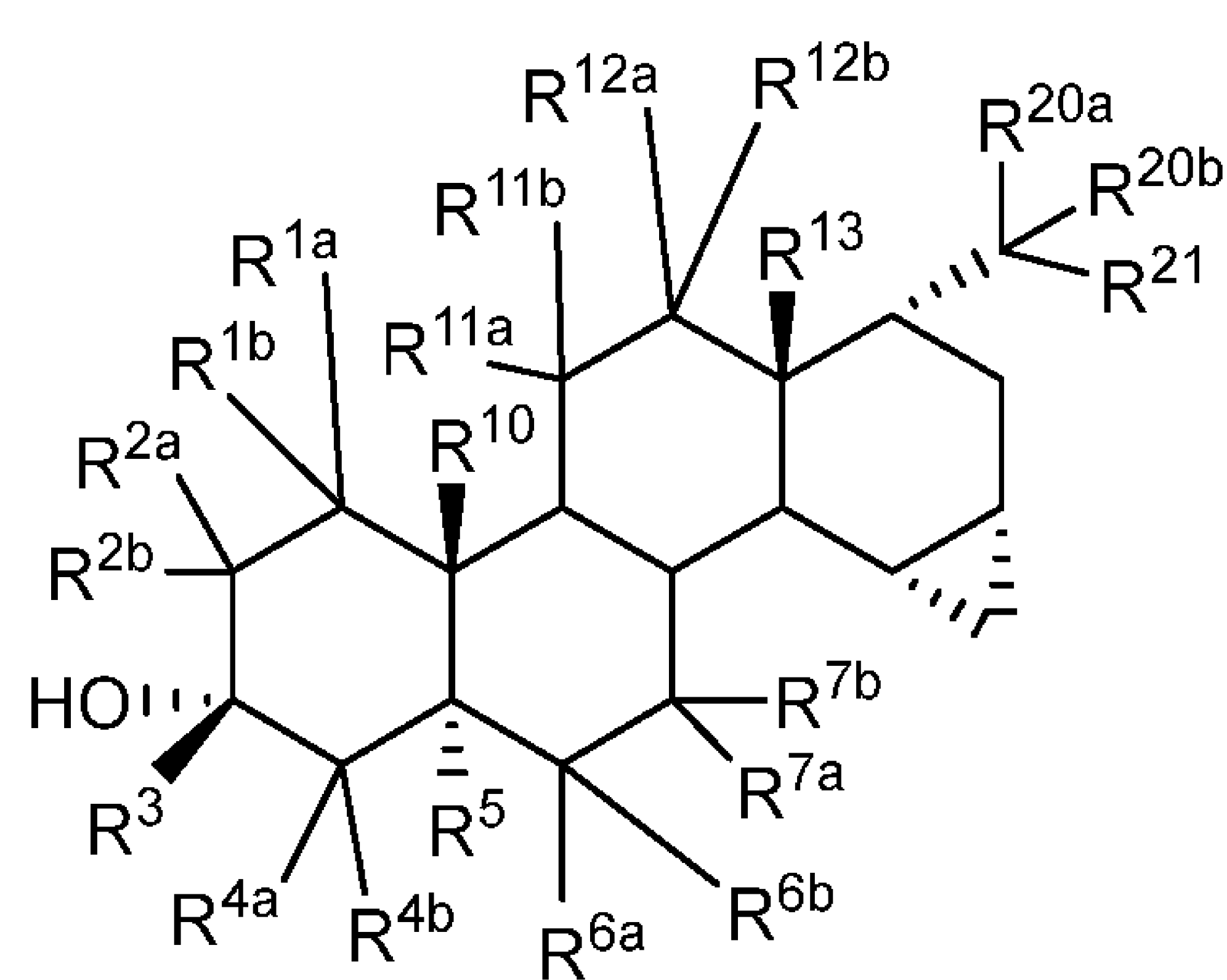
(II-B2a),



(II-B2b),



(II-B2c),



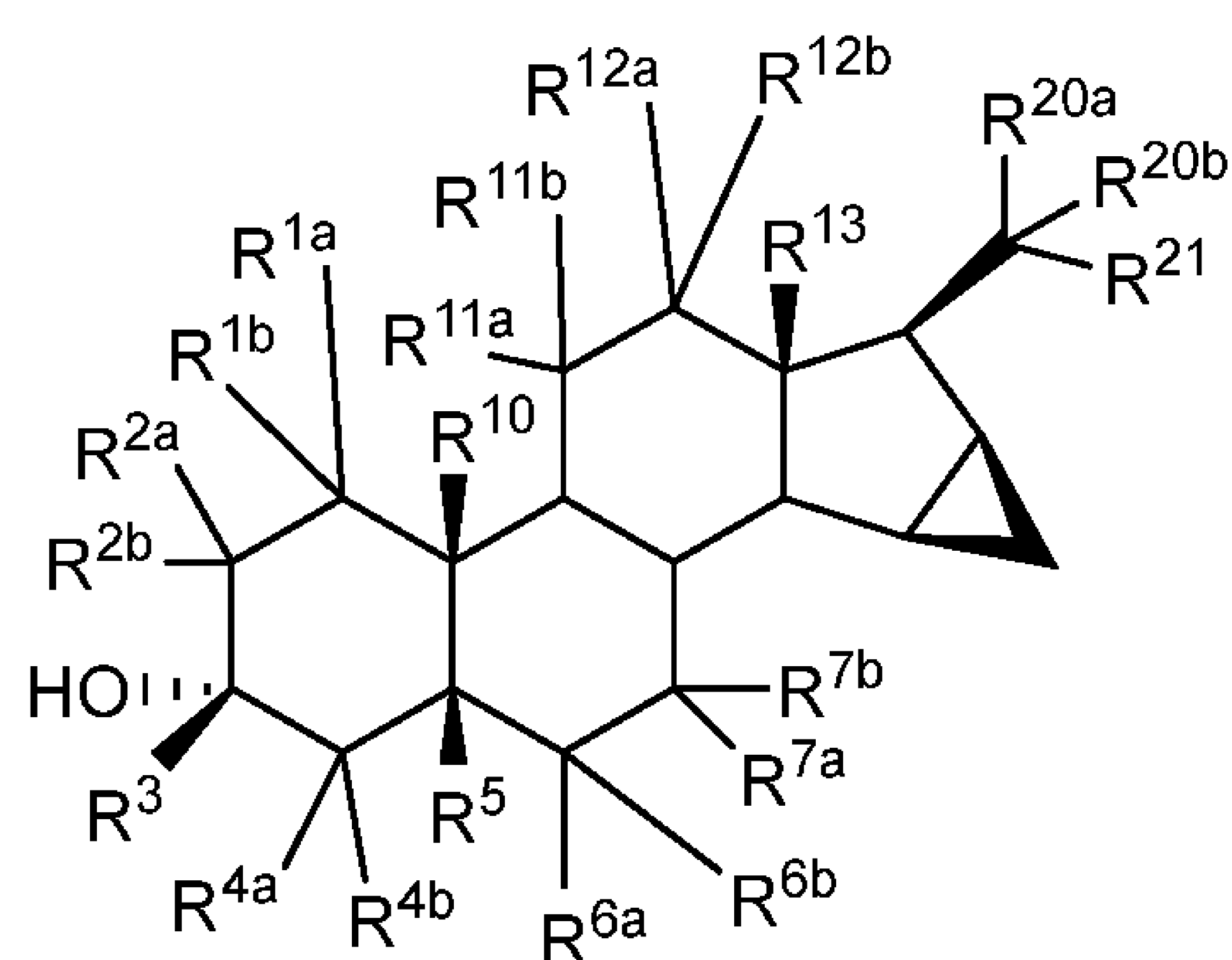
(II-B2d),

or

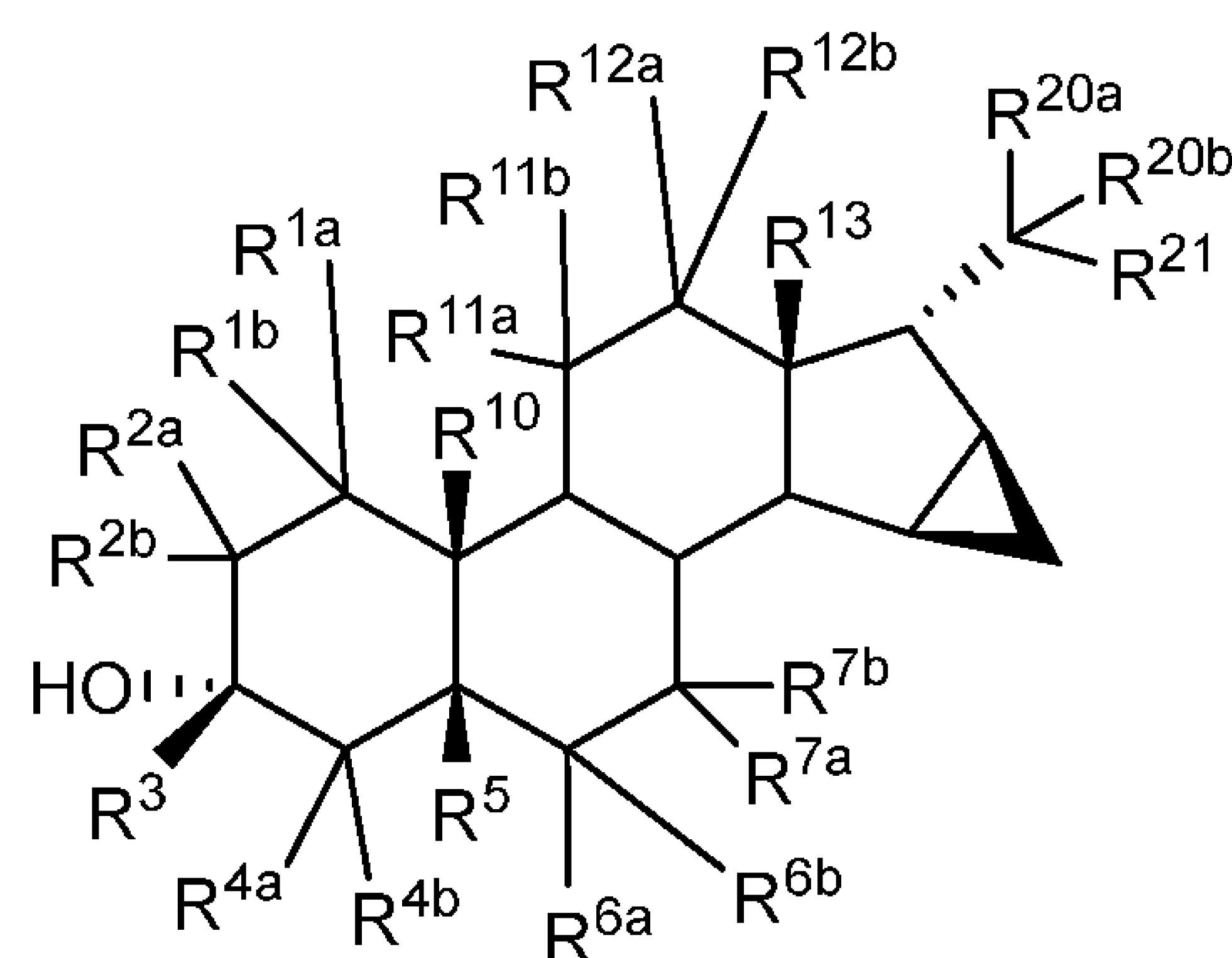
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-B), or (II-B2).

[0349] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl), R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

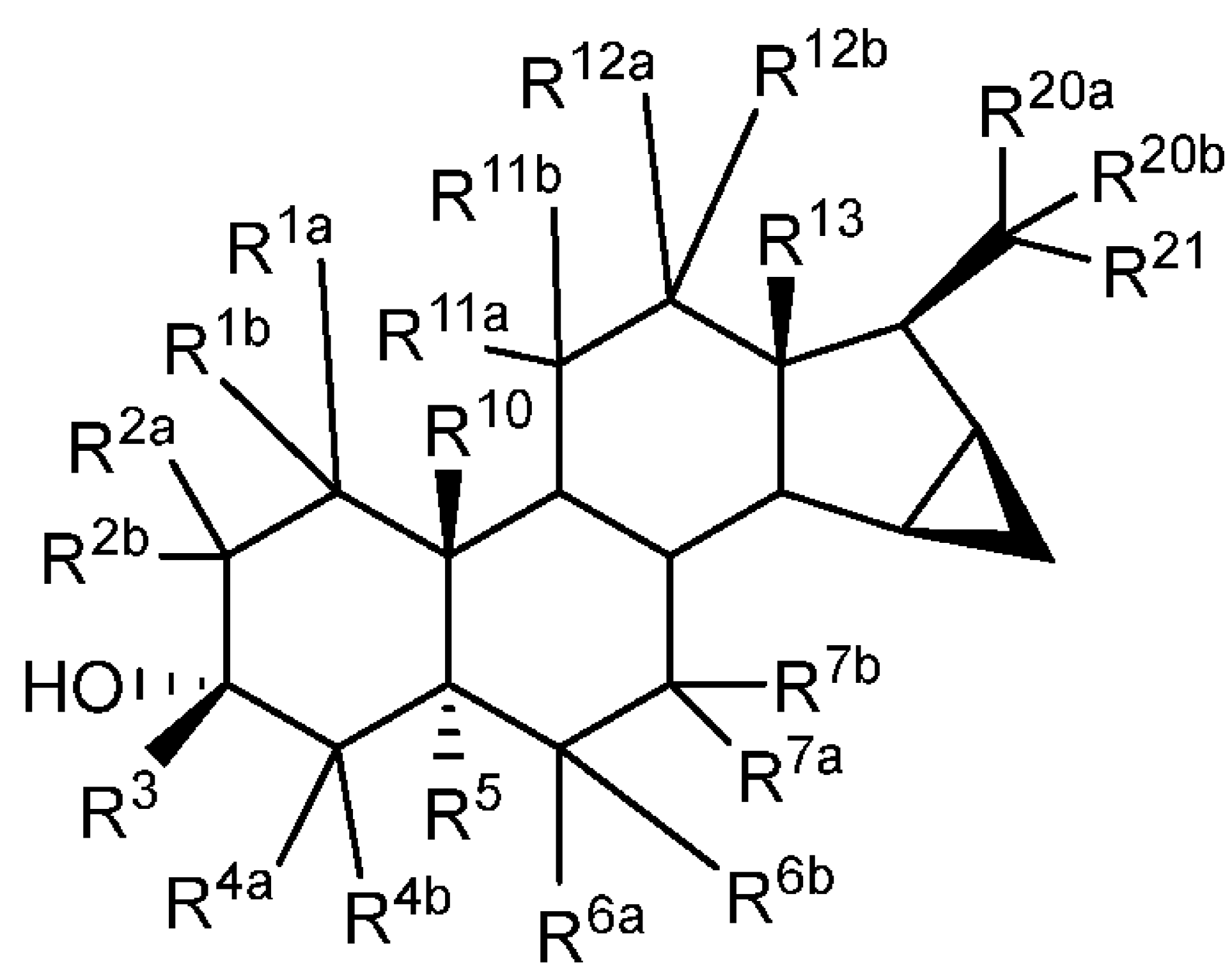
[0350] Another aspect of the present invention provides a compound of Formula (II-C1a), (II-C1b), (II-C1c) or (II-C1d)



(II-C1a),

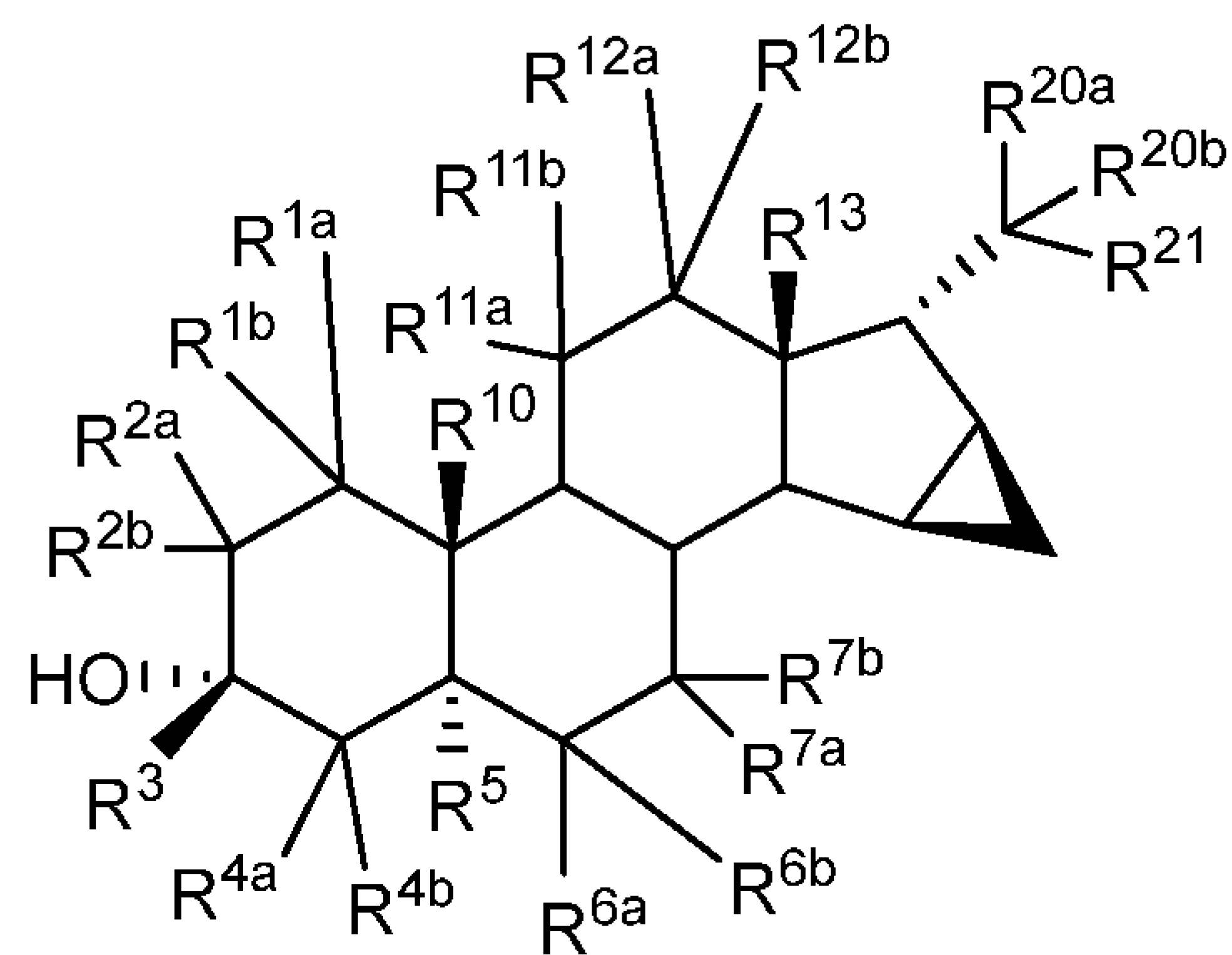


(II-C1b),



(II-C1c),

or

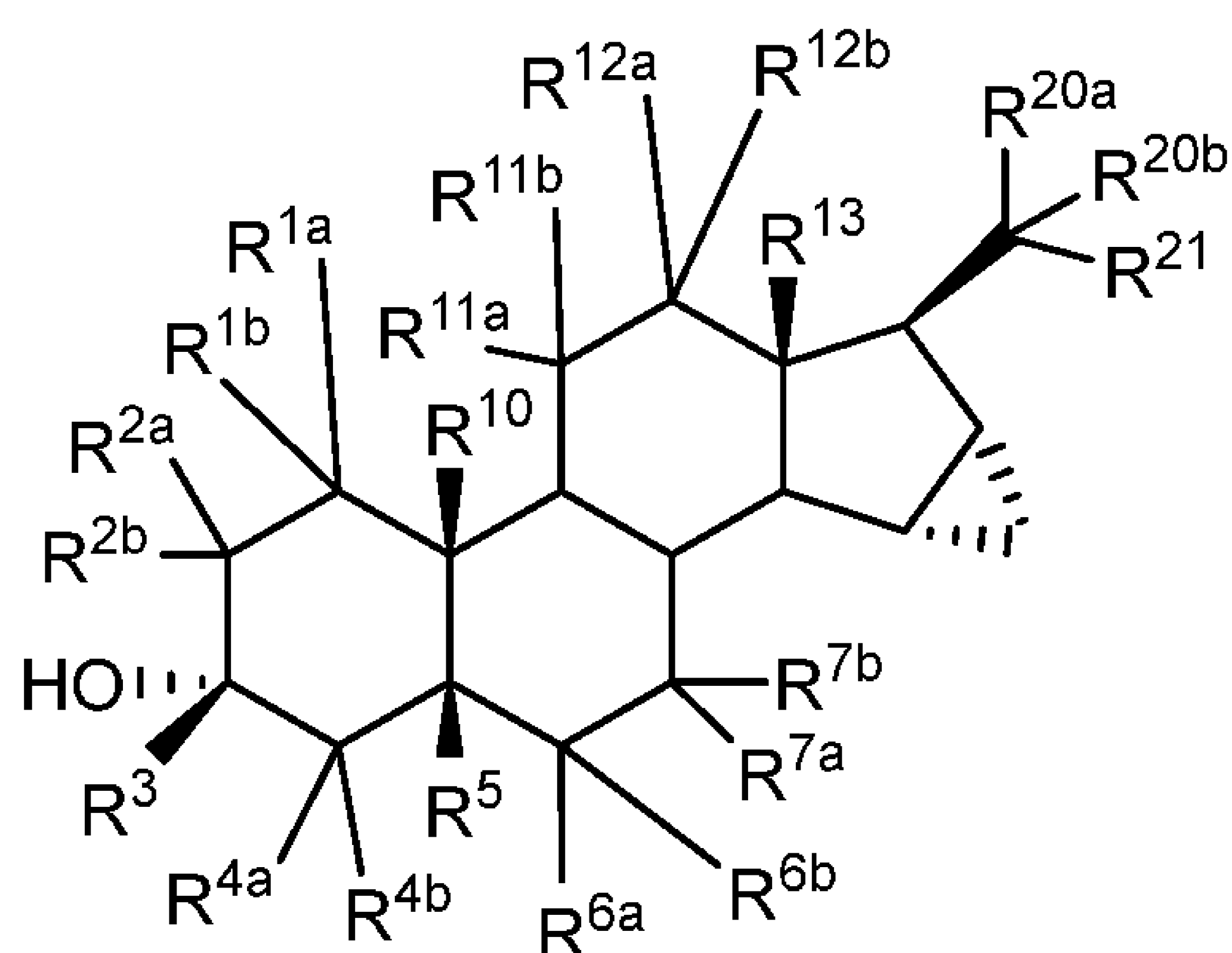


(II-C1d),

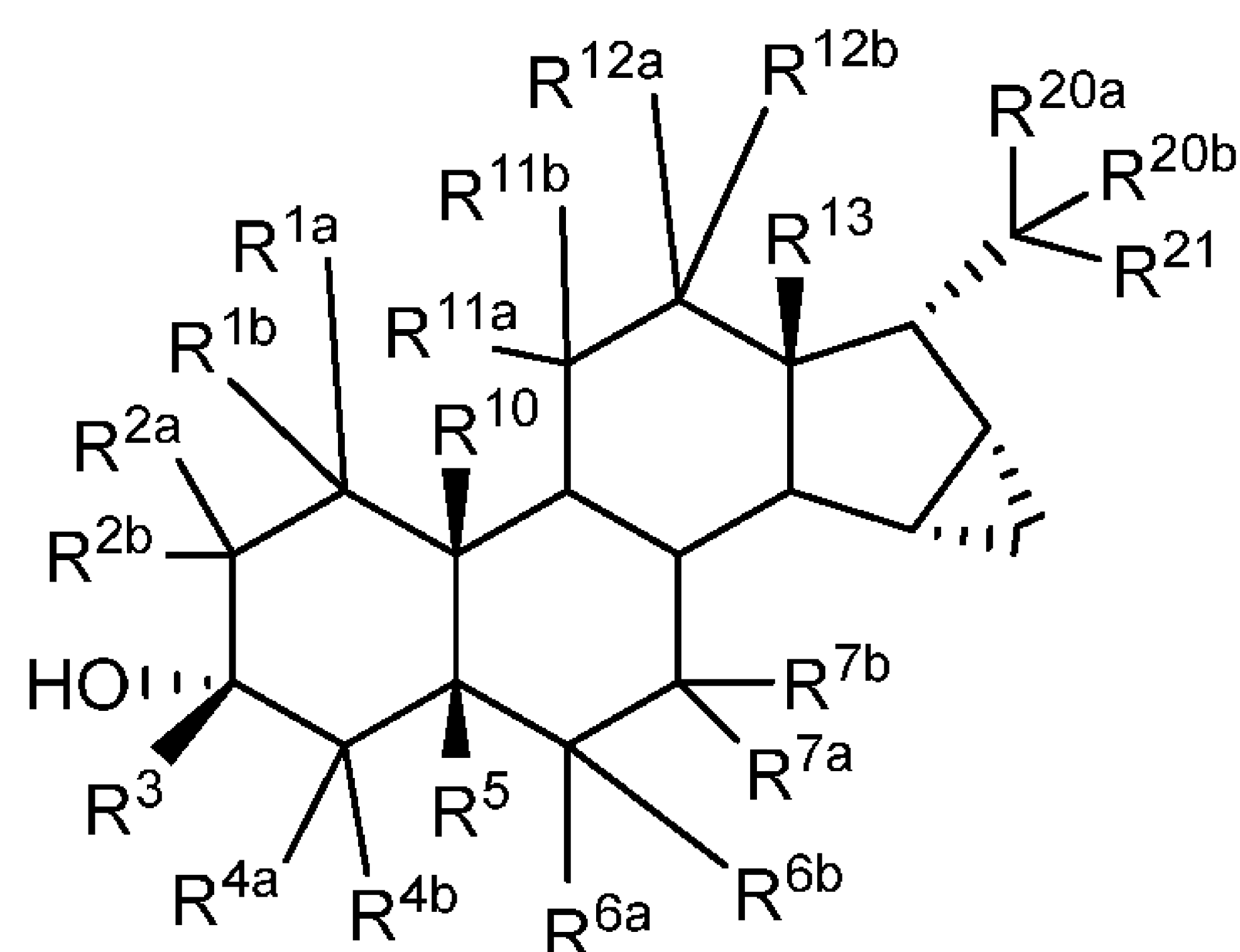
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-C), or (II-C1).

[0351] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl), R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

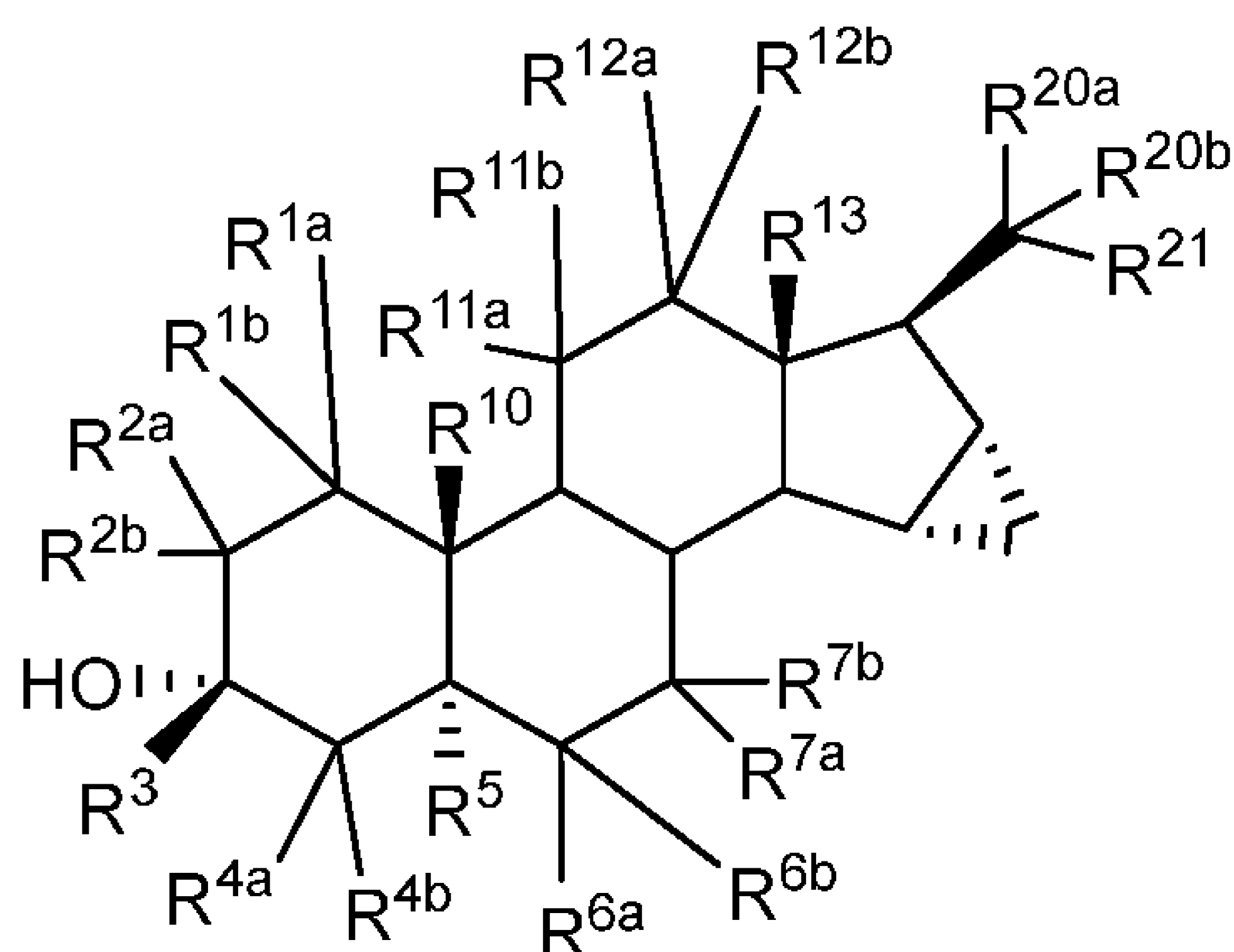
[0352] Another aspect of the present invention provides a compound of Formula (II-C2a), (II-C2b), (II-C2c) or (II-C2d)



(II-C2a),

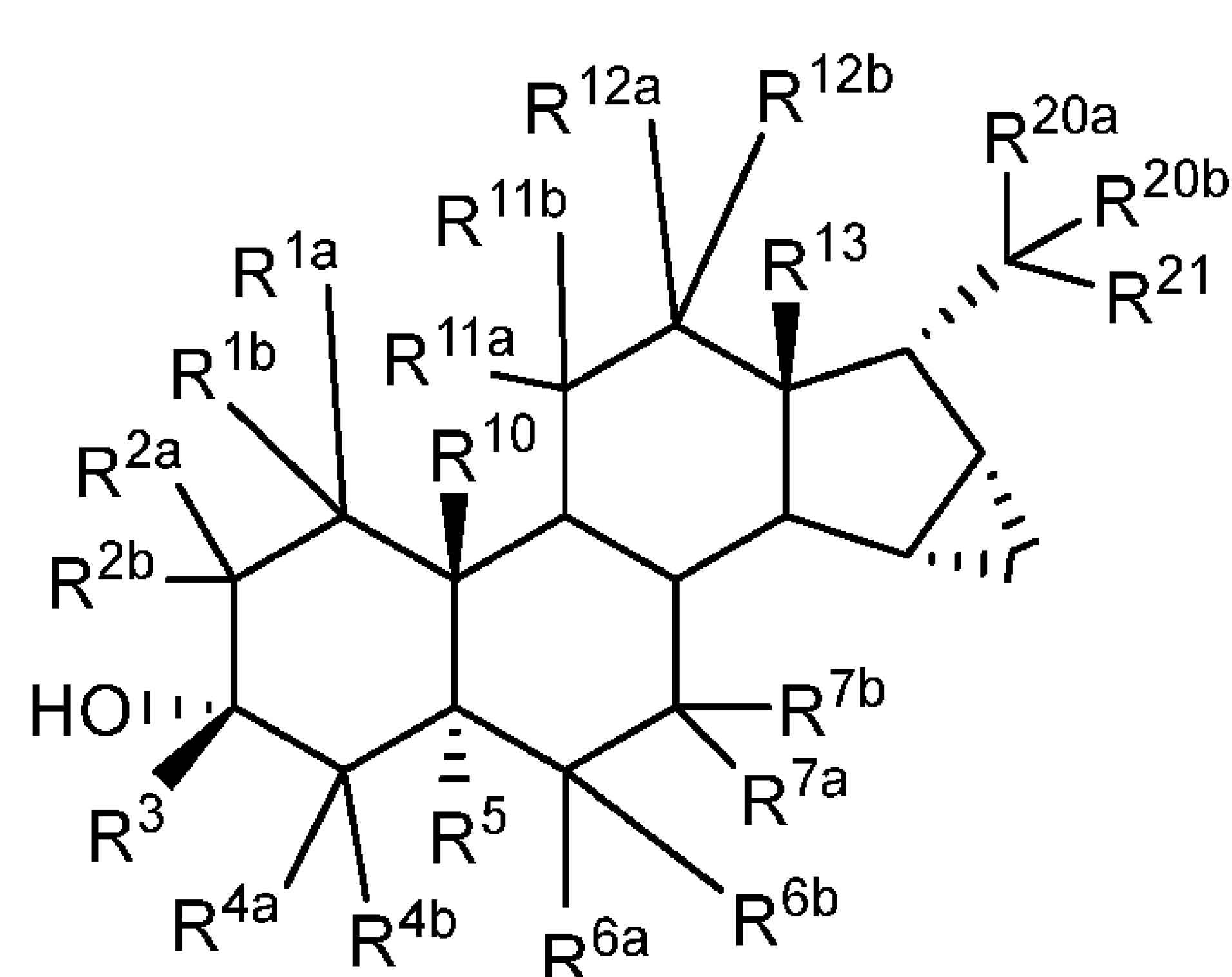


(II-C2b),



(II-C2c),

or

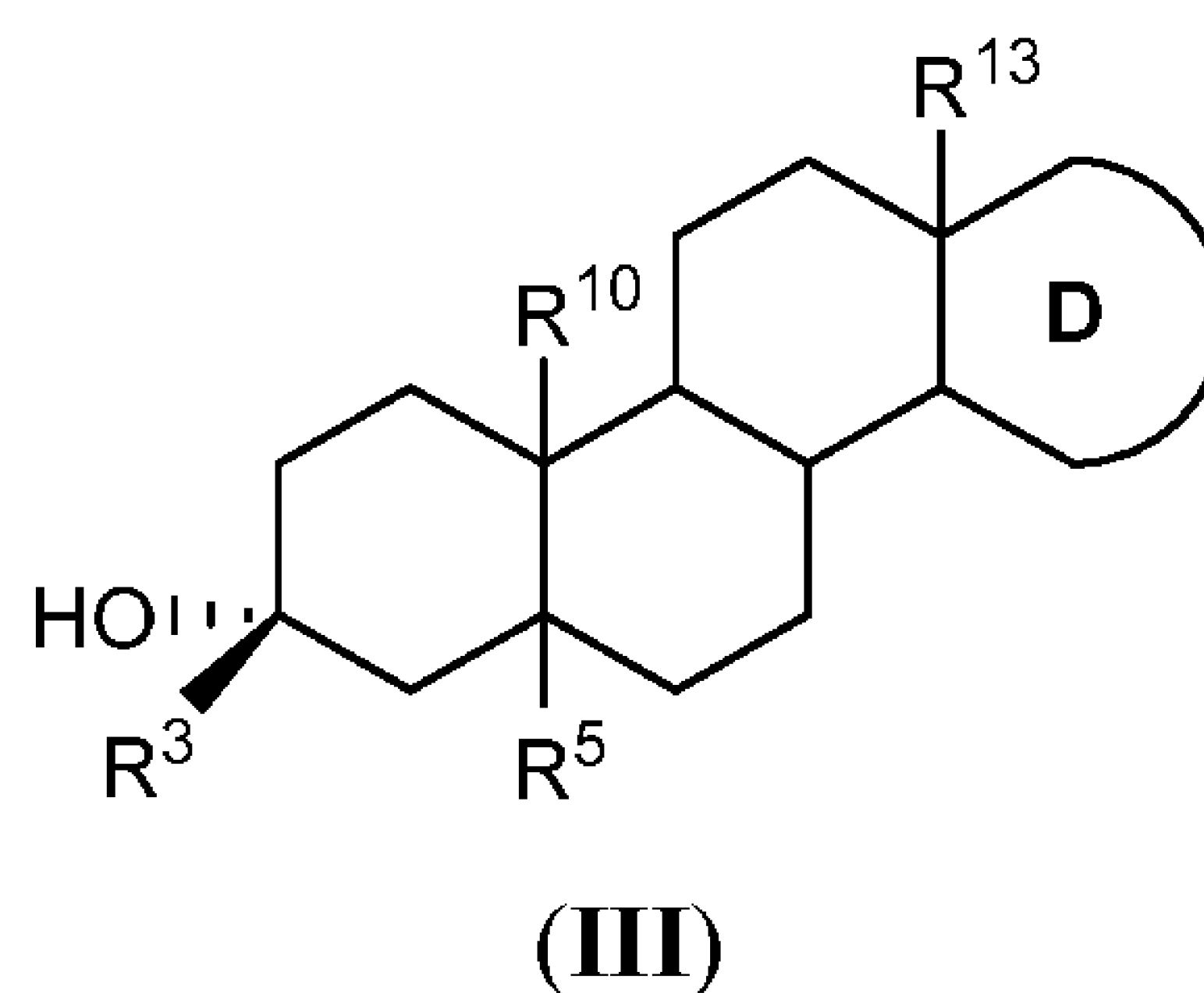


(II-C2d),

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (II-C), or (II-C2).

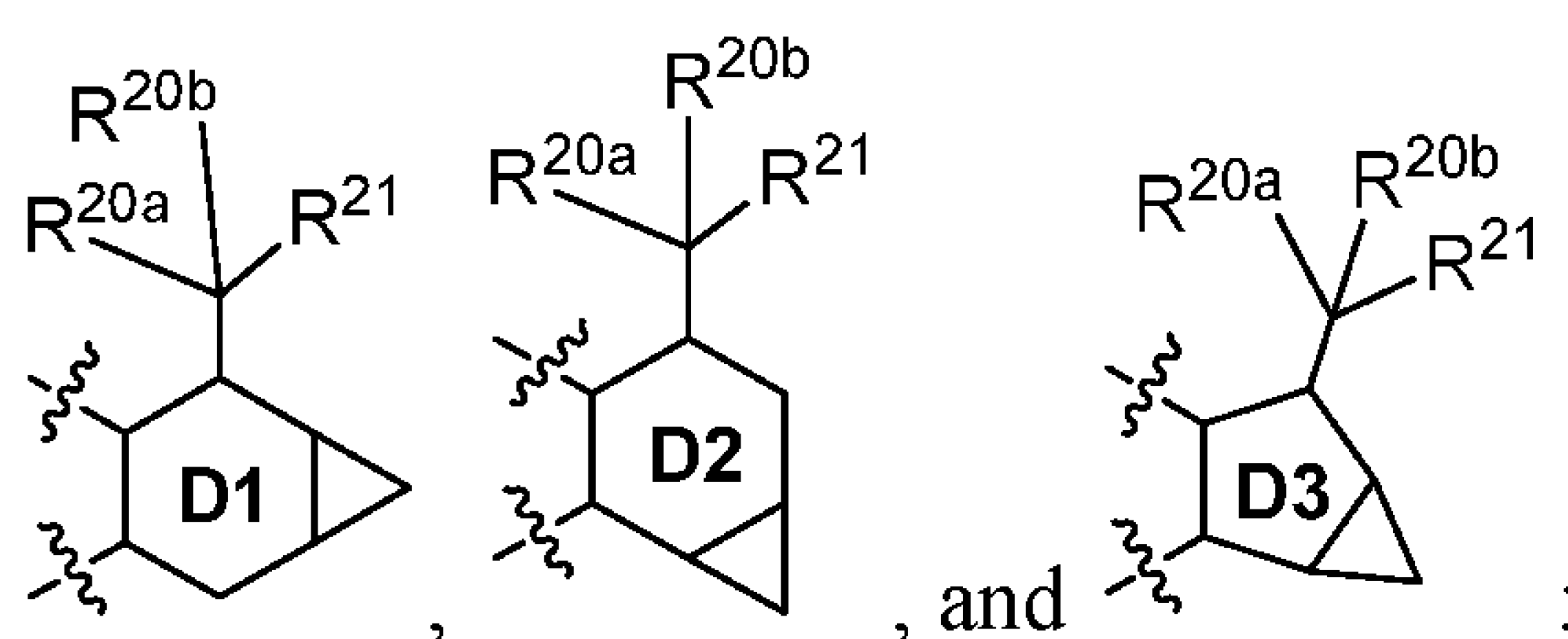
[0353] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl), R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or optionally substituted C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, or $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0354] Another aspect of the present invention provides a compound of Formula (III)



or a pharmaceutically acceptable salt thereof, wherein ring D, R^3 , R^5 , R^{10} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20a} , R^{20b} , R^{20c} , R^{21} , R^{31a} , R^{31b} and m are as defined in any of the embodiments of the compounds of Formula (I) or (II).

[0355] In some embodiments, Ring D is a fused bicyclic ring selected from



R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^{13} is $-H$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently $-H$, $-OH$, C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0356] In some embodiments, R^3 is C_{1-6} alkyl (e.g., C_{1-3} alkyl) or C_{1-6} alkyl- O - C_{1-6} alkyl (e.g., C_{1-3} alkyl- O - C_{1-3} alkyl). In some embodiments, R^3 is methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, neopentyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^3 is $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, or $-CH_2-O-CH_3$. And, in some embodiments, R^3 is $-CH_3$.

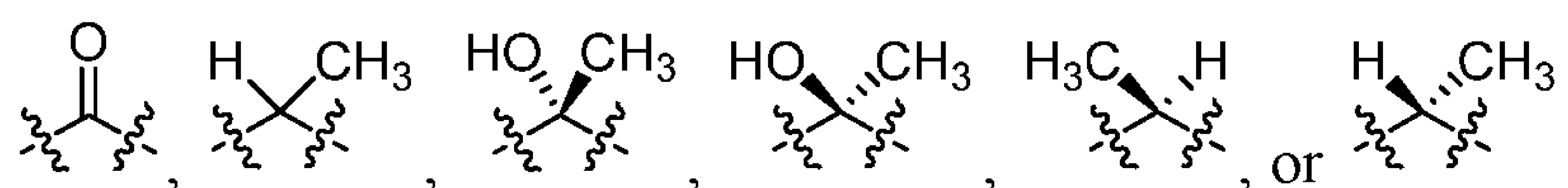
[0357] In some embodiments, R^5 is $-H$ or C_{1-3} alkyl. In some embodiments, R^5 is $-H$ or methyl.

[0358] In some embodiments, R^{10} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is

–H, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^{10} is –H or methyl.

[0359] In some embodiments, R^{13} is C_{1-6} alkyl (e.g., C_{1-3} alkyl). In some embodiments, R^{13} is methyl, ethyl, or propyl. In some embodiments, R^{13} is –H or methyl. And, in some embodiments, R^{13} is methyl.

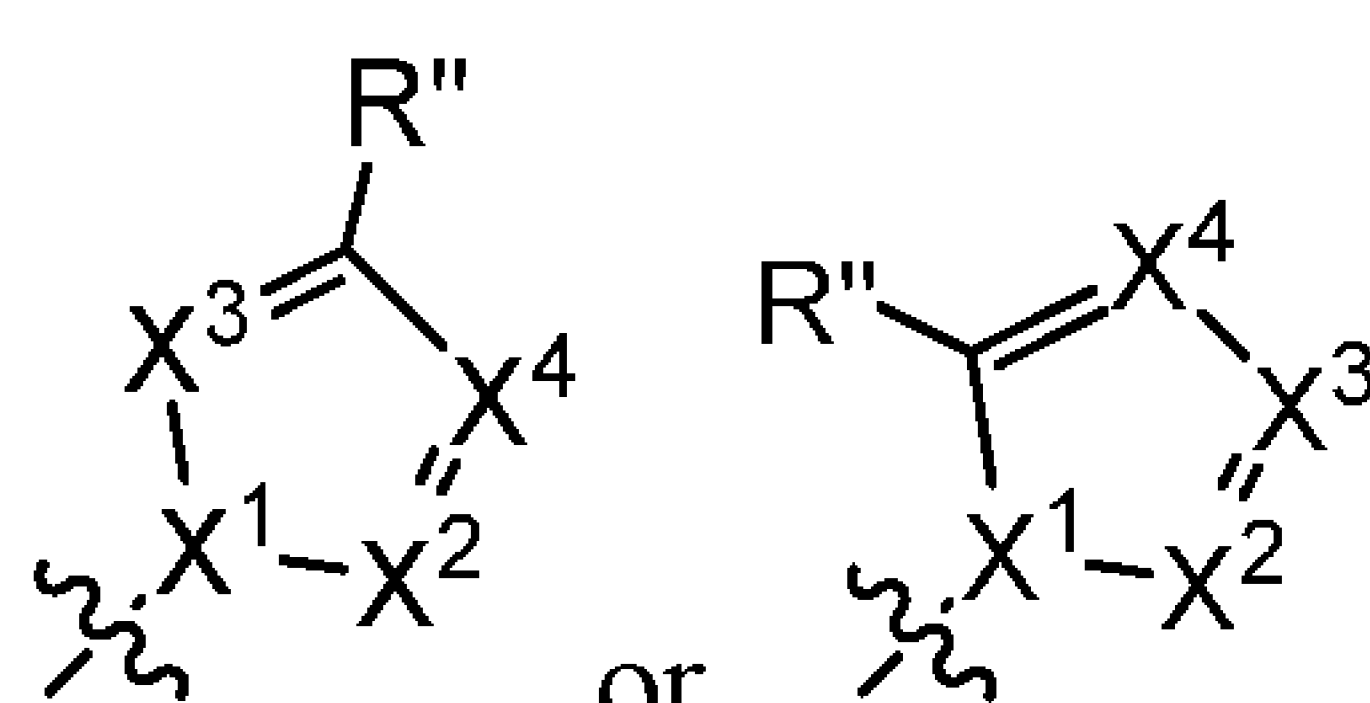
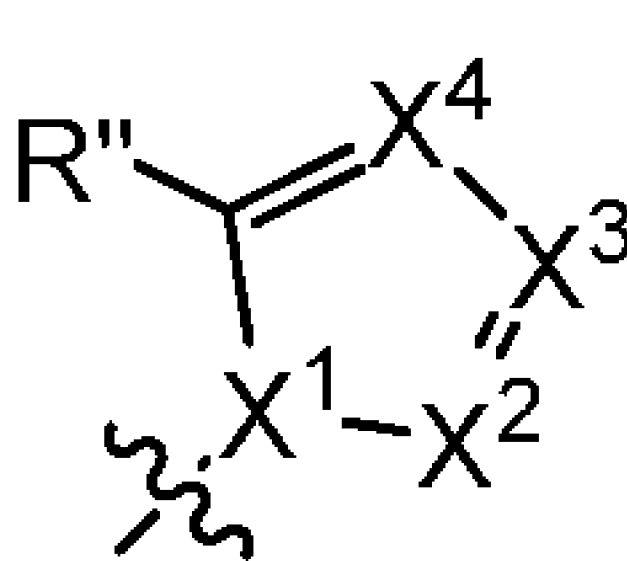
[0360] In some embodiments, R^{20a} and R^{20b} taken together form oxo. In some embodiments, one of R^{20a} and R^{20b} is –H, and the other of R^{20a} and R^{20b} is C_{1-6} alkyl (e.g., C_{1-3} alkyl). In some embodiments, one of R^{20a} and R^{20b} is C_{1-6} alkyl (e.g., C_{1-3} alkyl), and the other of R^{20a} and R^{20b} is –OH. In some embodiments, one of R^{20a} and R^{20b} is methyl, ethyl, or propyl, and the other of R^{20a} and R^{20b} is –OH. In some embodiments, R^{20a} , R^{20b} , and the carbon to which they are attached form



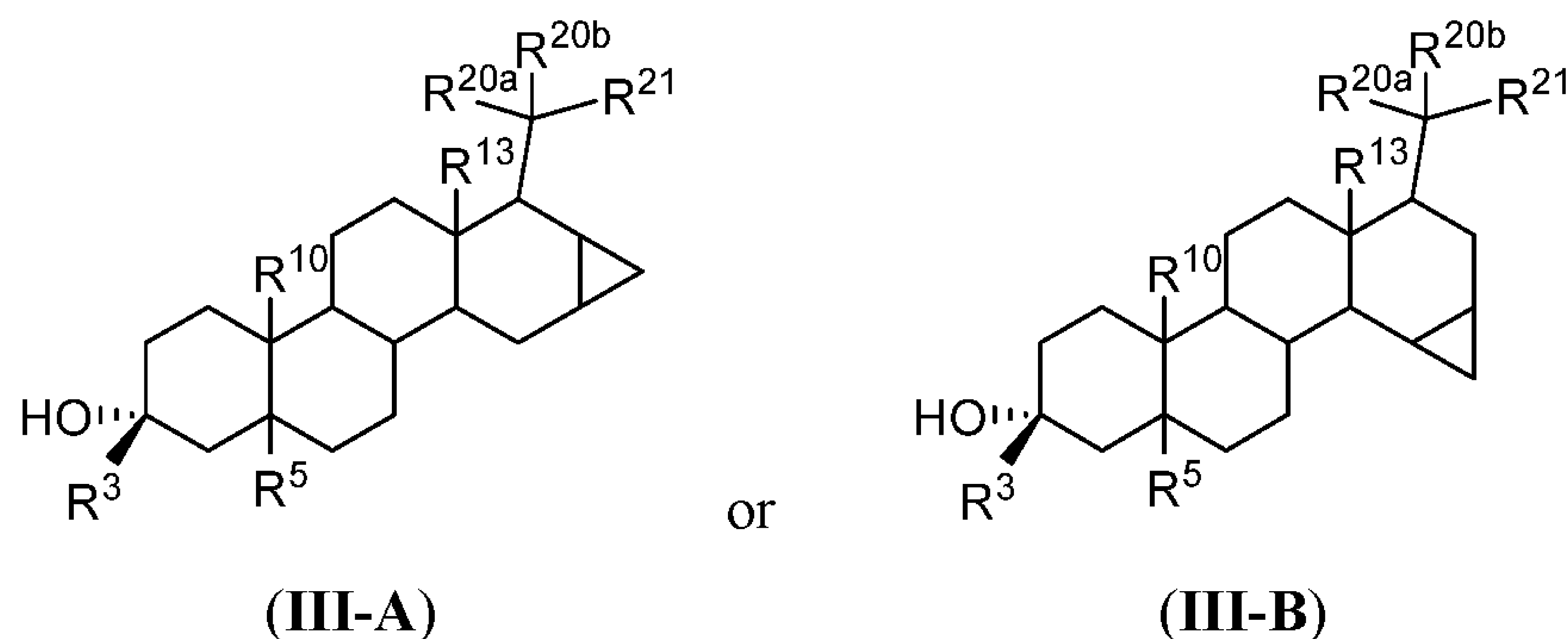
[0361] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-3} alkylene chain, or $-N(H)-$; and R^{30} is –H, –OH, –CN, –NO₂, –CF₃, or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, –CH₃, –CH₂OH, and –C(CH₃)₃. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, –CH₂–, –CH₂–CH₂–, or $-N(H)-$; and R^{30} is –H or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, –CH₃, –CH₂OH, and –C(CH₃)₃. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, –CH₂–, –CH₂–CH₂–, or $-N(H)-$; and R^{30} is a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from –CN, –NO₂, –CF₃, –CH₃, –CH₂OH, and –C(CH₃)₃. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, –CH₂–, or

$-N(H)-$; and R^{30} is , or , wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'', wherein each R'' is independently selected from –H, halo, –OH, –CN, –NO₂, –CF₃, –CH₃, –CH₂OH, and –C(CH₃)₃, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from

halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some

embodiments, R^{30} is  or , X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N and CR'' , wherein each R'' is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$, provided that no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$.

[0362] Another aspect of the present invention provides a compound of Formula (III-A) or (III-B)



or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), or (III).

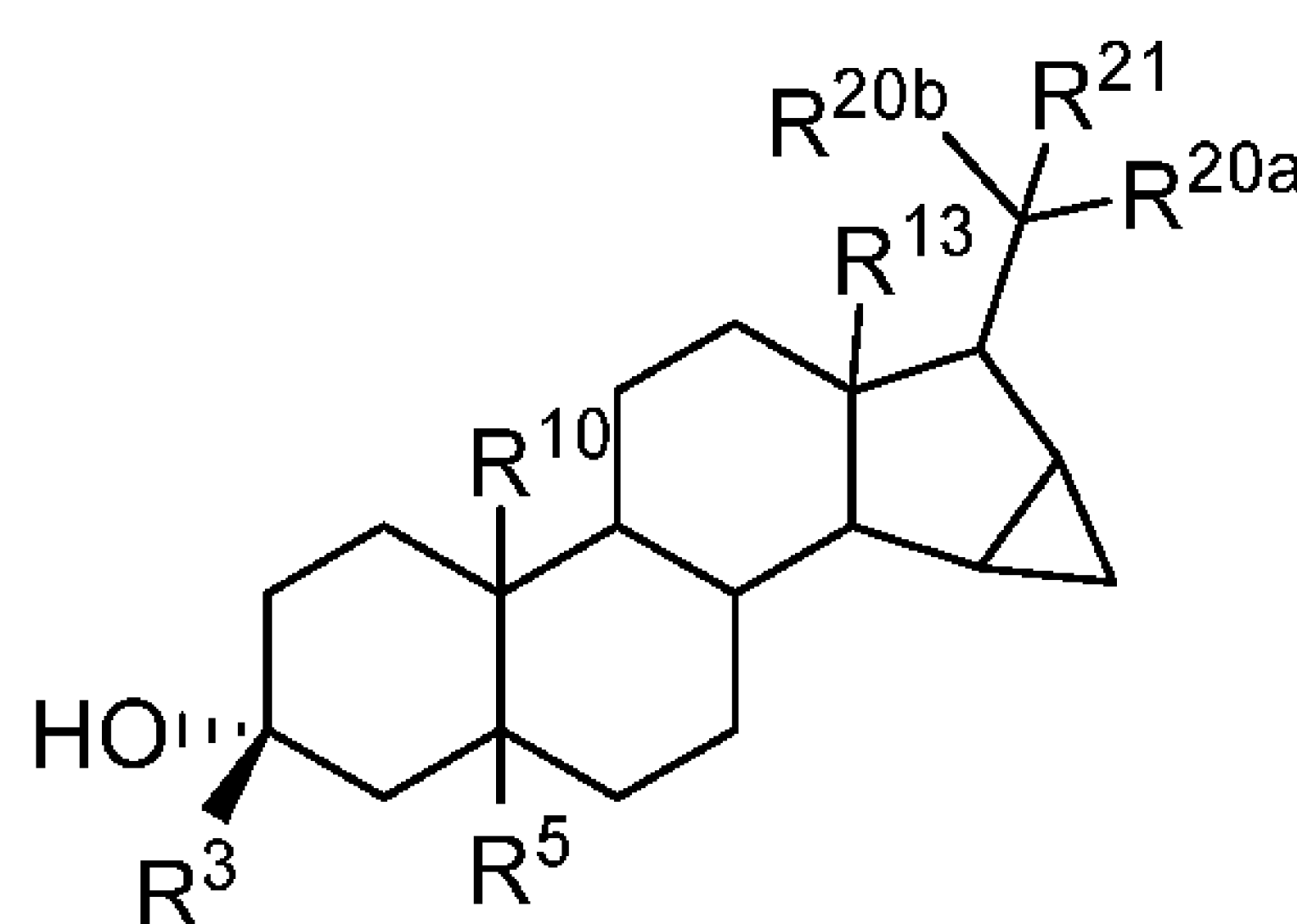
[0363] In some embodiments, R^3 is $-\text{H}$, C_{1-6} alkyl (e.g., C_{1-3} alkyl), or C_{1-6} alkyl-O- C_{1-6} alkyl (e.g., C_{1-3} alkyl-O- C_{1-3} alkyl); R^5 is $-\text{H}$ or C_{1-6} alkyl (e.g., C_{1-3} alkyl); R^{10} is $-\text{H}$, C_{1-6} alkyl (e.g., C_{1-3} alkyl), or C_{1-6} alkyl-O- C_{1-6} alkyl (e.g., C_{1-3} alkyl-O- C_{1-3} alkyl); R^{13} is $-\text{H}$ or C_{1-6} alkyl (e.g., C_{1-3} alkyl); each of R^{20a} and R^{20b} is independently selected from $-\text{H}$, $-\text{OH}$, and

C₁₋₆ alkyl (e.g., C₁₋₃ alkyl), or R^{20a} and R^{20b} taken together form oxo; R²¹ is -L^A-R³⁰; L^A is a bond, a branched or straight C₁₋₆ alkylene chain, or -N(H)-; and R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃.

[0364] In some embodiments, R³ is -H, C₁₋₃ alkyl, C₁₋₃ alkyl-O-C₁₋₃ alkyl; R⁵ is -H or methyl; R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; R¹³ is -H or C₁₋₃ alkyl; each of R^{20a} and R^{20b} is independently selected from -H, -OH, and C₁₋₃ alkyl, or R^{20a} and R^{20b} taken together form oxo; R²¹ is -L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain; and R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6- membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃. In some embodiments, the 5-6- membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

[0365] In some embodiments, R³ is methyl; R⁵ is -H; R¹⁰ is -H; R¹³ is -H or methyl; each of R^{20a} and R^{20b} is independently selected from -H, -OH, and methyl, or R^{20a} and R^{20b} taken together form oxo; R²¹ is -L^A-R³⁰; L^A is a bond, -NH-, or -CH₂-; R³⁰ is independently selected from pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C₁₋₆ alkyl (e.g., C₁₋₃ alkyl), or cyano.

[0366] Another aspect of the present invention provides a compound of Formula (III-C)



(III-C)

or a pharmaceutically acceptable salt thereof, wherein R³, R⁵, R¹⁰, R¹³, R^{20a}, R^{20b}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (II), or (III).

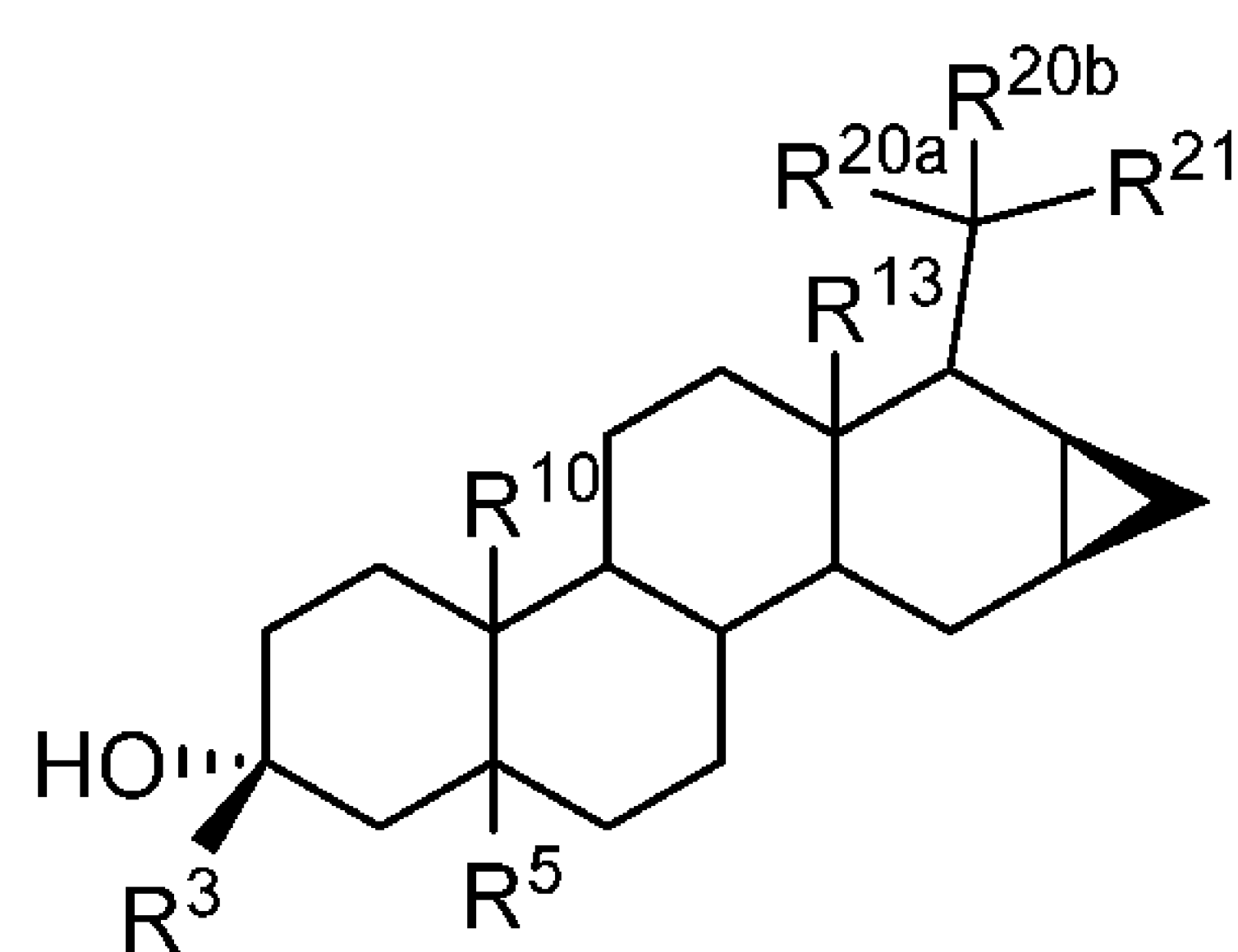
[0367] In some embodiments, R³ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; R⁵ is -H or C₁₋₆ alkyl; R¹⁰ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; R¹³ is -H or C₁₋₆ alkyl; each of R^{20a} and R^{20b} is independently selected from -H, -OH, and C₁₋₆ alkyl, or R^{20a} and R^{20b} taken together

form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

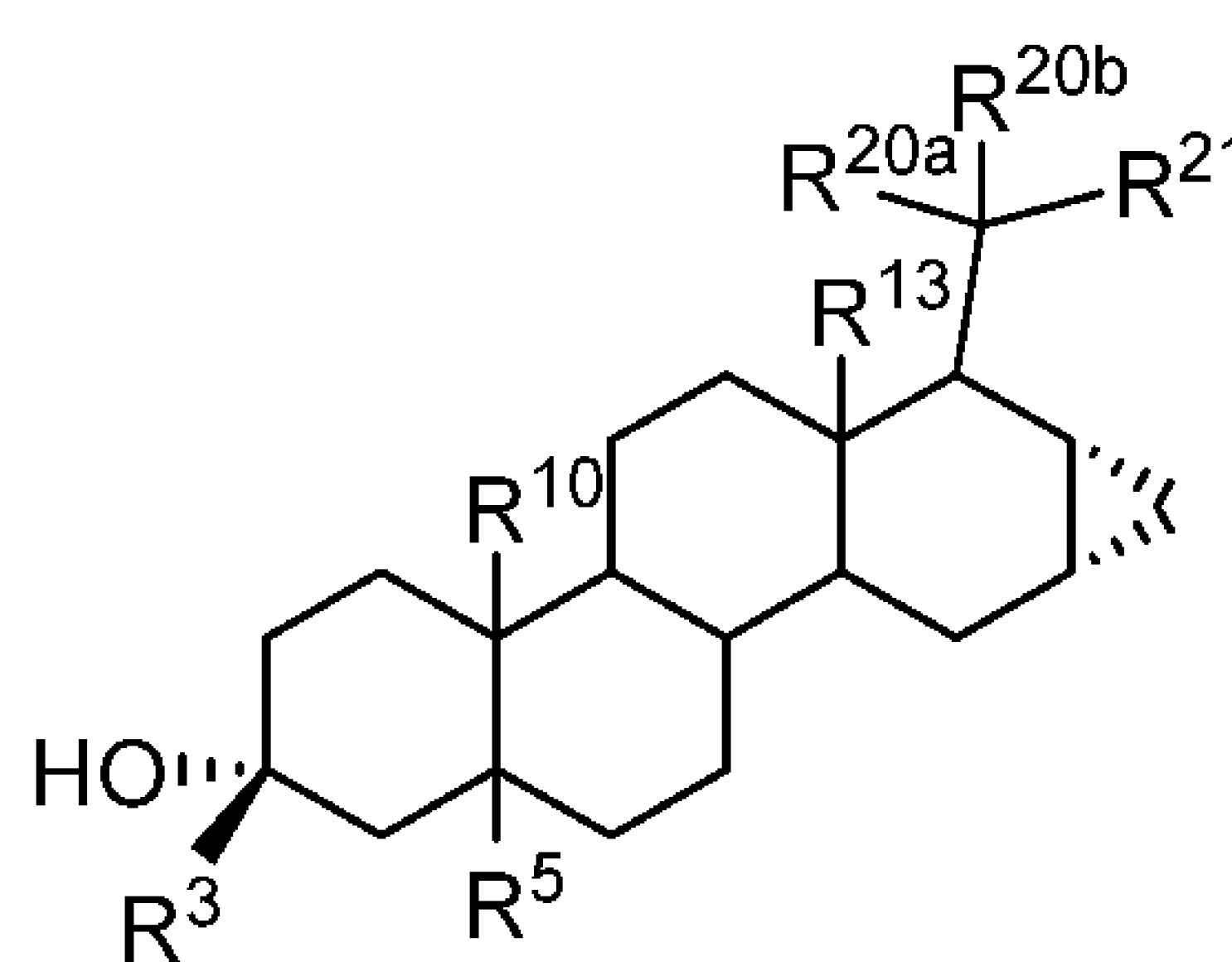
[0368] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl-O- C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl-O- C_{1-3} alkyl; R^{13} is $-H$ or C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or $-CH_3$.

[0369] In some embodiments, R^3 is methyl, ethyl, propyl, or methoxymethyl; R^5 is $-H$; R^{10} is $-H$; R^{13} is $-H$ or methyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and methyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, $-NH-$, or $-CH_2-$; R^{30} is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C_{1-6} alkyl, or cyano.

[0370] Another aspect of the present invention provides a compound of Formula (III-A1) or (III-A2)



(III-A1)



(III-A2)

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), or (III-A).

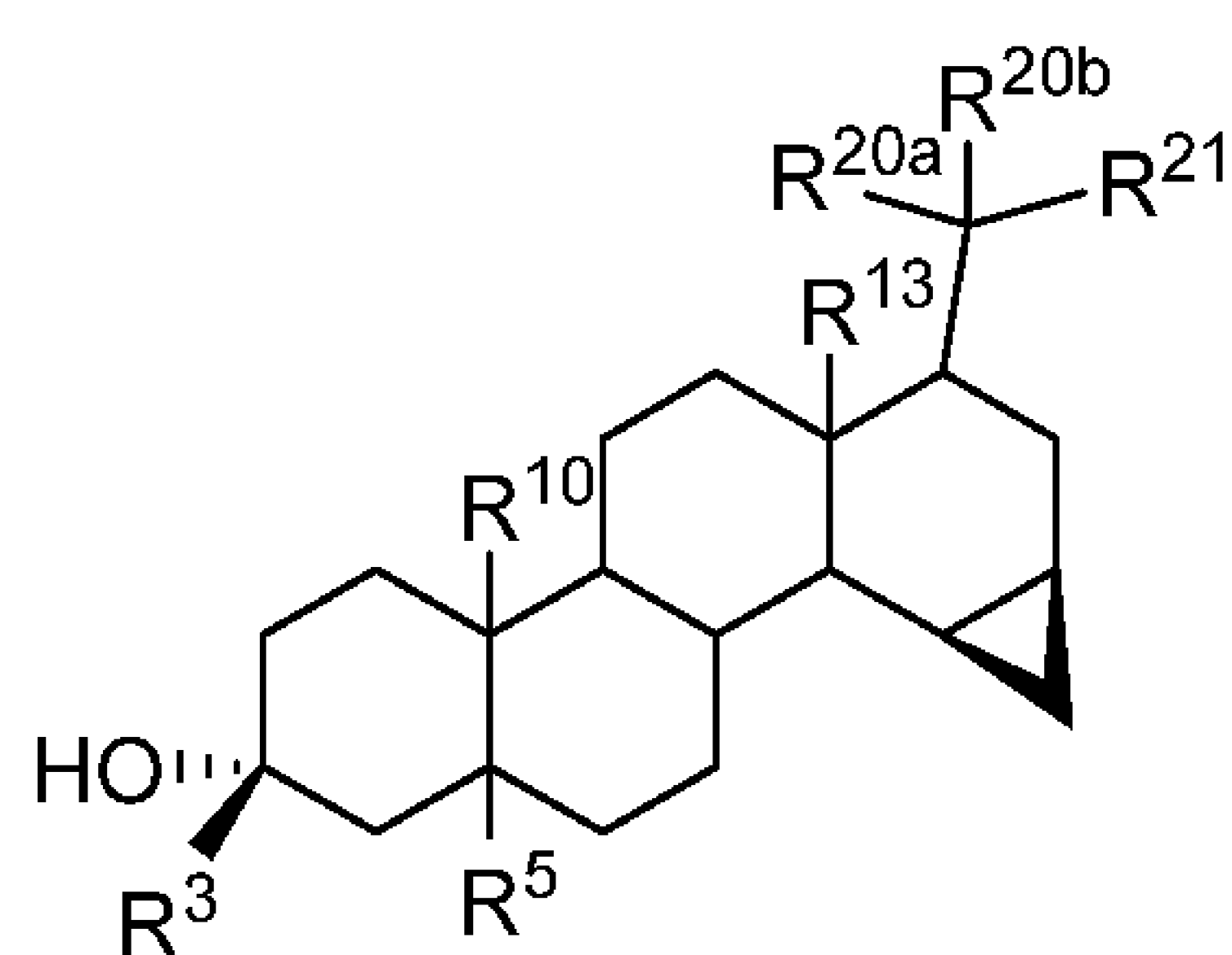
[0371] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl-O- C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl-O- C_{1-6} alkyl; R^{13} is $-H$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together

form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

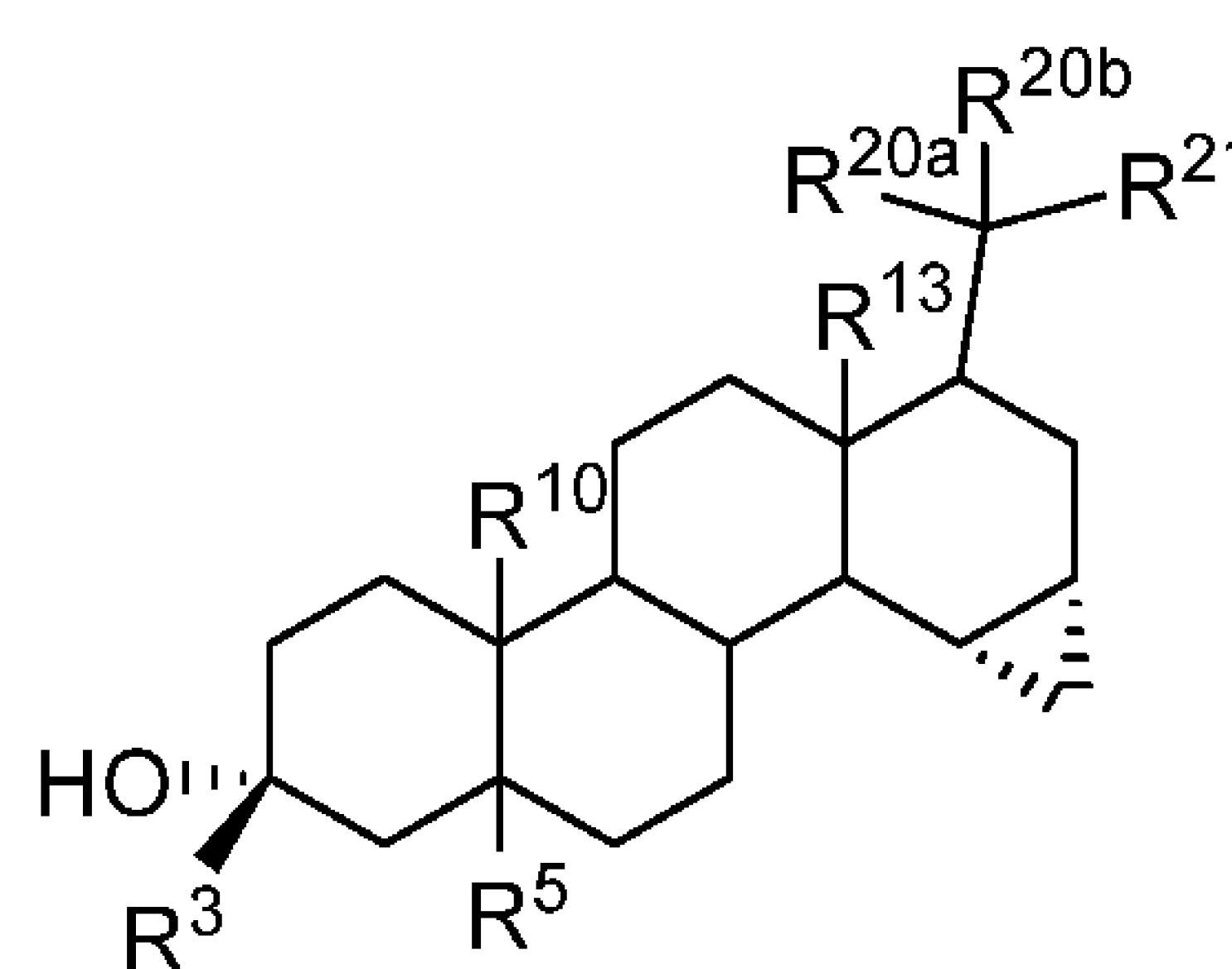
[0372] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl-O- C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl-O- C_{1-3} alkyl; R^{13} is $-H$ or C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0373] In some embodiments, R^3 is methyl, ethyl, propyl, or methoxymethyl; R^5 is $-H$; R^{10} is $-H$; R^{13} is $-H$ or methyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and methyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, $-NH-$, or $-CH_2-$; R^{30} is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C_{1-6} alkyl, or cyano.

[0374] Another aspect of the present invention provides a compound of Formula (III-B1) or (III-B2)



(III-B1)



(III-B2)

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), or (III-B).

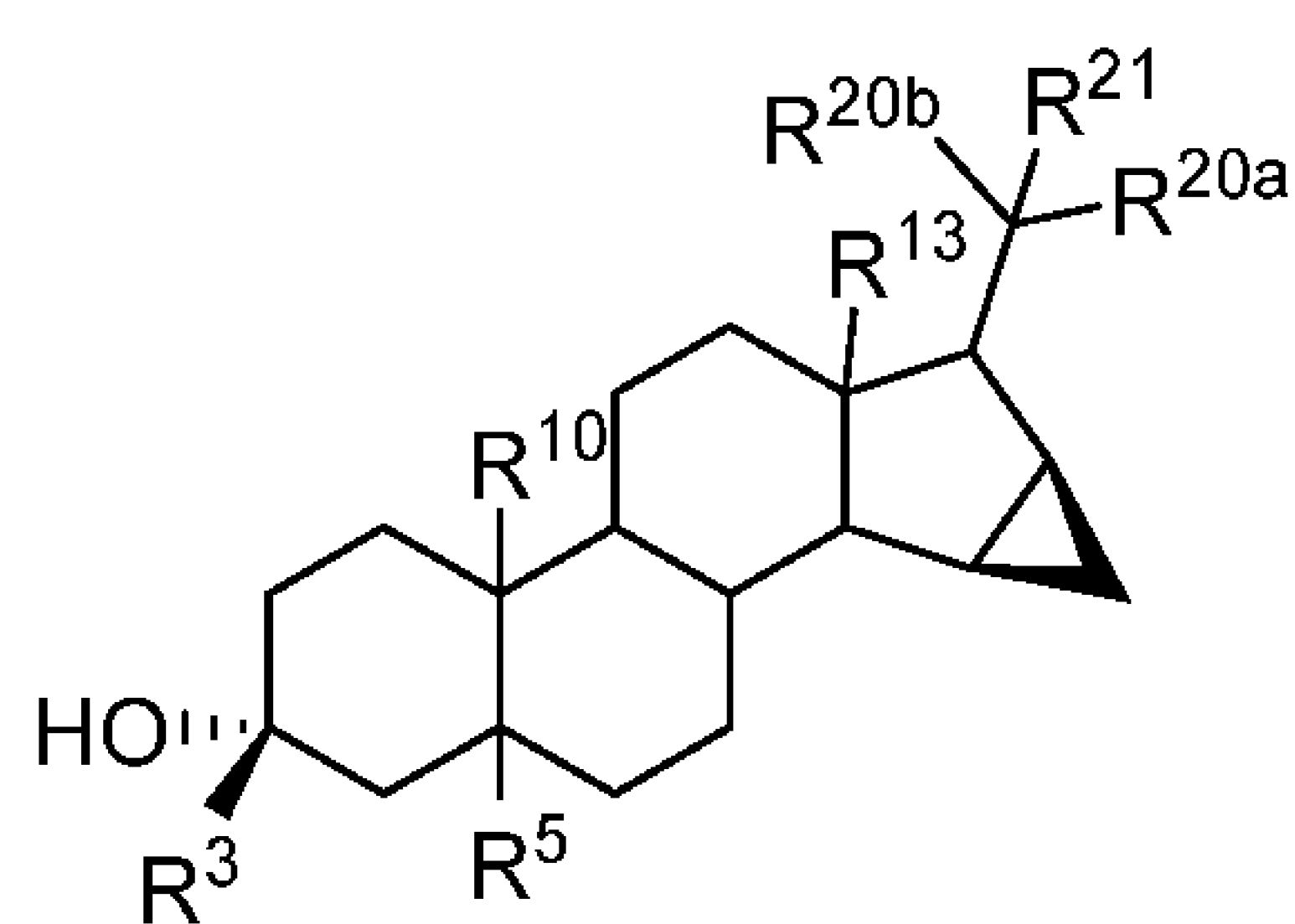
[0375] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl-O- C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl-O- C_{1-6} alkyl; R^{13} is $-H$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together

form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0376] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

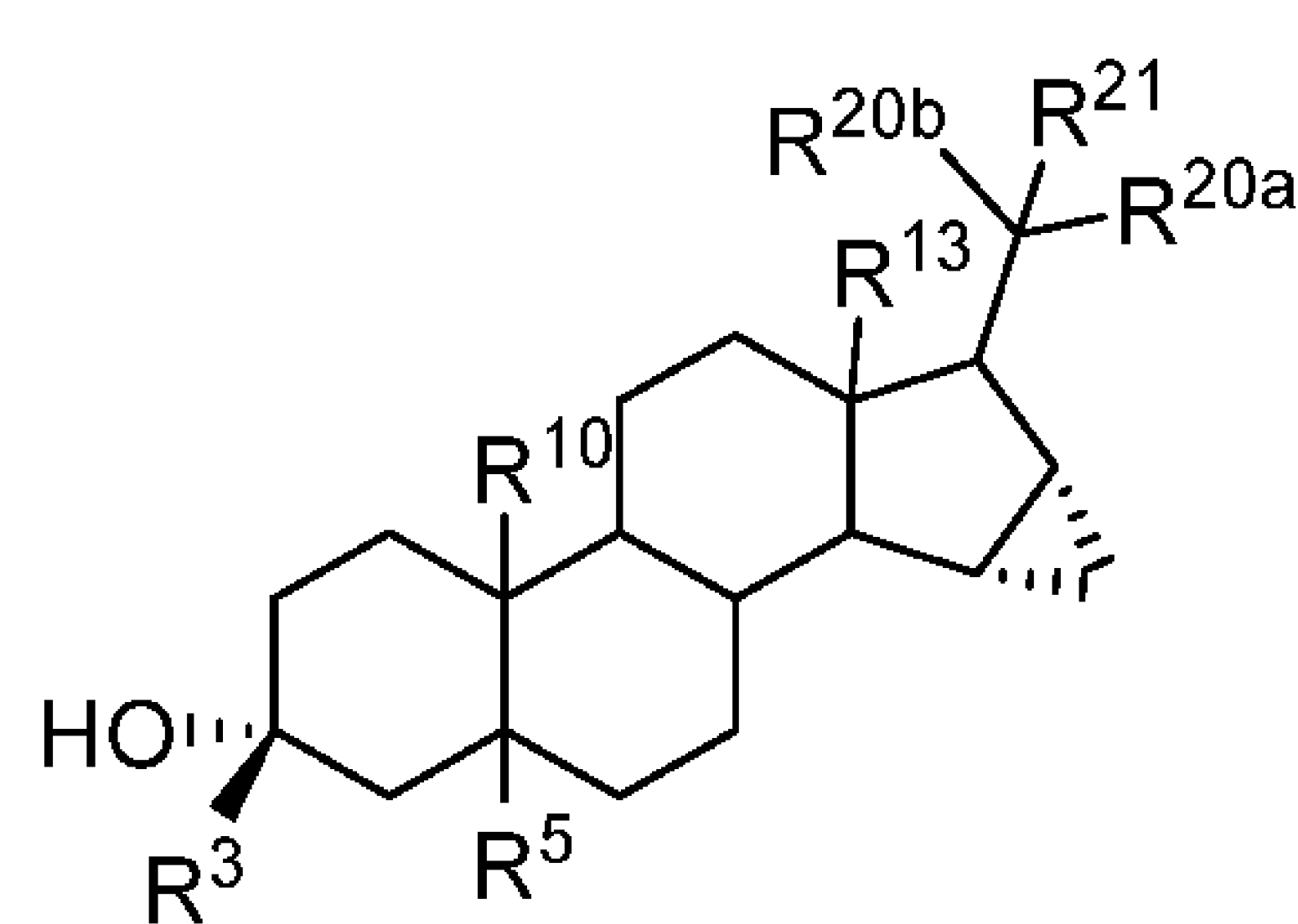
[0377] In some embodiments, R^3 is methyl, ethyl, propyl, or methoxymethyl; R^5 is $-H$; R^{10} is $-H$; R^{13} is $-H$ or methyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and methyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, $-NH-$, or $-CH_2-$; R^{30} is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C_{1-6} alkyl, or cyano.

[0378] Another aspect of the present invention provides a compound of Formula (III-C1) or (III-C2)



(III-C1)

or



(III-C2)

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), or (III-C).

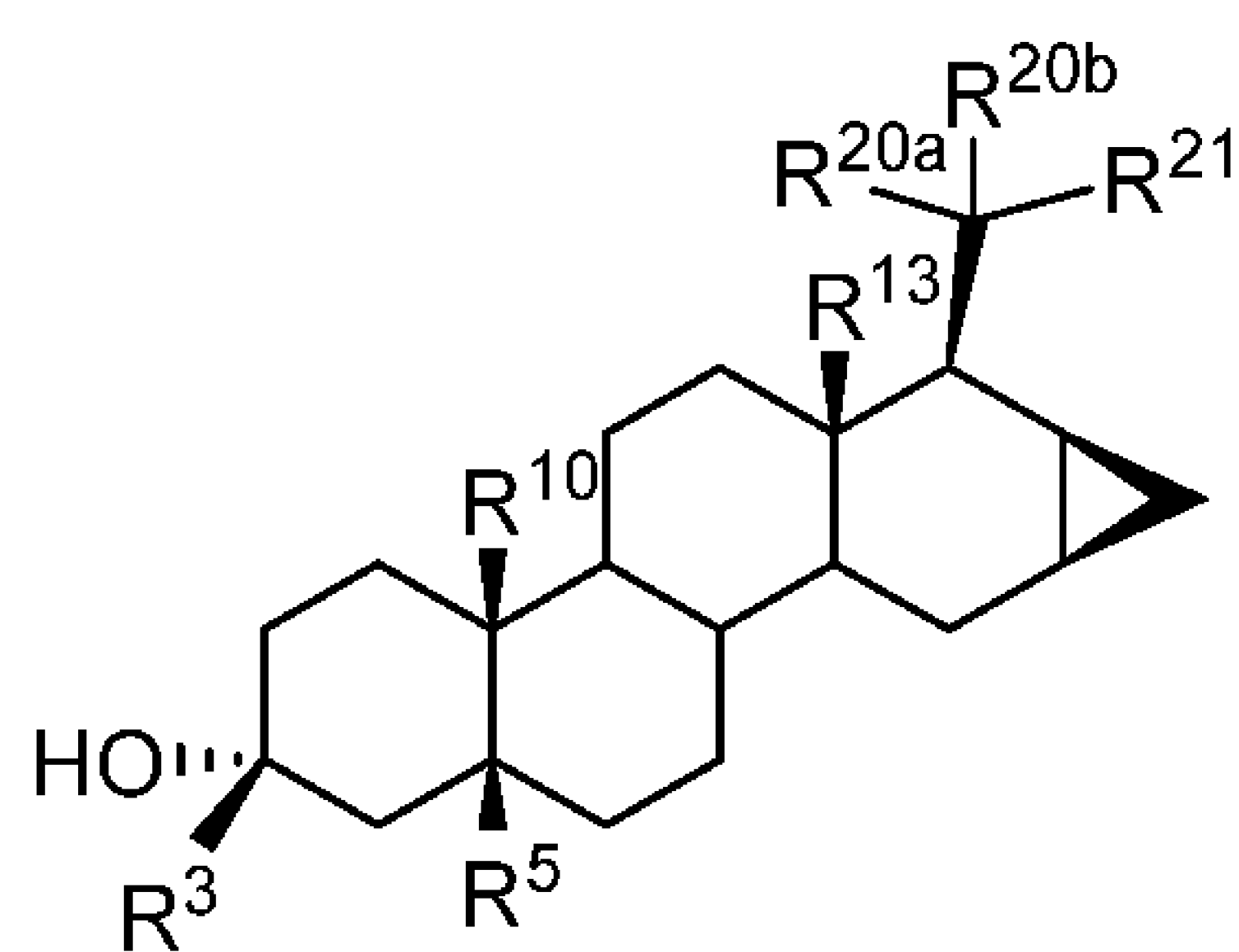
[0379] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^{13} is $-H$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together

form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

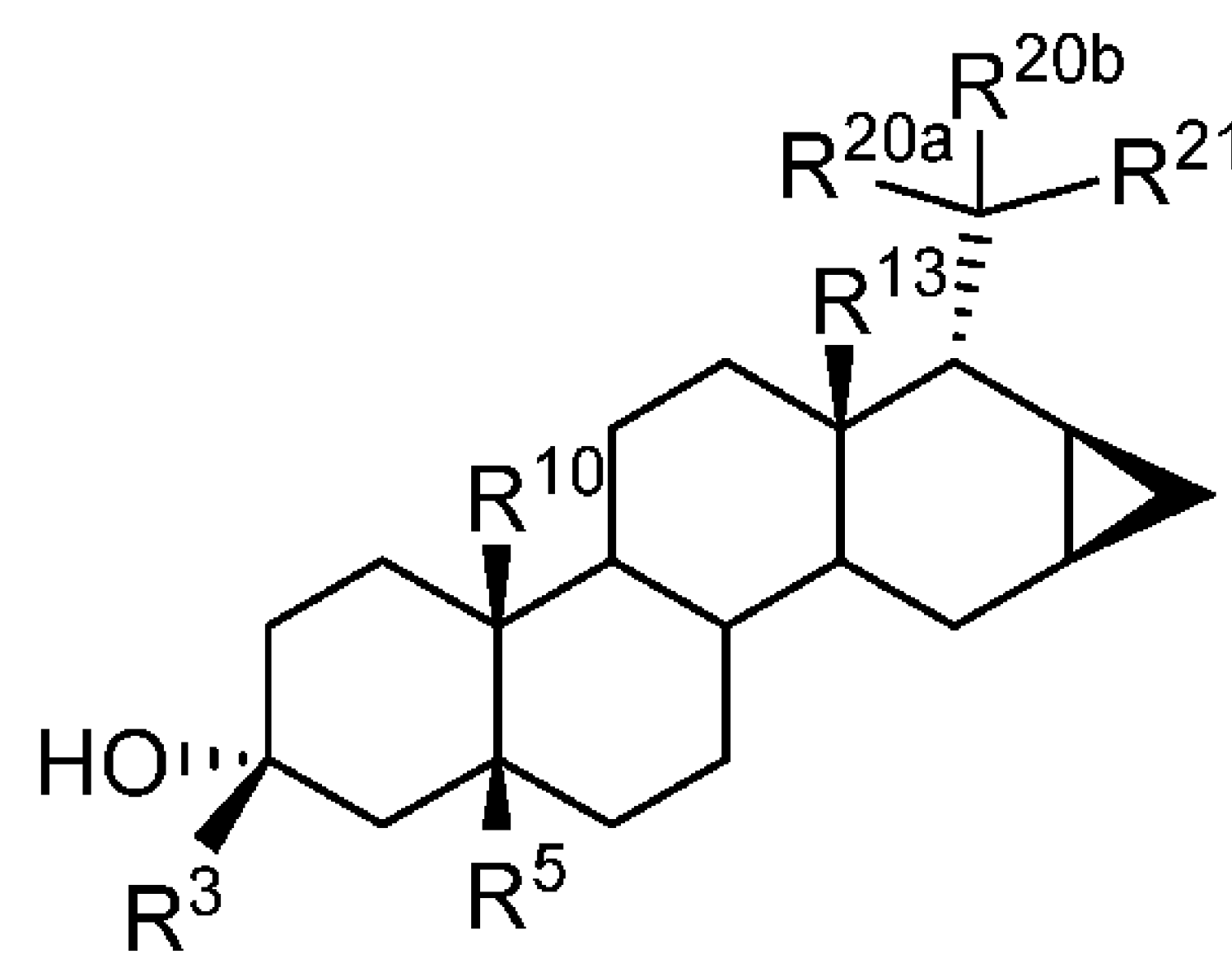
[0380] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0381] In some embodiments, R^3 is methyl, ethyl, propyl, or methoxymethyl; R^5 is $-H$; R^{10} is $-H$; R^{13} is $-H$ or methyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and methyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, $-NH-$, or $-CH_2-$; R^{30} is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C_{1-6} alkyl, or cyano.

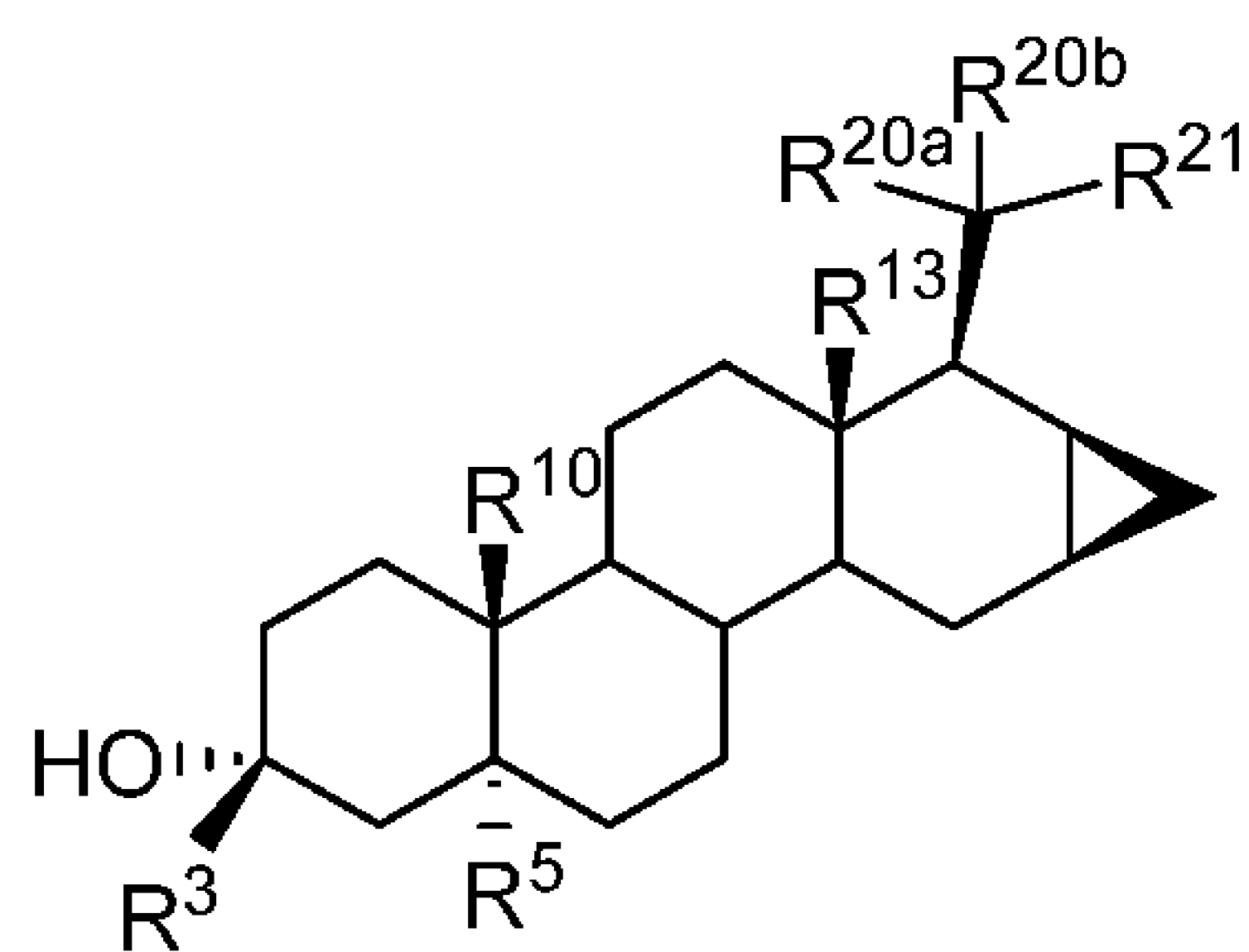
[0382] Another aspect of the present invention provides a compound of Formula (III-A1a), (III-A1b), (III-A1c), or (III-A1d)



(III-A1a),

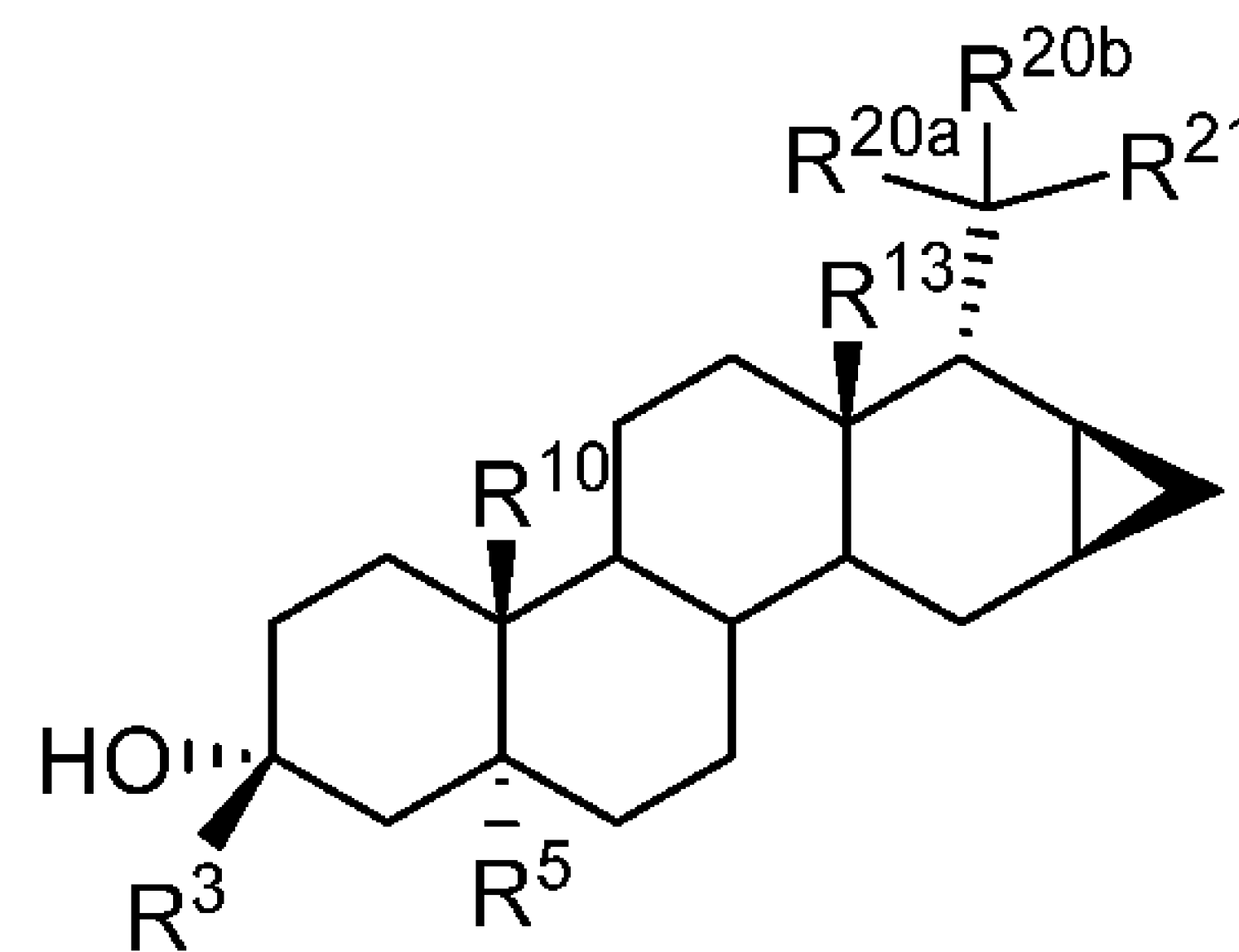


(III-A1b),



(III-A1c),

or



(III-A1d)

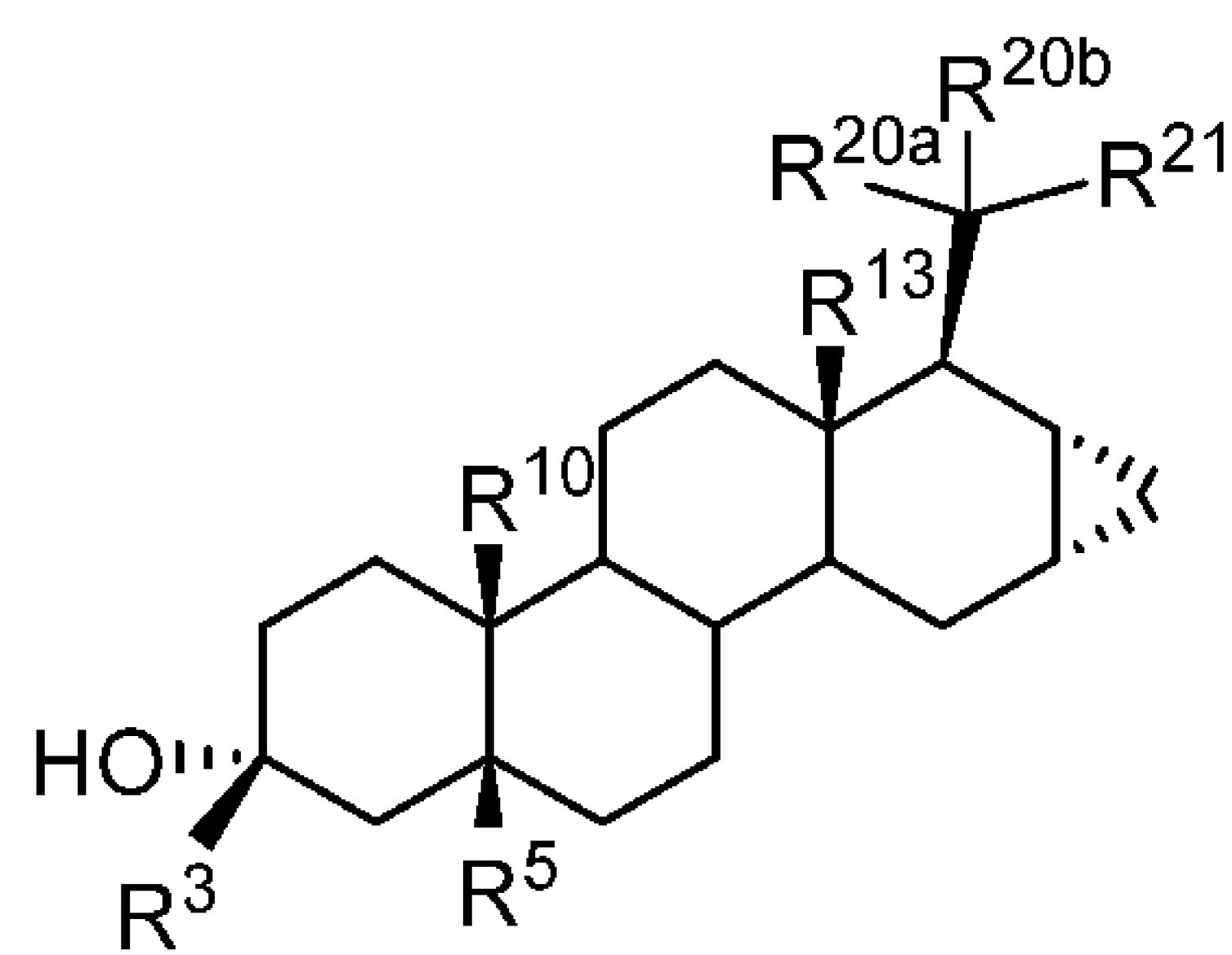
or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), (III-A), or (III-A1).

[0383] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^{13} is $-H$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

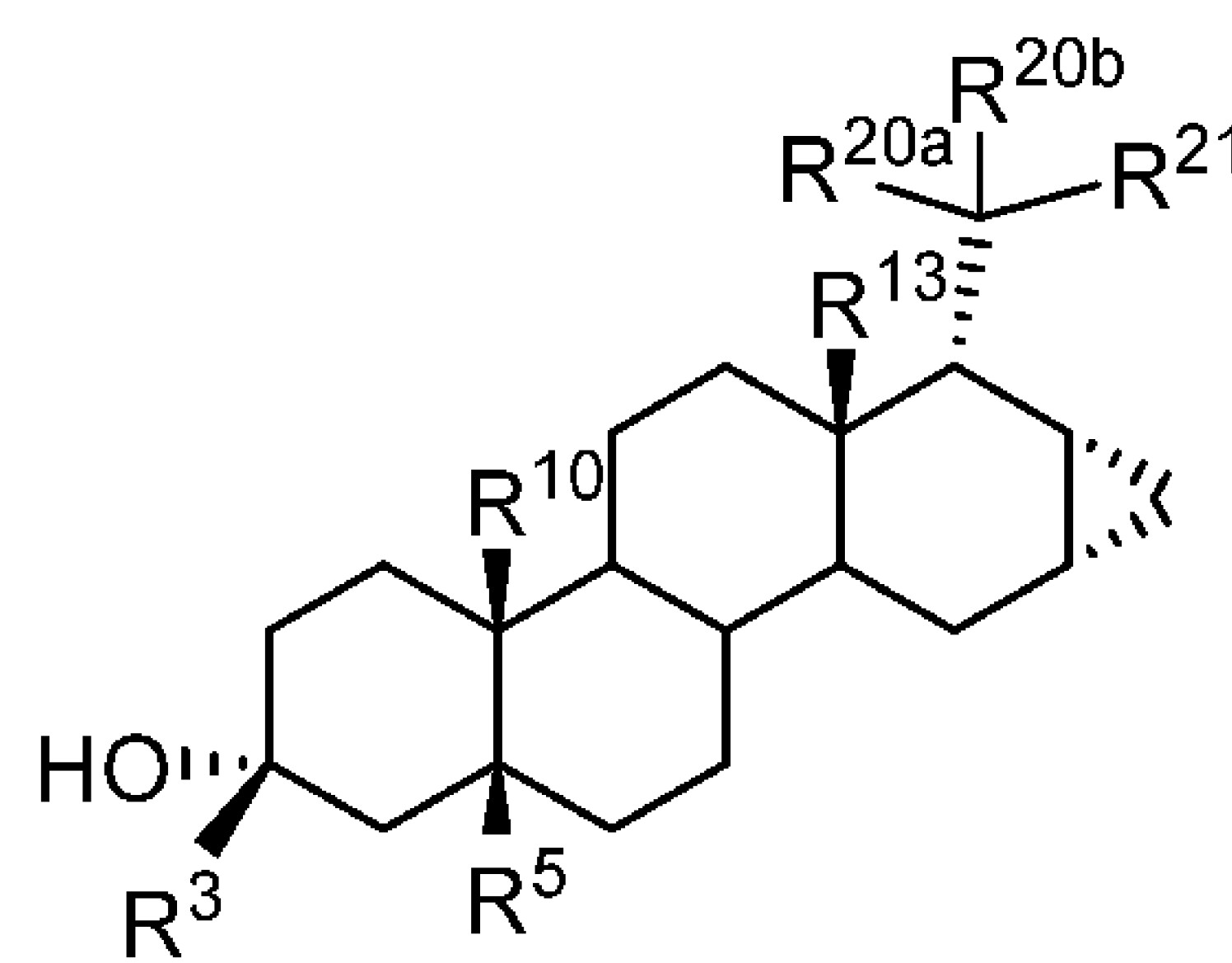
[0384] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0385] In some embodiments, R^3 is methyl, ethyl, propyl, or methoxymethyl; R^5 is $-H$; R^{10} is $-H$; R^{13} is $-H$ or methyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and methyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, $-NH-$, or $-CH_2-$; R^{30} is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C_{1-6} alkyl, or cyano.

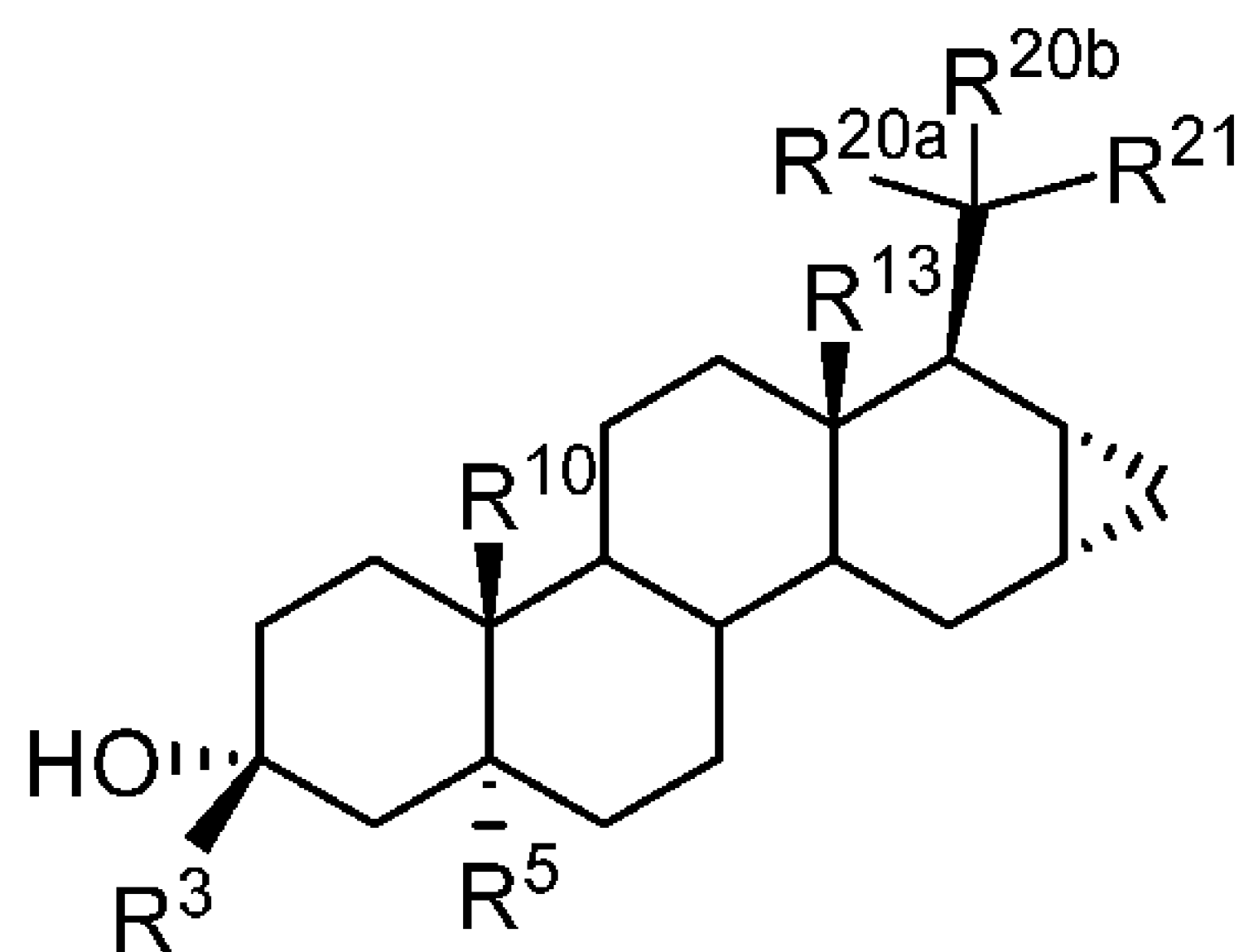
[0386] Another aspect of the present invention provides a compound of Formula (III-A2a), (III-A2b), (III-A2c), or (III-A2d)



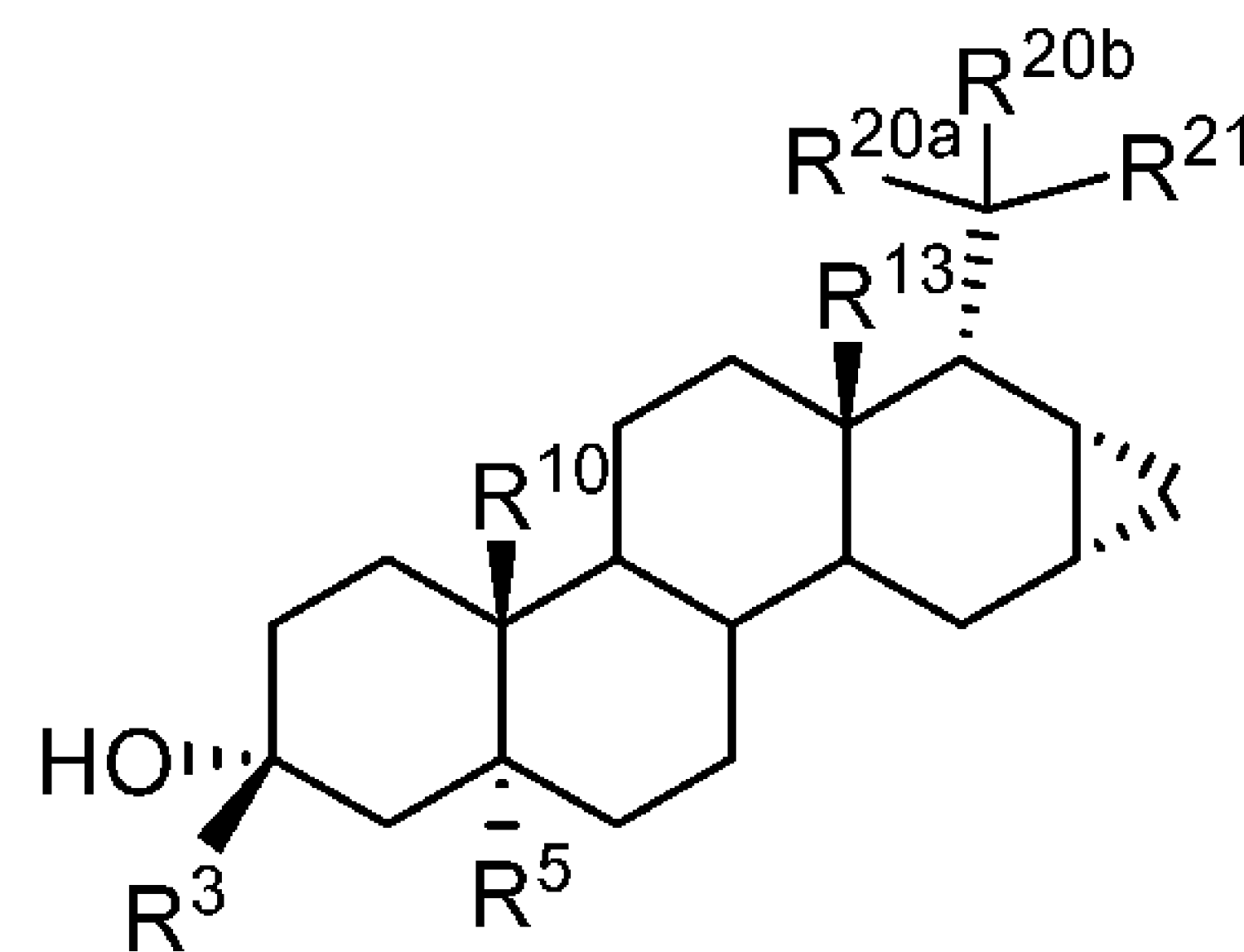
(III-A2a),



(III-A2b),



(III-A2c),



(III-A2d)

or

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), (III-A), or (III-A2).

[0387] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^{13} is $-H$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

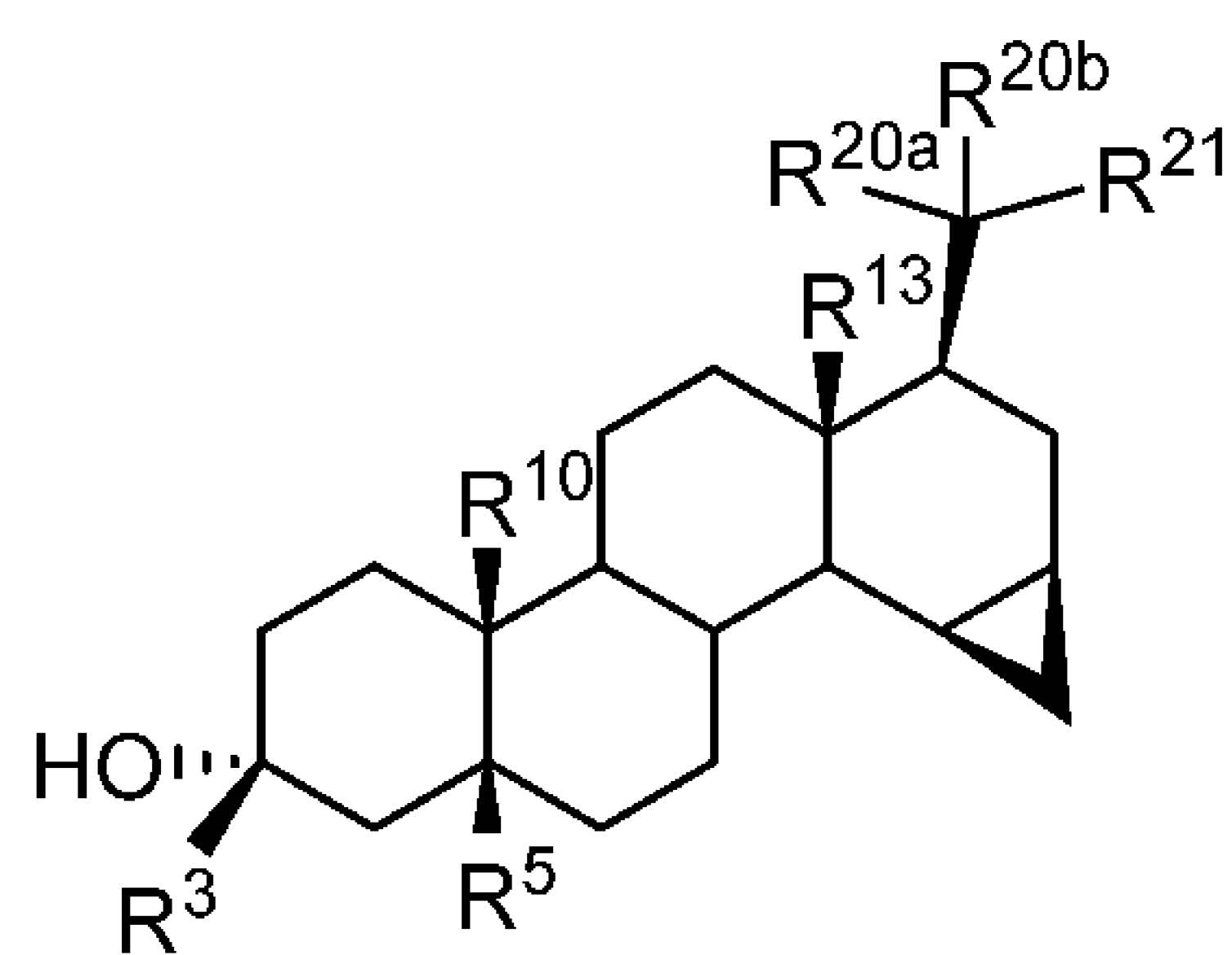
[0388] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups

independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$.

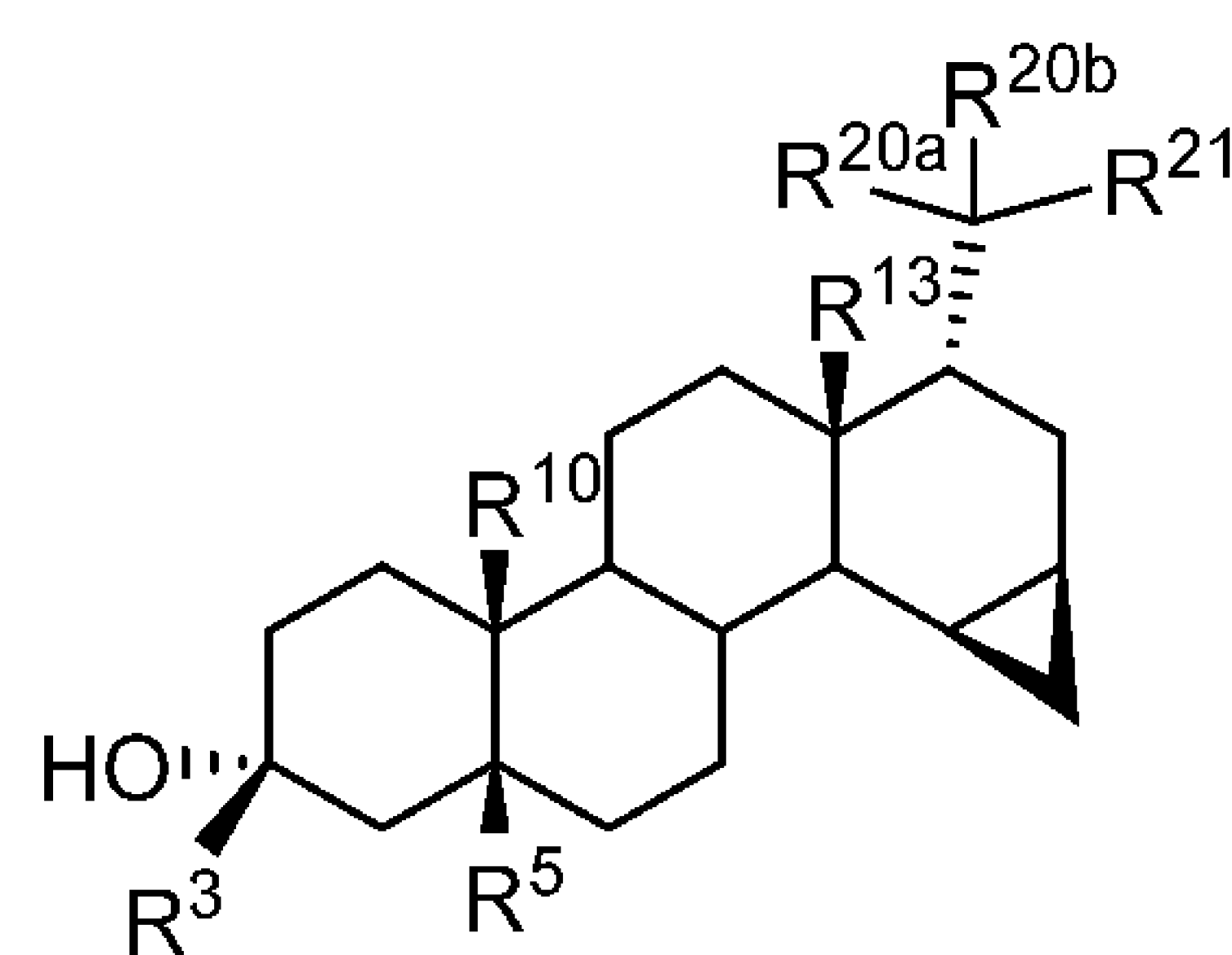
In some embodiments, the 5-6- membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, and $-\text{CH}_3$.

[0389] In some embodiments, R^3 is methyl, ethyl, propyl, or methoxymethyl; R^5 is $-\text{H}$; R^{10} is $-\text{H}$; R^{13} is $-\text{H}$ or methyl; each of R^{20a} and R^{20b} is independently selected from $-\text{H}$, $-\text{OH}$, and methyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-\text{L}^A-\text{R}^{30}$; L^A is a bond, $-\text{NH}-$, or $-\text{CH}_2-$; R^{30} is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C_{1-6} alkyl, or cyano.

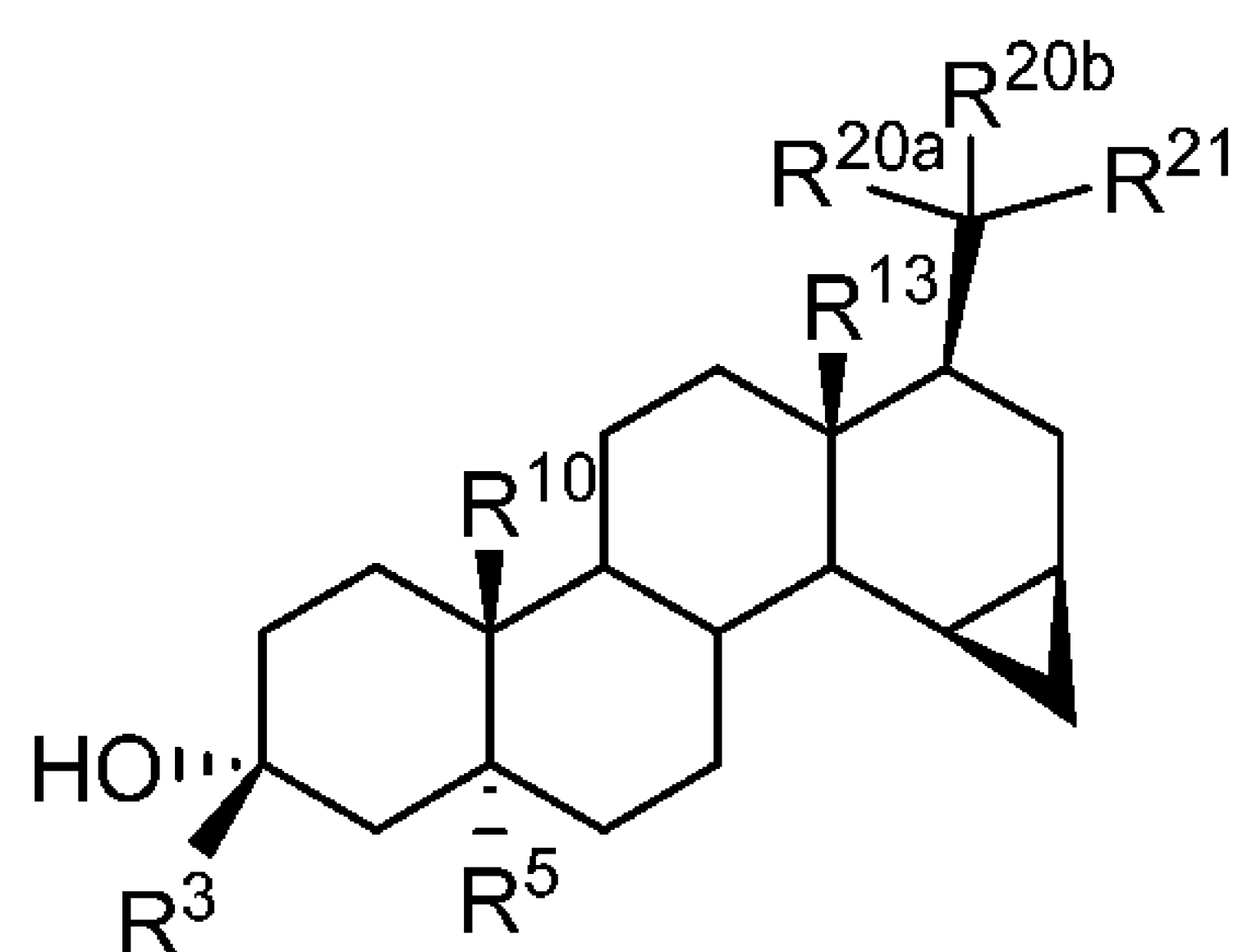
[0390] Another aspect of the present invention provides a compound of Formula **(III-B1a)**, **(III-B1b)**, **(III-B1c)**, or **(III-B1d)**



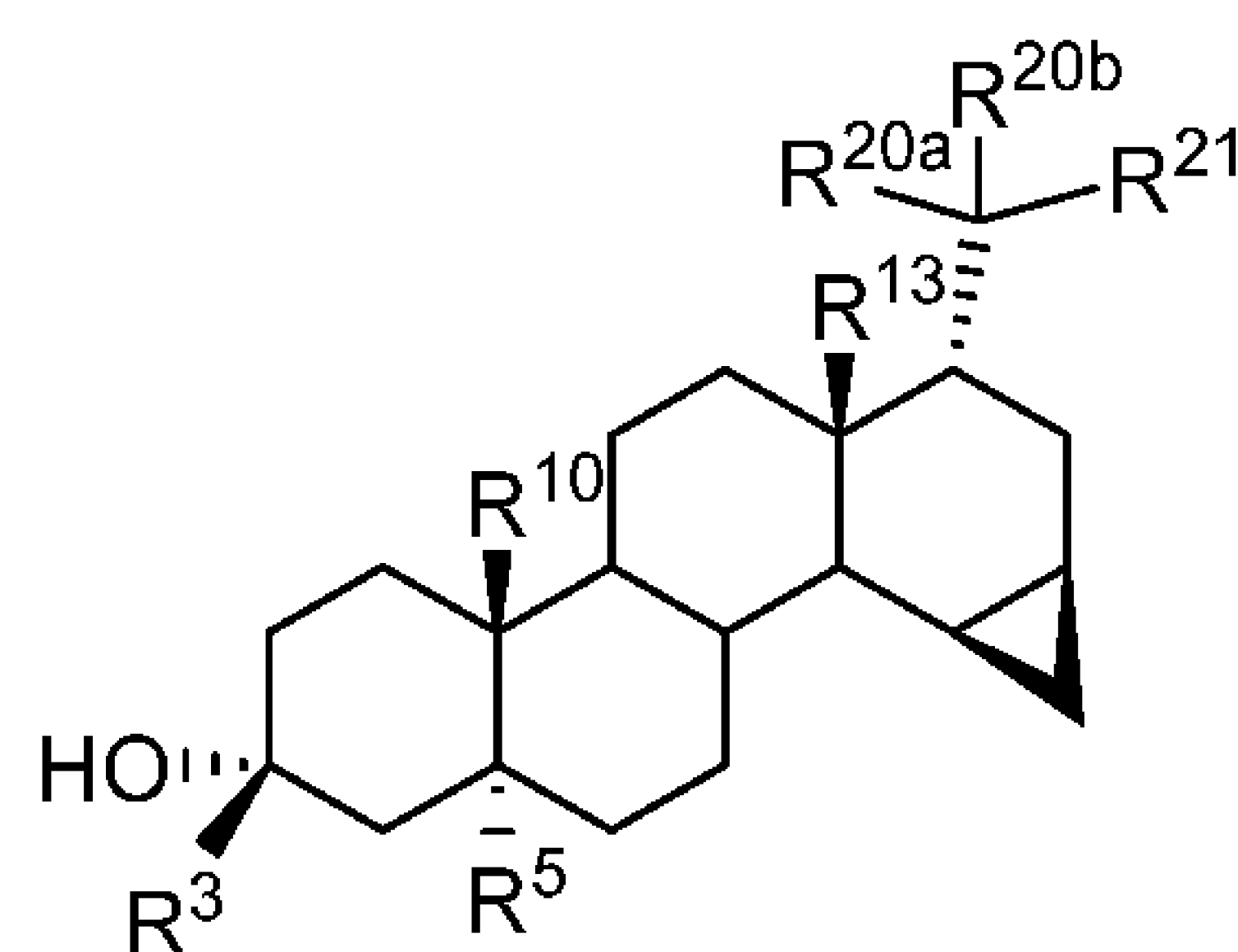
(III-B1a),



(III-B1b),



(III-B1c)



(III-B1d)

or

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula **(I)**, **(II)**, **(III)**, **(III-B)**, **(III-B1)**.

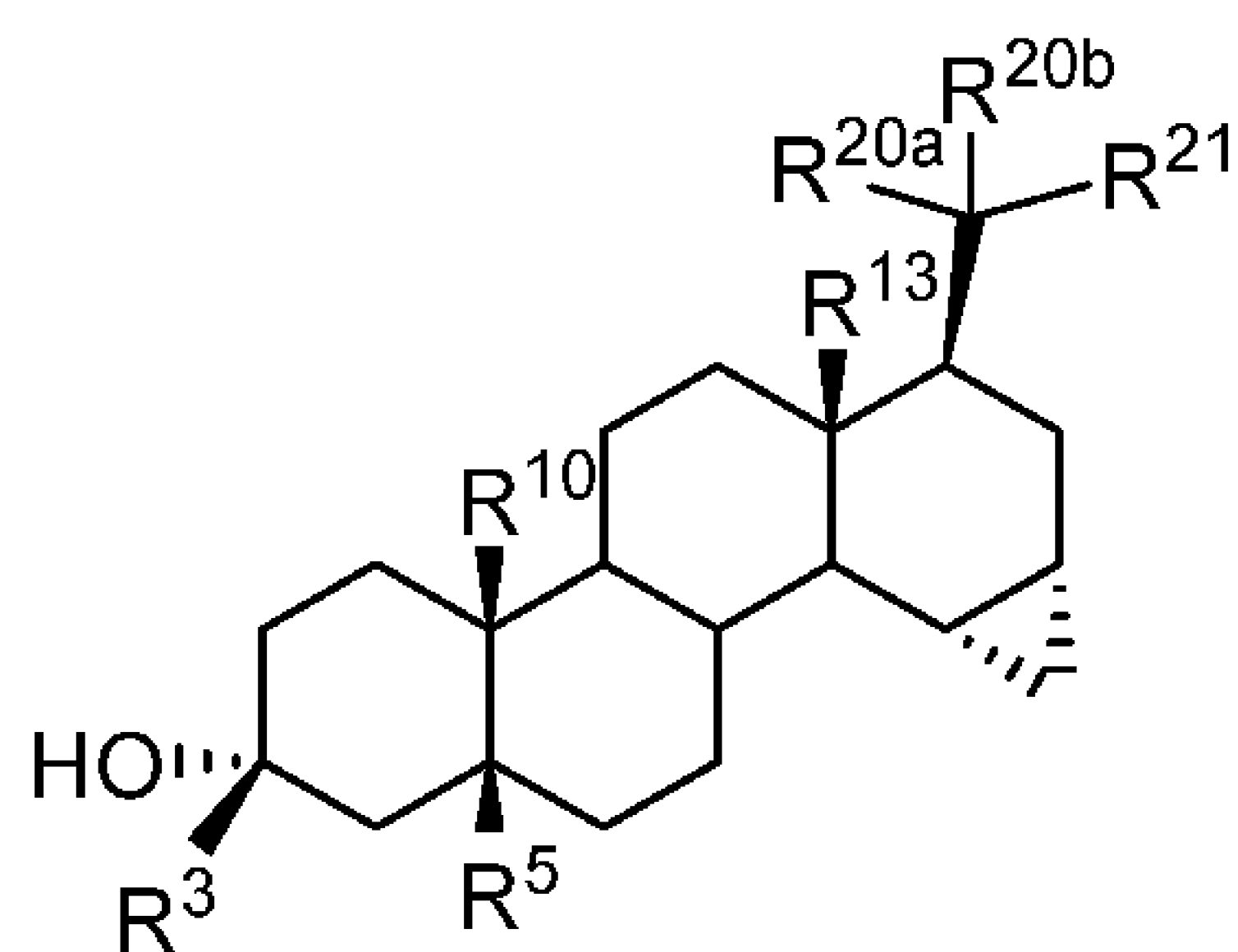
[0391] In some embodiments, R^3 is $-\text{H}$, C_{1-6} alkyl, or C_{1-6} alkyl- $\text{O}-\text{C}_{1-6}$ alkyl; R^5 is $-\text{H}$ or C_{1-6} alkyl; R^{10} is $-\text{H}$, C_{1-6} alkyl, or C_{1-6} alkyl- $\text{O}-\text{C}_{1-6}$ alkyl; R^{13} is $-\text{H}$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-\text{H}$, $-\text{OH}$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-\text{L}^A-\text{R}^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-\text{N}(\text{H})-$; and R^{30} is $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted

with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$.

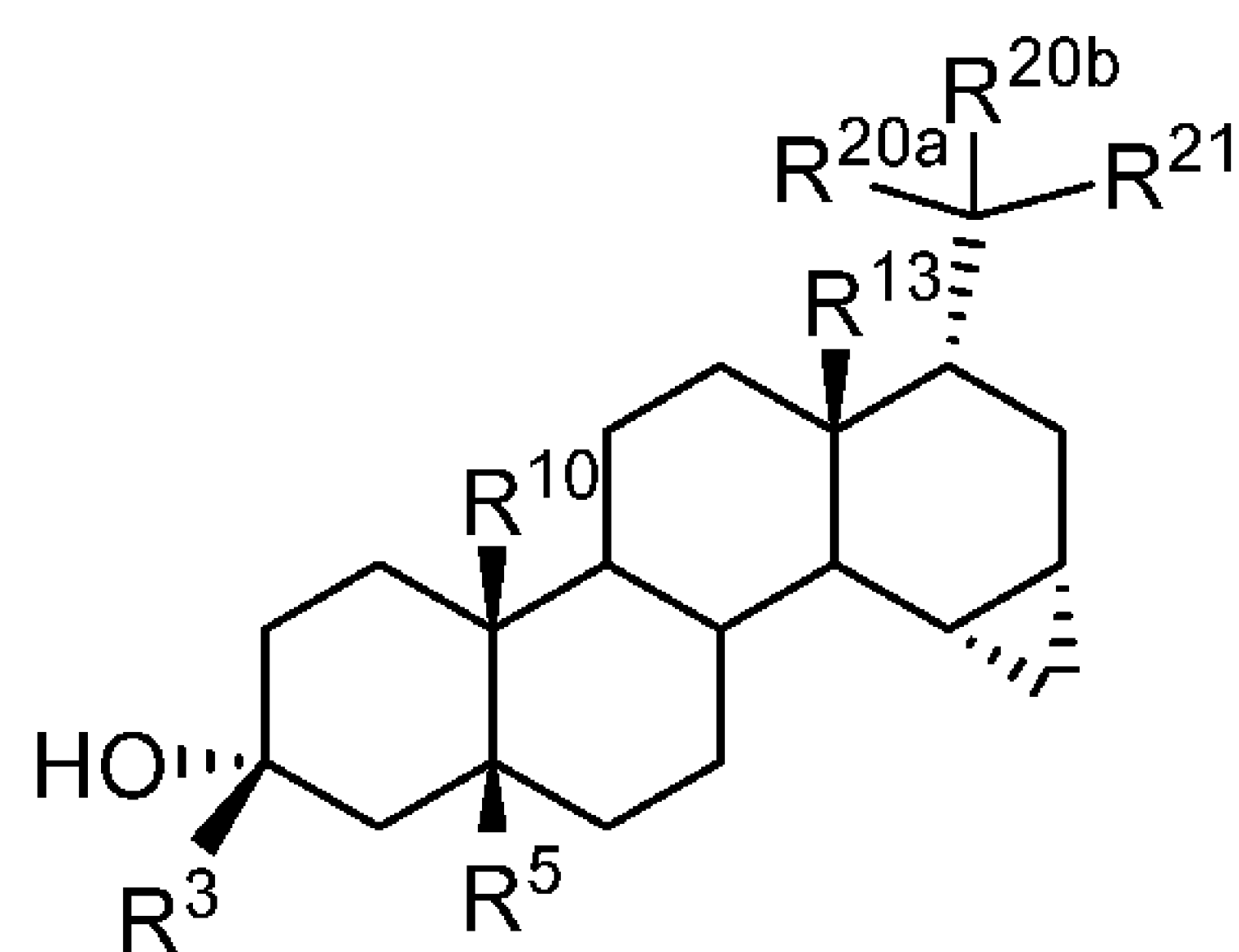
[0392] In some embodiments, R^3 is $-\text{H}$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-\text{H}$ or methyl; R^{10} is $-\text{H}$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-\text{H}$ or C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-\text{H}$, $-\text{OH}$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, and $-\text{CH}_3$.

[0393] In some embodiments, R^3 is methyl, ethyl, propyl, or methoxymethyl; R^5 is $-\text{H}$; R^{10} is $-\text{H}$; R^{13} is $-\text{H}$ or methyl; each of R^{20a} and R^{20b} is independently selected from $-\text{H}$, $-\text{OH}$, and methyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, $-\text{NH}-$, or $-\text{CH}_2-$; R^{30} is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C_{1-6} alkyl, or cyano.

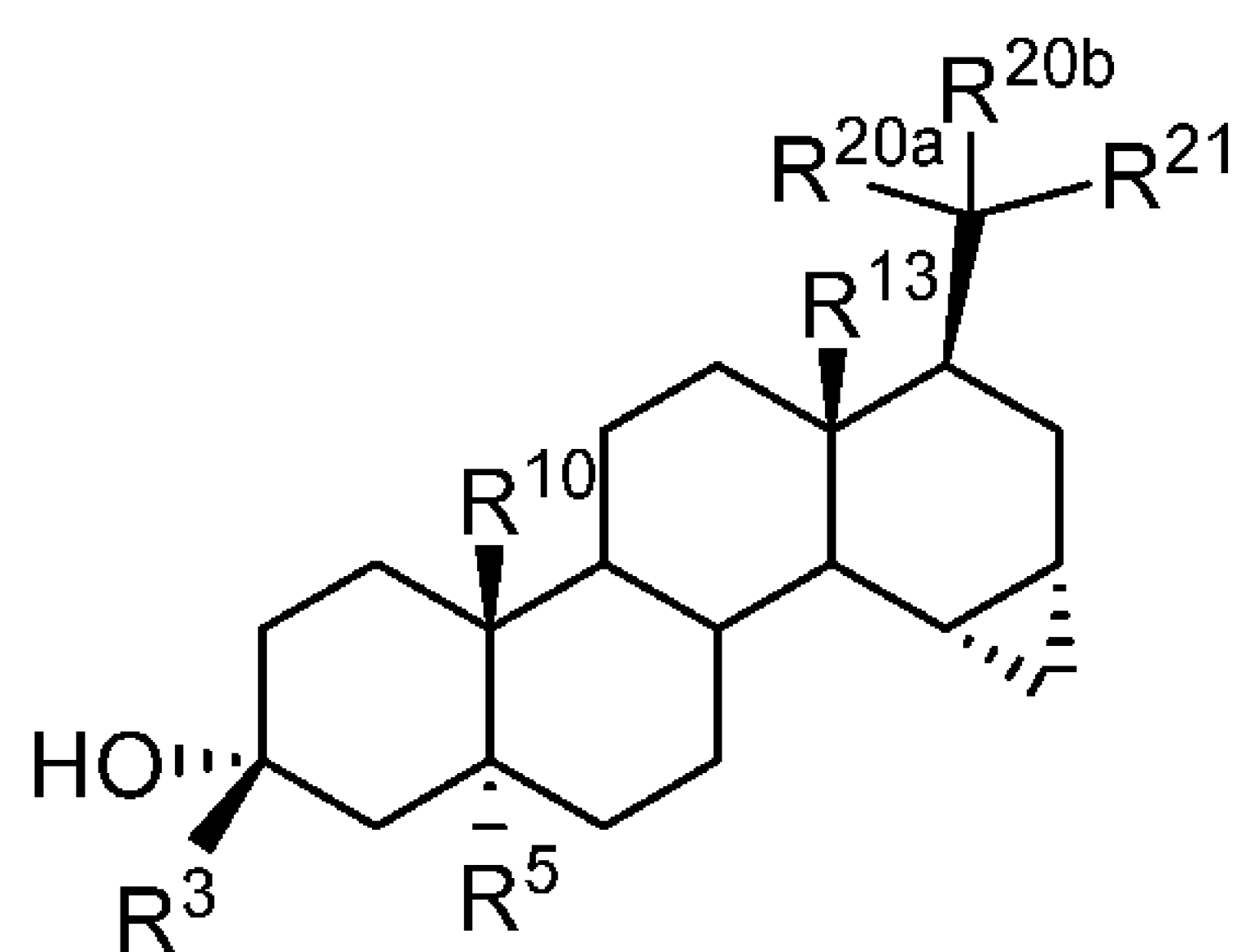
[0394] Another aspect of the present invention provides a compound of Formula (III-B2a), (III-B2b), (III-B2c), or (III-B2d)



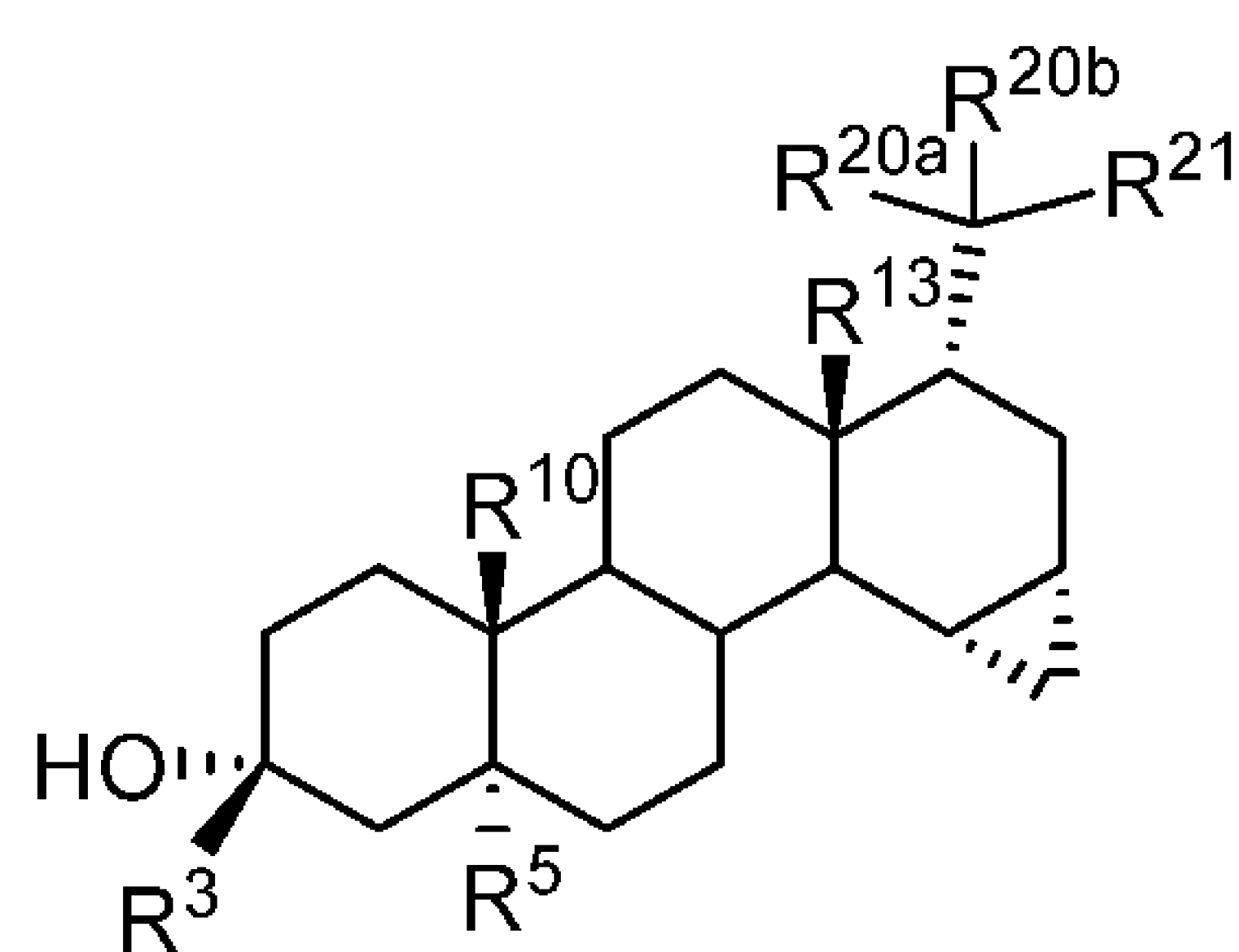
(III-B2a),



(III-B2b),



(III-B2c),



(III-B2d)

or

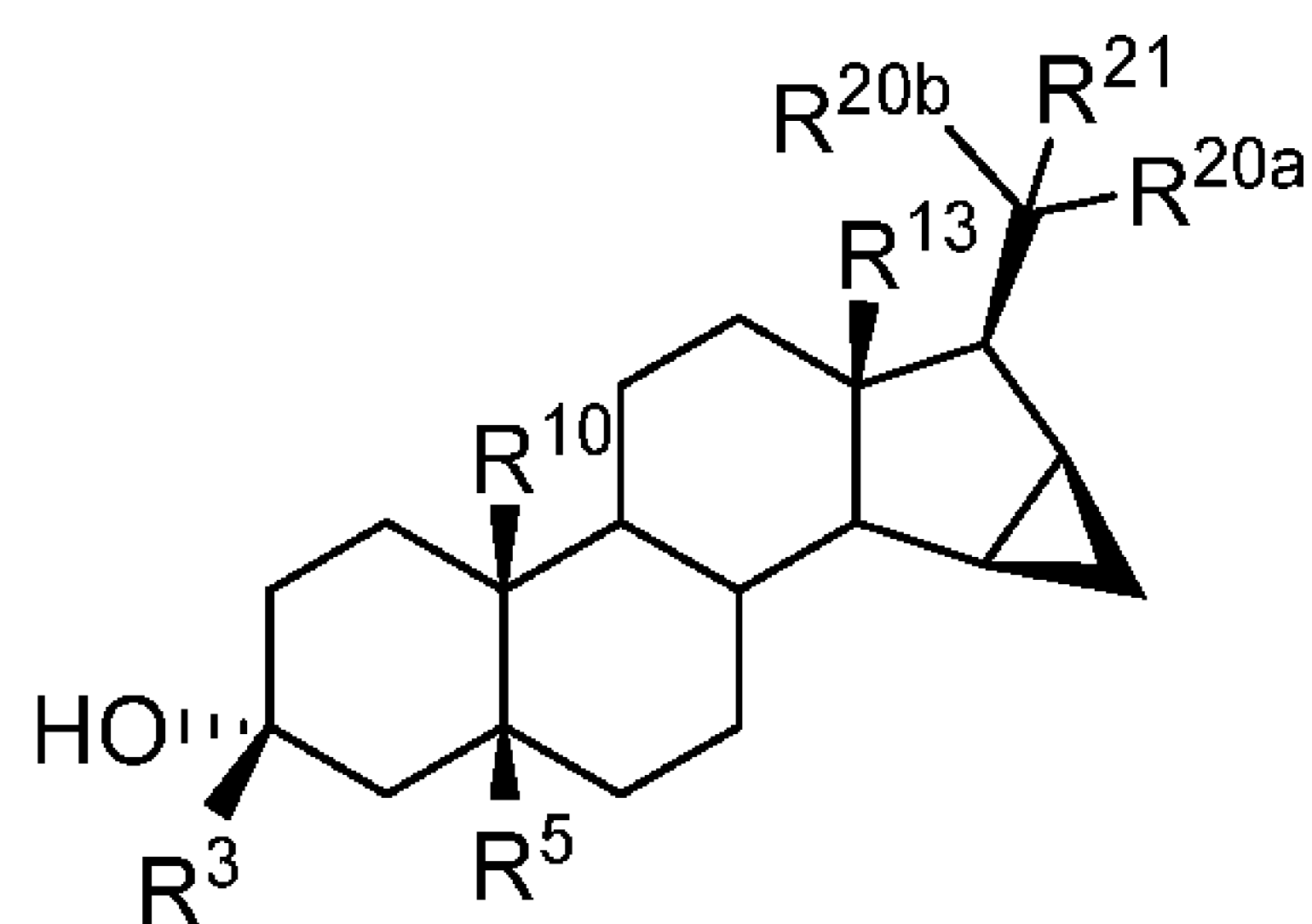
or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), (III-B), or (III-B2).

[0395] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^{13} is $-H$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

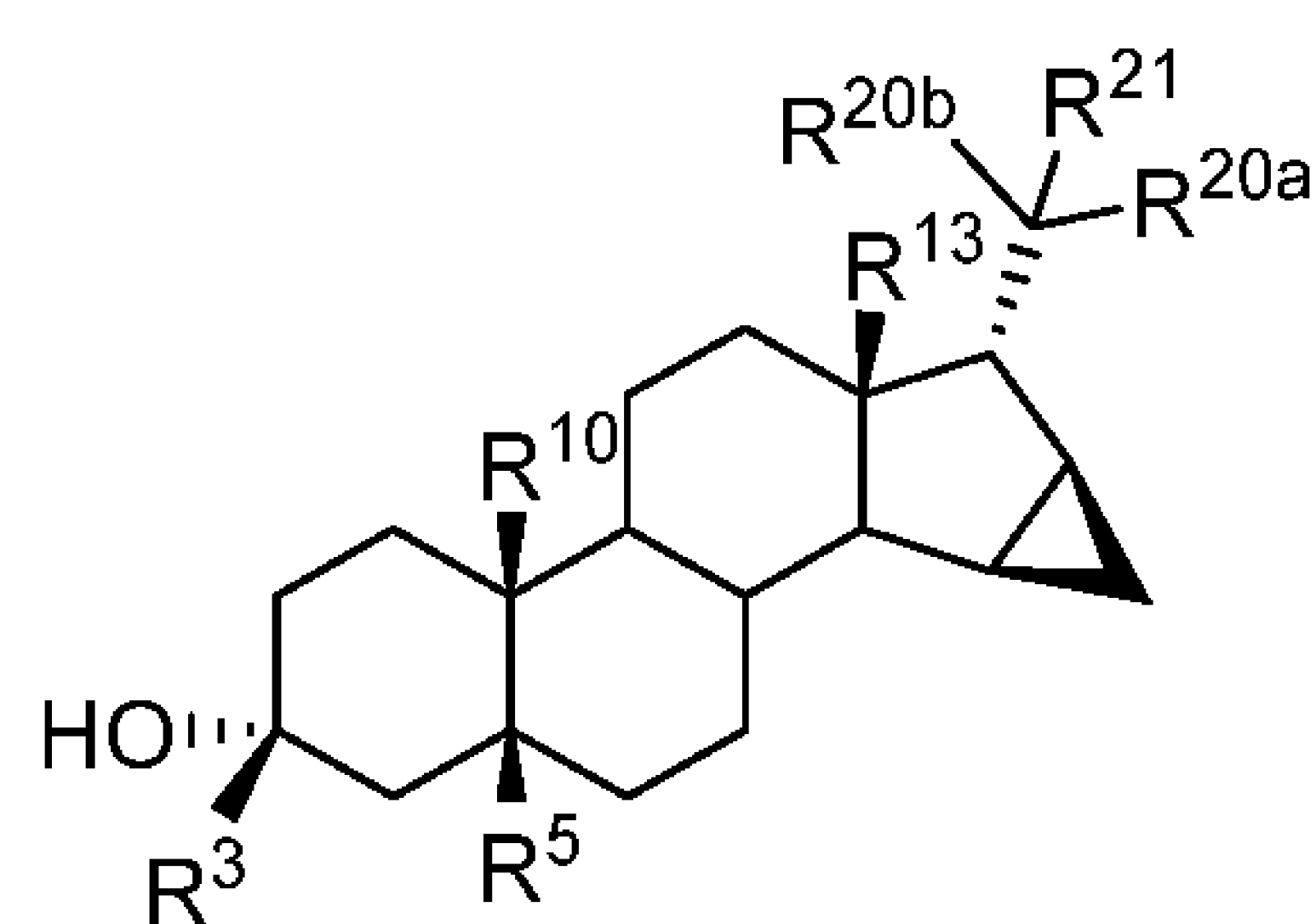
[0396] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6- membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, the 5-6- membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0397] In some embodiments, R^3 is methyl, ethyl, propyl, or methoxymethyl; R^5 is $-H$; R^{10} is $-H$; R^{13} is $-H$ or methyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and methyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, $-NH-$, or $-CH_2-$; R^{30} is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C_{1-6} alkyl, or cyano.

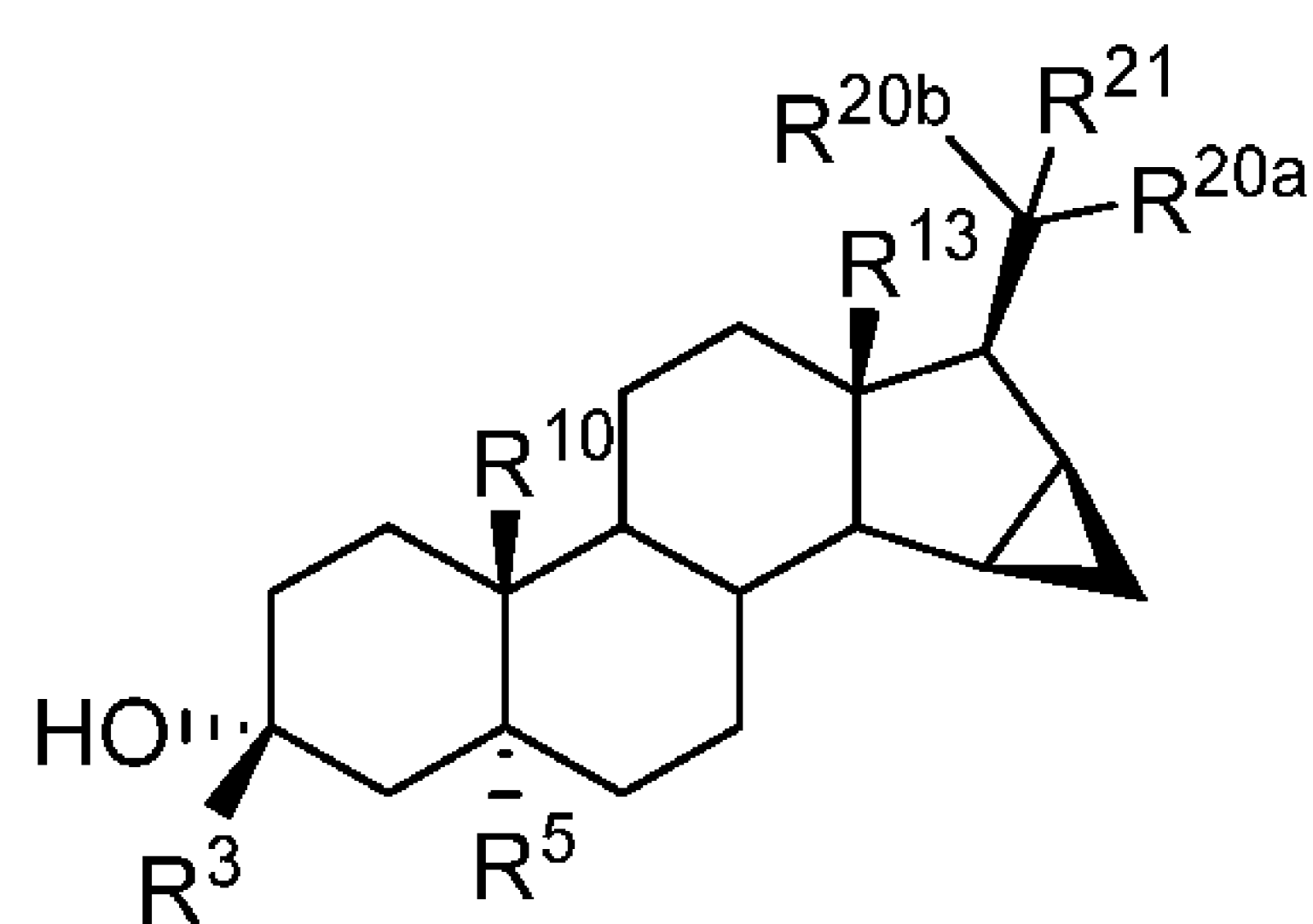
[0398] Another aspect of the present invention provides a compound of Formula (III-C1a), (III-C1b), (III-C1c), or (III-C1d)



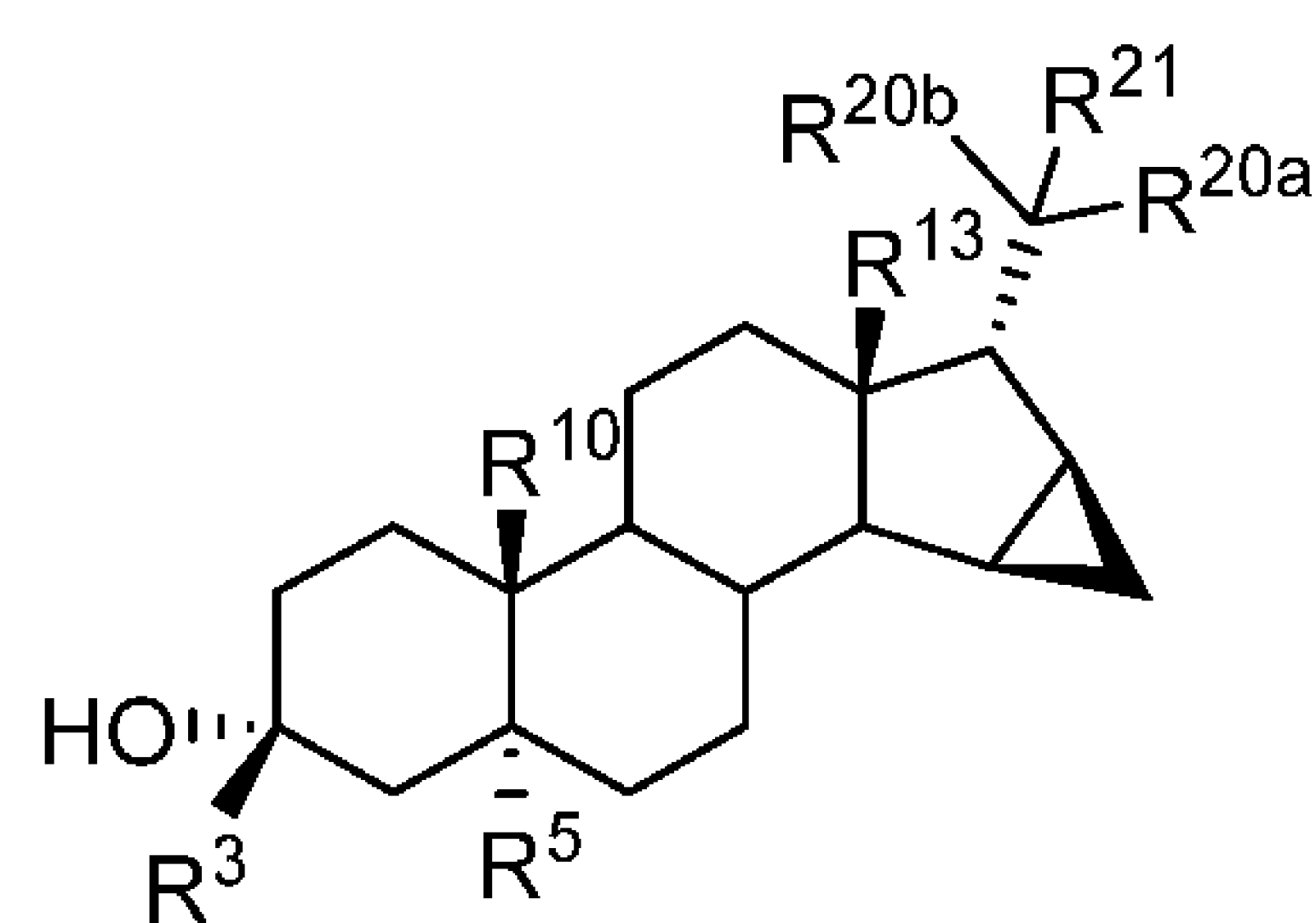
(III-C1a),



(III-C1b),



(III-C1c),



(III-C1d)

or

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), (III-C), or (III-C1).

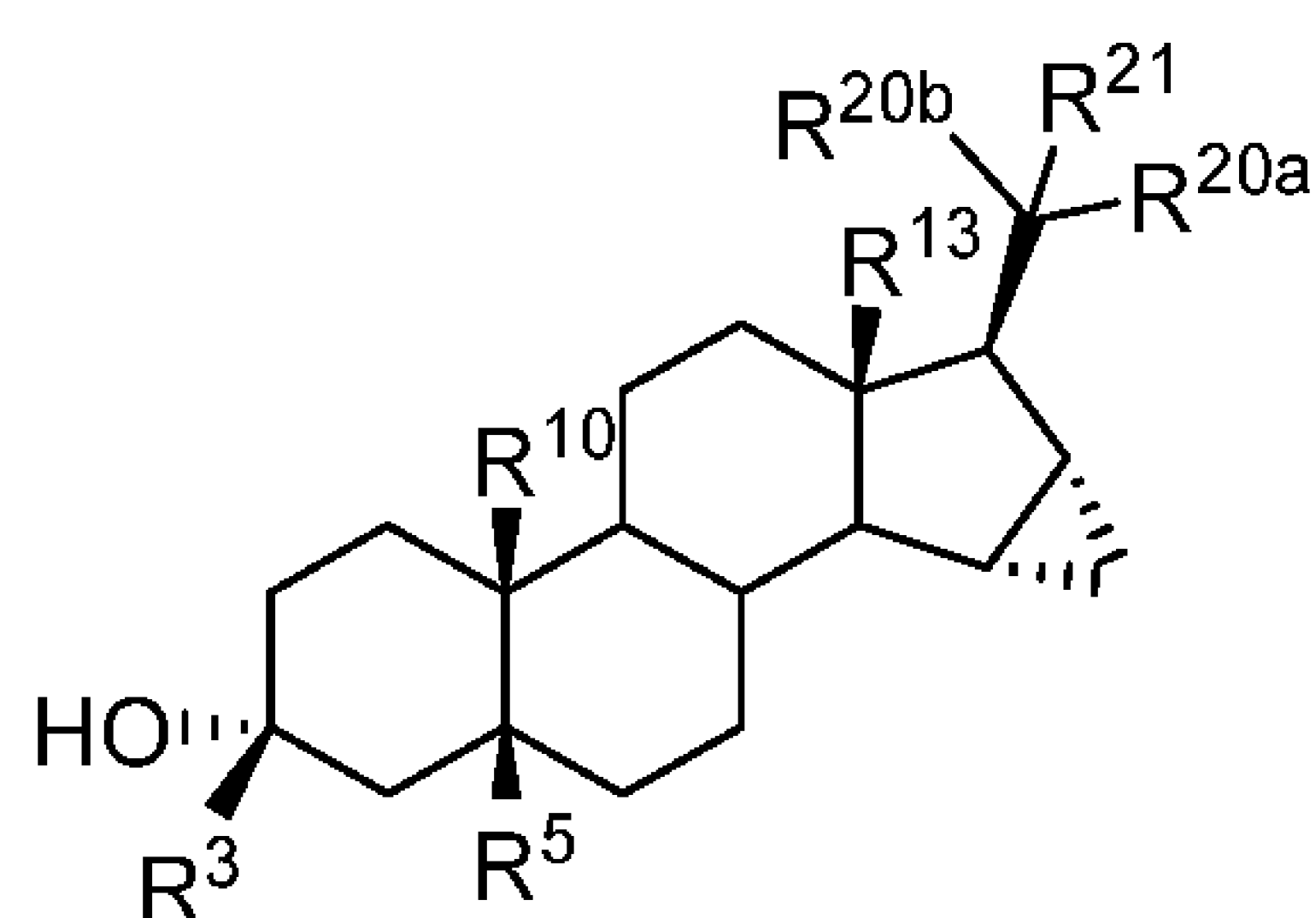
[0399] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^{13} is $-H$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0400] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

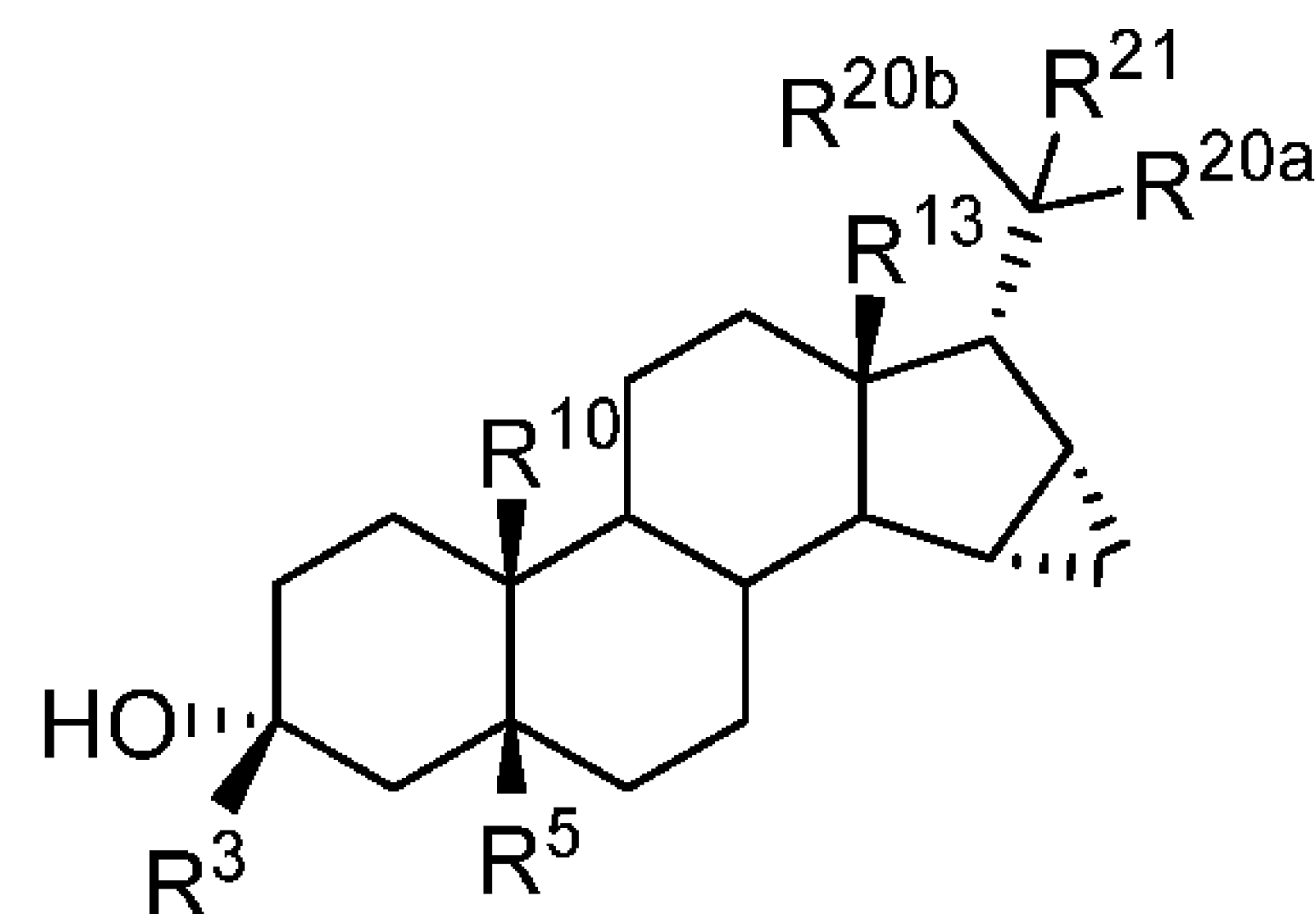
In some embodiment, the 5-6- membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0401] In some embodiments, R^3 is methyl, ethyl, propyl, or methoxymethyl; R^5 is $-H$; R^{10} is $-H$; R^{13} is $-H$ or methyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and methyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, $-NH-$, or $-CH_2-$; R^{30} is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C_{1-6} alkyl, or cyano.

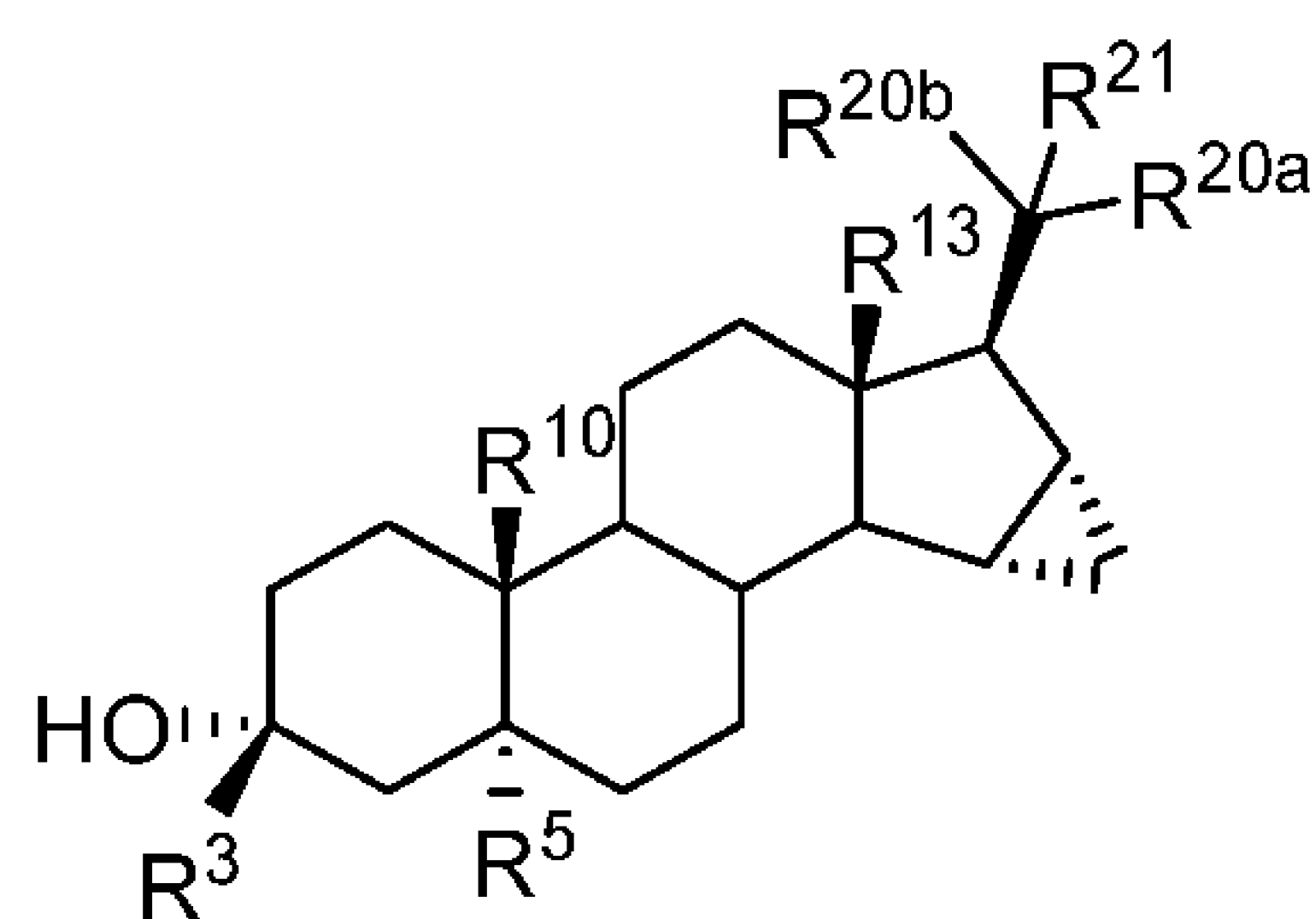
[0402] Another aspect of the present invention provides a compound of Formula (III-C2a), (III-C2b), (III-C2c), or (III-C2d)



(III-C2a),

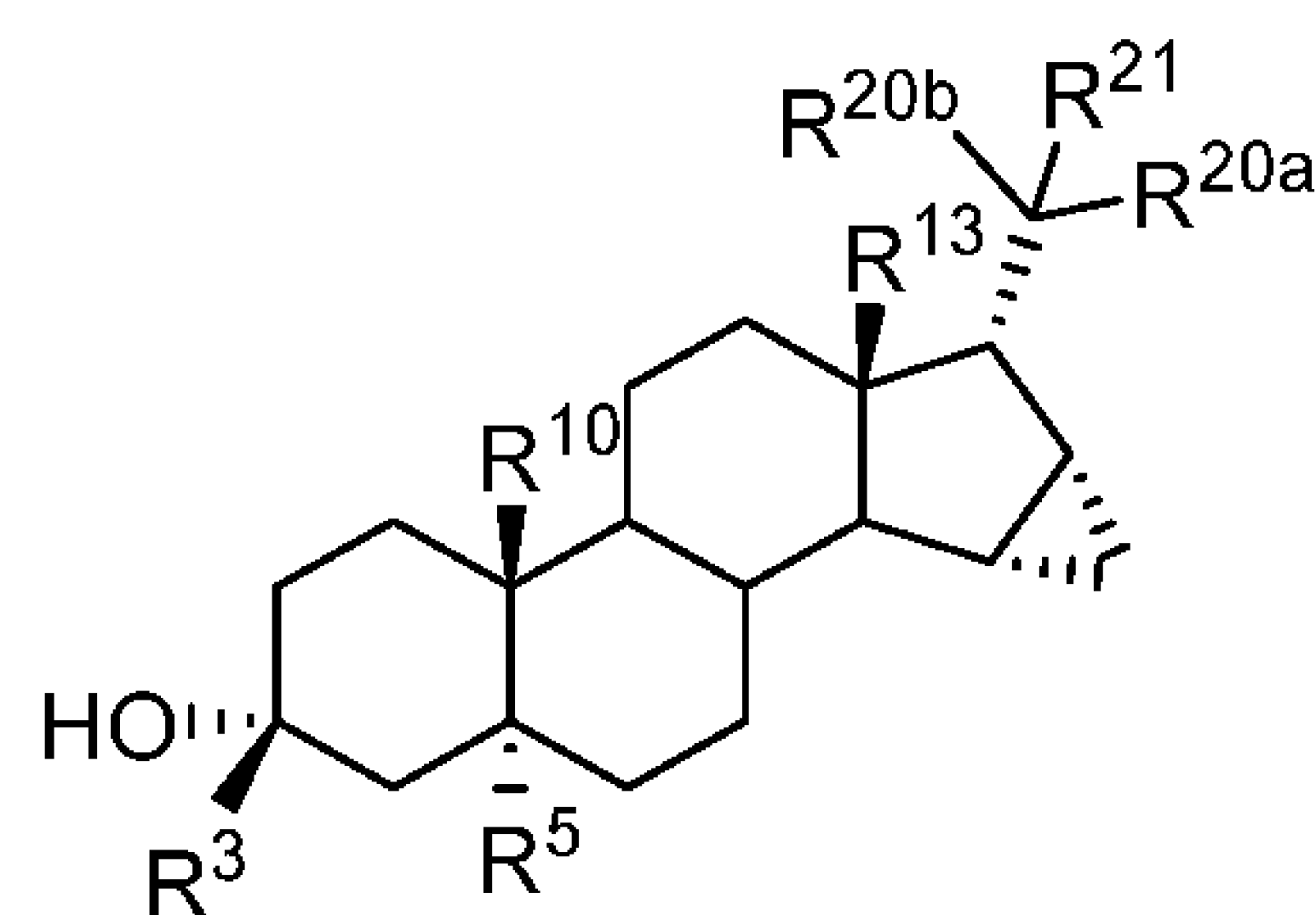


(III-C2b),



(III-C2c),

or



(III-C2d)

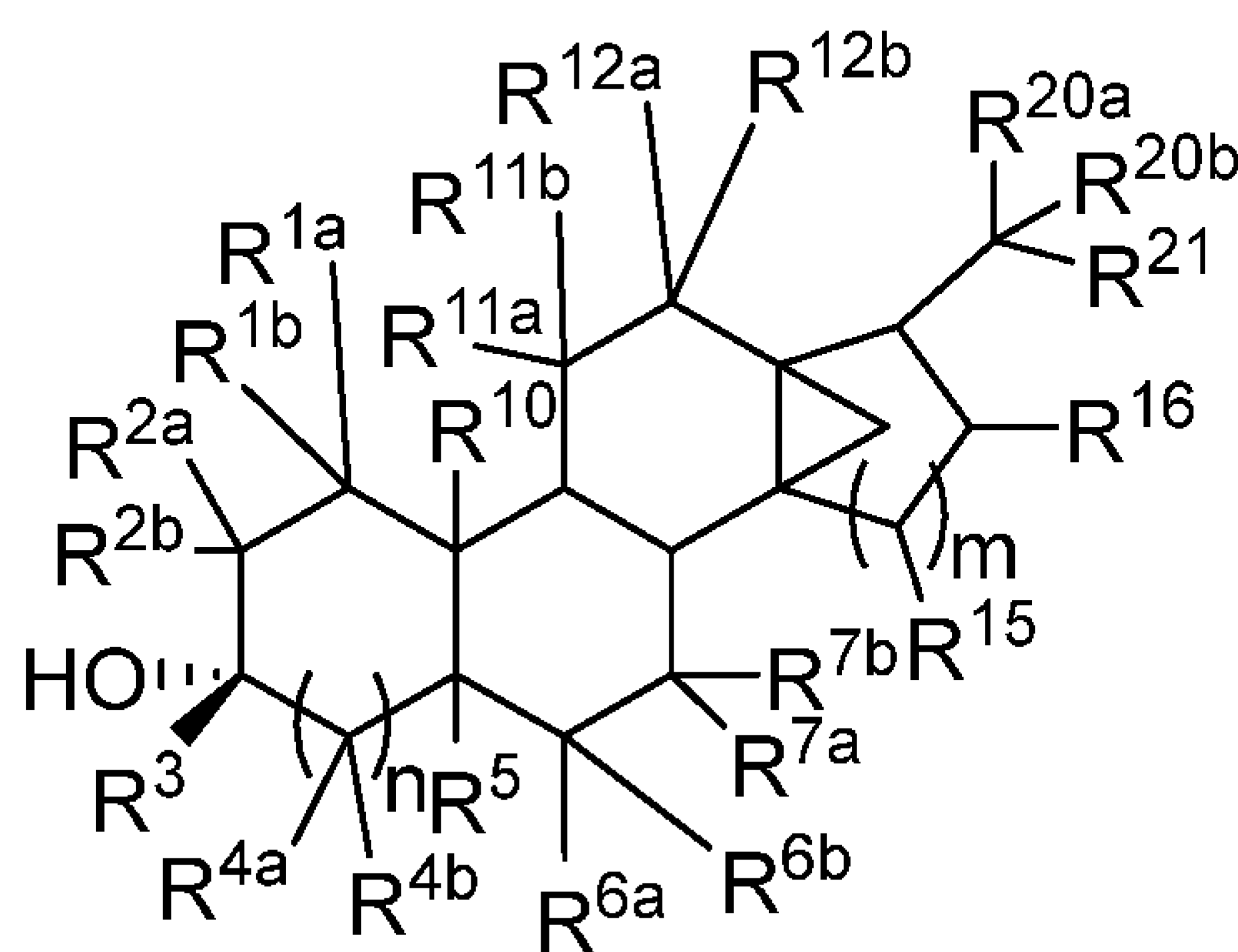
or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (II), (III), (III-C), or (III-C2).

[0403] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^{13} is $-H$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0404] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$ or C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0405] In some embodiments, R^3 is methyl, ethyl, propyl, or methoxymethyl; R^5 is $-H$; R^{10} is $-H$; R^{13} is $-H$ or methyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and methyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, $-NH-$, or $-CH_2-$; R^{30} is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C_{1-6} alkyl, or cyano.

[0406] Another aspect of the present invention provides a compound of Formula (IV)



(IV)

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{15} , R^{16} , R^{20a} , R^{20b} , R^{21} , m , and n are as defined in any of the embodiments of the compounds of Formula (I).

[0407] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{15} , R^{16} , R^{20a} , R^{20b} , and R^{21} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'-$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'-$, $-NR'S(O)_2-$, $-C(O)NR'NR'-$, $-NR'C(O)NR'-$, $-OC(O)NR'-$, $-NR'NR'-$,

$-\text{NR}'\text{S}(\text{O})_2\text{NR}'-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2-$; each R^{30} is independently selected from R' , halo, $-\text{CN}$, $-\text{NO}_2$, and $-\text{CF}_3$; each R' is independently selected from $-\text{H}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, or R^{1a} and R^{1b} taken together form oxo, or R^{2a} and R^{2b} taken together form oxo, or R^{4a} and R^{4b} taken together form oxo, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo, or R^{20a} and R^{20b} taken together form oxo; R^5 is $-\text{H}$ or C_{1-3} alkyl; R^{10} is $-\text{H}$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; m is 1 or 2; and n is 0, 1, or 2.

[0408] In some embodiments, each of R^{1a} and R^{1b} is independently selected from $-\text{H}$, C_{1-6} alkyl optionally substituted with R' , $-\text{N}(\text{R}')_2$, and $-\text{O}-\text{R}'$; or R^{1a} and R^{1b} taken together form oxo. In some embodiments, each of R^{1a} and R^{1b} is independently selected from $-\text{H}$ and C_{1-6} alkyl optionally substituted with R' ; or R^{1a} and R^{1b} taken together form oxo.

[0409] In some embodiments, one of R^{1a} and R^{1b} is $-\text{H}$, and the other is $-\text{H}$, C_{1-6} alkyl optionally substituted with R' , $-\text{N}(\text{R}')_2$, or $-\text{O}-\text{R}'$. In some embodiments, one of R^{1a} and R^{1b} is $-\text{H}$, and the other is $-\text{H}$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, one of R^{1a} and R^{1b} is $-\text{H}$, and the other is methyl. And, in some embodiments, each of R^{1a} and R^{1b} is $-\text{H}$.

[0410] In some embodiments, each of R^{2a} and R^{2b} is independently selected from $-\text{H}$, C_{1-6} alkyl optionally substituted with R' , $-\text{N}(\text{R}')_2$, and $-\text{O}-\text{R}'$, or R^{2a} and R^{2b} taken together form oxo. In some embodiments, each of R^{2a} and R^{2b} is independently selected from $-\text{H}$ and C_{1-6} alkyl optionally substituted with R' , or R^{2a} and R^{2b} taken together form oxo. In some embodiments, one of R^{2a} and R^{2b} is $-\text{H}$, and the other is $-\text{H}$, C_{1-6} alkyl optionally substituted with R' , $-\text{N}(\text{R}')_2$, or $-\text{O}-\text{R}'$. In some embodiments, one of R^{2a} and R^{2b} is $-\text{H}$, and the other is $-\text{H}$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, one of R^{2a} and R^{2b} is $-\text{H}$, and the other is methyl. And, in some embodiments, each of R^{2a} and R^{2b} is $-\text{H}$.

[0411] In some embodiments, R^3 is $-\text{H}$, C_{1-6} alkyl optionally substituted with R' , $-\text{N}(\text{R}')_2$, or $-\text{O}-\text{R}'$. In some embodiments, R^3 is $-\text{H}$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^3 is $-\text{H}$, $-\text{CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-CH}_3$, or $-\text{CH}_2\text{-O-CH}_3$. And, in some embodiments, R^3 is $-\text{H}$ or methyl.

[0412] In some embodiments, n is 0 and both of R^{4a} and R^{4b} are absent. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is methyl. And, in some embodiments, n is 1 and each of R^{4a} and R^{4b} is $-H$.

[0413] In some embodiments, R^5 is $-H$.

[0414] In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo. In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' . In some embodiments, two of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other two of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$. In some embodiments, three of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, three of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other is $-H$ or methyl. And, in some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is $-H$.

[0415] In some embodiments, R^{10} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl. And, in some embodiments, R^{10} is $-H$, methyl, or methoxymethyl.

[0416] In some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo. In some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' . In some embodiments, two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$. In some embodiments, two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are independently

selected from $-H$ and methyl. In some embodiments, three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other is $-H$ or methyl. And, in some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is $-H$.

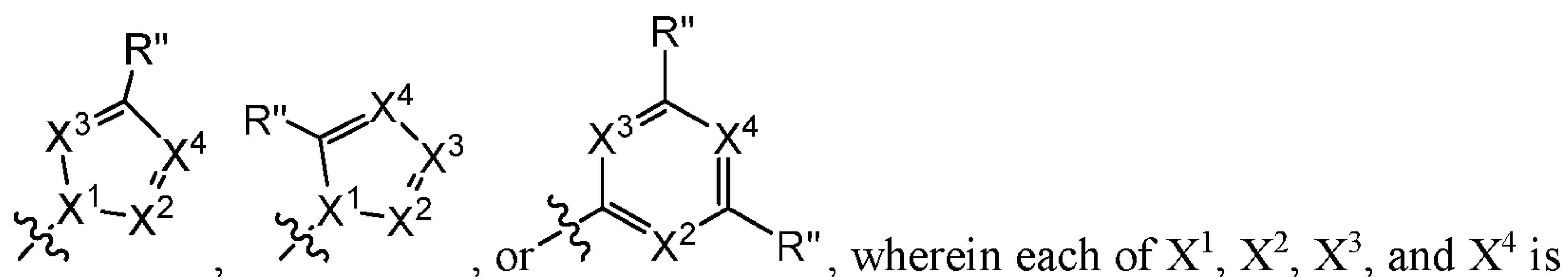
[0417] In some embodiments, m is 1 and R^{15} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, m is 1 and R^{15} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, m is 1 and R^{15} is $-H$ or C_{1-3} alkyl. In some embodiments, m is 1 and R^{15} is $-H$ or methyl. And, in some embodiments, m is 1 and R^{15} is $-H$.

[0418] In some embodiments, R^{16} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^{16} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^{16} is $-H$ or C_{1-3} alkyl. In some embodiments, R^{16} is $-H$ or methyl. And, in some embodiments, R^{16} is $-H$.

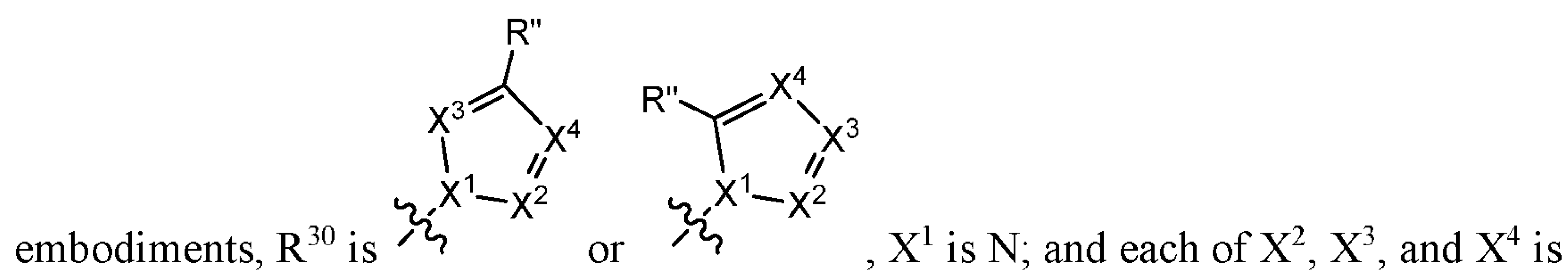
[0419] In some embodiments, each of R^{20a} and R^{20b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo. In some embodiments, each of R^{20a} and R^{20b} are independently selected from $-H$, C_{1-6} alkyl, $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo. In some embodiments, R^{20a} and R^{20b} taken together form oxo. In some embodiments, R^{20a} and R^{20b} are independently selected from $-H$, methyl, and $-OH$. In some embodiments, one of R^{20a} and R^{20b} is $-OH$, and the other is $-H$, or methyl. In some embodiments, R^{20a} and R^{20b} taken together form oxo.

[0420] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, or $-NH-$; and R^{30} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, or $-NH-$; and R^{30} is a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond or $-CH_2-$; and R^{30} is a 5-6-membered partially unsaturated or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-2

groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond or $-\text{CH}_2-$; and R^{30} is

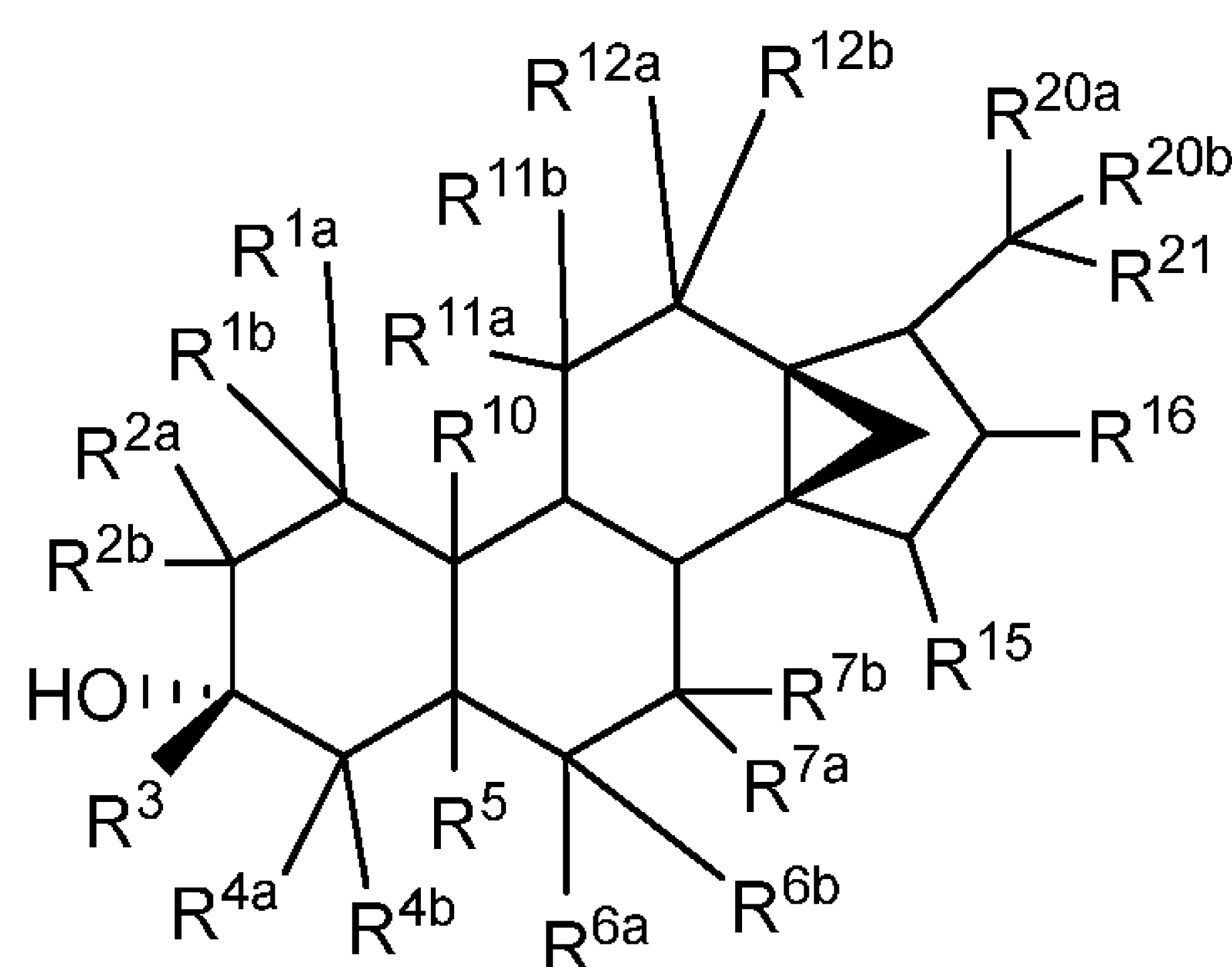


wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some



embodiments, R^{30} is X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N and CR'' , wherein each R'' is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$.

[0421] Another aspect of the present invention provides a compound of Formula (IV-A)



(IV-A)

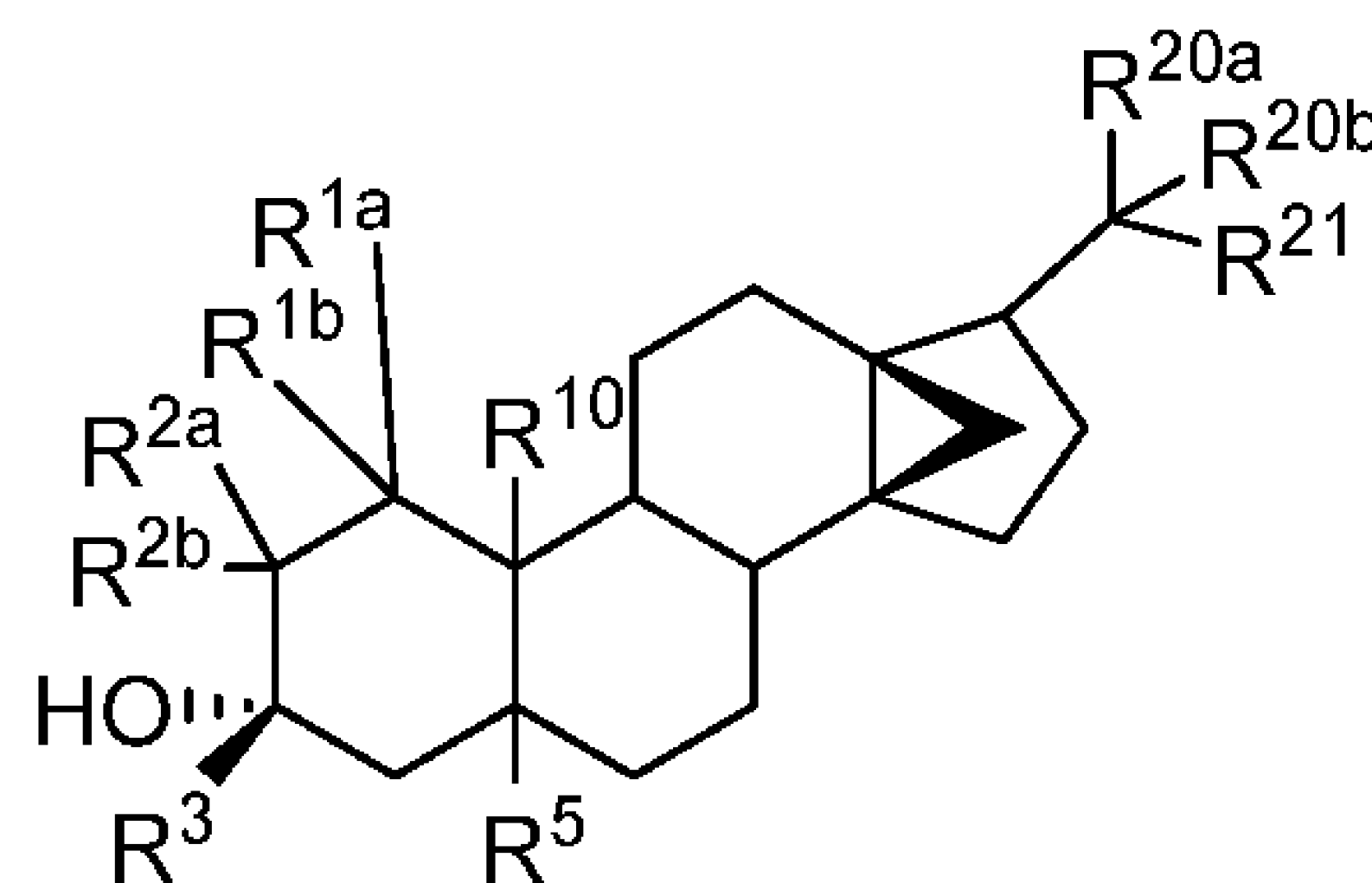
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{15} , R^{16} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I) or (IV).

[0422] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{15} , R^{16} , R^{20a} , R^{20b} , and R^{21} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; each R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$, or R^{20a} and R^{20b} taken together form oxo; R^5 is $-H$ or C_{1-3} alkyl; and R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl-O- C_{1-3} alkyl.

[0423] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{15} , and R^{16} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl); R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-5} alkyl-O- C_{1-6} alkyl; R^5 is $-H$ or C_{1-3} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl-O- C_{1-3} alkyl; each of R^{15} and R^{16} is independently $-H$ or C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl-OH, C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -,

–S–, –O–, –OC(O)–, –C(O)O–, –C(O)–, –C(O)C(O)–, –C(O)NR'–, –NR'C(O)–, –NR'C(O)O–, –S(O)₂NR'–, –NR'S(O)₂–, –C(O)NR'NR'–, –NR'C(O)NR'–, –OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, –S(O)–, or –S(O)₂–; R³⁰ is R', halo, –CN, –NO₂, and –CF₃; and each R' is independently selected from –H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, and –CH₃.

[0424] Another aspect of the present invention provides a compound of Formula (IV-A1)

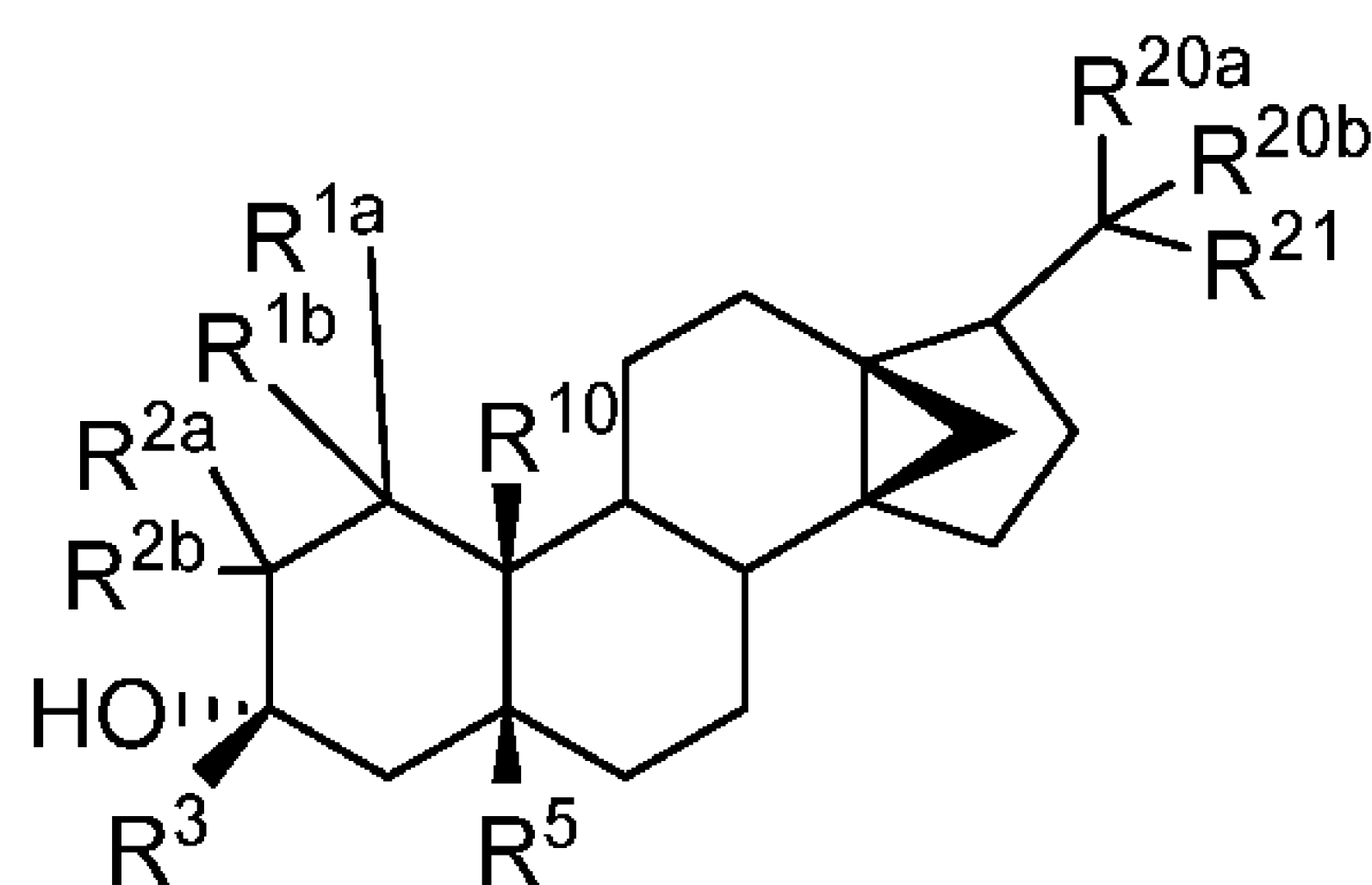


(IV-A1)

or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R⁵, R¹⁰, R^{20a}, R^{20b}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (IV), or (IV-A).

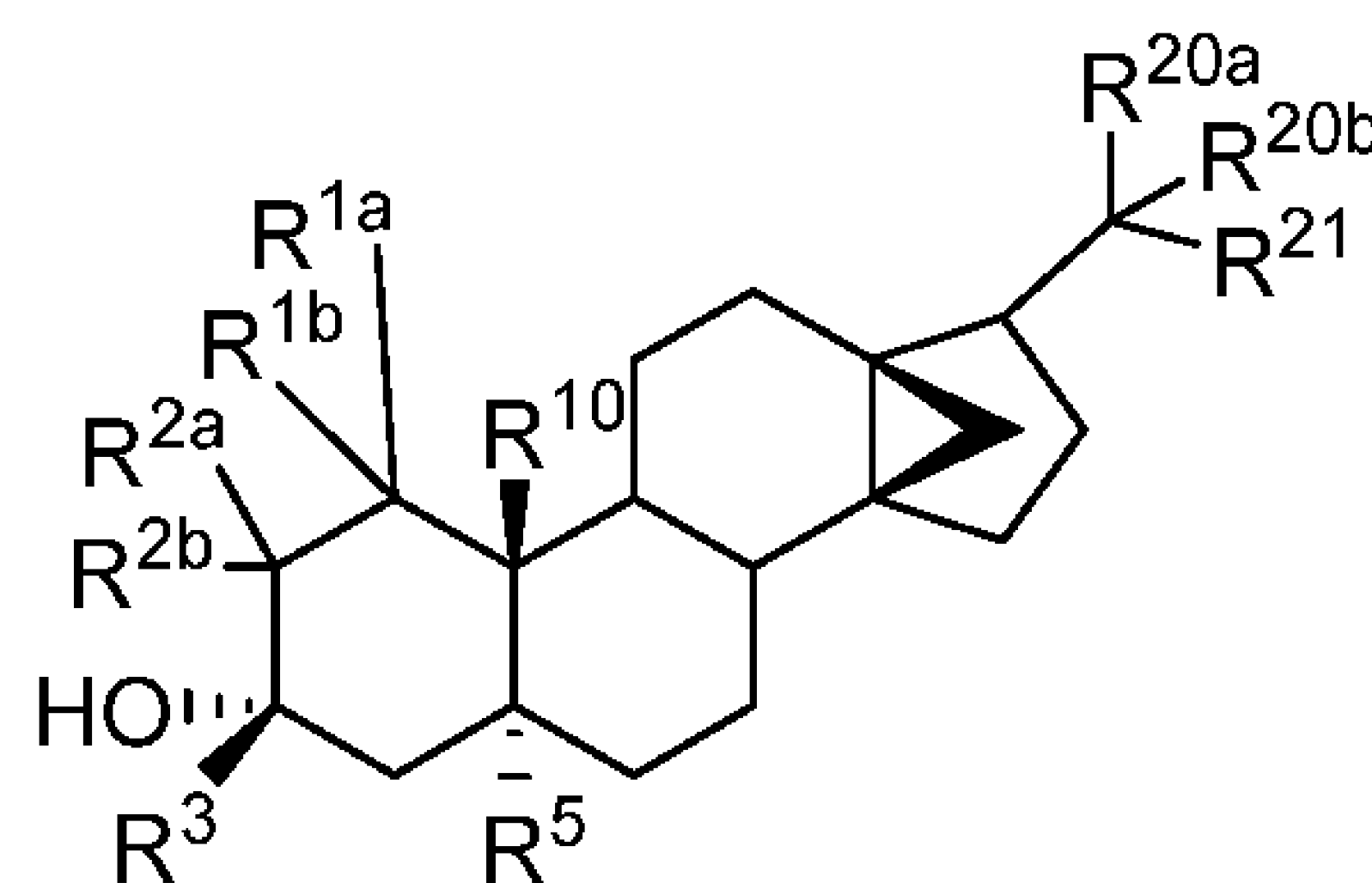
[0425] In some embodiments, each of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently selected from –H and C₁₋₃ alkyl; R³ is –H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₆ alkyl; R⁵ is –H or C₁₋₃ alkyl; R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; each of R^{20a} and R^{20b} is independently selected from –H, –OH, –CH₂OH, C₁₋₃ alkyl, and –NH₂, or R^{20a} and R^{20b} taken together form oxo; R²¹ is –L^A-R³⁰; L^A is a bond or a straight or branched C₁₋₃ alkylene chain; R³⁰ is R', halo, –CN, –NO₂, or –CF₃; and R' is –H, C₁₋₆ alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, and –CH₃.

[0426] Another aspect of the present invention provides a compound of Formula (IV-A1a) or (IV-A1b)



(IV-A1a)

or

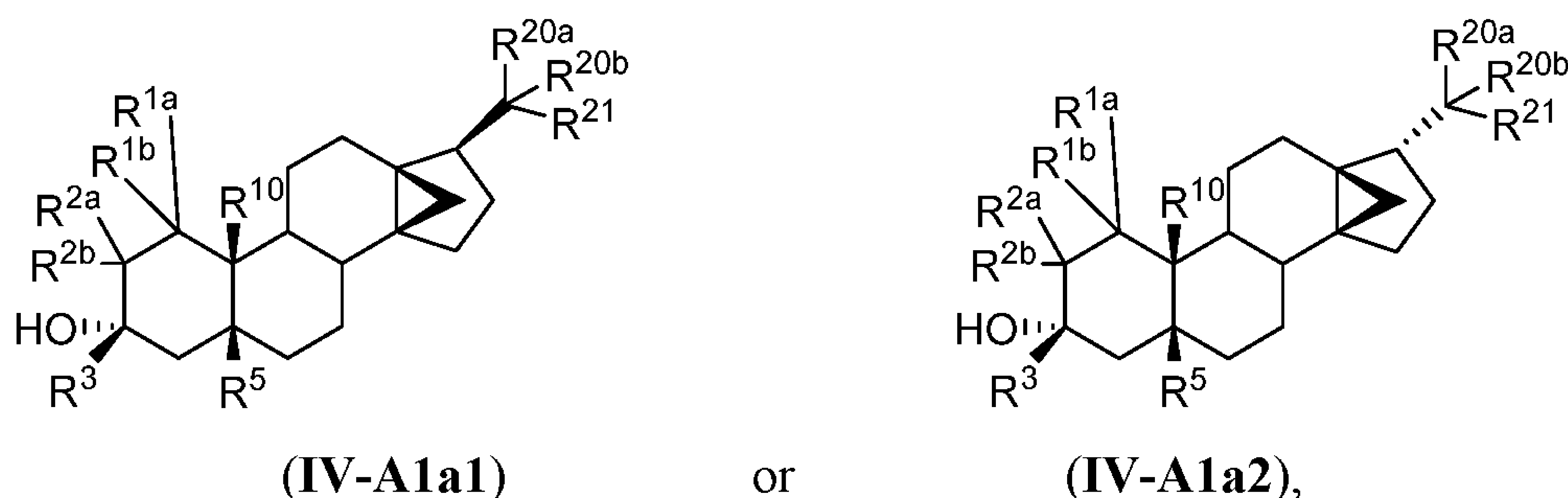


(IV-A1b)

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (IV), (IV-A), or (IV-A1).

[0427] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , and R^{2b} is selected from $-H$ and C_{1-3} alkyl; R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or C_{1-3} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-CH_2OH$, C_{1-3} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or a straight or branched C_{1-3} alkylene chain; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and R' is $-H$, C_{1-6} alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

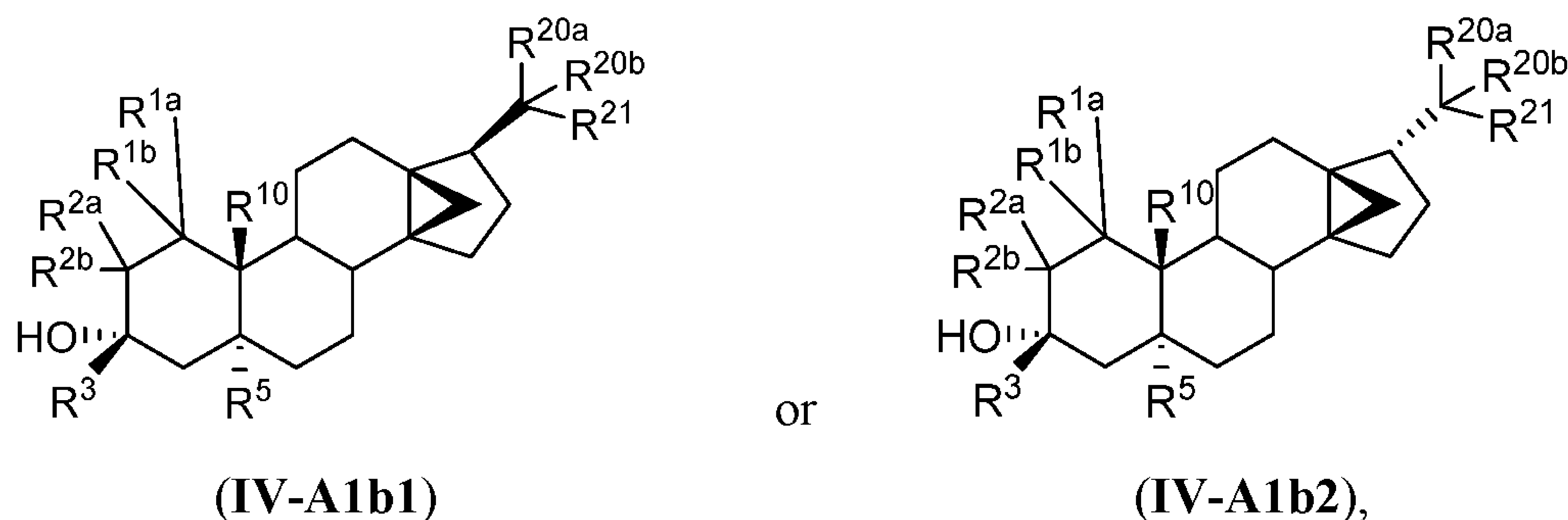
[0428] Another aspect of the present invention provides a compound of Formula (IV-A1a1) or (IV-A1a2)



or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (IV), (IV-A), (IV-A1), or (IV-A1a).

[0429] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , and R^{2b} is independently selected from $-H$ and C_{1-3} alkyl; R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or C_{1-3} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-CH_2OH$, C_{1-3} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or a straight C_{1-3} alkylene chain; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and R' is $-H$, C_{1-6} alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

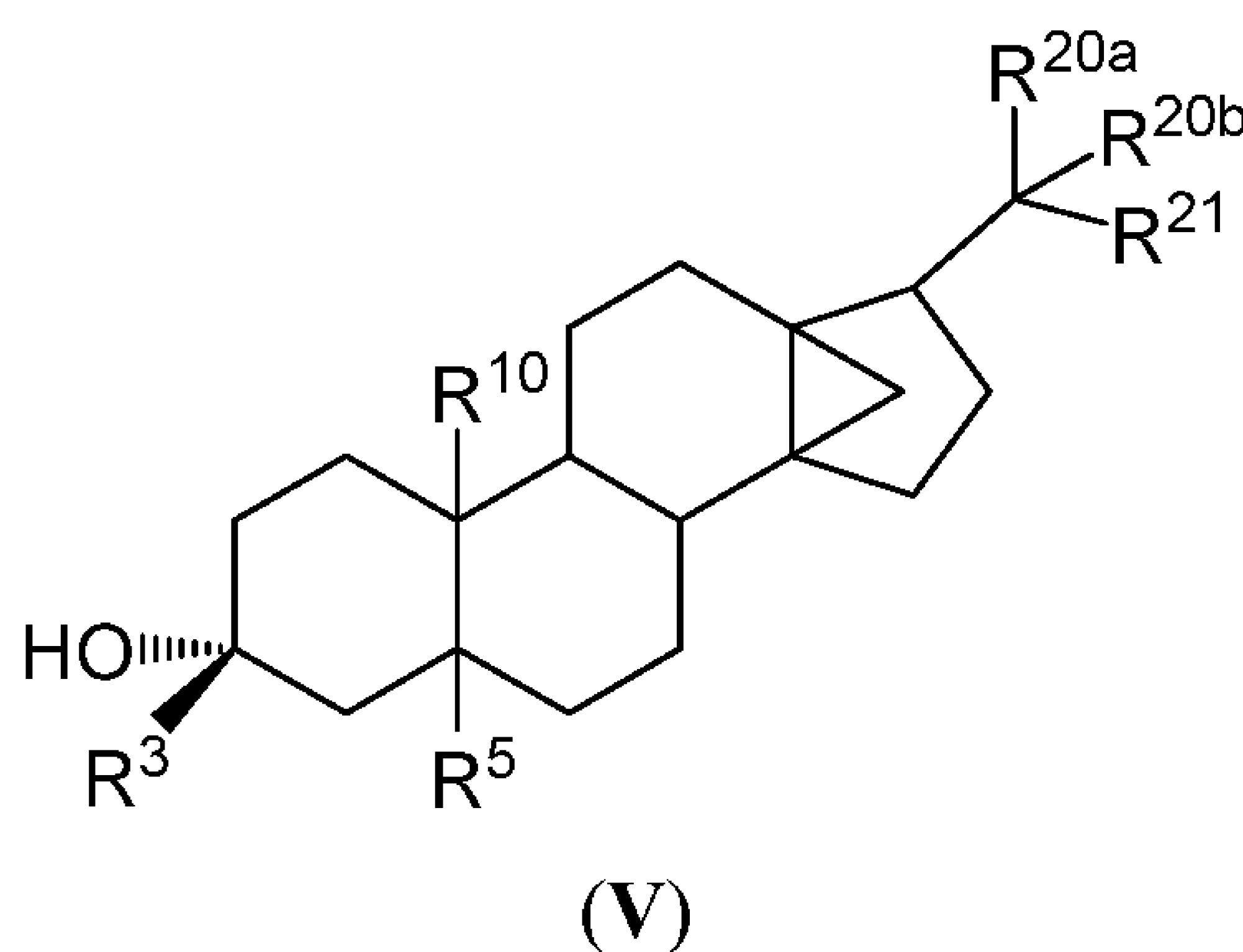
[0430] Another aspect of the present invention provides a compound of Formula (IV-A1b1) or (IV-A1b2)



or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} , are as defined in any of the embodiments of the compounds of Formula (I), (IV), (IV-A), (IV-A1), or (IV-A1b).

[0431] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , and R^{2b} is independently selected from $-H$ and C_{1-3} alkyl; R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or C_{1-3} alkyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-CH_2OH$, C_{1-3} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or a straight C_{1-3} alkylene chain; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and R' is $-H$, C_{1-6} alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0432] Another aspect of the present invention provides a compound of Formula (V)



or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I) or (IV).

[0433] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl (e.g., C_{1-3} alkyl- O - C_{1-3} alkyl); R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken

together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

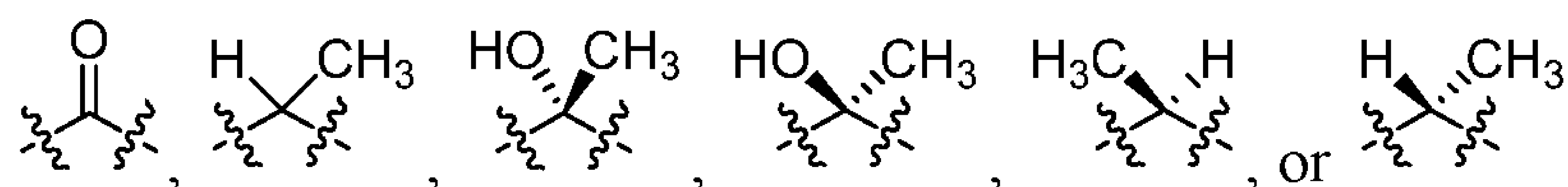
[0434] In some embodiments, R^3 is C_{1-6} alkyl (e.g., C_{1-3} alkyl) or C_{1-6} alkyl-O- C_{1-6} alkyl (e.g., C_{1-3} alkyl-O- C_{1-3} alkyl). In some embodiments, R^3 is methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, neopentyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^3 is $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, or $-CH_2-O-CH_3$. And, in some embodiments, R^3 is $-CH_3$.

[0435] In some embodiments, R^5 is $-H$ or C_{1-3} alkyl. In some embodiments, R^5 is $-H$ or methyl.

[0436] In some embodiments, R^{10} is $-H$, C_{1-6} alkyl (e.g., C_{1-3} alkyl), or C_{1-3} alkyl-O- C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl-O- C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^{10} is $-H$ or methyl.

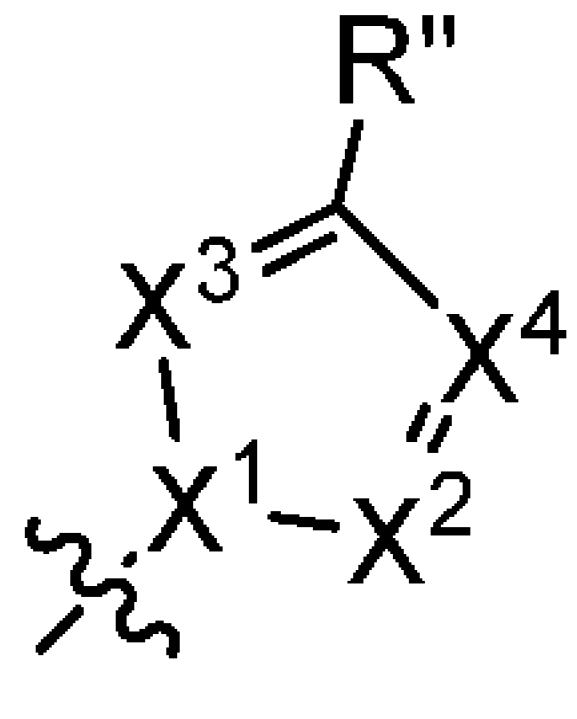
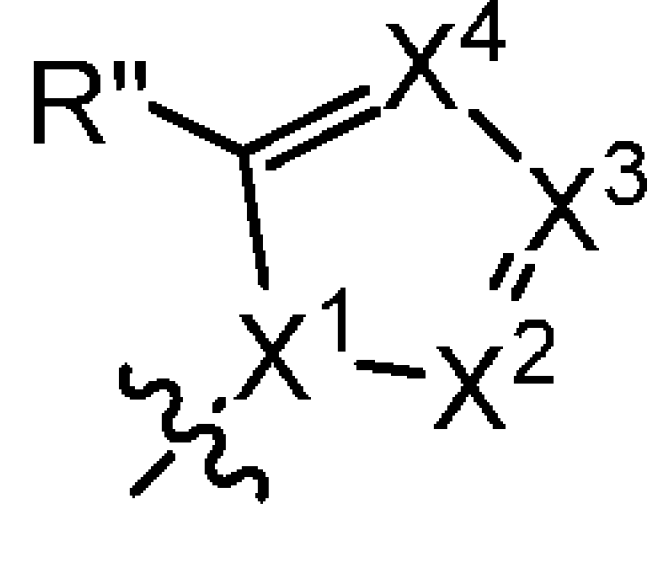
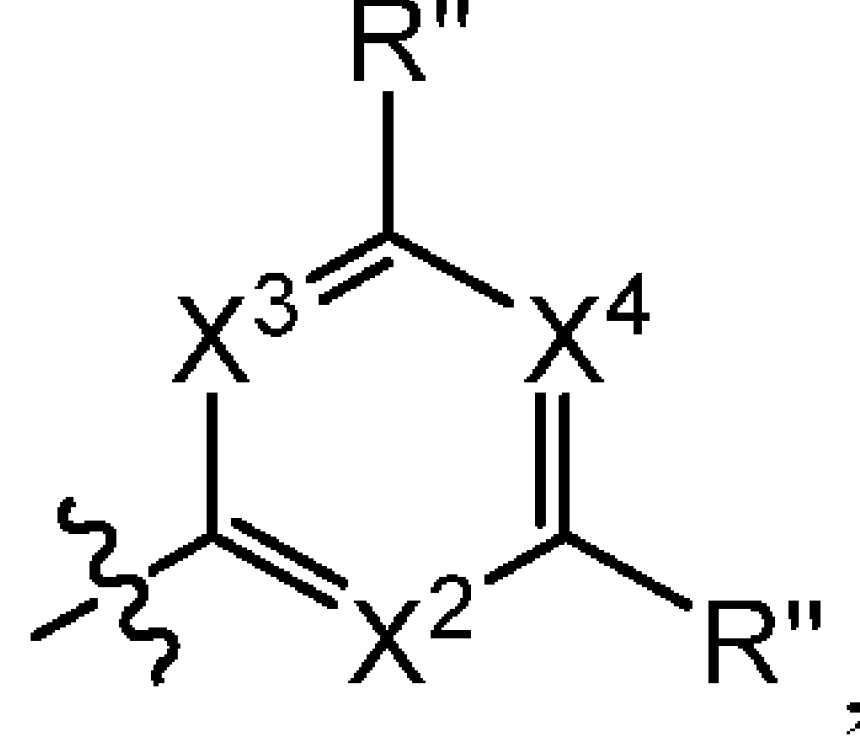
[0437] In some embodiments, R^{13} is C_{1-6} alkyl (e.g., C_{1-3} alkyl). In some embodiments, R^{13} is methyl, ethyl, or propyl. In some embodiments, R^{13} is $-H$ or methyl. And, in some embodiments, R^{13} is methyl.

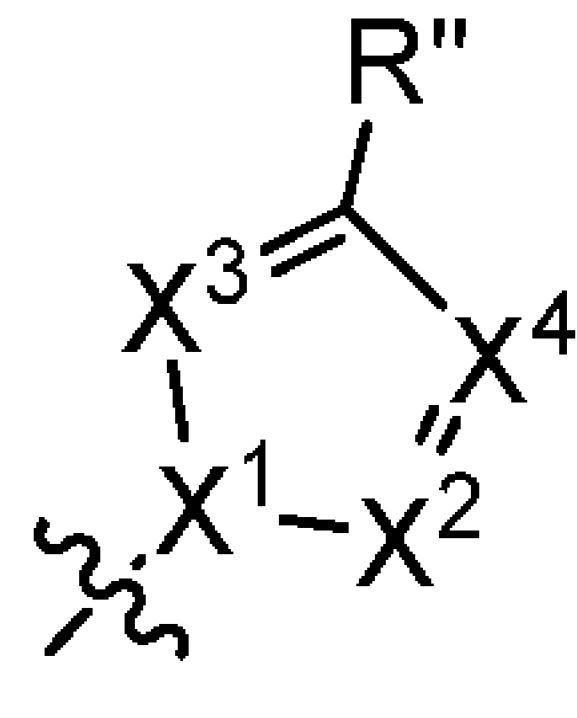
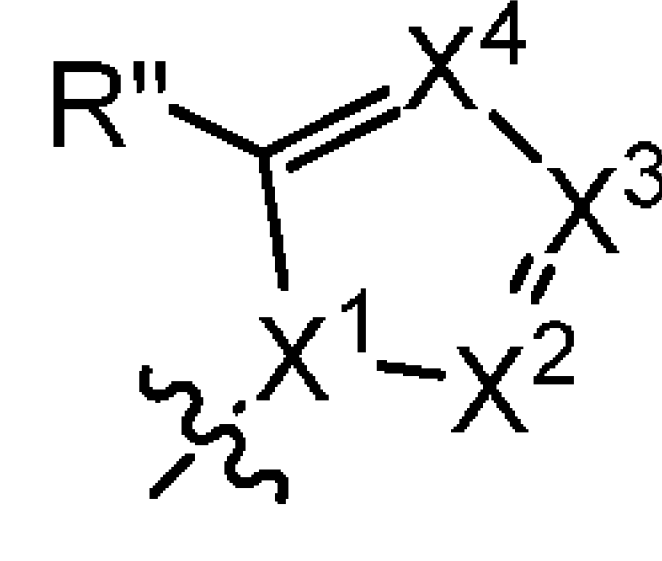
[0438] In some embodiments, R^{20a} and R^{20b} taken together form oxo. In some embodiments, one of R^{20a} and R^{20b} is $-H$, and the other of R^{20a} and R^{20b} is C_{1-6} alkyl (e.g., C_{1-3} alkyl). In some embodiments, one of R^{20a} and R^{20b} is C_{1-6} alkyl (e.g., C_{1-3} alkyl), and the other of R^{20a} and R^{20b} is $-OH$. In some embodiments, one of R^{20a} and R^{20b} is methyl, ethyl, or propyl, and the other of R^{20a} and R^{20b} is $-OH$. In some embodiments, R^{20a} , R^{20b} , and the carbon to which they are attached form



[0439] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-3} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6 membered ring of R^{30} is optionally

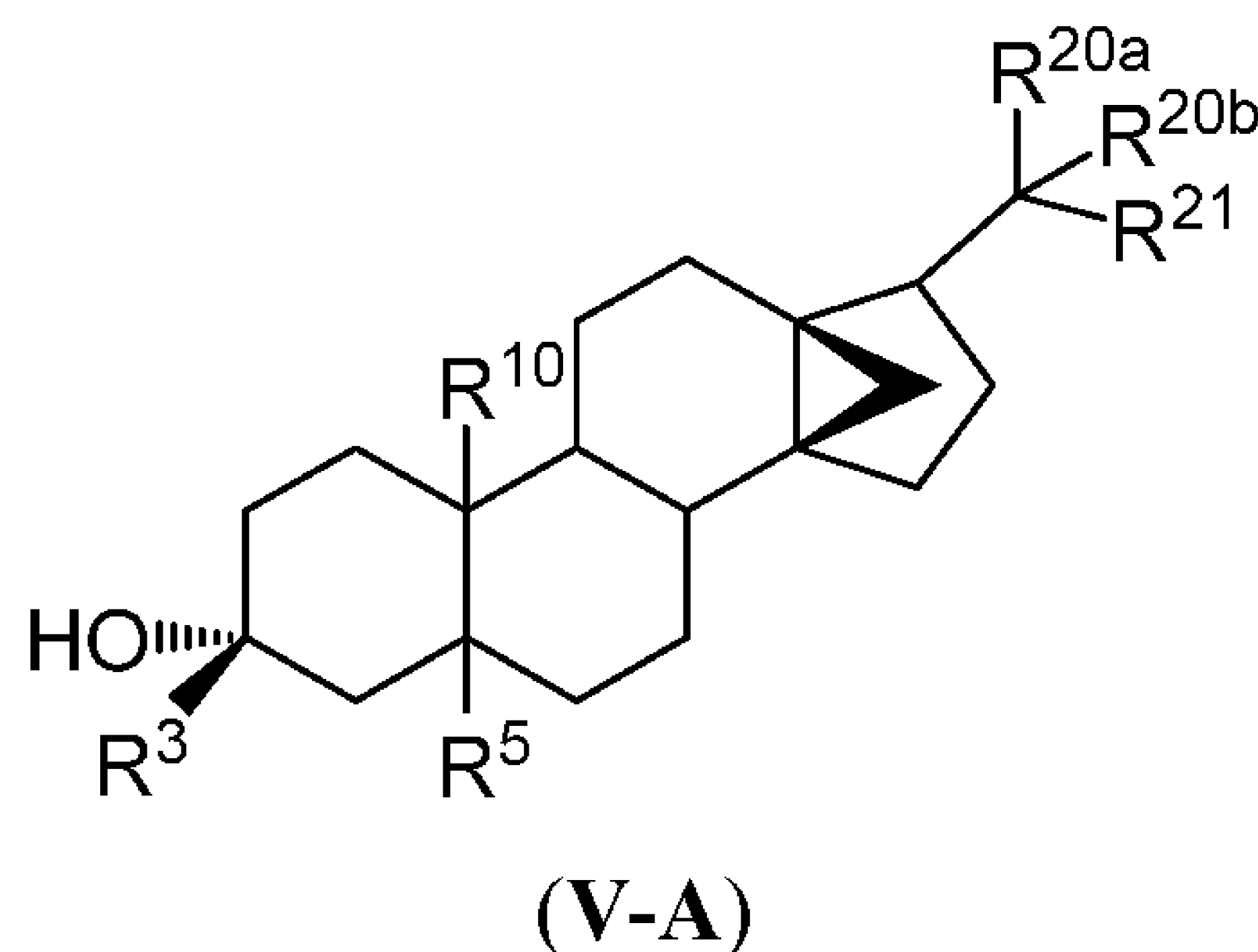
substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, or $-\text{N}(\text{H})-$; and R^{30} is $-\text{H}$ or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, or $-\text{N}(\text{H})-$; and R^{30} is a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, $-\text{CH}_2-$, or

$-\text{N}(\text{H})-$; and R^{30} is , , or , wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some

embodiments, R^{30} is  or , X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N and CR'' , wherein each R'' is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$, provided that no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of

X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$.

[0440] Another aspect of the present invention provides a compound of Formula (V-A)

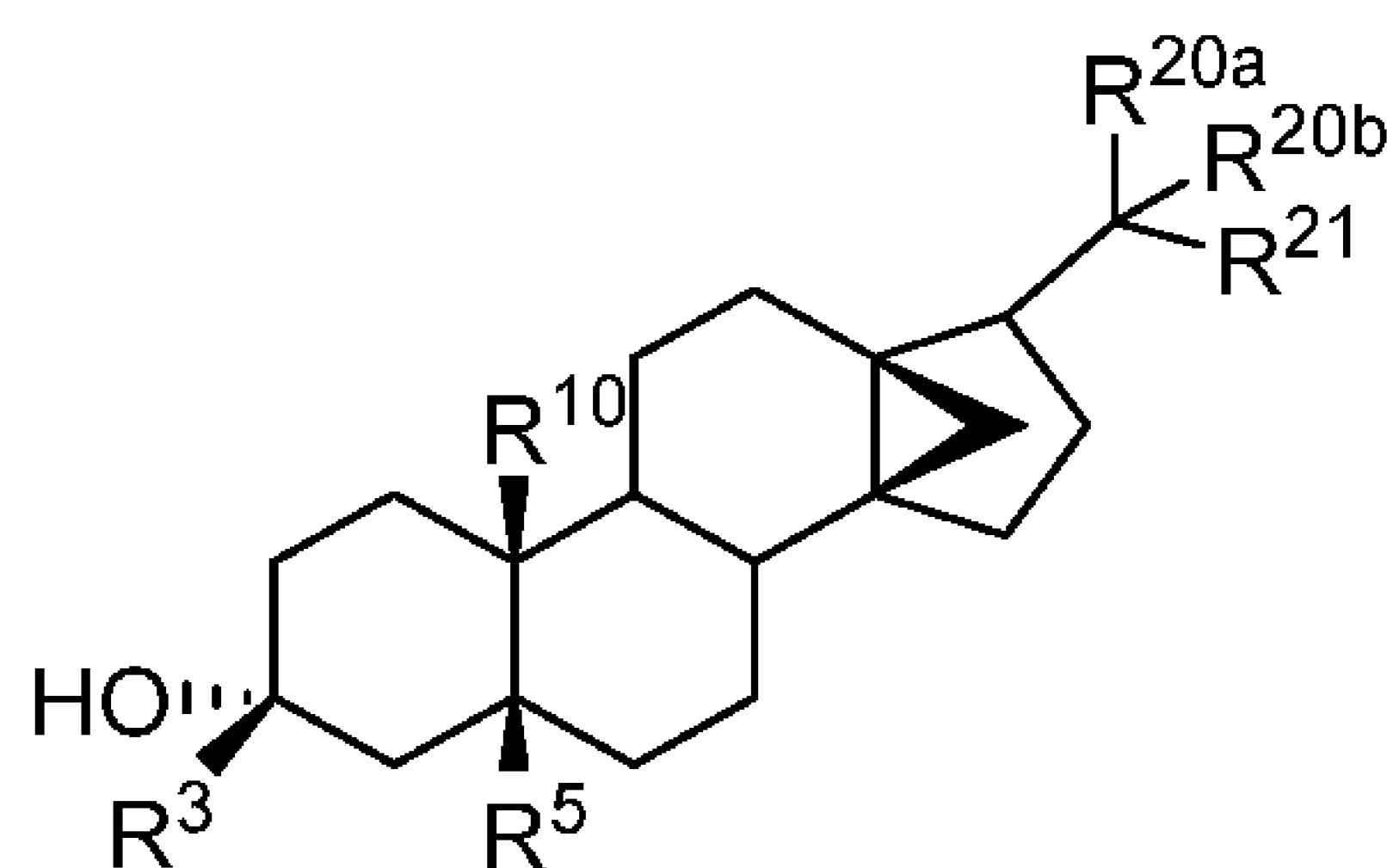


or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} , are as defined in any of the embodiments of the compounds of Formula (I), (IV), or (V).

[0441] In some embodiments, R^3 is $-\text{H}$, C_{1-6} alkyl (e.g., C_{1-3} alkyl), or C_{1-6} alkyl- O - C_{1-6} alkyl (e.g., C_{1-3} alkyl- O - C_{1-3} alkyl); R^5 is $-\text{H}$ or C_{1-6} alkyl (e.g., C_{1-3} alkyl); R^{10} is $-\text{H}$, C_{1-6} alkyl (e.g., C_{1-3} alkyl), or C_{1-6} alkyl- O - C_{1-6} alkyl (e.g., C_{1-3} alkyl- O - C_{1-3} alkyl); each of R^{20a} and R^{20b} is independently selected from $-\text{H}$, $-\text{OH}$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, a branched or straight C_{1-6} alkylene chain, or $-\text{N}(\text{H})-$; and R^{30} is $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$.

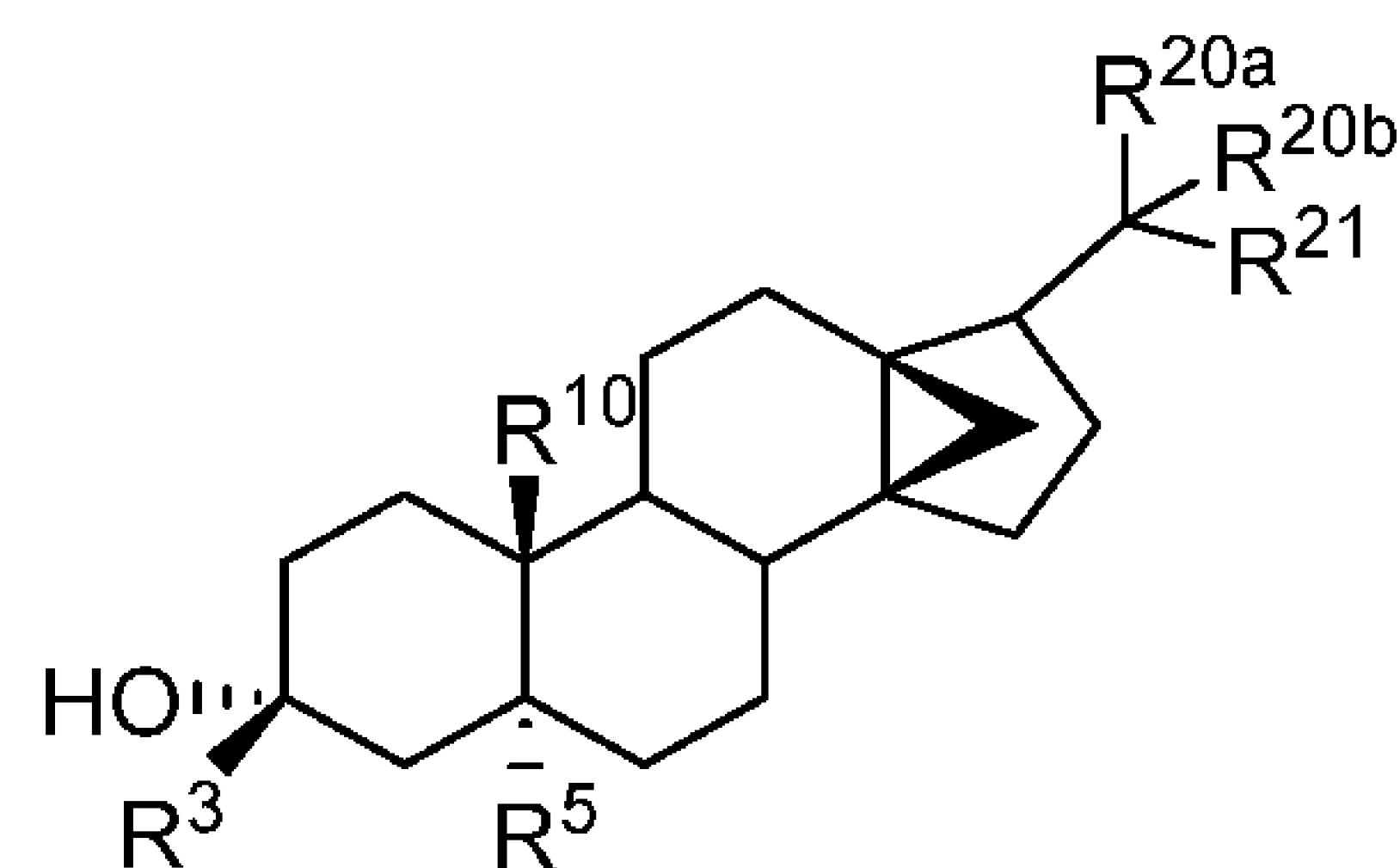
[0442] In some embodiments, R^3 is $-\text{H}$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-\text{H}$ or methyl; R^{10} is $-\text{H}$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-\text{H}$, $-\text{OH}$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$.

[0443] Another aspect of the present invention provides a compound of Formula (V-A1) or (V-A2)



(V-A1)

or



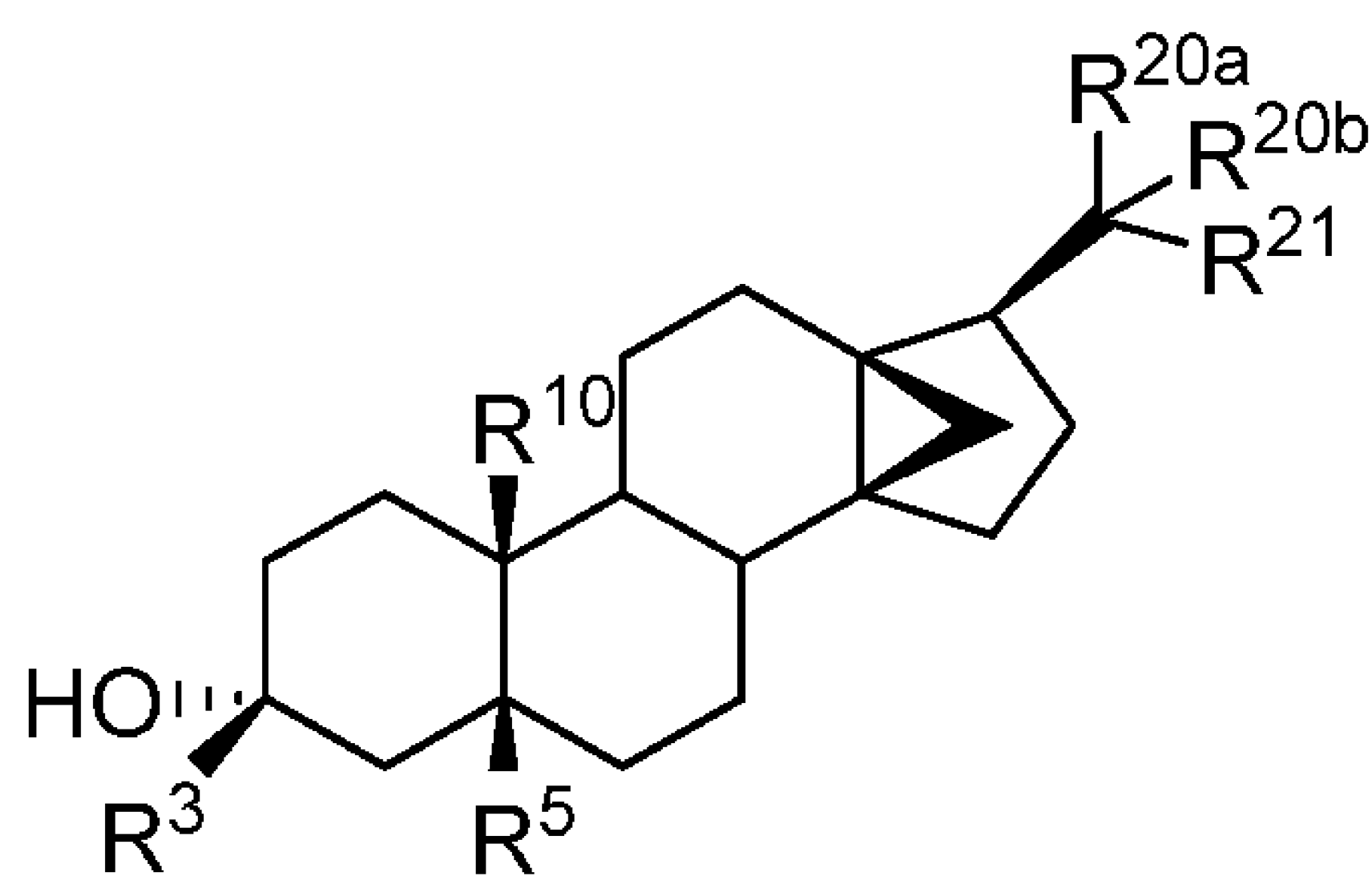
(V-A2),

or a pharmaceutically acceptable salt thereof, wherein R³, R⁵, R¹⁰, R^{20a}, R^{20b}, and R²¹, are as defined in any of the embodiments of the compounds of Formula (I), (IV), (V), or (V-A).

[0444] In some embodiments, R³ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; R⁵ is -H or C₁₋₆ alkyl; R¹⁰ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; each of R^{20a} and R^{20b} is independently selected from -H, -OH, and C₁₋₆ alkyl, or R^{20a} and R^{20b} taken together form oxo; R²¹ is -L^A-R³⁰; L^A is a bond, a branched or straight C₁₋₆ alkylene chain, or -N(H)-; and R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃.

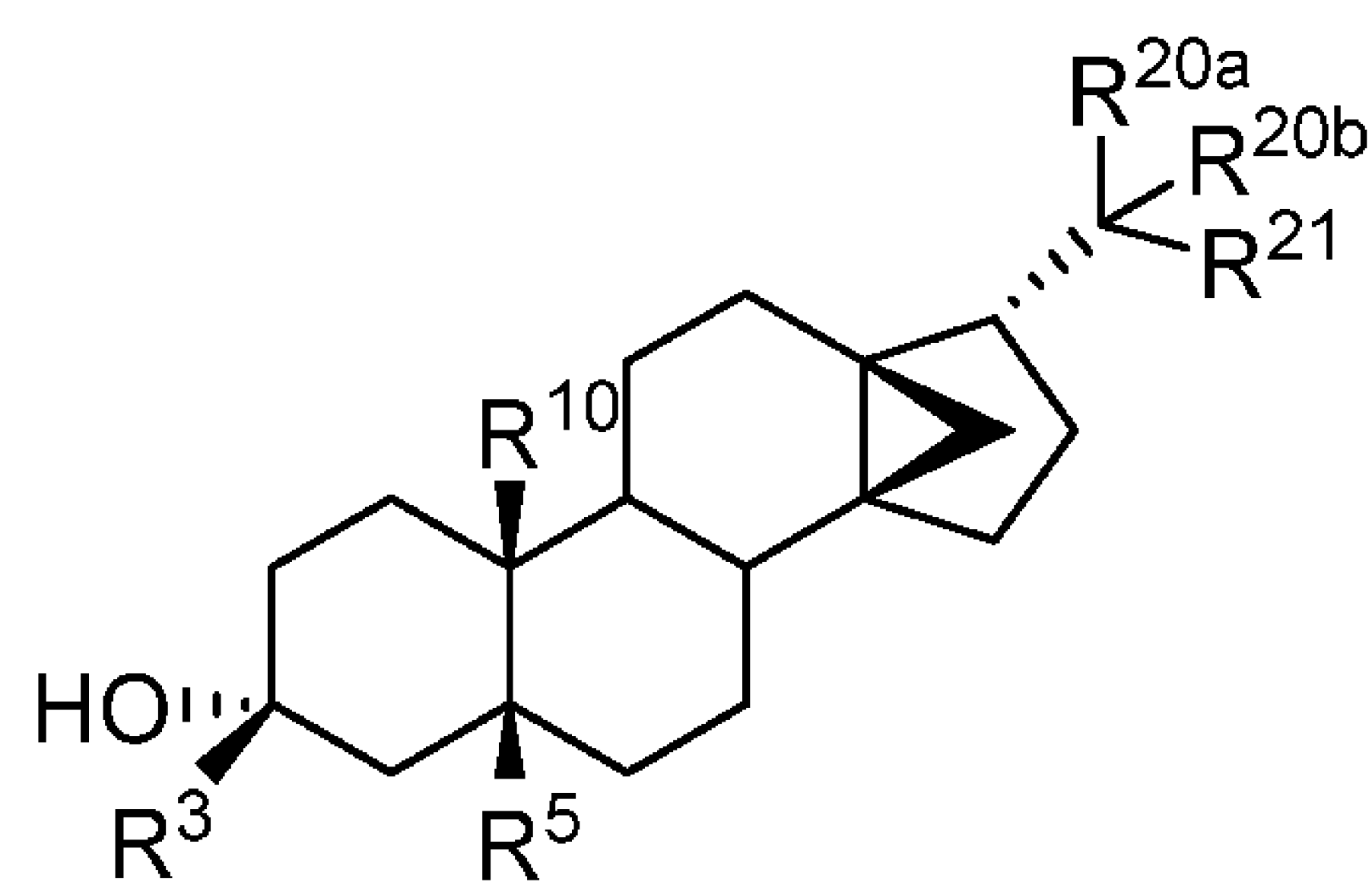
[0445] In some embodiments, R³ is -H, C₁₋₃ alkyl, C₁₋₃ alkyl-O-C₁₋₃ alkyl; R⁵ is -H or methyl; R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; each of R^{20a} and R^{20b} is independently selected from -H, -OH, and C₁₋₃ alkyl, or R^{20a} and R^{20b} taken together form oxo; R²¹ is -L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain; and R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃.

[0446] Another aspect of the present invention provides a compound of Formula (V-A1a) or (V-A1b)



(V-A1a)

or



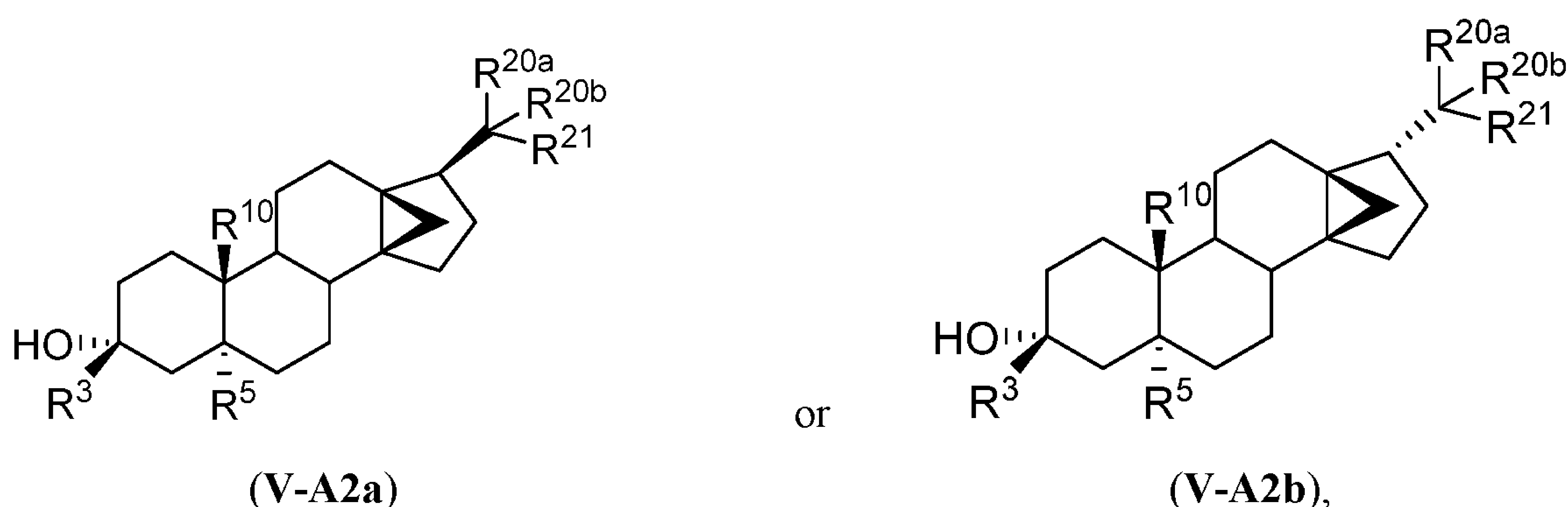
(V-A1b),

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} , are as defined in any of the embodiments of the compounds of Formula (I), (IV), (V), (V-A), or (V-A1).

[0447] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0448] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6- membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0449] Another aspect of the present invention provides a compound of Formula (V-A2a) or (V-A2b)



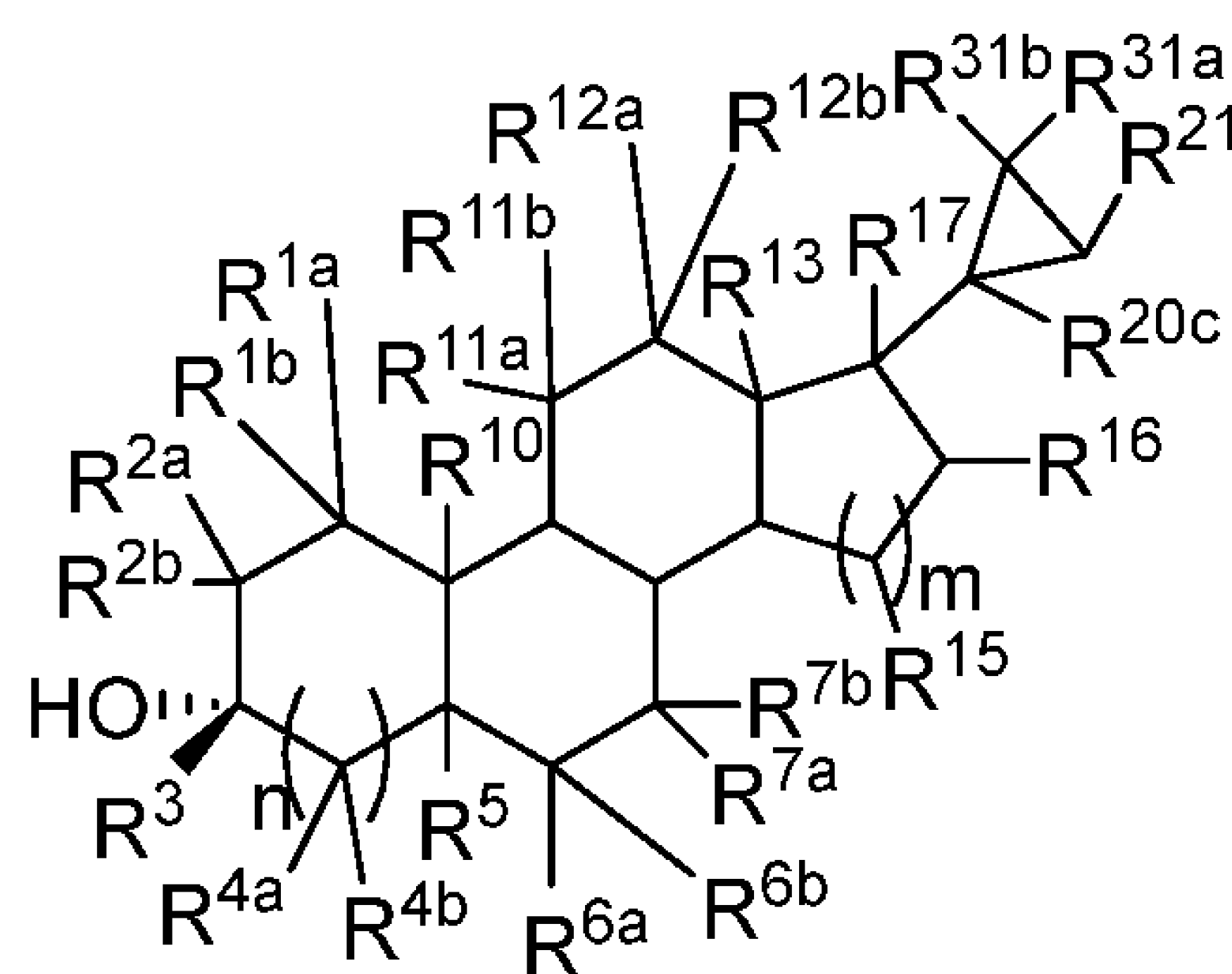
or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{20a} , R^{20b} , and R^{21} , are as defined in any of the embodiments of the compounds of Formula (I), (IV), (V), (V-A), or (V-A2).

[0450] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^{20a} and R^{20b} is independently

selected from $-H$, $-OH$, and C_{1-6} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0451] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl-O- C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl-O- C_{1-3} alkyl; each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0452] Another aspect of the present invention provides a compound of Formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20c} , R^{21} , R^{31a} , R^{31b} , m , and n are as defined in any of the embodiments of the compounds of Formula (I).

[0453] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , and R^{21} is $-L^A-R^{30}$; each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'-$, $-S-$, $-O-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-C(O)C(O)-$, $-C(O)NR'-$, $-NR'C(O)-$, $-NR'C(O)O-$, $-S(O)_2NR'-$, $-NR'S(O)_2-$, $-C(O)NR'NR'-$, $-NR'C(O)NR'-$, $-OC(O)NR'-$, $-NR'NR'-$, $-NR'S(O)_2NR'-$, $-S(O)-$, or $-S(O)_2-$; each R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; each R' is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}

alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃, or R^{1a} and R^{1b} taken together form oxo, or R^{2a} and R^{2b} taken together form oxo, or R^{4a} and R^{4b} taken together form oxo, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo; each of R⁵ and R^{20c} is independently selected from -H and methyl; R¹⁰ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl; each of R^{31a} and R^{31b} is (i) independently selected from -H, halo, and C₁₋₆ alkyl, or (ii) when one of R^{31a} and R^{31b} is -H, the other of R^{31a} and R^{31b} is -H, halo, C₁₋₆ alkyl, or -OR³², wherein R³² is -H, C₁₋₆ alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S; n is 0, 1, or 2; and m is 1 or 2.

[0454] In some embodiments, each of R^{1a} and R^{1b} is independently selected from -H, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, and -O-R', or R^{1a} and R^{1b} taken together form oxo. In some embodiments, each of R^{1a} and R^{1b} is independently selected from -H and C₁₋₆ alkyl optionally substituted with R', or R^{1a} and R^{1b} taken together form oxo. In some embodiments, one of R^{1a} and R^{1b} is -H, and the other is -H, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, or -O-R'. In some embodiments, one of R^{1a} and R^{1b} is -H, and the other is -H or C₁₋₆ alkyl optionally substituted with R'. In some embodiments, one of R^{1a} and R^{1b} is -H, and the other is methyl. And, in some embodiments, each of R^{1a} and R^{1b} is -H.

[0455] In some embodiments, each of R^{2a} and R^{2b} is independently selected from -H, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, and -O-R', or R^{2a} and R^{2b} taken together form oxo. In some embodiments, each of R^{2a} and R^{2b} is independently selected from -H and C₁₋₆ alkyl optionally substituted with R', or R^{2a} and R^{2b} taken together form oxo. In some embodiments, one of R^{2a} and R^{2b} is -H, and the other is -H, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, or -O-R'. In some embodiments, one of R^{2a} and R^{2b} is -H, and the other is -H or C₁₋₆ alkyl optionally substituted with R'. In some embodiments, one of R^{2a} and R^{2b} is -H, and the other is methyl. And, in some embodiments, each of R^{2a} and R^{2b} is -H.

[0456] In some embodiments, R³ is -H, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, or -O-R'. In some embodiments, R³ is -H or C₁₋₆ alkyl optionally substituted with R'. In some embodiments, R³ is -H, -CH₃, -CH₂-CH₂-CH₃, or -CH₂-O-CH₃. In some embodiments, R³ is -H or methyl.

[0457] In some embodiments, n is 0 and both of R^{4a} and R^{4b} are absent. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{4a} and R^{4b} taken together form oxo. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is methyl. And, in some embodiments, n is 1 and each of R^{4a} and R^{4b} is $-H$.

[0458] In some embodiments, R^5 is $-H$ or methyl. In some embodiments, R^5 is $-H$.

[0459] In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo. In some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' . In some embodiments, two of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other two of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$. In some embodiments, three of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, three of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other is $-H$ or methyl. And, in some embodiments, each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is $-H$.

[0460] In some embodiments, R^{10} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl. And, in some embodiments, R^{10} is $-H$, methyl, or methoxymethyl.

[0461] In some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo. In some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' . In some embodiments, two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$. In some embodiments, two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are independently

selected from $-H$ and methyl. In some embodiments, three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other is $-H$ or methyl. And, in some embodiments, each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is $-H$.

[0462] In some embodiments, R^{13} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^{13} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^{13} is $-H$ or C_{1-3} alkyl (e.g., methyl or ethyl). In some embodiments, R^{13} is $-H$. And, in some embodiments, R^{13} is $-CH_3$ (methyl). In some embodiments, R^{13} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{13} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl. In some embodiments, R^{13} is $-H$ or C_{1-3} alkyl. In some embodiments, R^{13} is $-H$, methyl, or methoxymethyl. And, in some embodiments, R^{13} is methyl.

[0463] In some embodiments, m is 1 and R^{15} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, m is 1 and R^{15} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, m is 1 and R^{15} is $-H$ or C_{1-3} alkyl (e.g., methyl or ethyl). And, in some embodiments, R^{15} is $-H$.

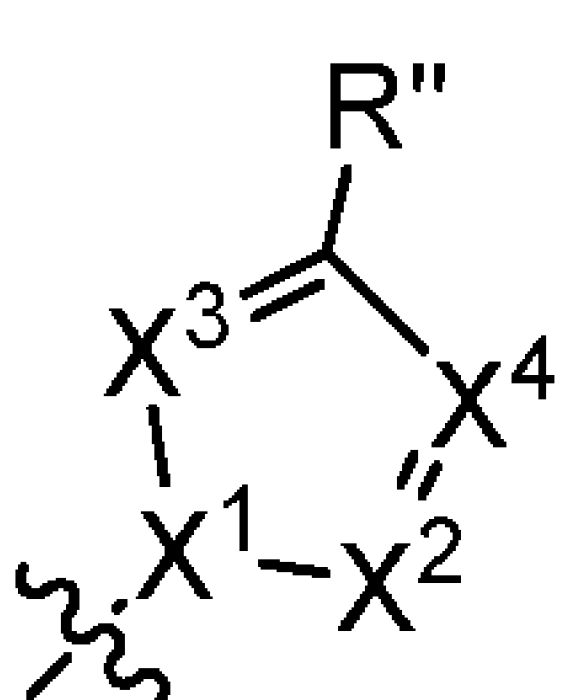
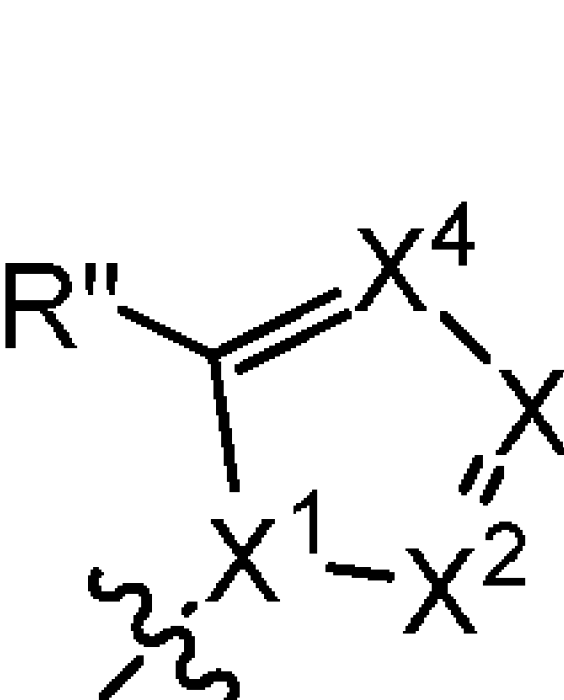
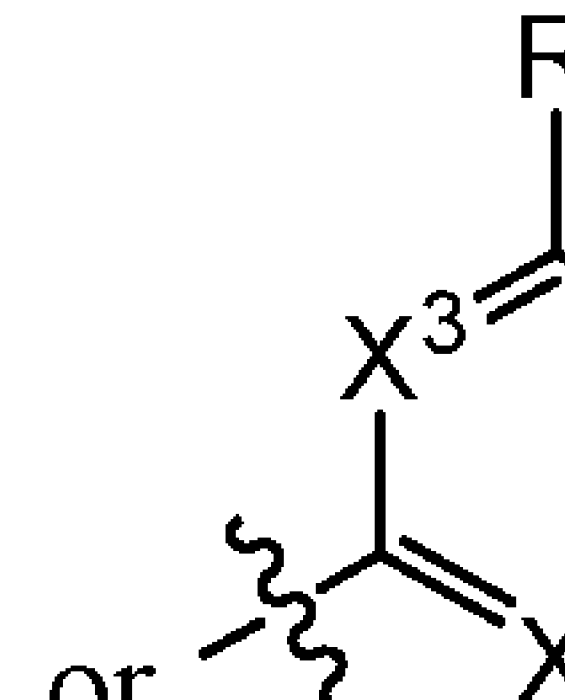
[0464] In some embodiments, R^{16} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^{16} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^{16} is $-H$ or C_{1-3} alkyl (e.g., methyl or ethyl). And, in some embodiments, R^{16} is $-H$.

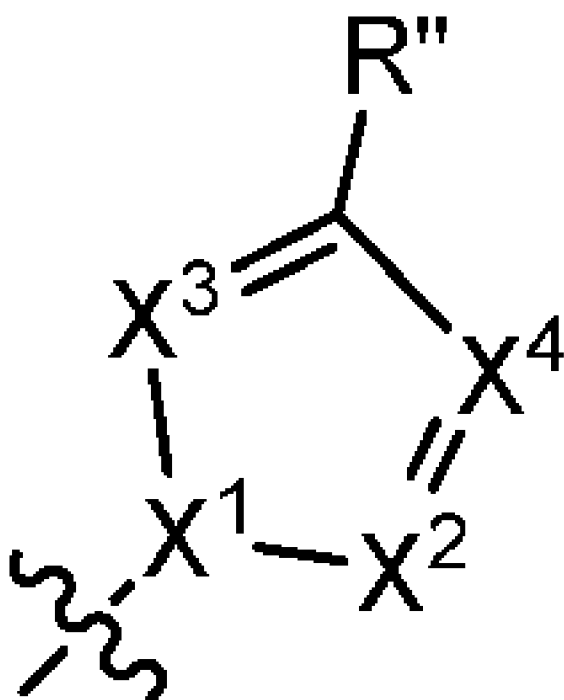
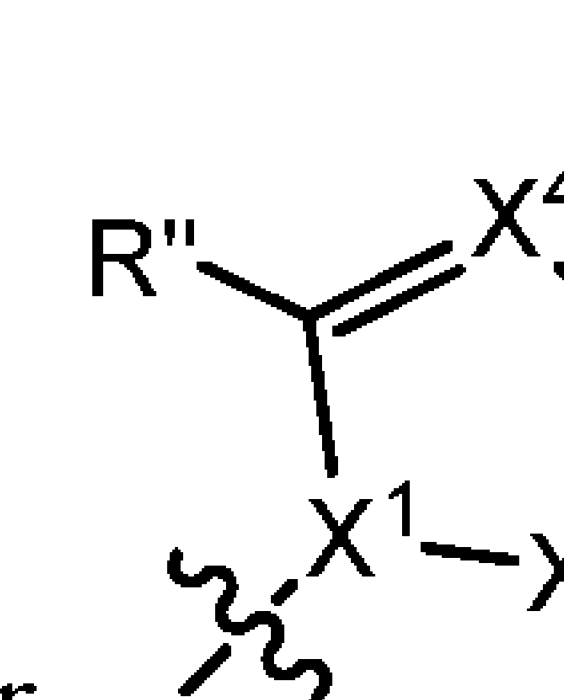
[0465] In some embodiments, R^{17} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$. In some embodiments, R^{17} is $-H$ or C_{1-6} alkyl optionally substituted with R' . In some embodiments, R^{17} is $-H$ or C_{1-3} alkyl (e.g., methyl or ethyl). And, in some embodiments, R^{17} is $-H$.

[0466] In some embodiments, R^{20c} is $-H$.

[0467] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-CH_2-$, or $-CH_2-CH_2-$; and R^{30} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond or $-CH_2-$; and R^{30} is a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6-membered ring is optionally substituted with 1-3 groups

independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond or $-\text{CH}_2-$; and R^{30} is a 5-6-membered partially unsaturated or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-2 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$. In some embodiments, R^{21} is

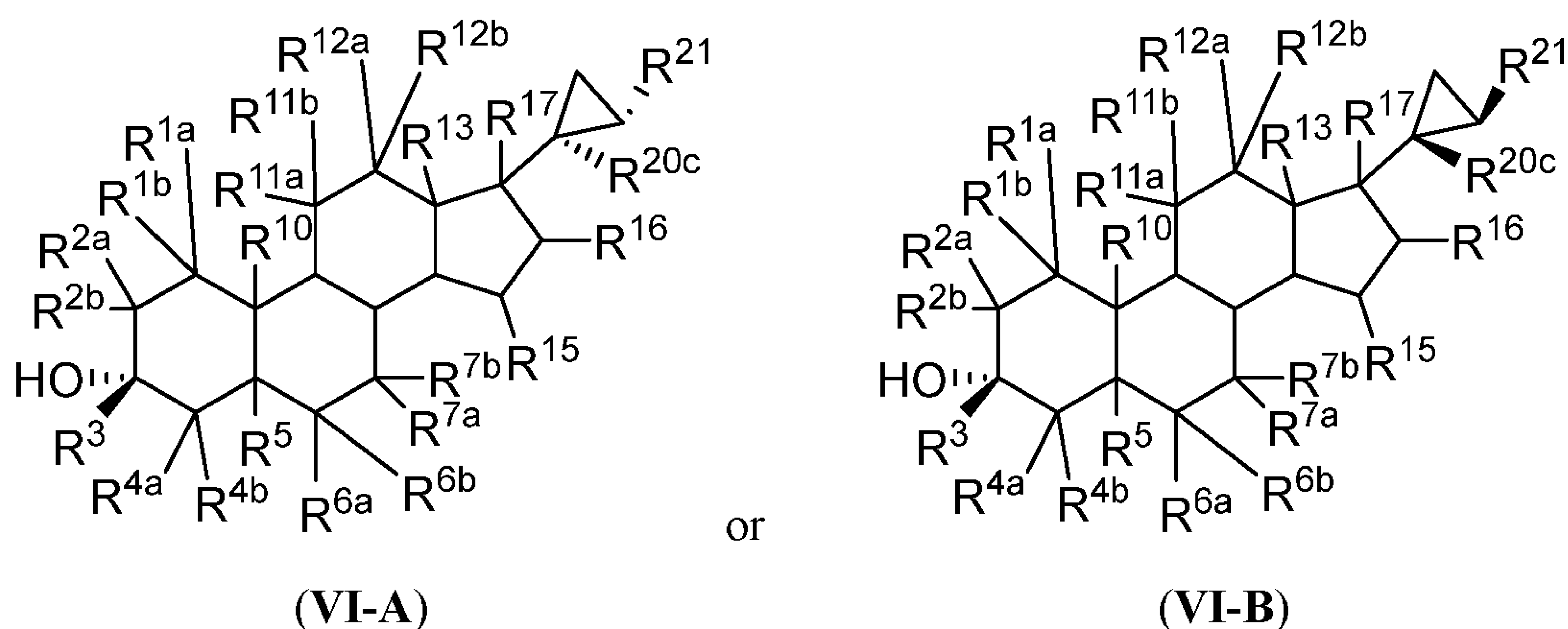
$-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond or $-\text{CH}_2-$; and R^{30} is , , or , wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$,

$-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, R^{30} is , or , X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N and CR'' , wherein each R'' is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$, provided that no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$.

[0468] In some embodiments, each of $\text{R}^{31\text{a}}$ and $\text{R}^{31\text{b}}$ is independently selected from $-\text{H}$, halo, and C_{1-6} alkyl, or when one of $\text{R}^{31\text{a}}$ and $\text{R}^{31\text{b}}$ is $-\text{H}$, the other is $-\text{H}$, halo, C_{1-6} alkyl, or $-\text{OR}^{32}$, wherein R^{32} is $-\text{H}$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully

unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S. In some embodiments, one of R^{31a} and R^{31b} is $-H$, and the other is $-H$, halo, C_{1-6} alkyl, or $-OR^{32}$, wherein R^{32} is $-H$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S. In some embodiments, each of R^{31a} and R^{31b} is independently selected from $-H$, halo, and C_{1-6} alkyl. In some embodiments, one of R^{31a} and R^{31b} is $-H$, and the other is $-OH$, $-O-C_{1-6}$ alkyl, $-O$ -phenyl, or $-O-C_{3-6}$ cycloalkyl. In some embodiments, each of R^{31a} and R^{31b} is $-H$.

[0469] Another aspect of the present invention provides a compound of Formula (VI-A) or (VI-B)

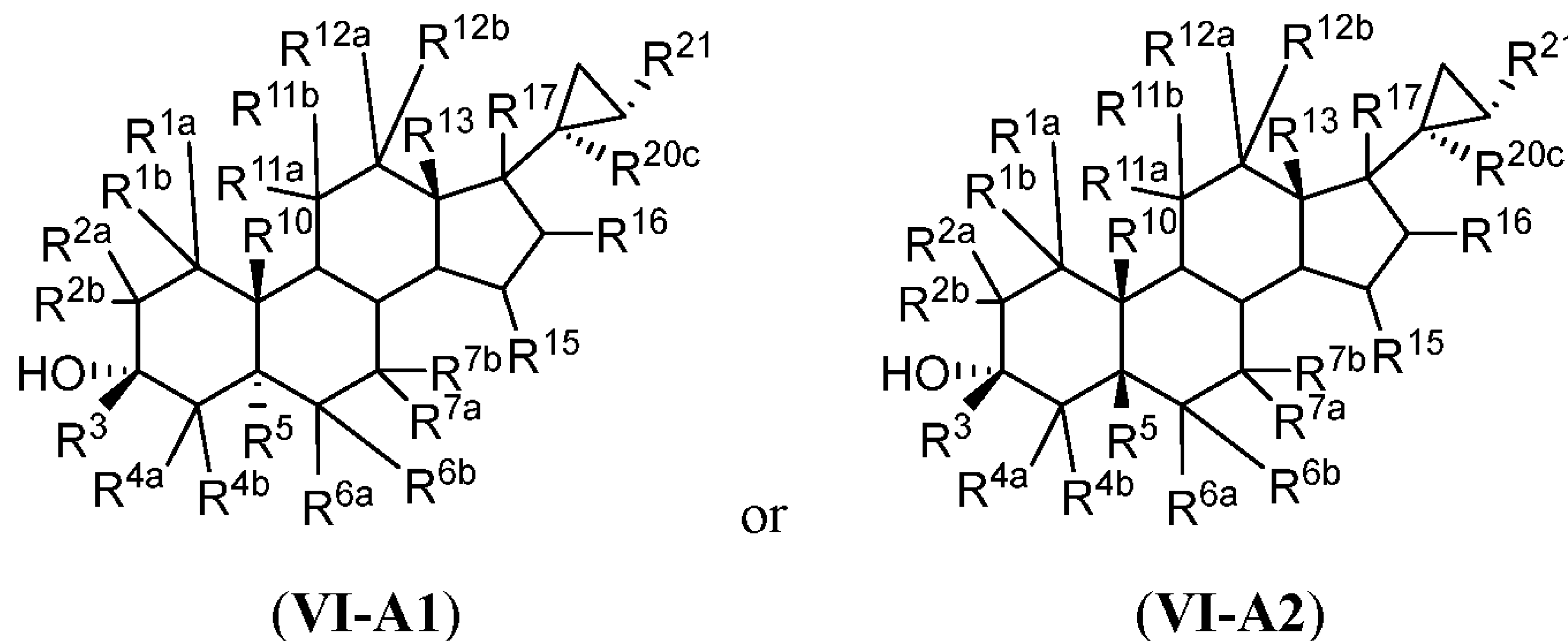


or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20c} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I) or (VI).

[0470] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , and R^{17} is independently selected from $-H$ and C_{1-6} alkyl; R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^5 and R^{20c} is independently selected from $-H$ and methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms,

wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

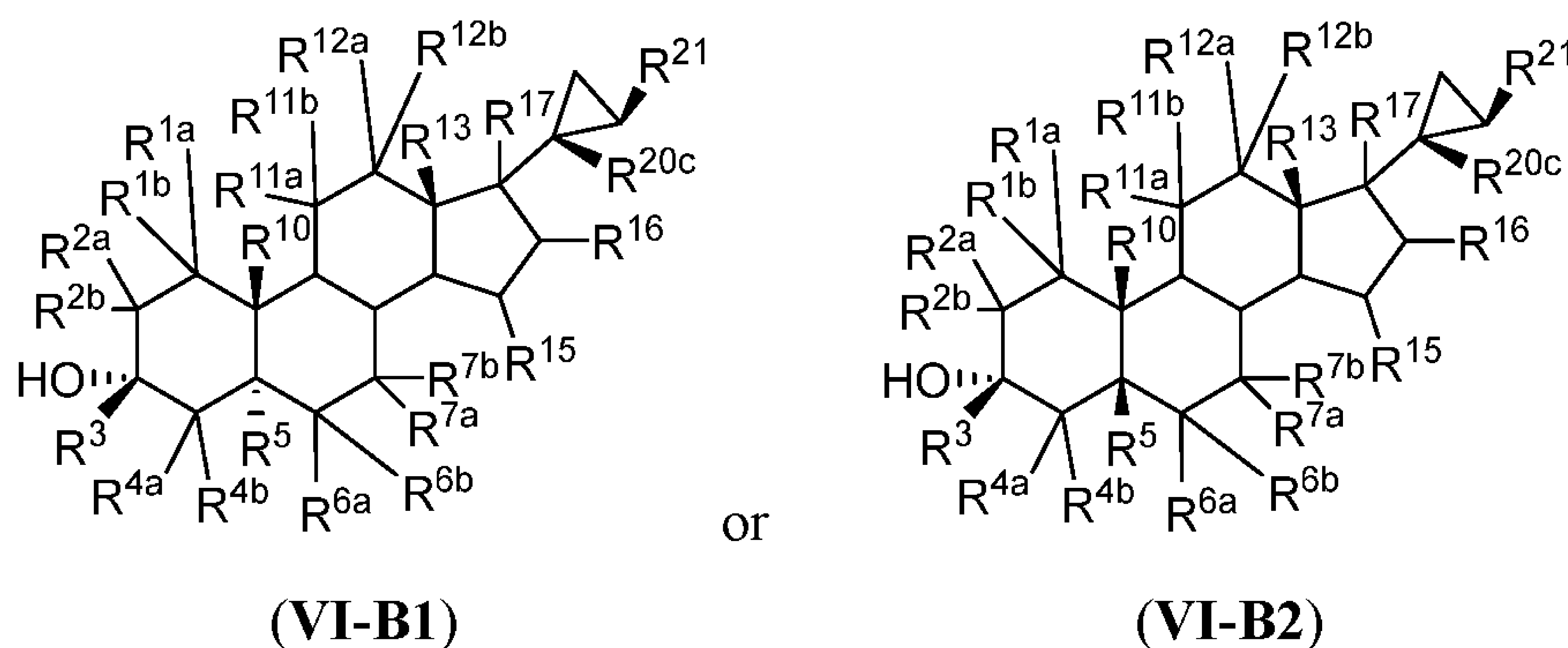
[0471] Another aspect of the present invention provides a compound of Formula **(VI-A1)** or **(VI-A2)**



or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R^{4a}, R^{4b}, R⁵, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R¹⁰, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R¹⁵, R¹⁶, R¹⁷, R^{20c}, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (VI), or (VI-A).

[0472] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , and R^{17} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl); R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^5 and R^{20c} is independently selected from $-H$ and methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

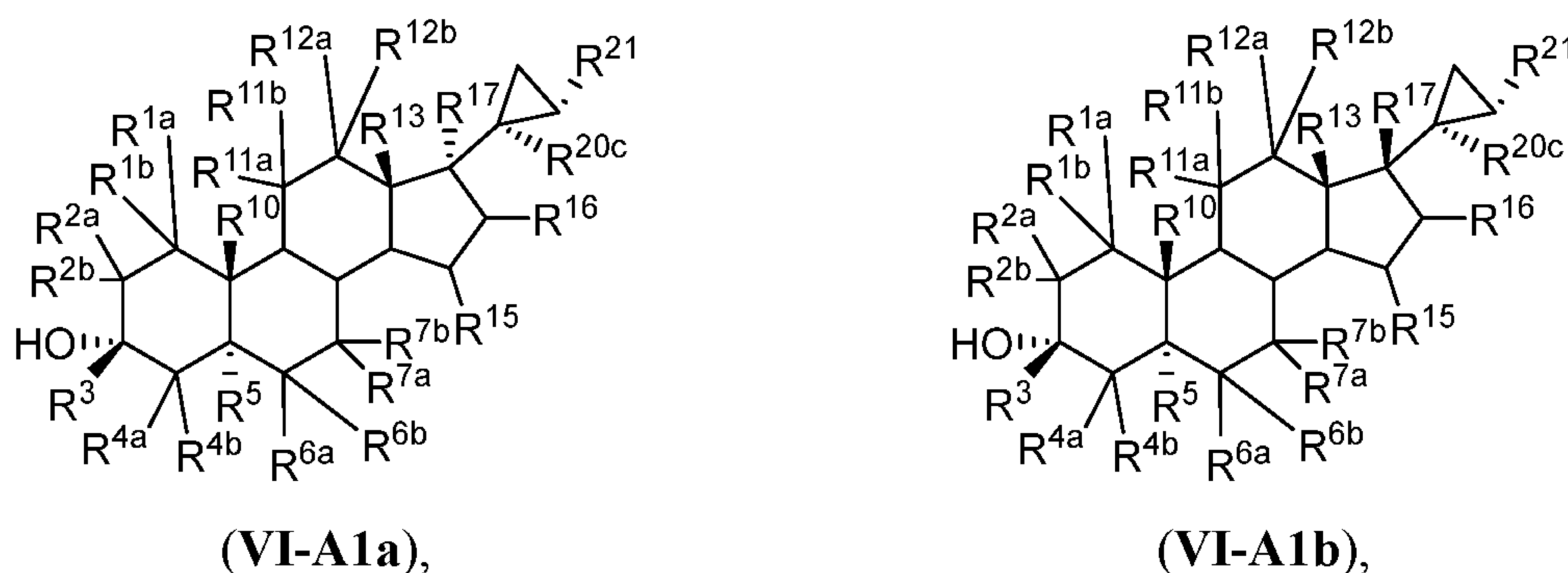
[0473] Another aspect of the present invention provides a compound of Formula **(VI-B1)** or **(VI-B2)**

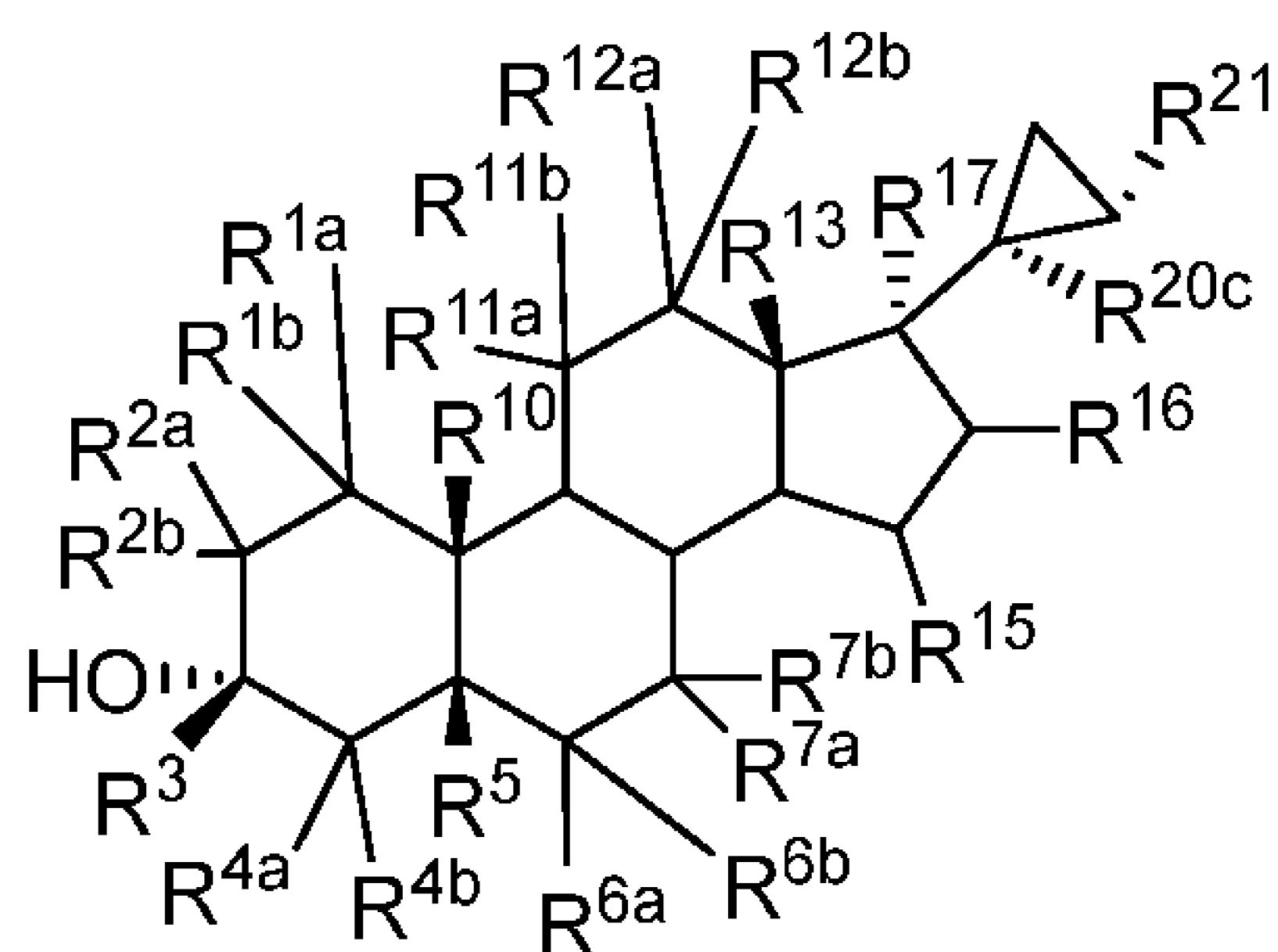


or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20c} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), or (VI-B).

[0474] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , and R^{17} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl); R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^5 and R^{20c} is independently selected from $-H$ and methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

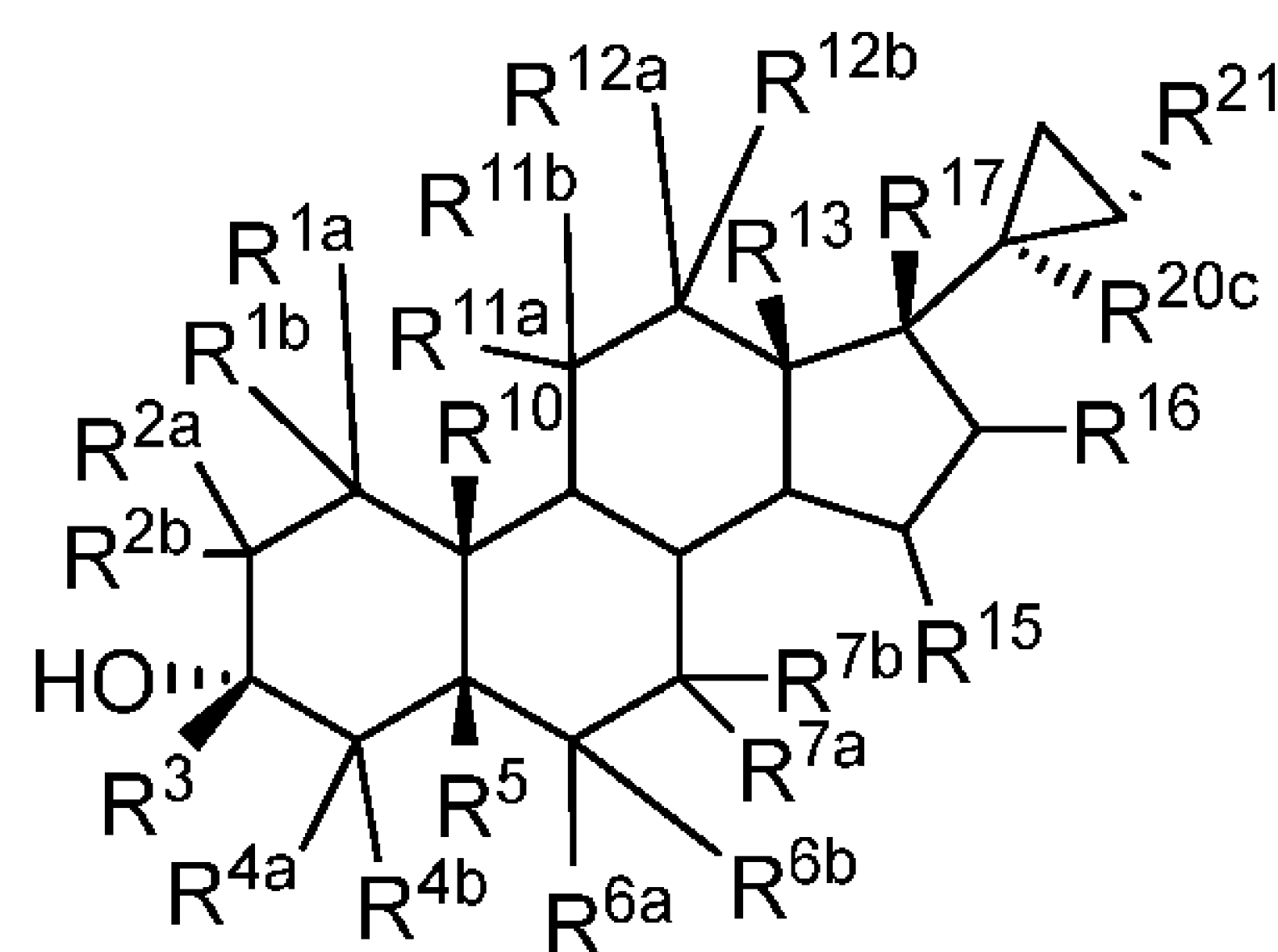
[0475] Another aspect of the present invention provides a compound of Formula (VI-A1a), (VI-A1b), (VI-A1c), or (VI-A1d)





(VI-A1c),

or

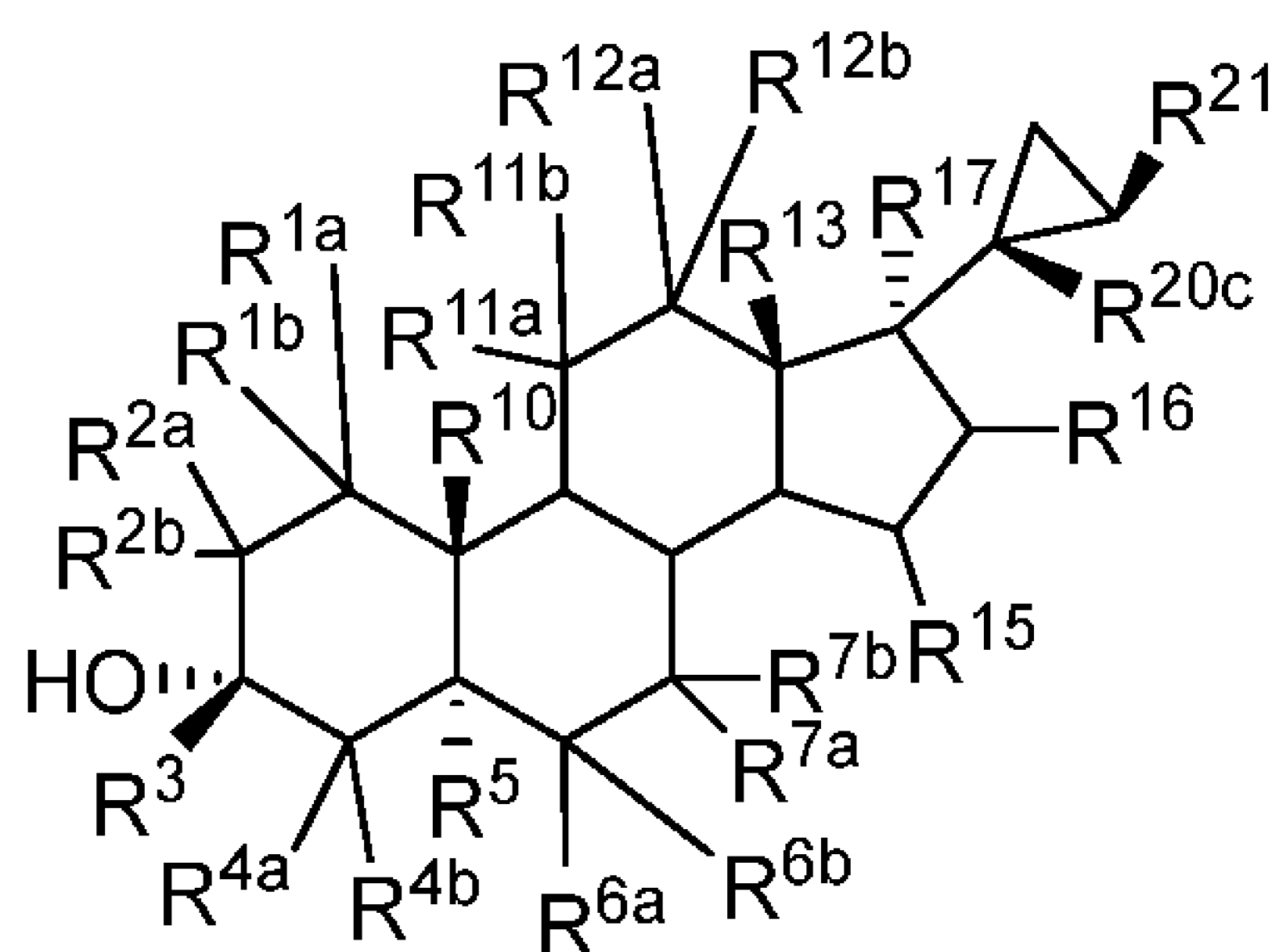


(VI-A1d),

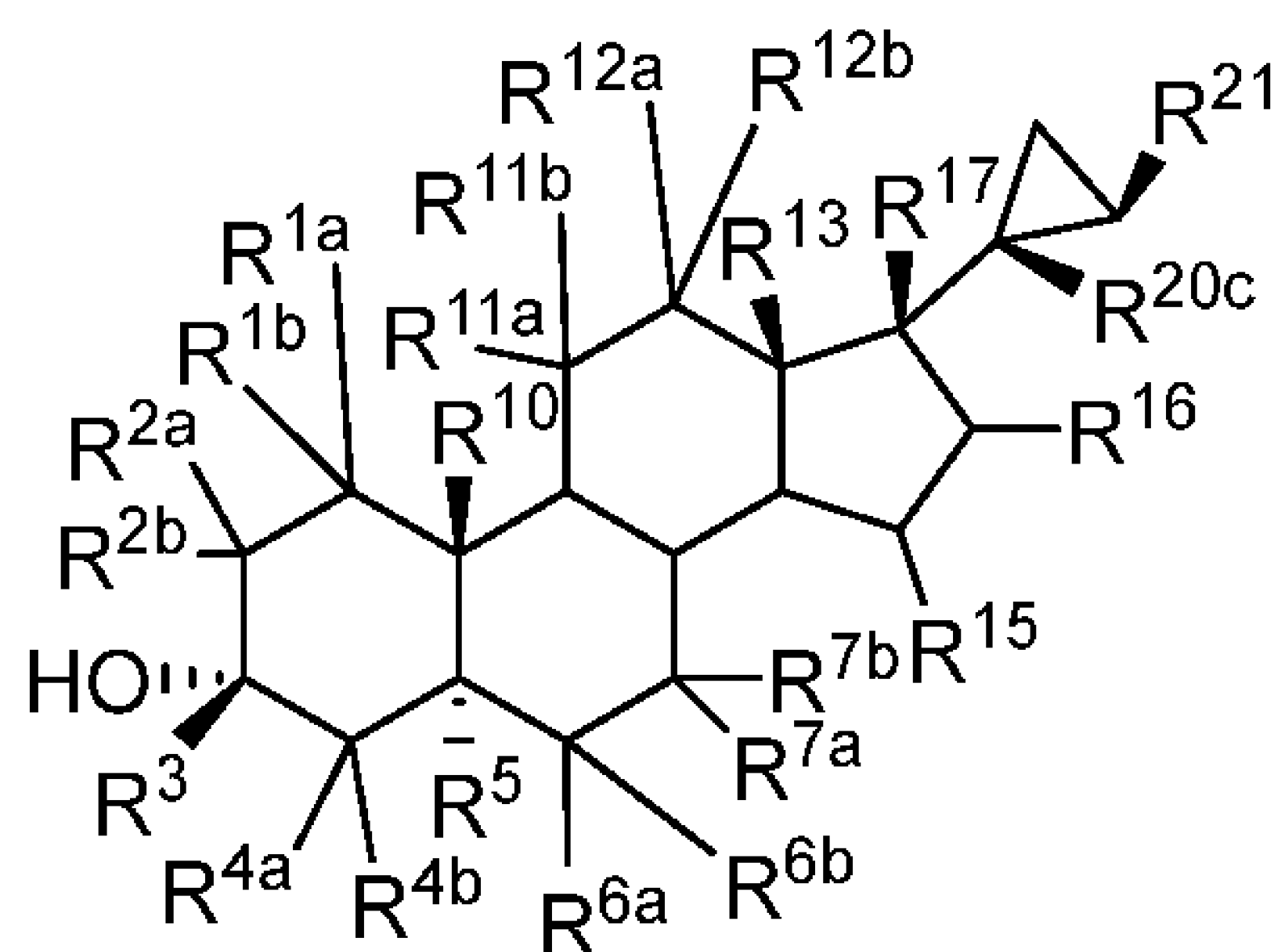
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20c} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VI-A), (VI-A1), or (VI-A2).

[0476] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , and R^{17} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl); R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^5 and R^{20c} is independently selected from $-H$ and methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

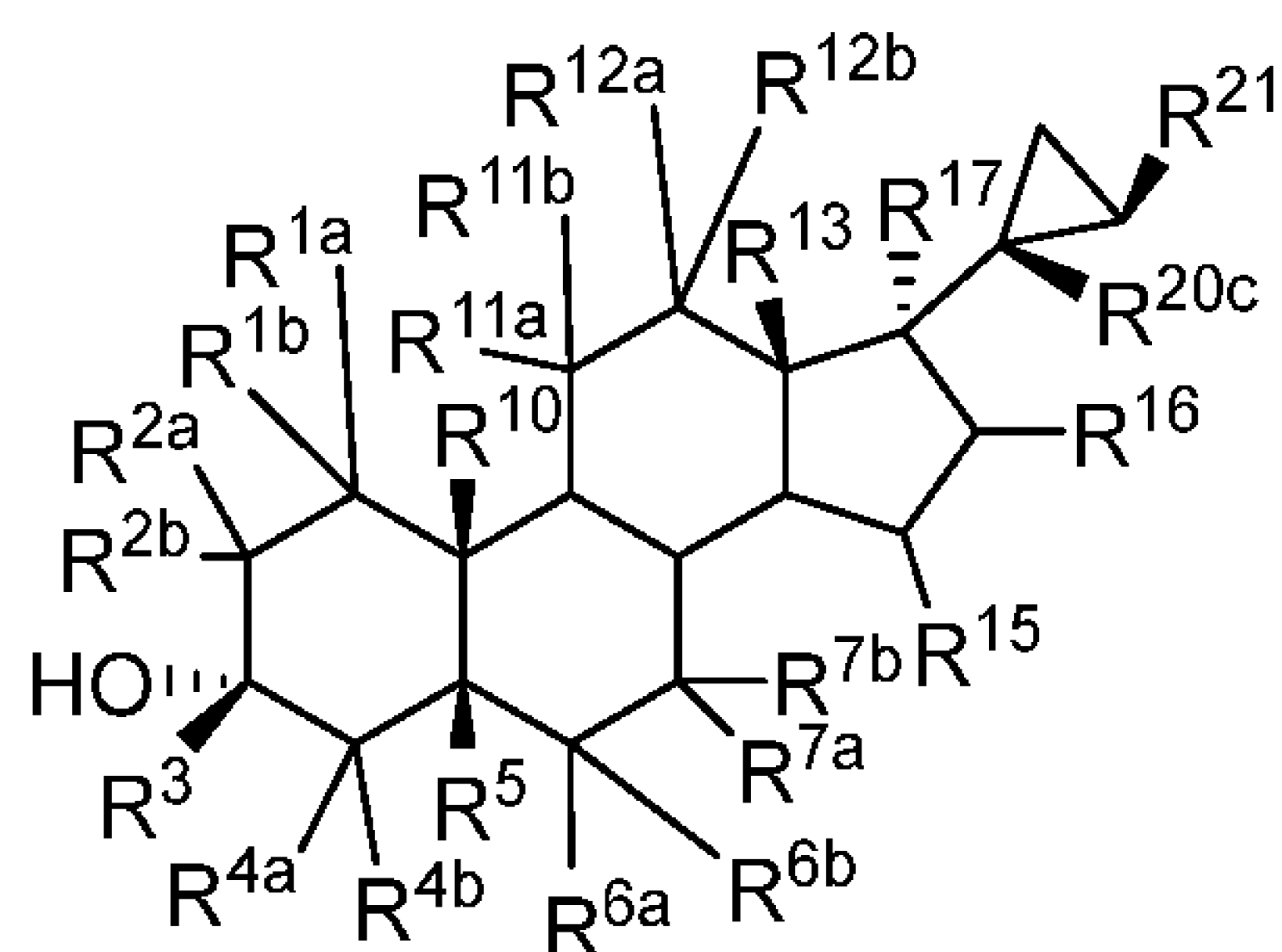
[0477] Another aspect of the present invention provides a compound of Formula (VI-B1a), (VI-B1b), (VI-B1c), or (VI-B1d)



(VI-B1a),

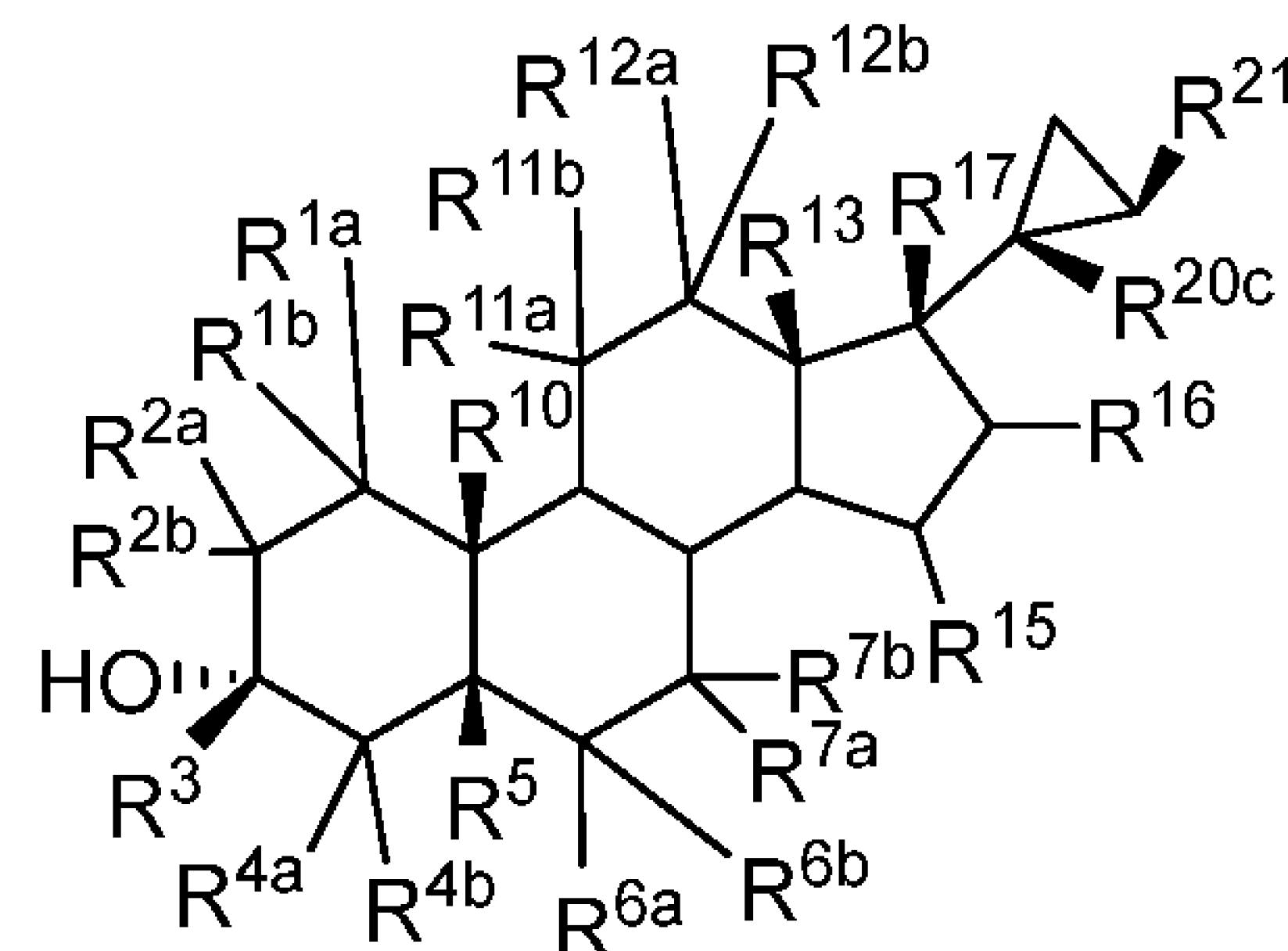


(VI-B1b),



(VI-B1c),

or

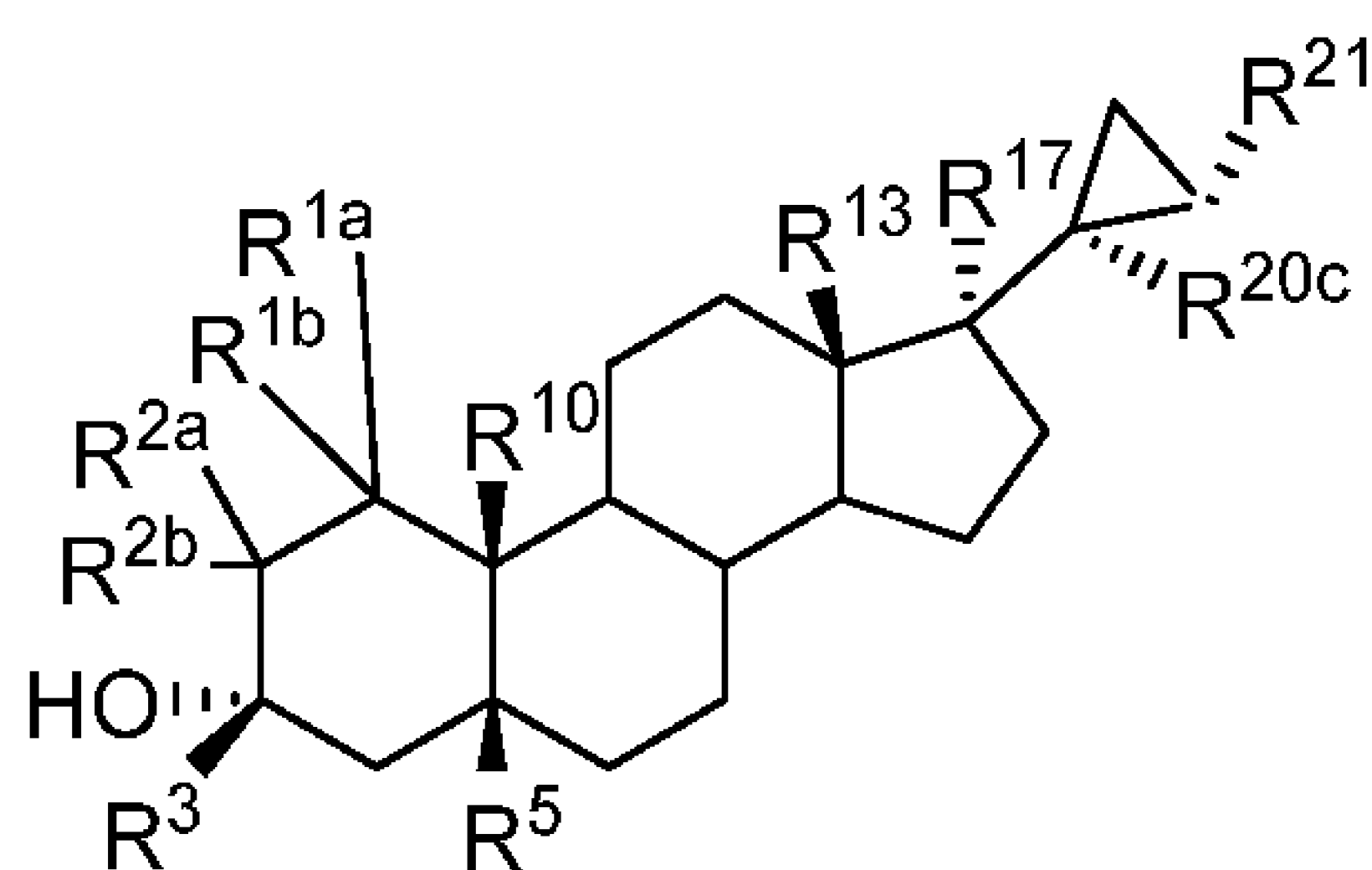


(VI-B1d),

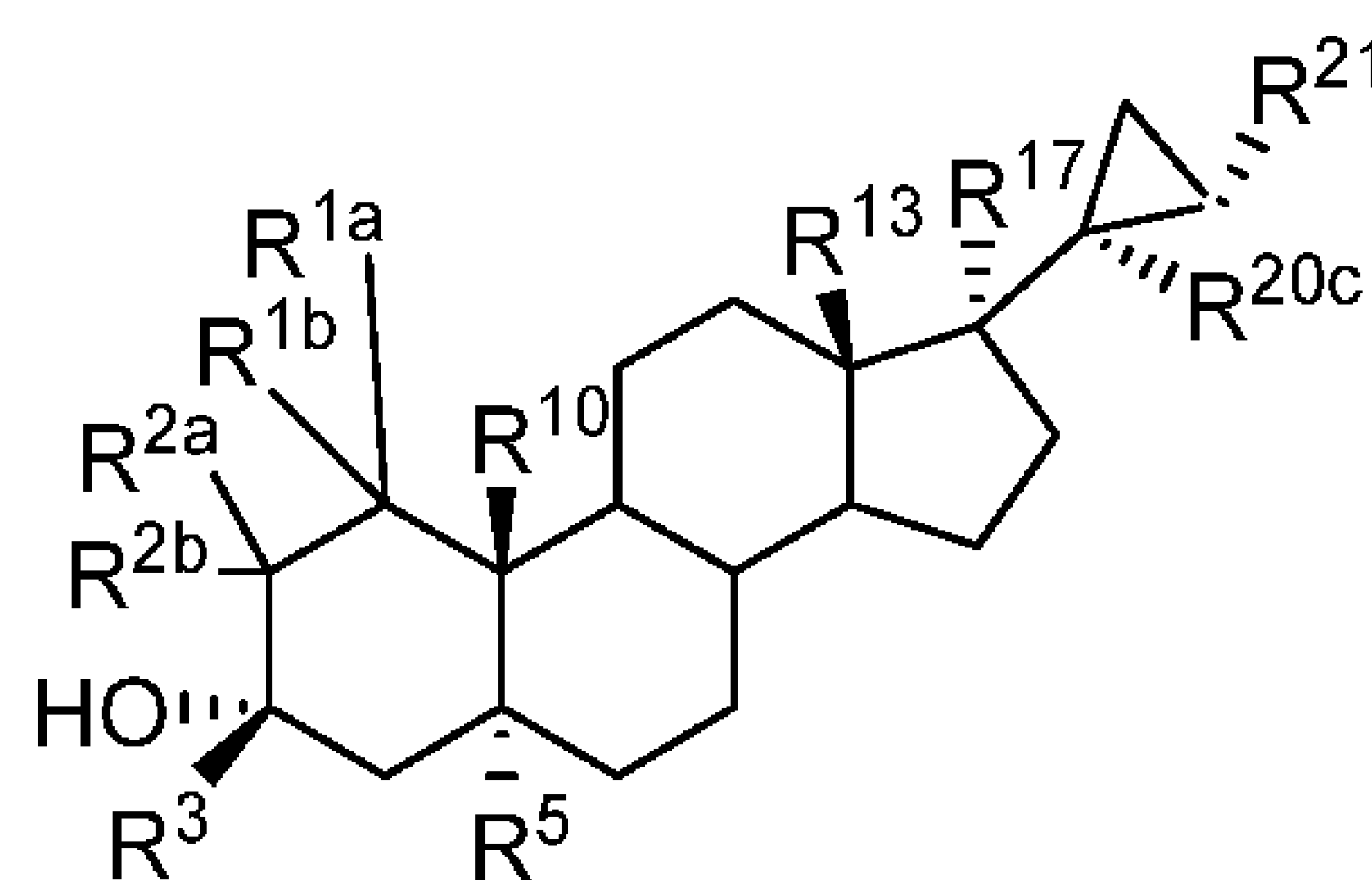
or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^5 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{10} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20c} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VI-B), (VI-B1), or (VI-B2).

[0478] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , and R^{17} is independently selected from $-H$ and C_{1-6} alkyl (e.g., C_{1-3} alkyl); R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; each of R^5 and R^{20c} is independently selected from $-H$ and methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

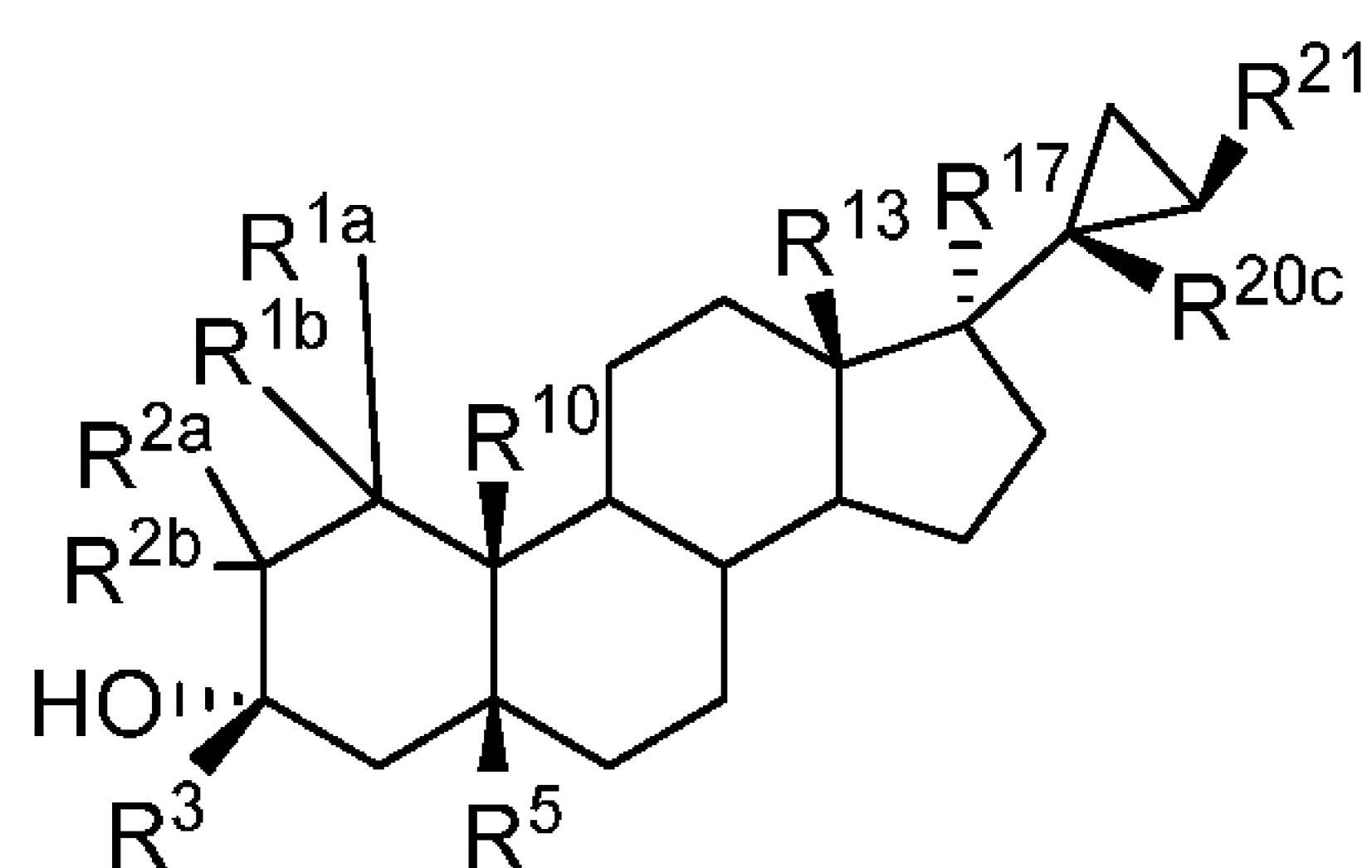
[0479] Another aspect of the present invention provides a compound of Formula (VI-A3a), (VI-A3b), (VI-B3a), or (VI-B3b)



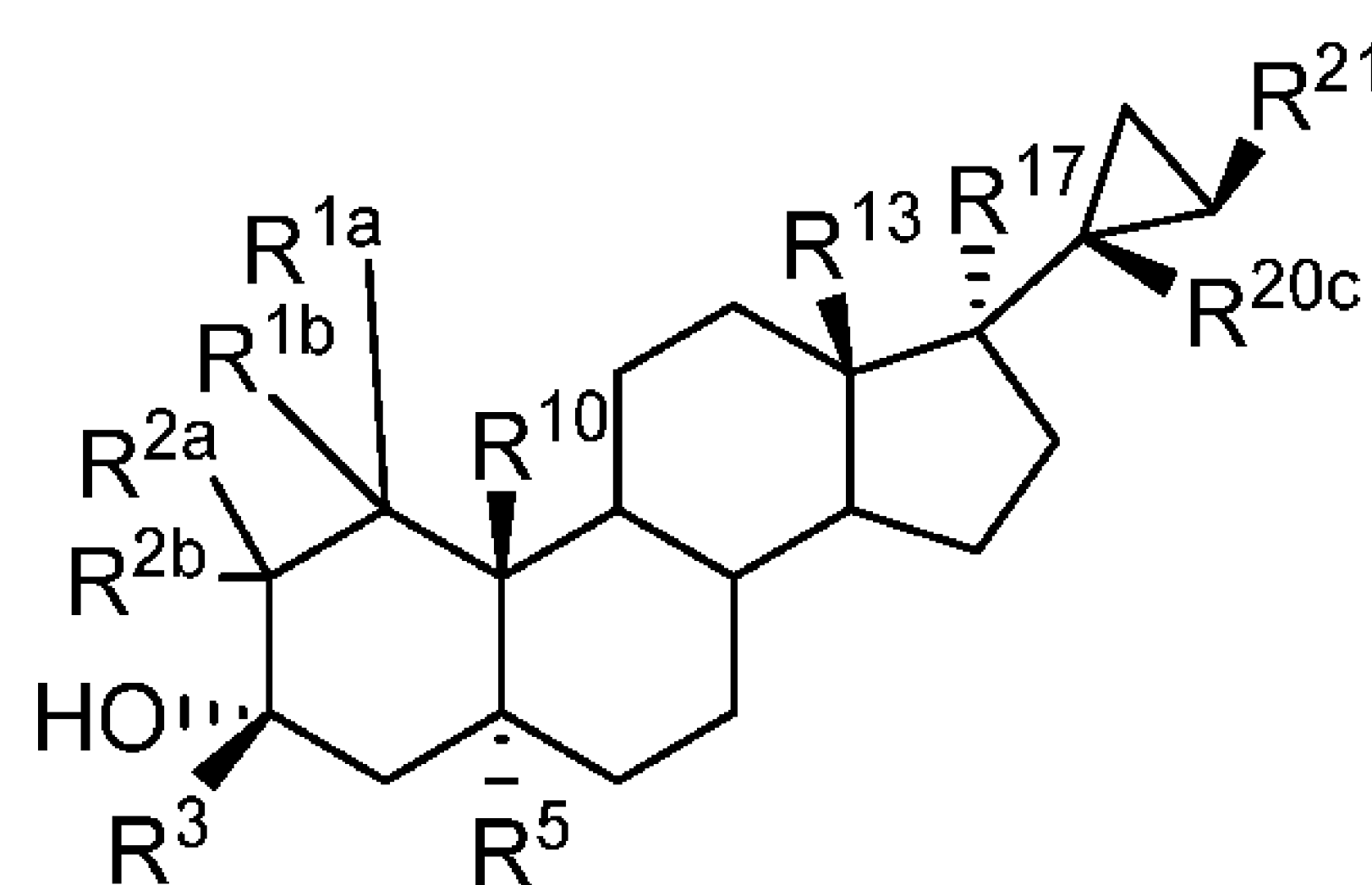
(VI-A3a),



(VI-A3b),



(VI-B3a),



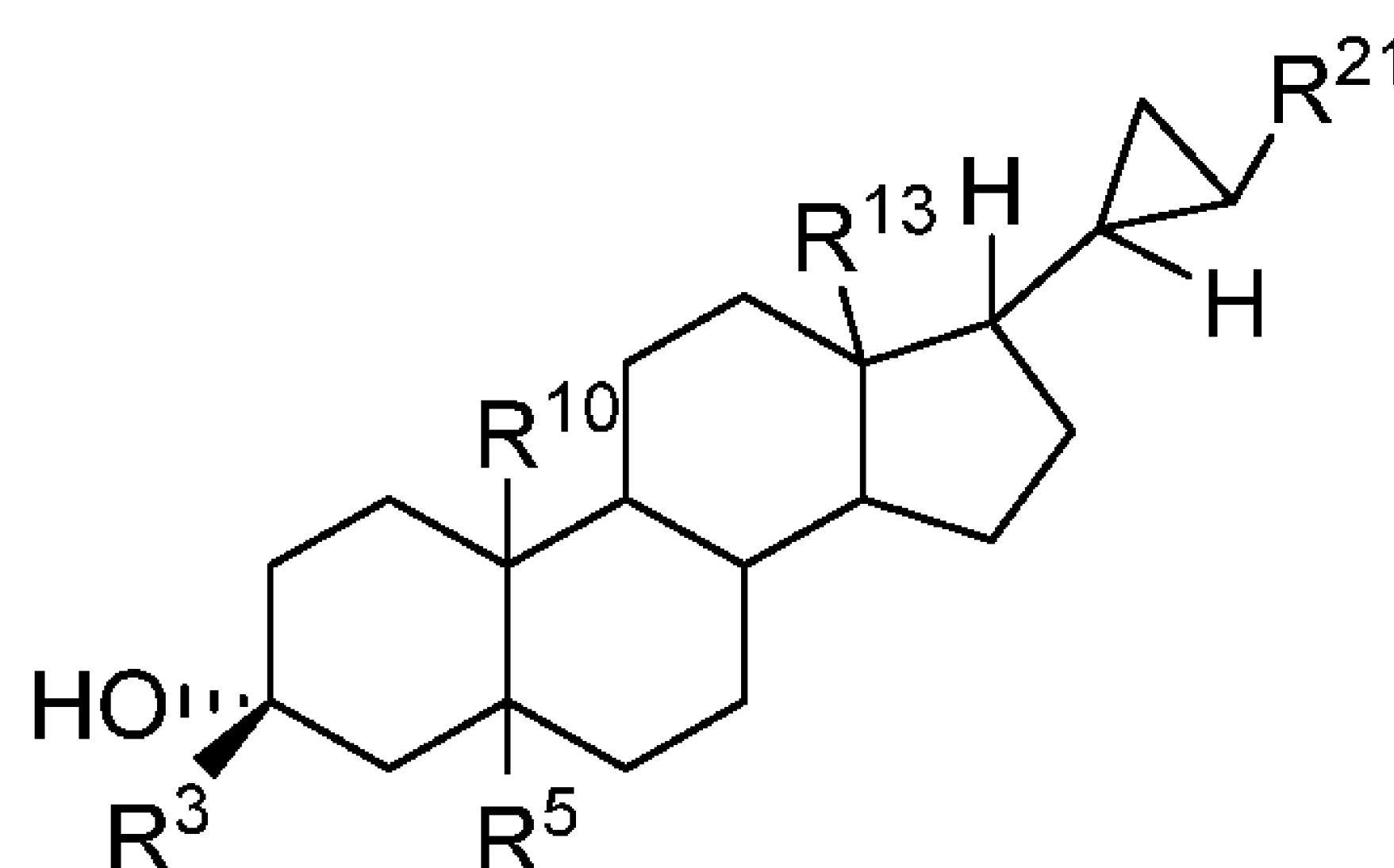
(VI-B3b),

or

or a pharmaceutically acceptable salt thereof, wherein R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^5 , R^{10} , R^{13} , R^{17} , R^{20c} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), or (VI-B1d), as applicable.

[0480] In some embodiments, each of R^{1a} , R^{1b} , R^{2a} , and R^{2b} is independently selected from $-H$ and C_{1-3} alkyl; R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; each of R^5 , R^{13} , R^{17} , and R^{20c} is independently selected from $-H$ and methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or a straight C_{1-3} alkylene chain; R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

[0481] Another aspect of the present invention provides a compound of Formula (VII)



(VII)

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I) or (VI).

[0482] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N,

O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

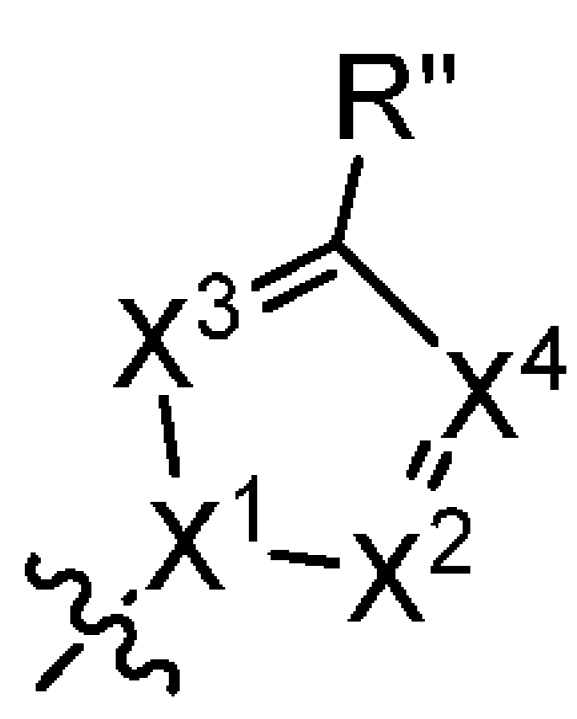
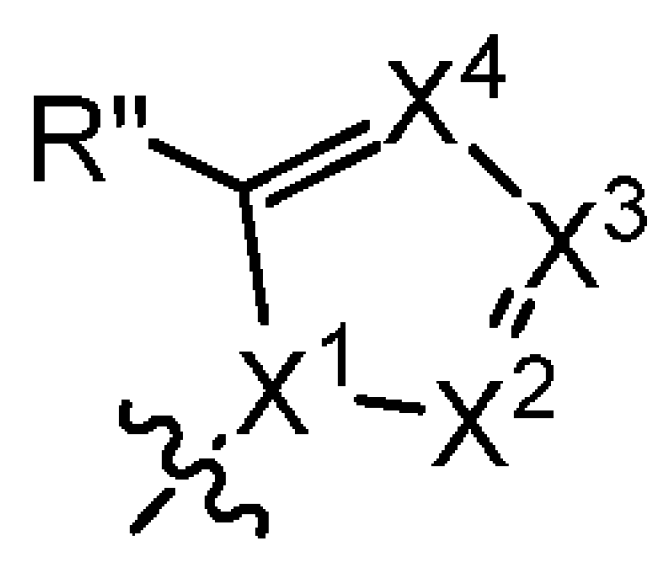
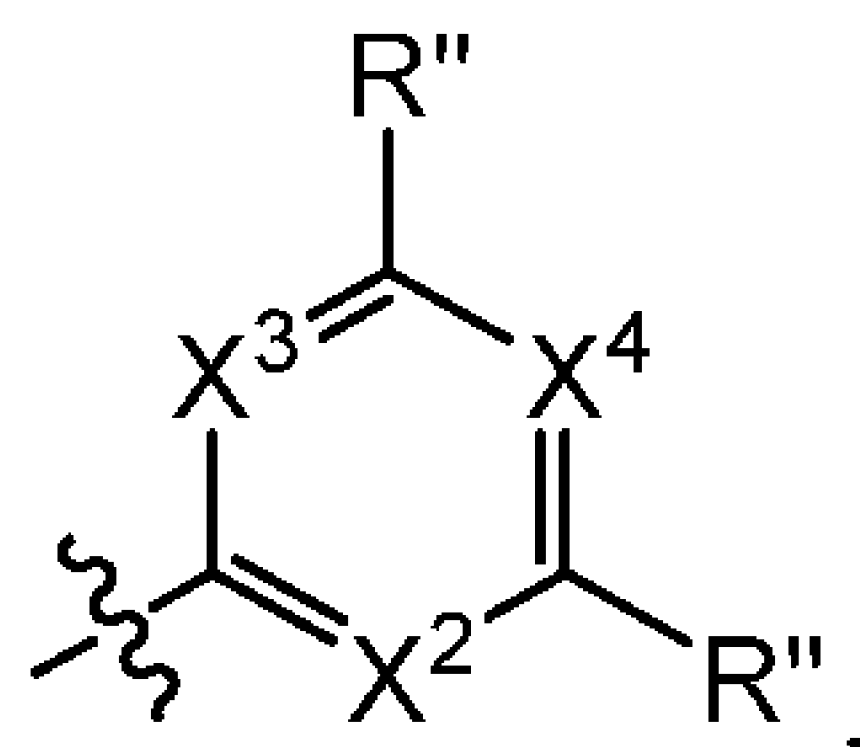
[0483] In some embodiments, R^3 is C_{1-6} alkyl or C_{1-6} alkyl- O - C_{1-6} alkyl. In some embodiments, R^3 is methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, neopentyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^3 is $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, or $-CH_2-O-CH_3$. And, in some embodiments, R^3 is $-CH_3$.

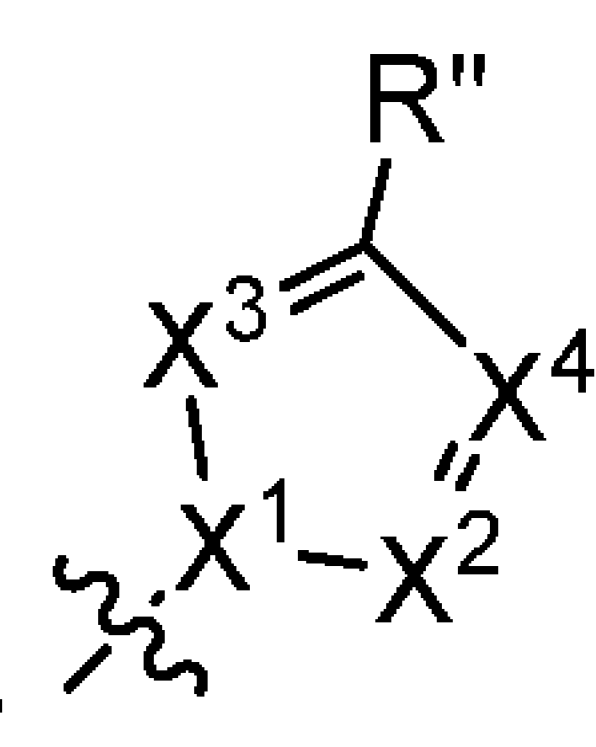
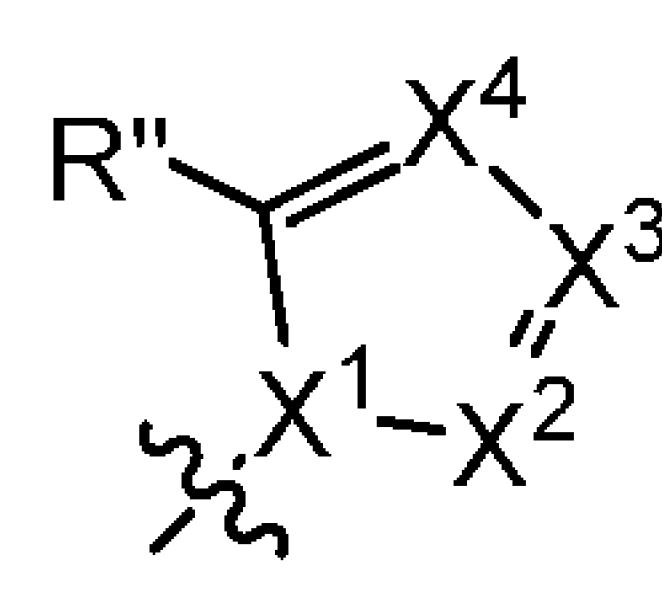
[0484] In some embodiments, R^5 is $-H$ or C_{1-3} alkyl. In some embodiments, R^5 is $-H$ or methyl.

[0485] In some embodiments, R^{10} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{10} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^{10} is $-H$ or methyl.

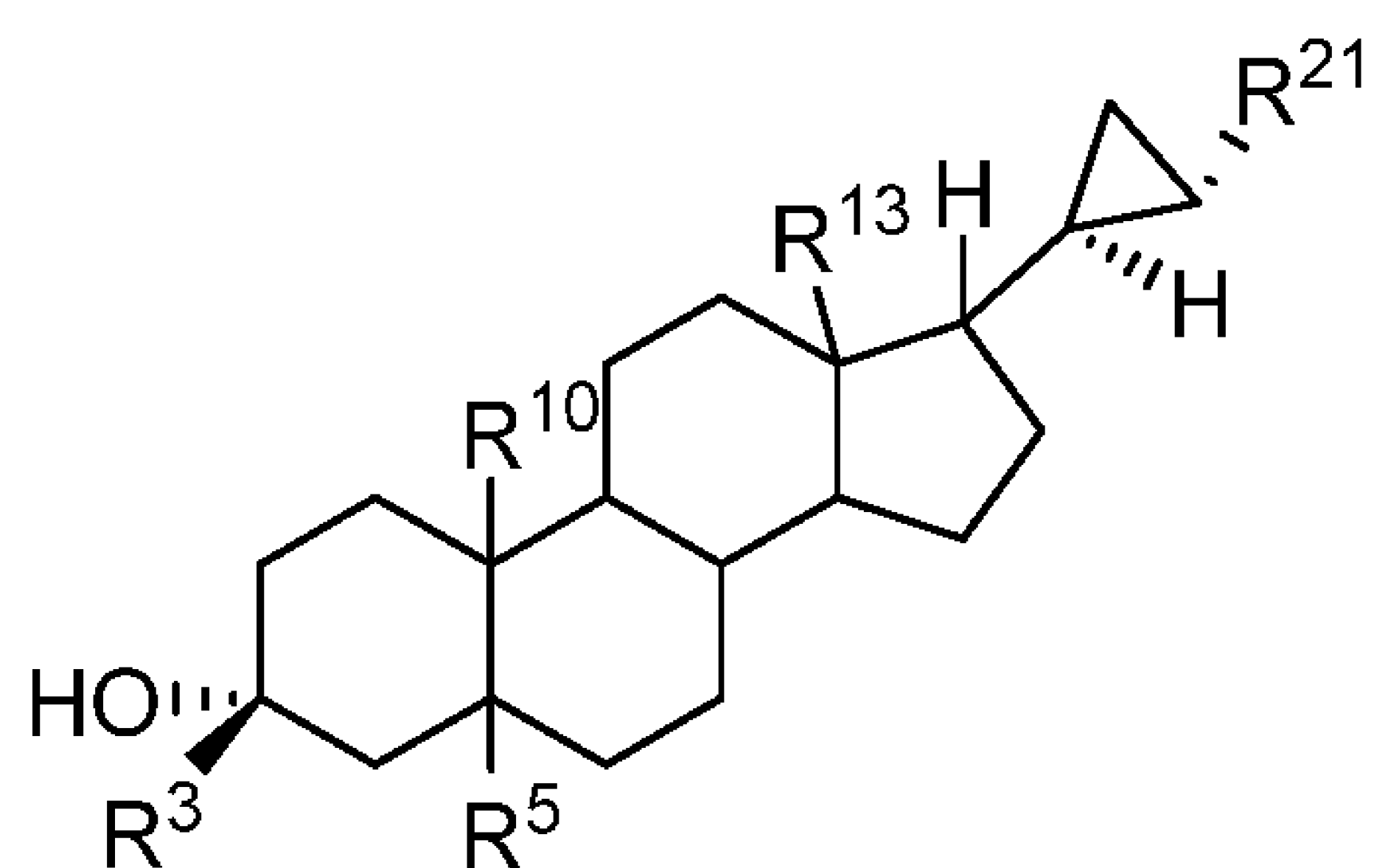
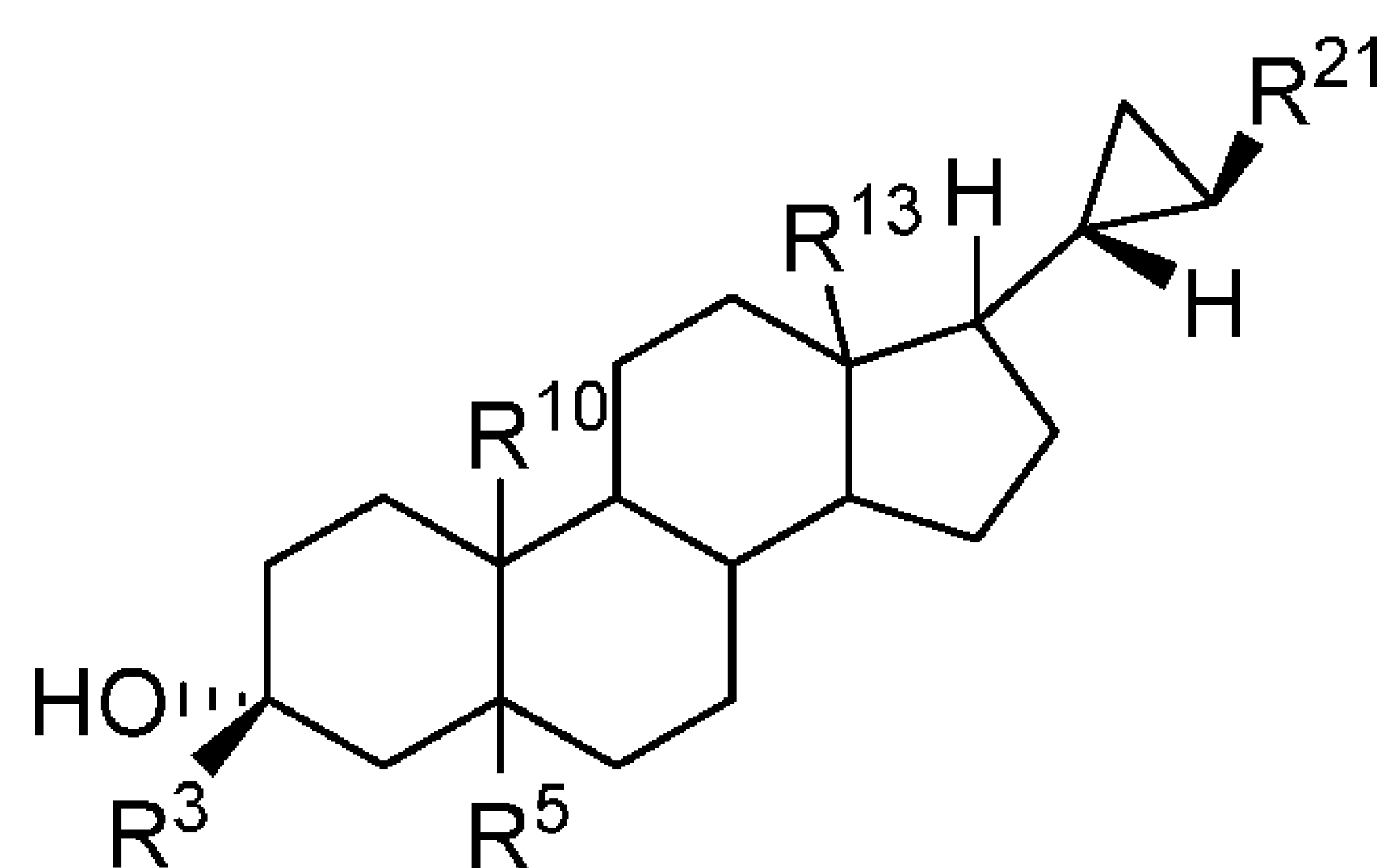
[0486] In some embodiments, R^{13} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{13} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl. In some embodiments, R^{13} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl. In some embodiments, R^{13} is $-H$ or methyl. And, in some embodiments, R^{13} is methyl.

[0487] In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-3} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, or $-N(H)-$; and R^{30} is $-H$ or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, or $-N(H)-$; and R^{30} is a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$. In some embodiments, R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, or

$-\text{N}(\text{H})-$; and R^{30} is , , or , wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some

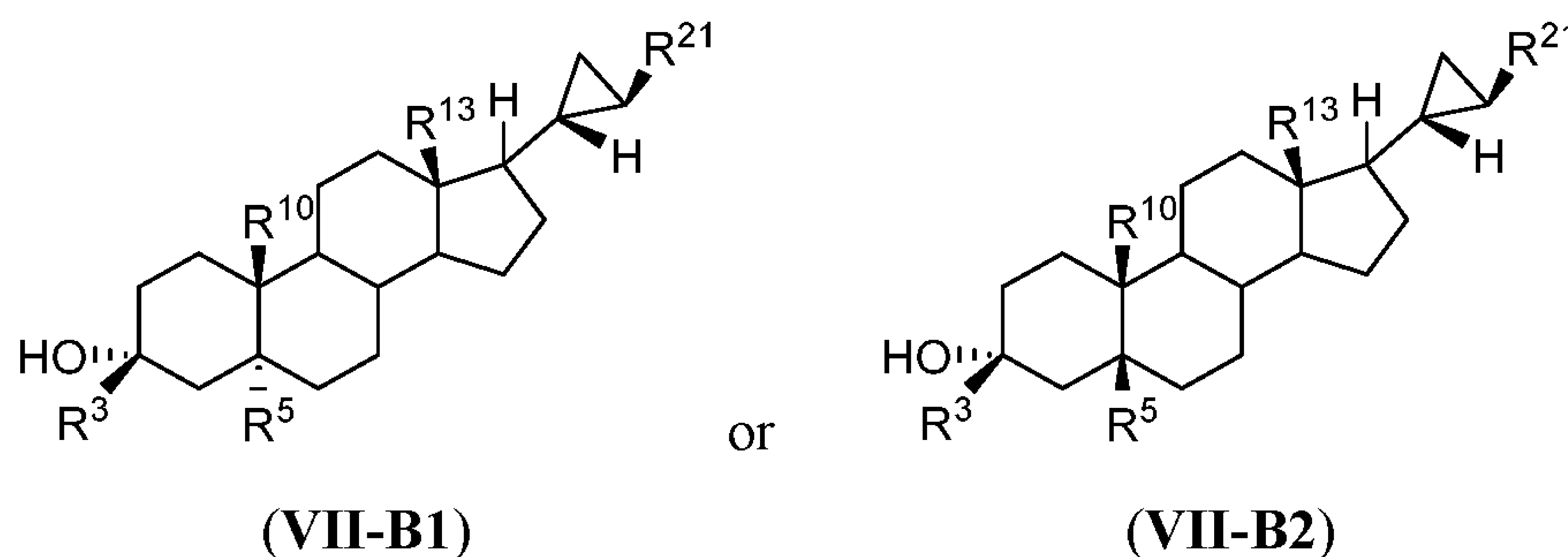
embodiments, R^{30} is  or , X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N and CR'' , wherein each R'' is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$, provided that no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least one of X^1 , X^2 , X^3 , and X^4 is N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N, and no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$. In some embodiments, at least two of X^1 , X^2 , X^3 , and X^4 are N and no greater than 1 instance of R'' is halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, or $-\text{CH}_2\text{OH}$.

[0488] Another aspect of the present invention provides a compound of Formula **(VII-A)** or **(VII-B)**

**(VII-A)** or**(VII-B)**

[0493] In some embodiments, R³ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; R⁵ is -H or methyl; R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; R¹³ is -H, or C₁₋₃ alkyl; R²¹ is -L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain; and R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃.

[0494] Another aspect of the present invention provides a compound of Formula **(VII-B1)** or **(VII-B2)**

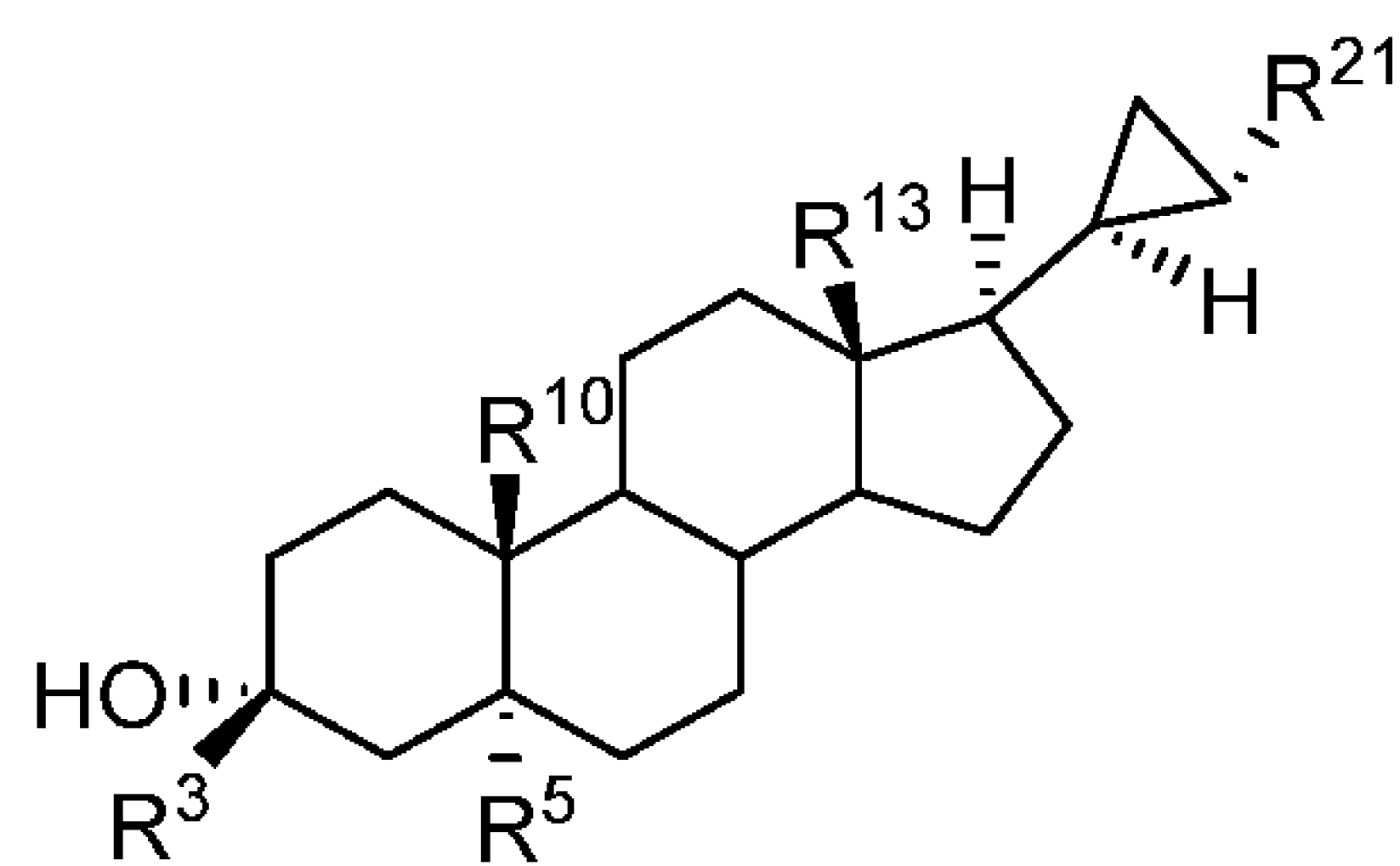


or a pharmaceutically acceptable salt thereof, wherein R³, R⁵, R¹⁰, R¹³, and R²¹ are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VII), or (VII-B).

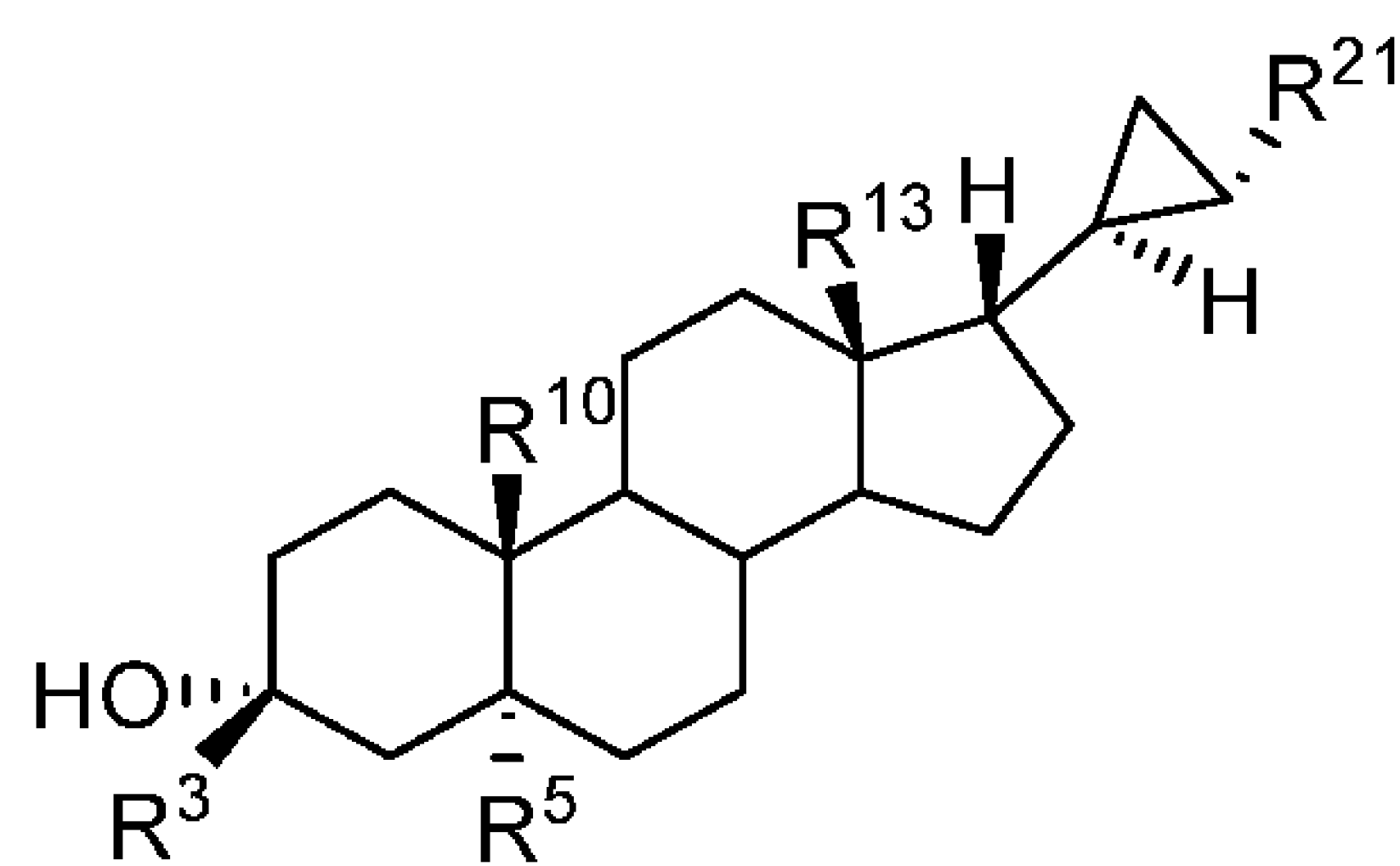
[0495] In some embodiments, R³ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl; R⁵ is -H or C₁₋₆ alkyl; each of R¹⁰ and R¹³ is independently selected from -H, C₁₋₆ alkyl, and C₁₋₆ alkyl-O-C₁₋₆ alkyl; R²¹ is -L^A-R³⁰; L^A is a bond, a branched or straight C₁₋₆ alkylene chain, or -N(H)-; and R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃.

[0496] In some embodiments, R³ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; R⁵ is -H or methyl; R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl; R¹³ is -H, or C₁₋₃ alkyl; R²¹ is -L^A-R³⁰; L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain; and R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃.

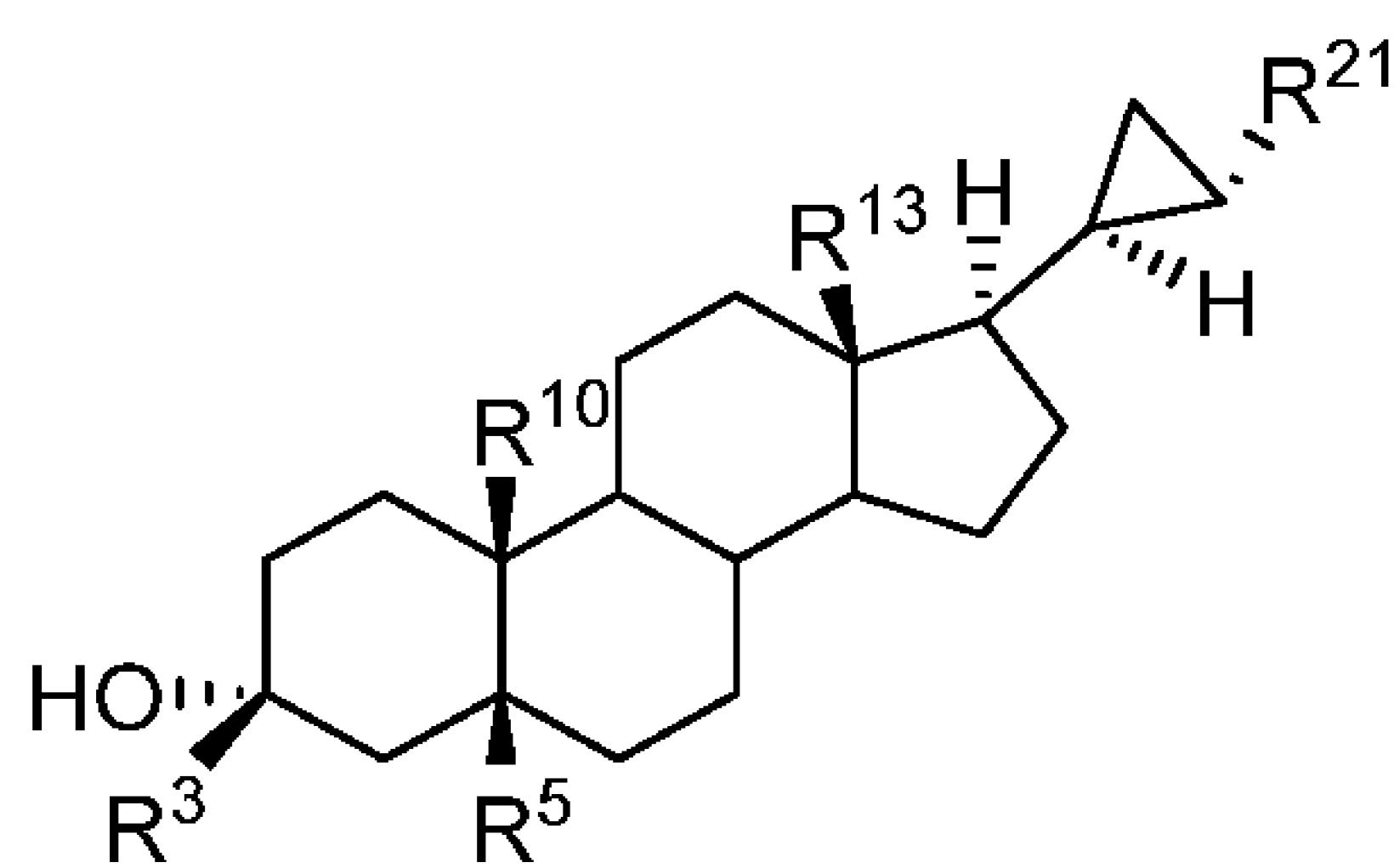
[0497] Another aspect of the present invention provides a compound of Formula (VII -A1a), (VII -A1b), (VII -A1c), or (VII -A1d)



(VII-A1a),

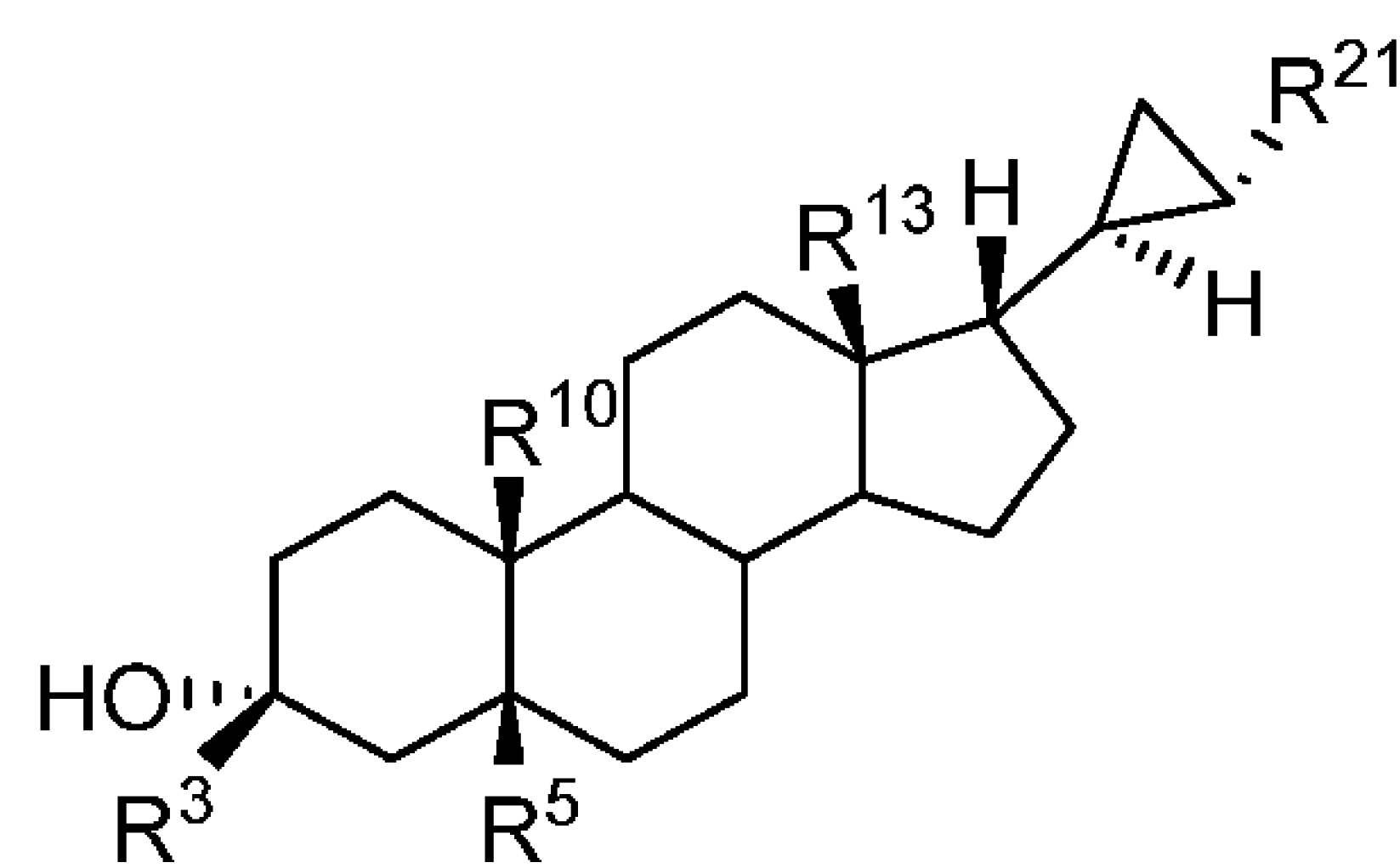


(VII-A1b),



(VII-A1c),

or



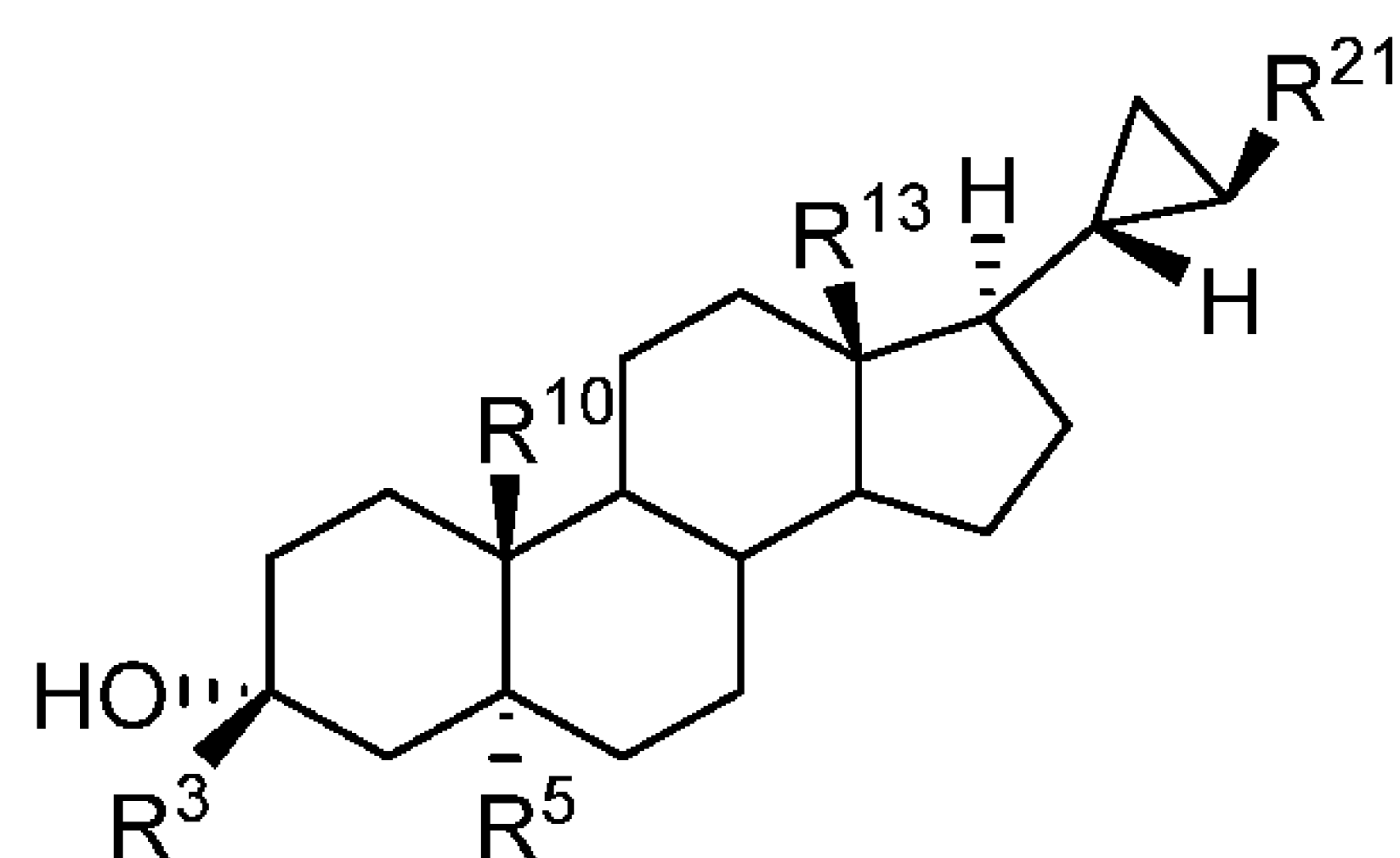
(VII-A1d),

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VII), (VII-A), (VII-A1), or (VII-A2).

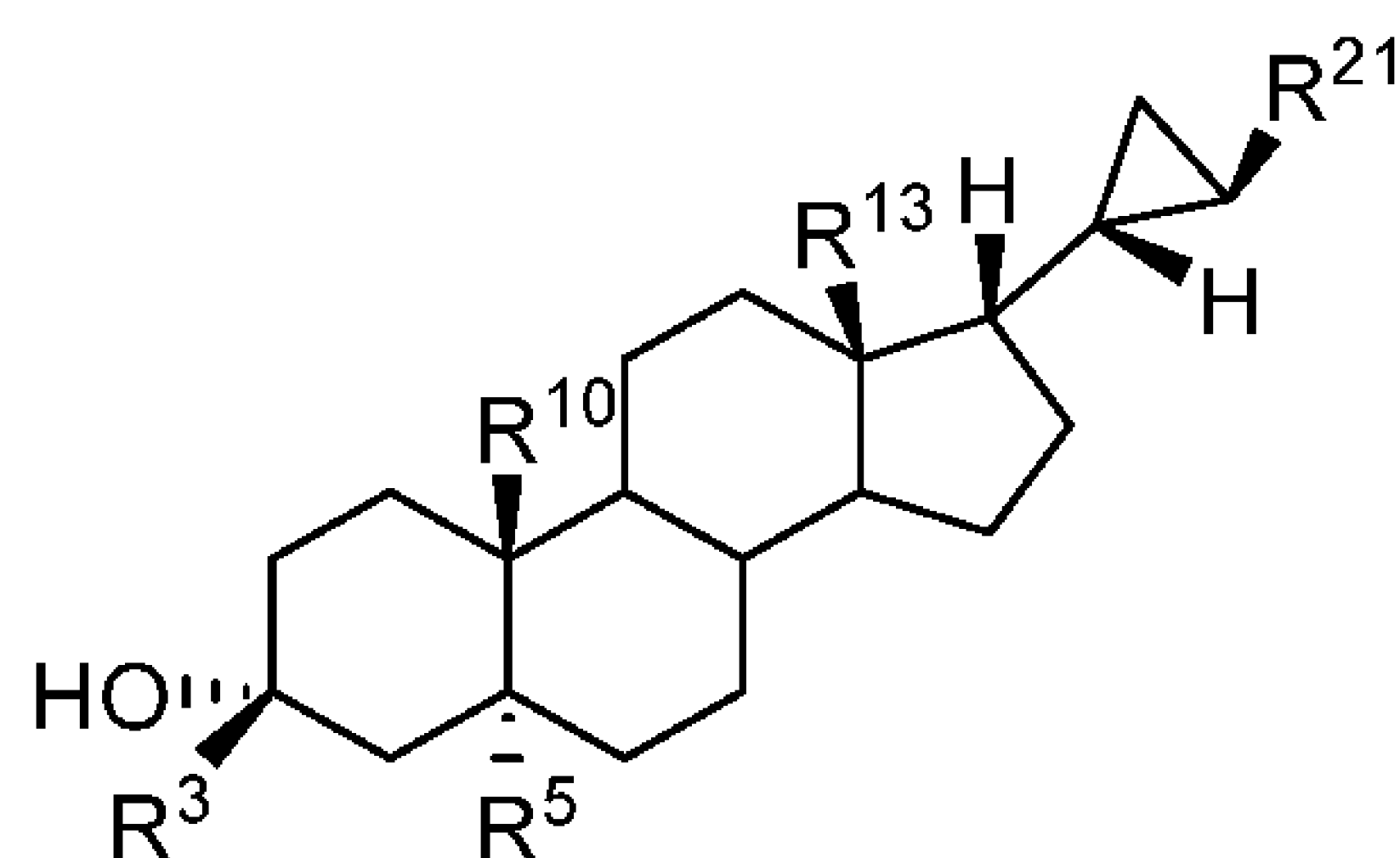
[0498] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0499] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$, or C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

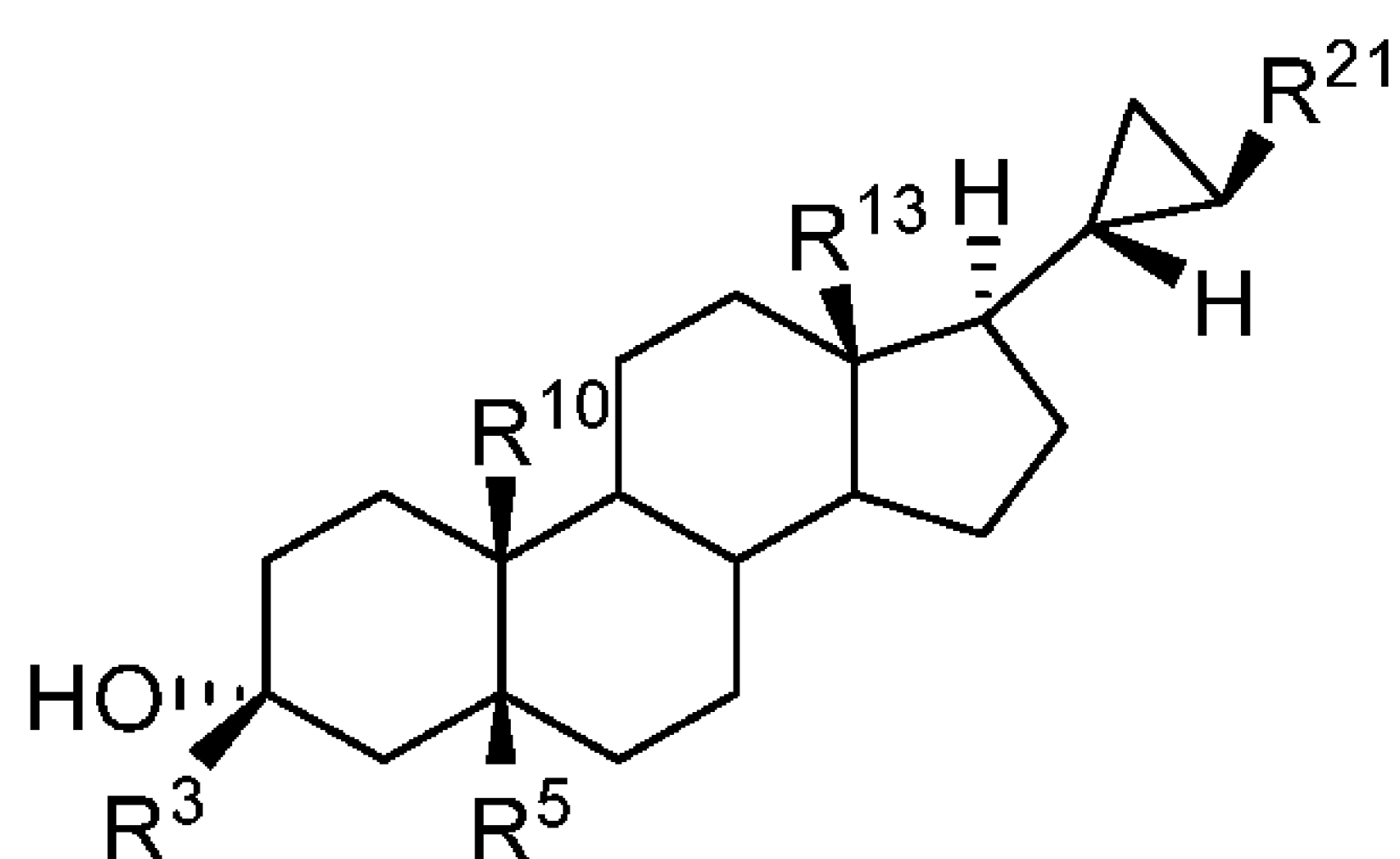
[0500] Another aspect of the present invention provides a compound of Formula (VII-B1a), (VII-B1b), (VII-B1c), or (VII-B1d)



(VII-B1a),

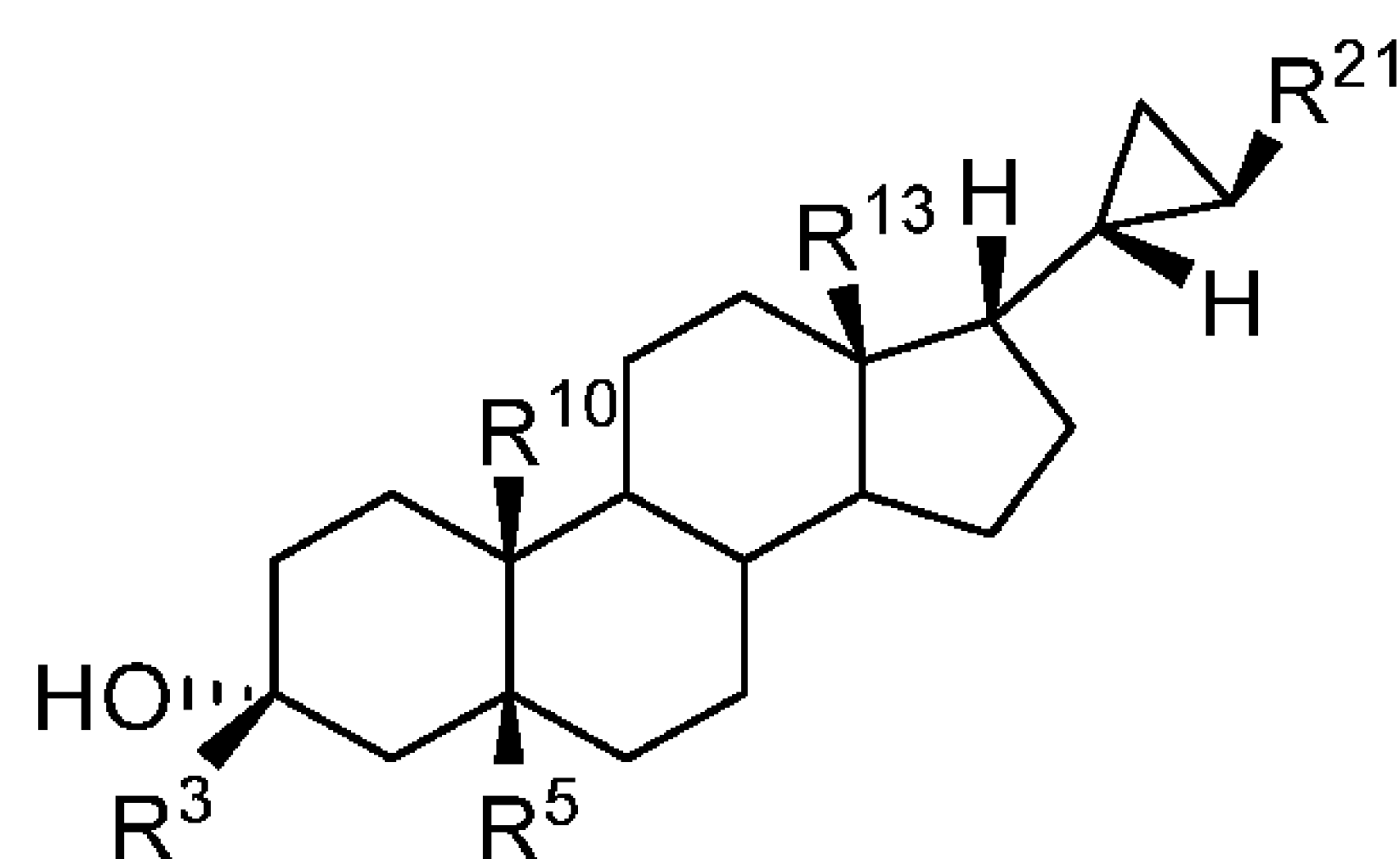


(VII-B1b),



(VII-B1c),

or



(VII-B1d),

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^5 , R^{10} , R^{13} , and R^{21} are as defined in any of the embodiments of the compounds of Formula (I), (VI), (VII), (VII-B), (VII-B1), or (VII-B2).

[0501] In some embodiments, R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl; R^5 is $-H$ or C_{1-6} alkyl; each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

[0502] In some embodiments, R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^5 is $-H$ or methyl; R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl; R^{13} is $-H$, or C_{1-3} alkyl; R^{21} is $-L^A-R^{30}$; L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain; and R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

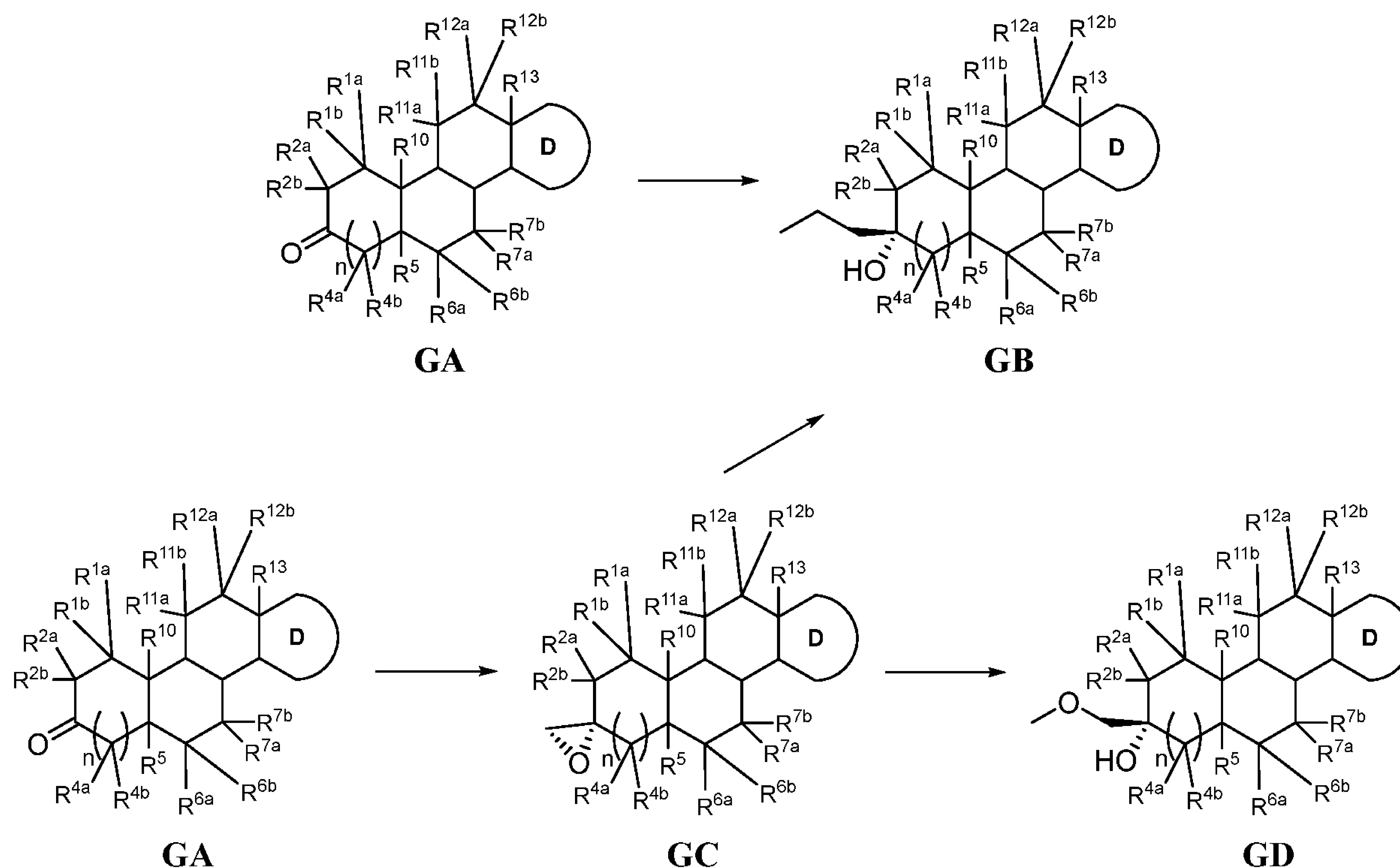
[0503] D. General Synthetic Schemes

[0504] Compounds of the present invention can be generated according to the following synthetic schemes. In the following general schemes, it will be understood that all variables used in the schemes carry the definition provide herein. As used in the general schemes, LG

means “leaving group” and PG means “protecting group”. Enantiomerically pure compounds of the general schemes are envisioned by the use of stereospecific reaction conditions or chiral resolution using methods known to those having skill in the art and/or detailed in the specific examples provided herein.

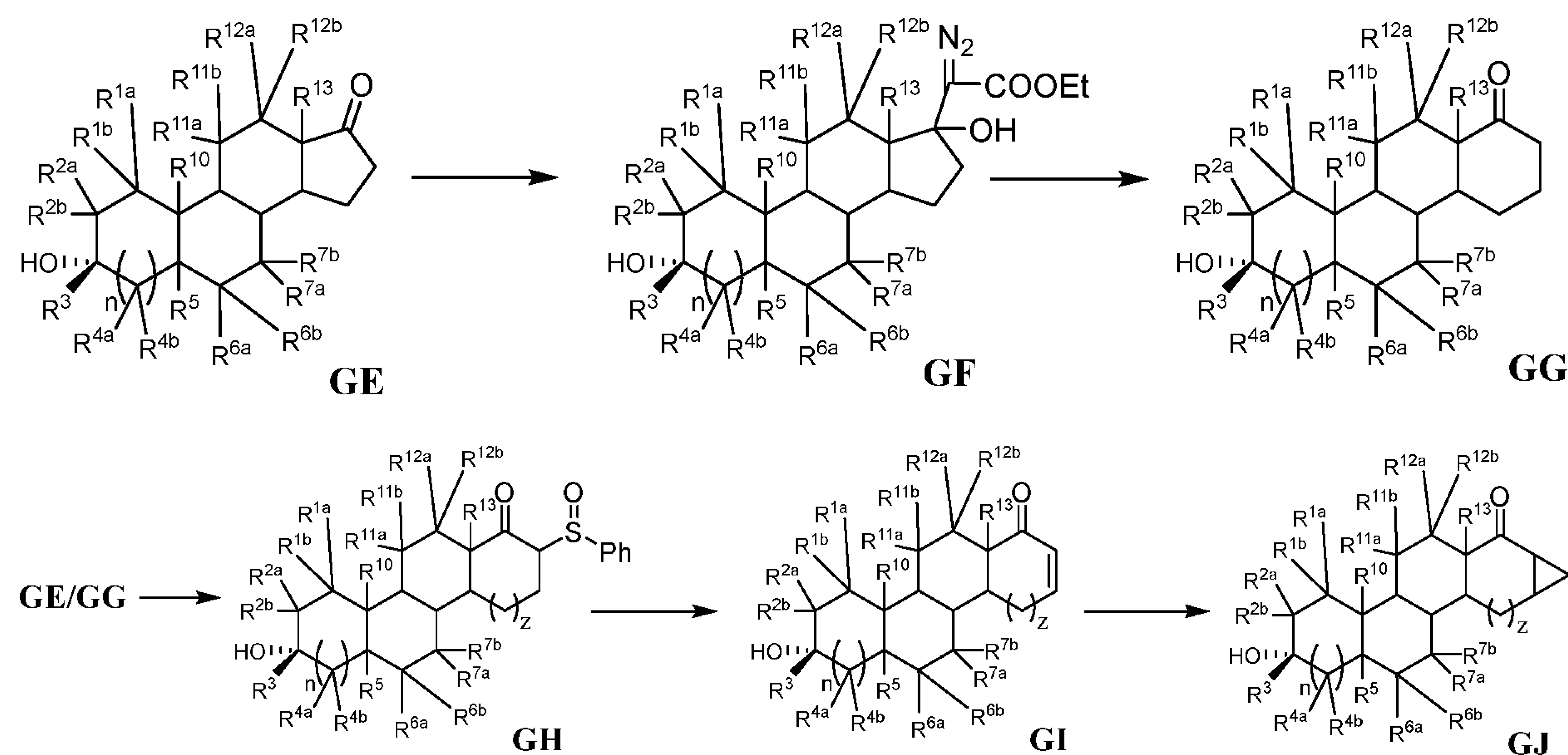
[0505] Compounds of the general formulas GB and GD can be made according to Scheme 1 below. Compounds of formula GA, with a carbonyl functionality on the C3 carbon of the steroid scaffold, can be purchased or made from the corresponding C3 alcohol through the use of an oxidizing agent such as the Dess–Martin periodinane (DMP). Compounds of formula GB can be made by direct exposure of a compound of formula GA with an alkyl magnesium bromide/chloride reagent (Grignard reagent), such as propylmagnesium bromide, as pictured in Scheme 1, or methylmagnesium bromide. Compounds of formula GB can also be made by first converting the C3 carbonyl group to an oxirane functionality to produce a compound of formula GC, followed by exposure to a Grignard reagent as detailed above. Compounds of the general formula GC can be made by the reaction of a compound of formula GA with an oxidizing agent such as trimethylsulfoxonium iodide (Me₃SOI) in the presence of a base. A compound of the general formula GC can also be converted to the corresponding alkoxymethyl compound by exposure to the appropriate alkoxide, such as methoxide pictured in Scheme 1.

[0506] Scheme 1: Synthesis of compounds of the general formula GD



[0507] Compounds of the general formula GE can be converted to compounds of formula GG, and then either a compound of formula GE or GG can be converted to a compound of formula GJ, wherein z is 0 or 1, according to Scheme 2. Compounds of formula GG can be made by first reacting a compound of formula GE with ethyl diazoacetate to produce a diazo compound of formula GF. The compound of formula GF can then be reacted with a reagent such as $\text{Rh}_2(\text{OAc})_4$ to achieve an intramolecular carbon insertion reaction to provide a compound of GG. Compounds of formula GE or GG can be converted to a compound of formula GJ, wherein z is 0 or 1, by first reacting with a reagent such as methyl benzenesulfinate in the presence of a base to provide an intermediate compound of formula GH, which can then be exposed to elimination conditions to provide a compound of formula GI. Treating a compound of formula GI with an oxidizing agent such as trimethylsulfoxonium iodide (Me_3SOI) in the presence of a base can provide a compound of formula GJ, which bears a fused cyclopropyl moiety.

[0508] Scheme 2: Synthesis of compounds of the general formula GJ



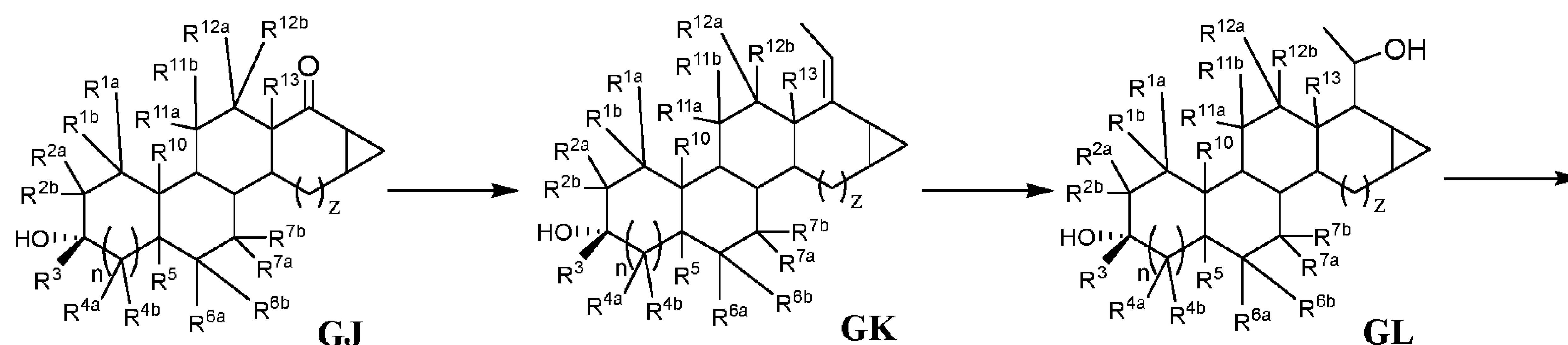
[0509] Compounds of the general formula GR and GS can be synthesized according to Scheme 3. A compound of formula GJ can be converted to a compound of GK by reacting with the reagent ethyltriphenylphosphenium bromide (EtPh_3PBr), or other analogous reagent, in the presence of a base. The resulting compound of formula GK can be converted into a secondary alcohol compound of formula GL using the appropriate borane reduction agent, optionally in the presence of hydrogen peroxide. Compounds of formula GL can be converted to ketone compounds of formula GM using an appropriate oxidizing agent such as DMP or pyridinium chlorochromate (PCC). Compounds of formula GN can be synthesized

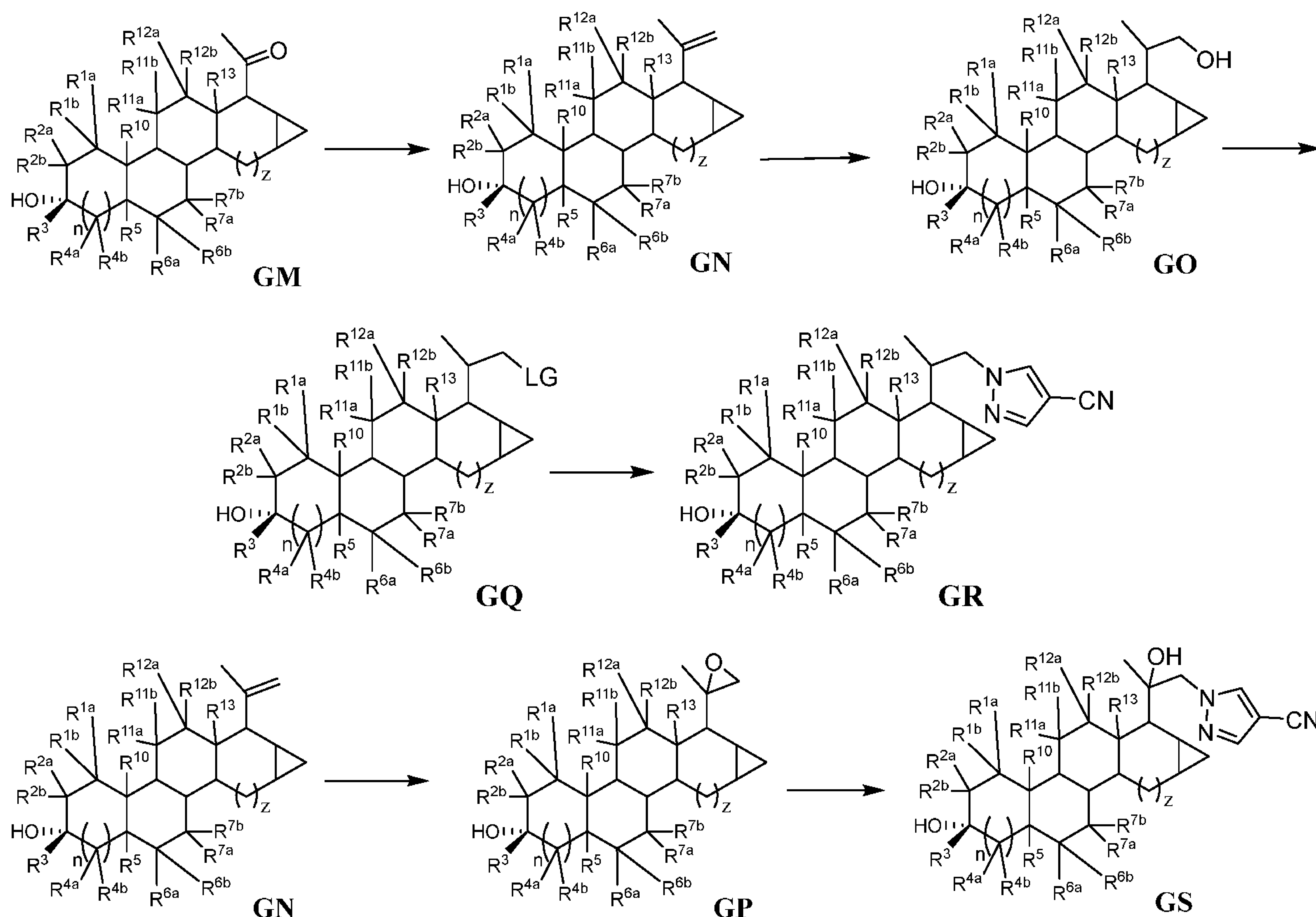
from compounds of formula GM by reacting with methyltriphenylphosphenium bromide (MePh₃PBr), or other analogous reagent, in the presence of a base.

[0510] Compounds of the formula GR can be synthesized from compounds of formula GN by first reacting a compound of formula GN with an appropriate borane reduction agent optionally in the presence of hydrogen peroxide, for example BH₃-Me₂S in the presence of hydrogen peroxide and sodium hydroxide, to provide a compound of formula GO. The alcohol functionality of the compound of formula GO can then be converted into a leaving group (LG) using methods known to those skilled in the art, for example by tosylation, mesylation, or triflation of the hydroxyl functionality, to form a compound of the formula GQ. The compound of formula GQ can be converted to a compound of formula GR by reacting with a nucleophilic compound, for example 4-cyanopyrazole as pictured in Scheme 3. It will be known that the number of nucleophilic compounds that could be used in this step to make compounds of formula GR are virtually limitless, and other specific examples are provided herein. Optionally, a compound of formula GO can be exposed to Mitsunobu conditions to provide a compound of formula GR, only forming the compound of formula GQ *in situ*.

[0511] Compounds of formula GS can be synthesized from compounds of formula GN by reacting with an appropriate oxidizing agent, such as m-CPBA or Me₃SOI, to provide oxirane compounds of formula GP. Compounds of formula GP can be converted to compounds of formula GS by reacting with a nucleophilic compound, for example 4-cyanopyrazole as pictured in Scheme 3. As stated above, it will be known that the number of nucleophilic compounds that could be used in this step to make compounds of formula GS are virtually limitless, and other specific examples are provided herein.

[0512] Scheme 3: Synthesis of compounds of the general formulas GR and GS





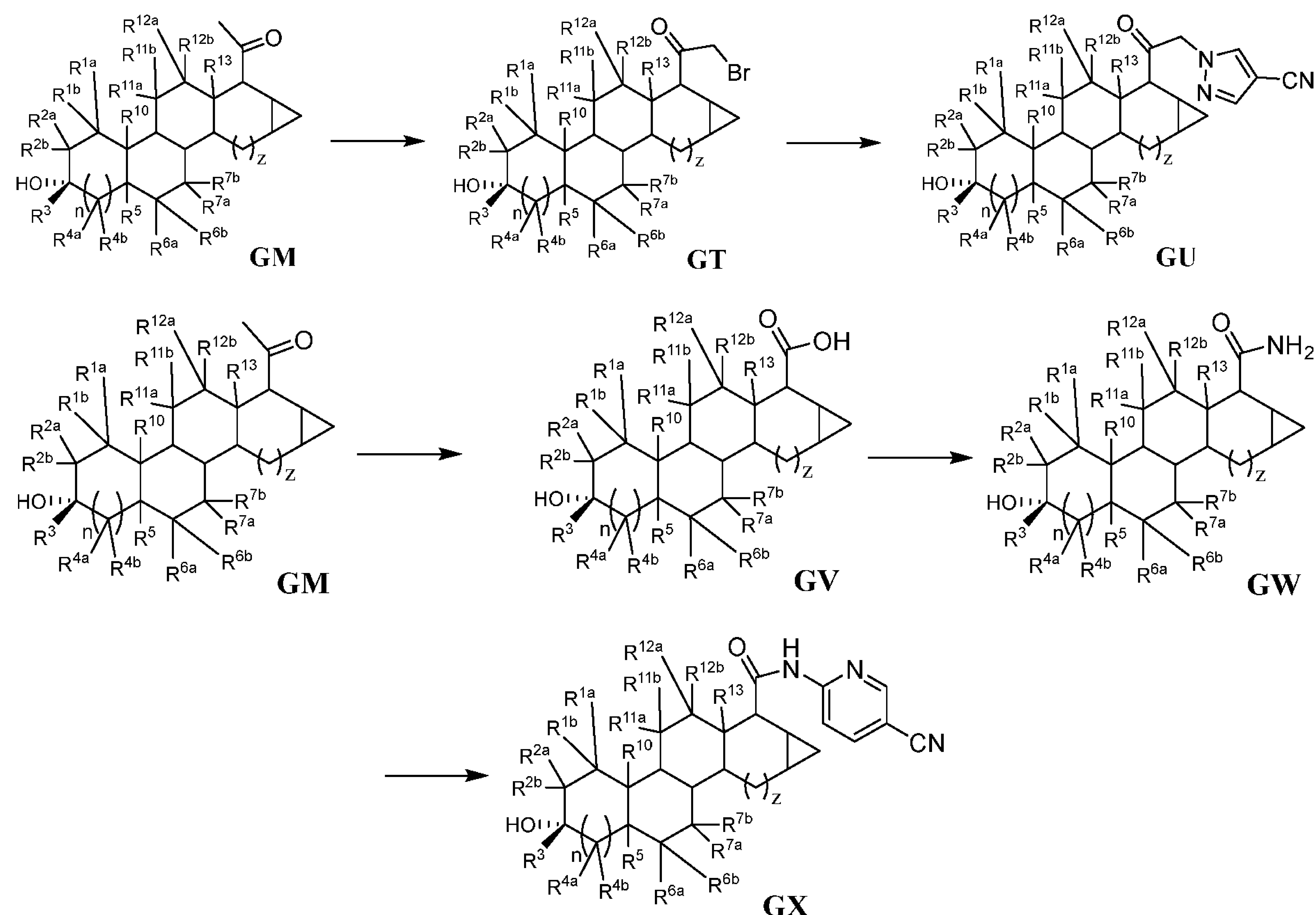
[0513] Compounds of formula GU and GX can be synthesized according to Scheme 4.

[0514] Compounds of formula GU can be synthesized by first reacting a compound of formula GM with a brominating agent, such as molecular bromide in the presence of HBr to provide a compound of formula GT. Reacting a compound of GT with a nucleophilic compound, for example 4-cyanopyrazole as pictured in Scheme 3, provides a compound of formula GU. As stated above, it will be known that the number of nucleophilic compounds that could be used in this step to make compounds of formula GU are virtually limitless, and other specific examples are provided herein.

[0515] Compounds of formula GX can be synthesized by first reacting a compound of GM with molecular bromide in the presence of sodium hydroxide under aqueous conditions to provide a carboxylic acid compound of the formula GV. Conversion of the carboxylic acid functionality of the compound of formula GV to the corresponding carboxamide of formula GW can be accomplished by reacting with ammonium chloride under coupling conditions, or alternatively by first converting the carboxylic acid to the acid chloride and then reacting with ammonium chloride in the presence of a base. Reacting the resulting compound of formula GW with an aryl compound under coupling conditions, such as palladium catalyzed coupling conditions, provides the compound of formula GX. It will be known that the number of aryl

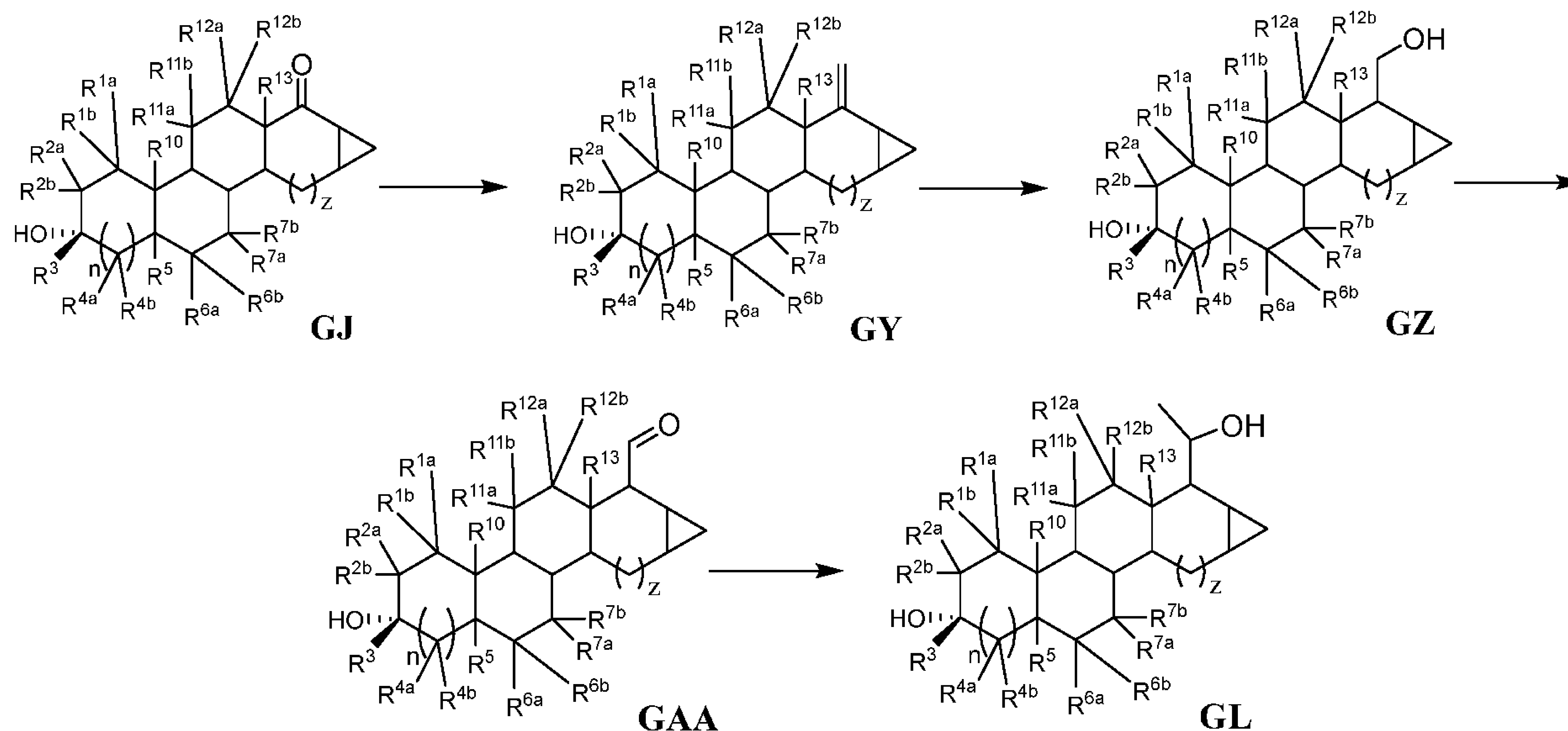
compounds that could be used in the coupling step to make compounds of formula GX are virtually limitless.

[0516] Scheme 4: Synthesis of compounds of the general formulas GU and GX



[0517] Intermediate compounds of formula GL can alternatively be synthesized according to Scheme 5 below. Compounds of formula GL can be synthesized by first reacting a compound of formula GJ with TMSCH₂Li, or other analogous reagent to provide a compound of formula GY. Reacting a compound of formula GY with an appropriate borane reduction agent, optionally in the presence of hydrogen peroxide, for example BH₃-Me₂S in the presence of hydrogen peroxide and sodium hydroxide, can provide a compound of formula GZ. The resulting compound of formula GZ can then be oxidized, using an oxidizing reagent such as DMP, to provide an aldehyde compound of formula GAA, which can then be treated with an alkylmagnesium bromide reagent, such as methylmagnesium bromide as pictured in Scheme 5, to provide a compound of formula GL.

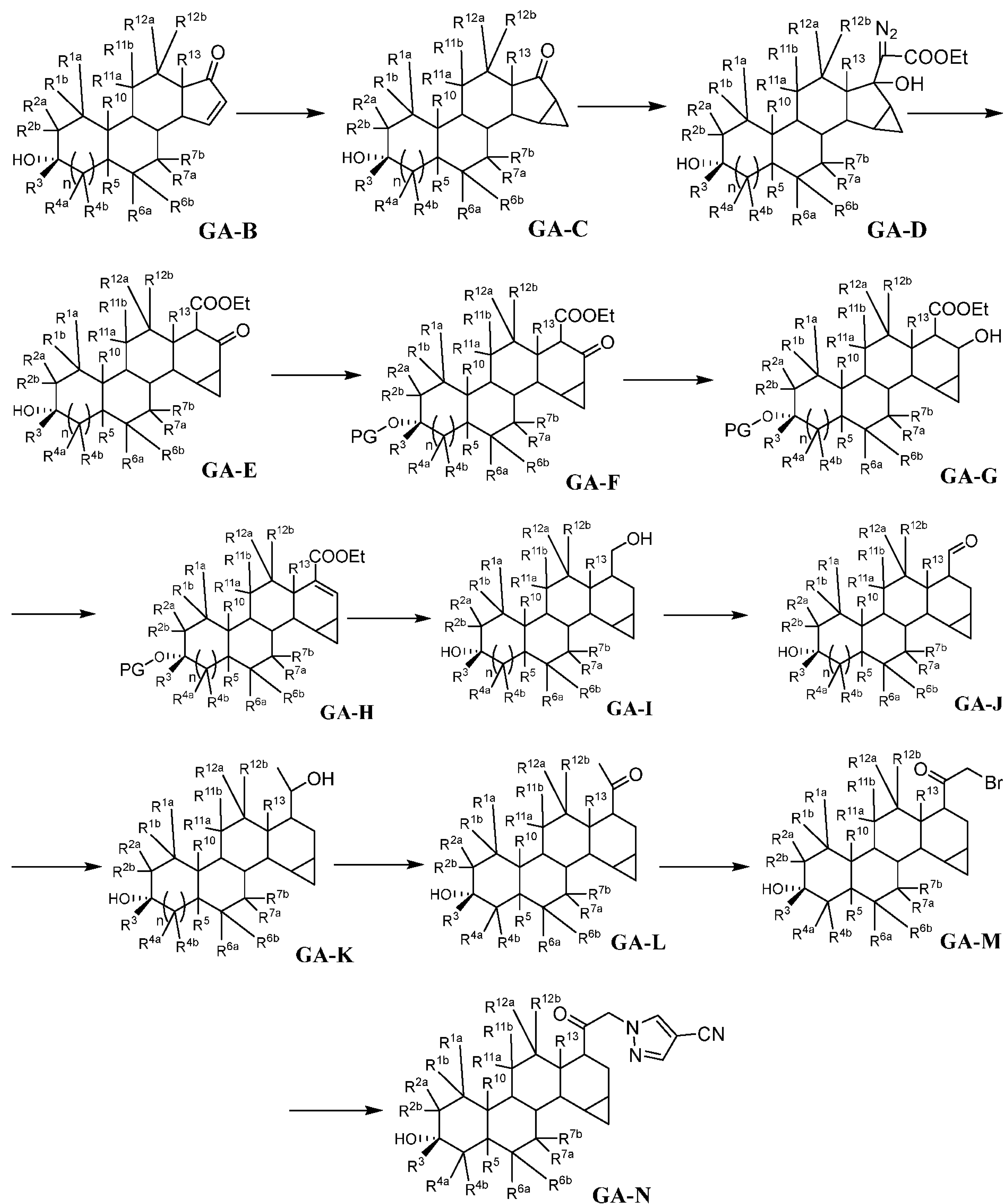
[0518] Scheme 5: Alternative synthesis of intermediate compounds of the general formula GL



[0519] Compounds of the general formula GA-N can be synthesized according to Scheme 6 below. Compounds of formula GA-B can be treated with an oxidizing agent such as trimethylsulfoxonium iodide (Me_3SOI) in the presence of a base to provide compounds of formula GA-C, which bears a fused cyclopropyl moiety. The resulting compounds of GA-C can then be treated with ethyl diazoacetate to produce diazo compounds of formula GA-D. A compound of formula GA-D can then be reacted with a reagent such as $\text{Rh}_2(\text{OAc})_4$ to achieve an intramolecular carbon insertion reaction to provide a compound of GA-E. Protecting a compound of formula GA-E using methods known to those having skill in the art results in a compound of formula GA-F, which can then be reduced to a β -hydroxy compound of formula GA-G. Conversion of the hydroxyl moiety of a compound of formula GA-G to a sulfonate compound with a reagent such as methanesulfonyl chloride in the presence of a base provides an elimination product compound of formula GA-H. Reduction of a compound of formula GA-H, and removal of the protecting group results in a primary alcohol compound of formula GA-I. Oxidation of the compound of formula GA-I to the aldehyde compound of formula GA-J, and subsequent treatment with an alkylmagnesium bromide reagent, such as methylmagnesium bromide as pictured in Scheme 6, provides a compound of formula GA-K. Oxidation of the secondary alcohol functionality of a compound of formula GA-K using an oxidizing agent such as DMP, provides a ketone compound of GA-L, which can then be brominated using a brominating reagent such as molecular bromine in the presence of HBr, or the like, to provide a compound of formula GA-M. Compounds of formula GA-M can be

converted to compounds of formula GA-N by reacting with a nucleophilic compound, for example 4-cyanopyrazole as pictured in Scheme 6. As stated above, it will be known that the number of nucleophilic compounds that could be used in this step to make compounds of formula GA-N are virtually limitless.

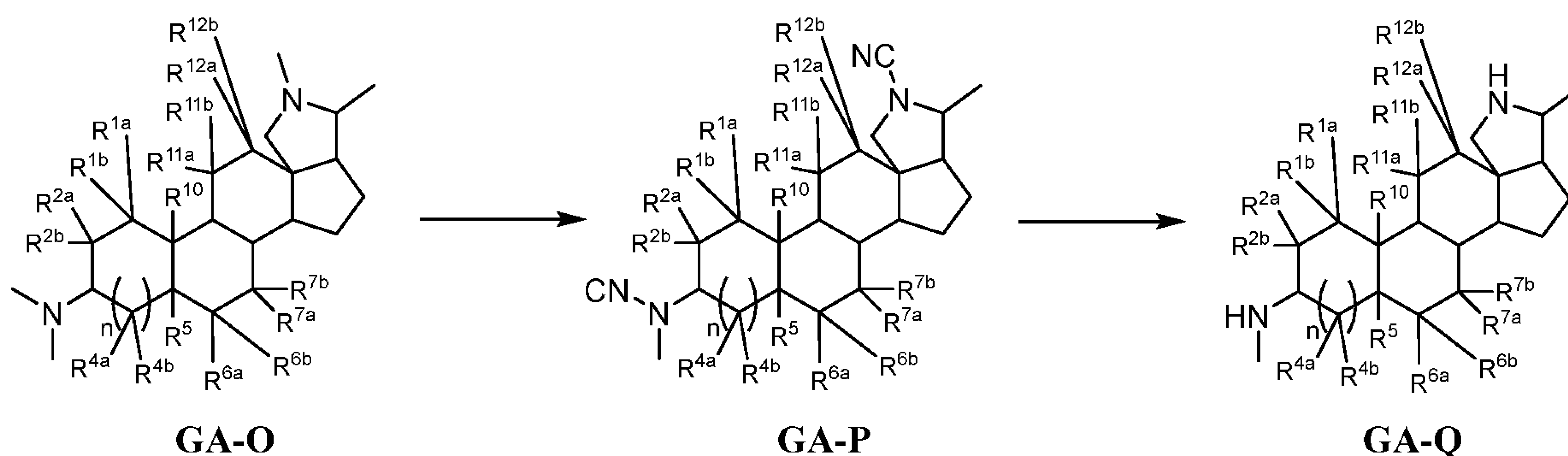
[0520] Scheme 6: Synthesis of compounds of the general formula GA-N

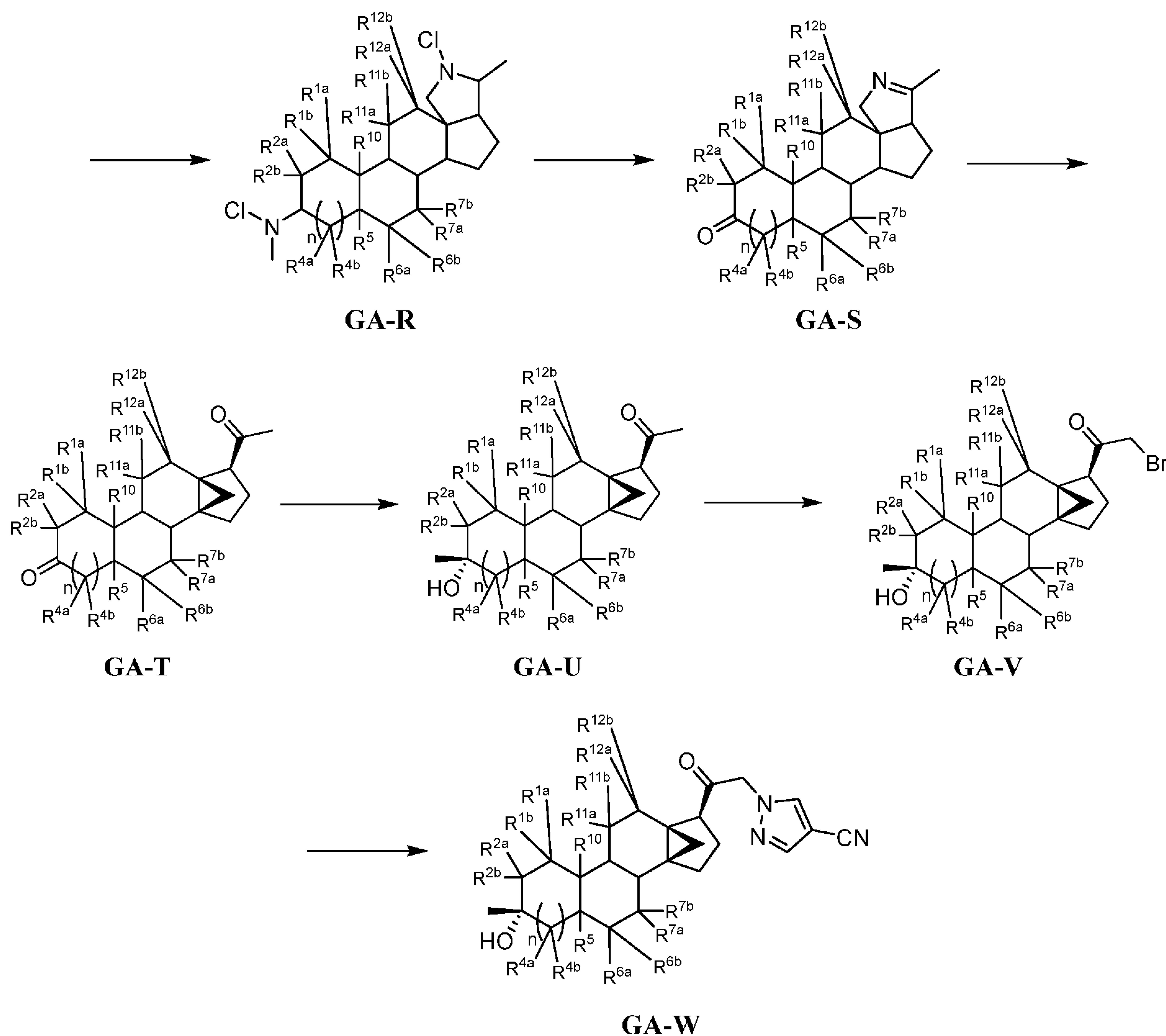


[0521] Compounds of the general formula GA-W can be made from starting material GA-O according to Scheme 7. If starting material has any unsaturation, the compound of formula GA-O can be achieved by reduction with an appropriate reducing agent, such as hydrogen with a palladium catalyst. A compound of formula GA-O can then be reacted with BrCN, or an equivalent reagent, to produce a bis-cyano compound of formula GA-P. The compound of formula GA-P can then be exposed to aqueous hydroxide conditions to remove the cyano group and produce a compound of formula GA-Q. The overall transformation from the compound of formula GA-O to the compound of formula GA-Q being the loss of methyl groups on all methylamino moieties of the compound. The compound of formula GA-Q can then be reacted with N-chlorosuccinimide to produce a bis-N-chloro compound of formula GA-R, which can then be transformed to a compound of formula GA-S when exposed to methoxide/methanol conditions. The ring-opening and cyclopropane formation necessary to produce a compound of formula GA-T can be achieved by reacting a compound of formula GA-S with NaNO₂, or a functionally equivalent reagent. A compound of formula GA-U can be made by direct exposure of a compound of formula GA-T with an alkyl magnesium bromide/chloride reagent (Grignard reagent), such as methylmagnesium bromide, as pictured in Scheme 7, to react with the carbonyl functionality on C3.

[0522] Compounds of formula GA-W can be synthesized by first reacting a compound of formula GA-U with a brominating agent, such as molecular bromide in the presence of HBr to provide a compound of formula GA-V. Reacting a compound of GA-V with a nucleophilic compound, for example 4-cyanopyrazole as pictured in Scheme 7, provides a compound of formula GA-W. It will be known that the number of nucleophilic compounds that could be used in this step to make compounds of formula GA-W are virtually limitless, and other specific examples can be envisioned, such as a tetrazole-based nucleophile.

[0523] Scheme 7: Synthesis of compounds of the general formula GA-W



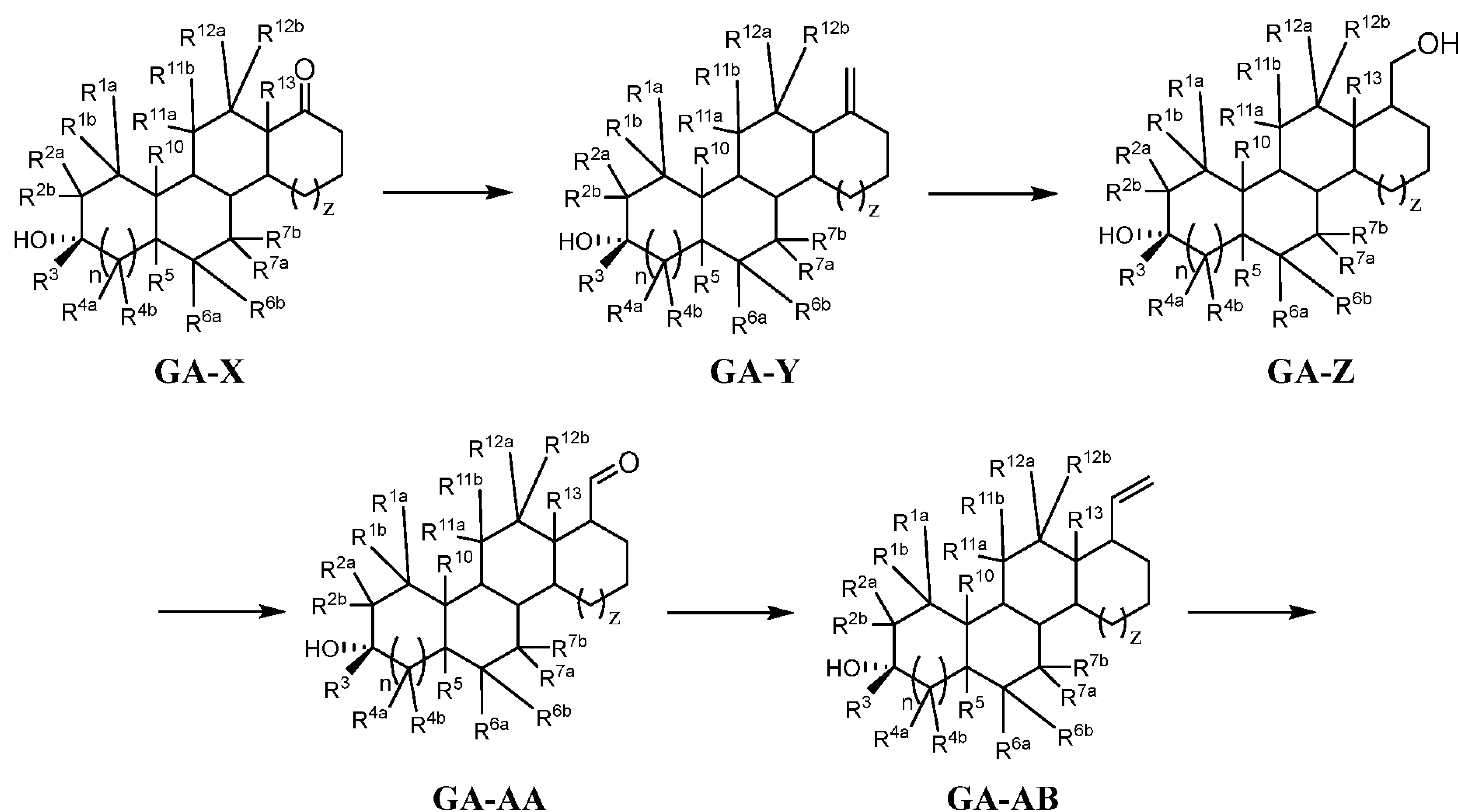


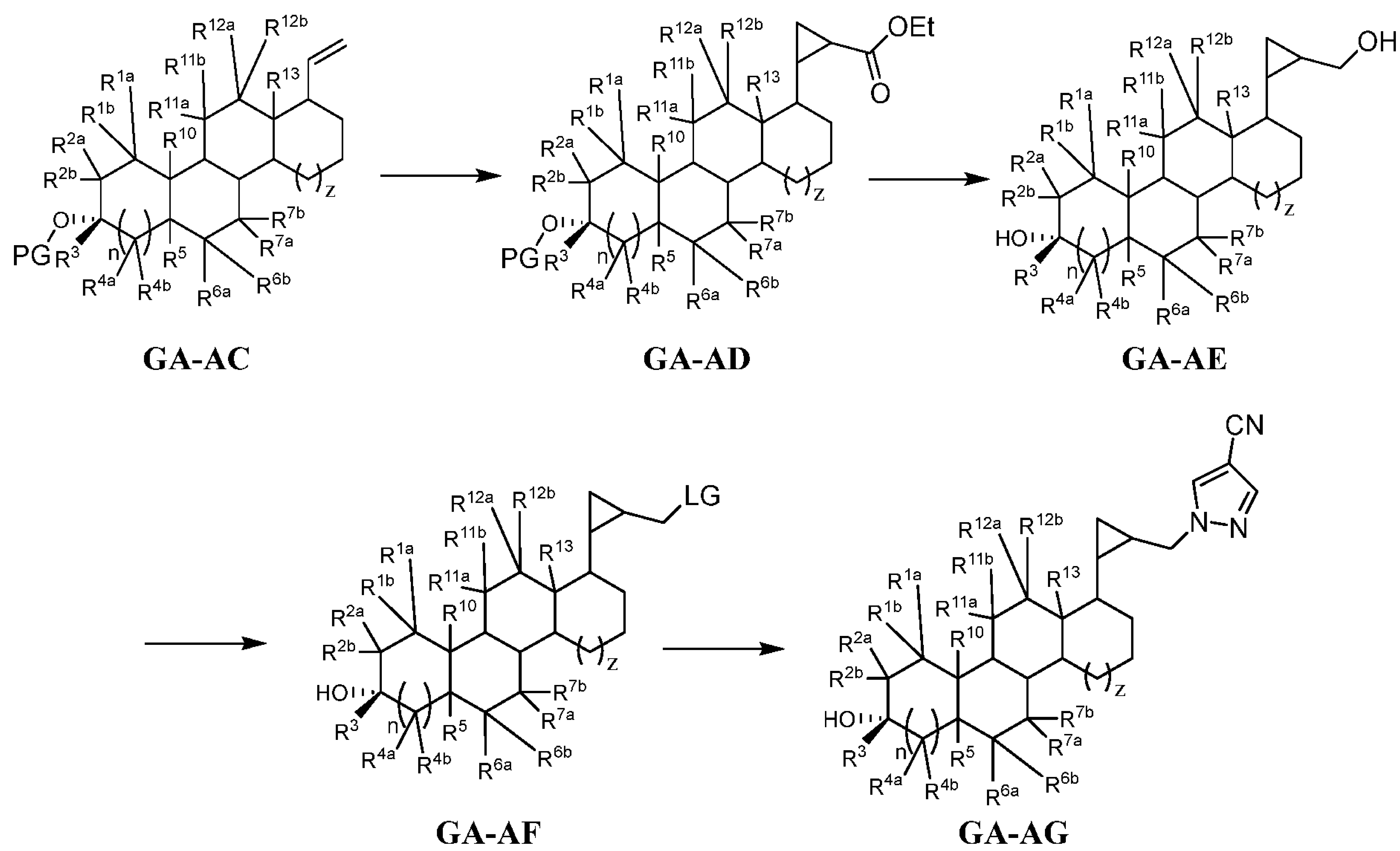
[0524] Compounds of formula GK, wherein z is 0 or 1, can be synthesized according to Scheme 8 below, by first reacting a compound of formula GA-X with methyltriphenylphosphenium bromide (MePh₃PBr), or other analogous reagent to provide a compound of formula GA-Y. Reacting a compound of formula GA-Y with an appropriate borane reduction agent, optionally in the presence of hydrogen peroxide, for example 9-BBN dimer in the presence of hydrogen peroxide and sodium hydroxide, can provide a compound of formula GA-Z. The resulting compound of formula GA-Z can then be oxidized, using an oxidizing reagent such as pyridinium chlorochromate (PCC), to provide an aldehyde compound of formula GA-AA, which can then be treated again with methyltriphenylphosphenium bromide (MePh₃PBr), or other analogous reagent to form an olefin from the aldehyde functionality and provide a compound of formula GA-AB. A compound of formula GA-AD can be synthesized by first protecting the alcohol functionality on C3 of a compound of formula GA-AB using methods known to those having skill in the

art to provide a compound of formula GA-AC, and then contacting the compound of formula GA-AC with ethyl diazoacetate in the presence of rhodium (ii) acetate dimer to form a cyclopropyl moiety from the olefin functionality and provide the compound of formula GA-AD. A compound of formula GA-AD can then be reduced and deprotected to provide a compound of formula GA-AE.

[0525] The alcohol functionality of the compound of formula GA-AE can then be converted into a leaving group (LG) using methods known to those skilled in the art, for example by tosylation, mesylation, or triflation of the hydroxyl functionality, to form a compound of the formula GA-AF. The compound of formula GA-AF can be converted to a compound of formula GA-AG by reacting with a nucleophilic compound, for example 4-cyanopyrazole as pictured in Scheme 8. It will be known that the number of nucleophilic compounds that could be used in this step to make compounds of formula GA-AG are virtually limitless, and other specific examples are envisioned. Optionally, a compound of formula GA-AE can be exposed to Mitsunobu conditions to provide a compound of formula GA-AG, only forming the compound of formula GA-AF *in situ*.

[0526] Scheme 8: Synthesis of compounds of the general formula GA-AG

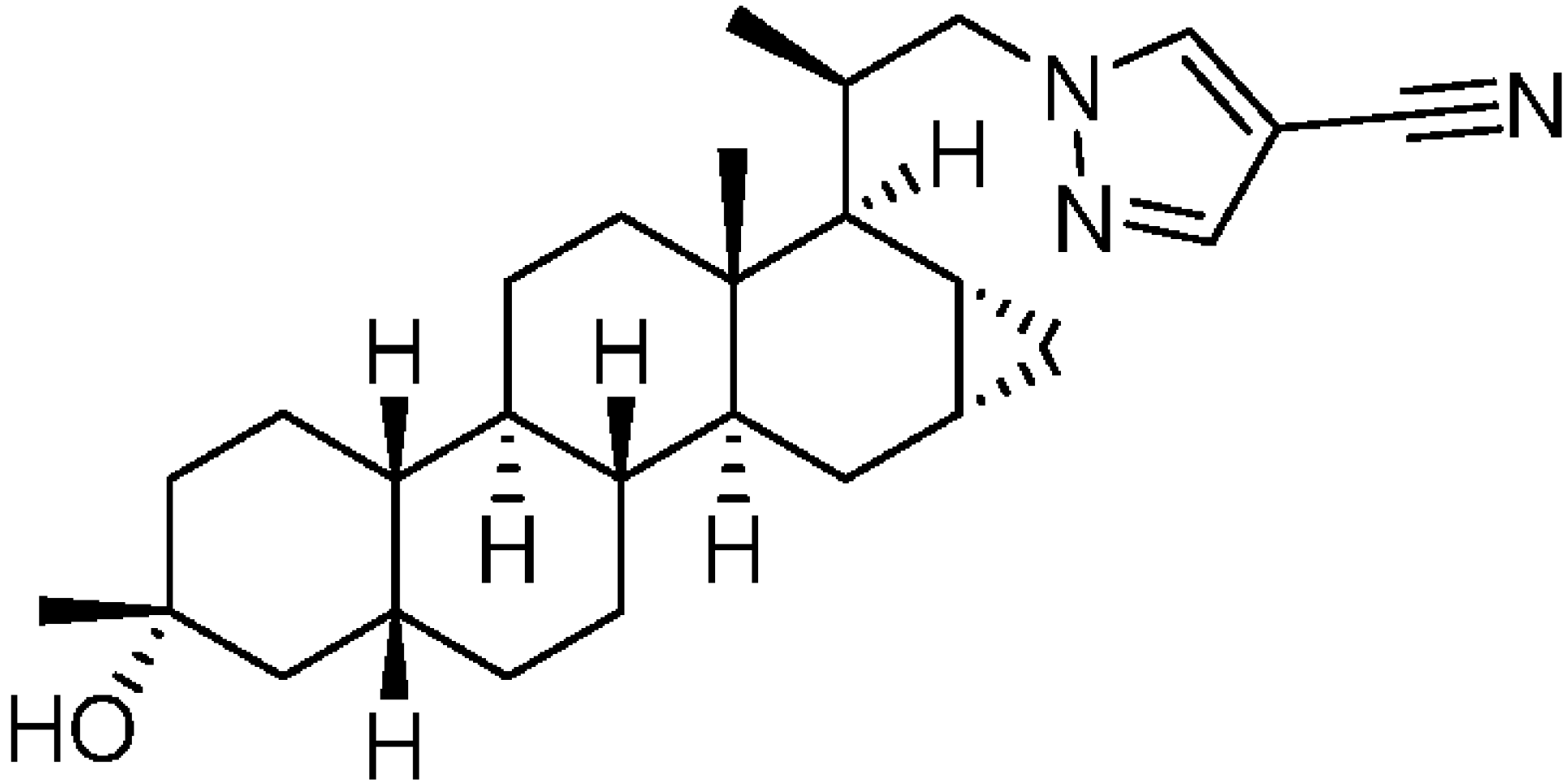
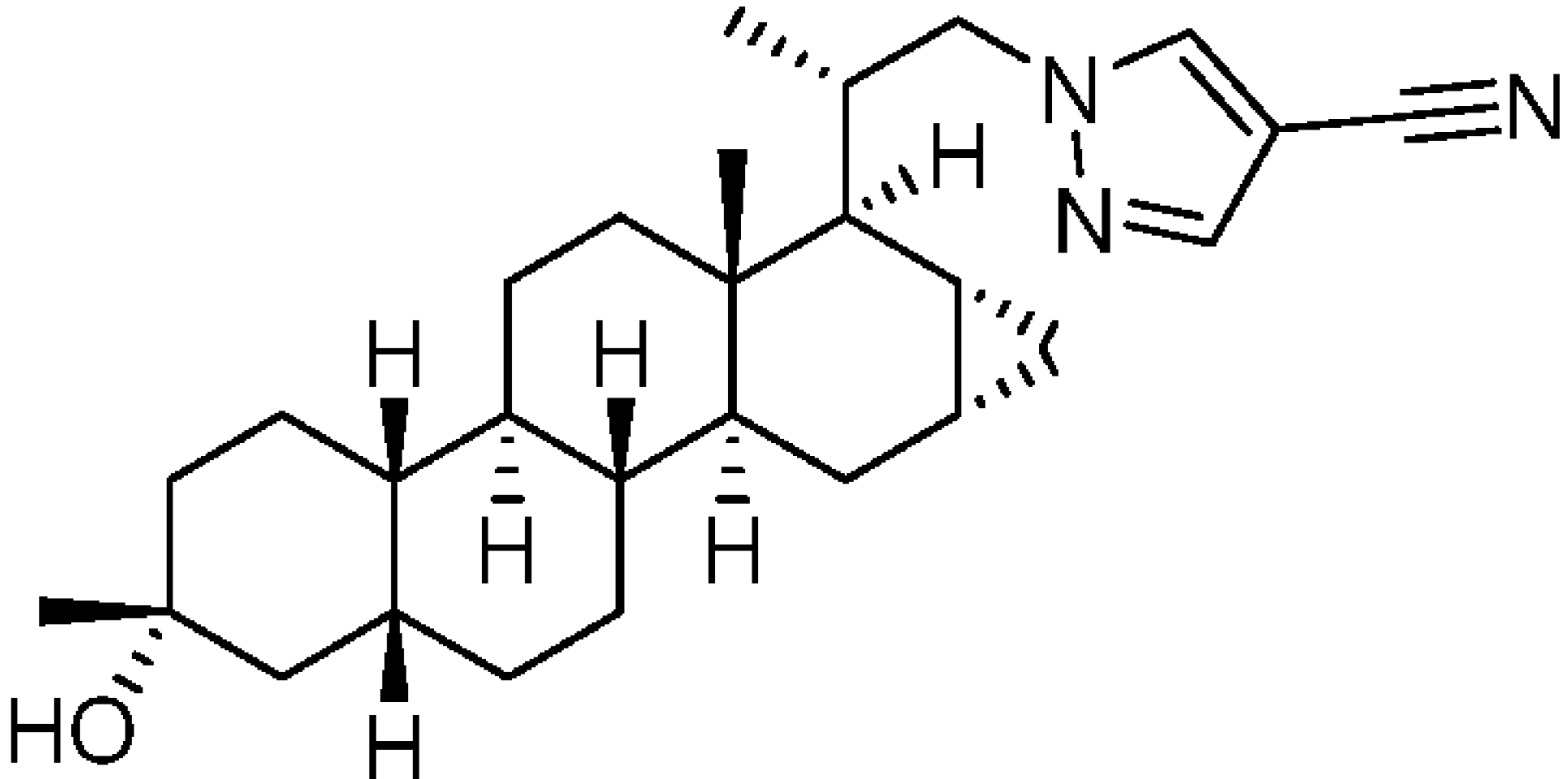
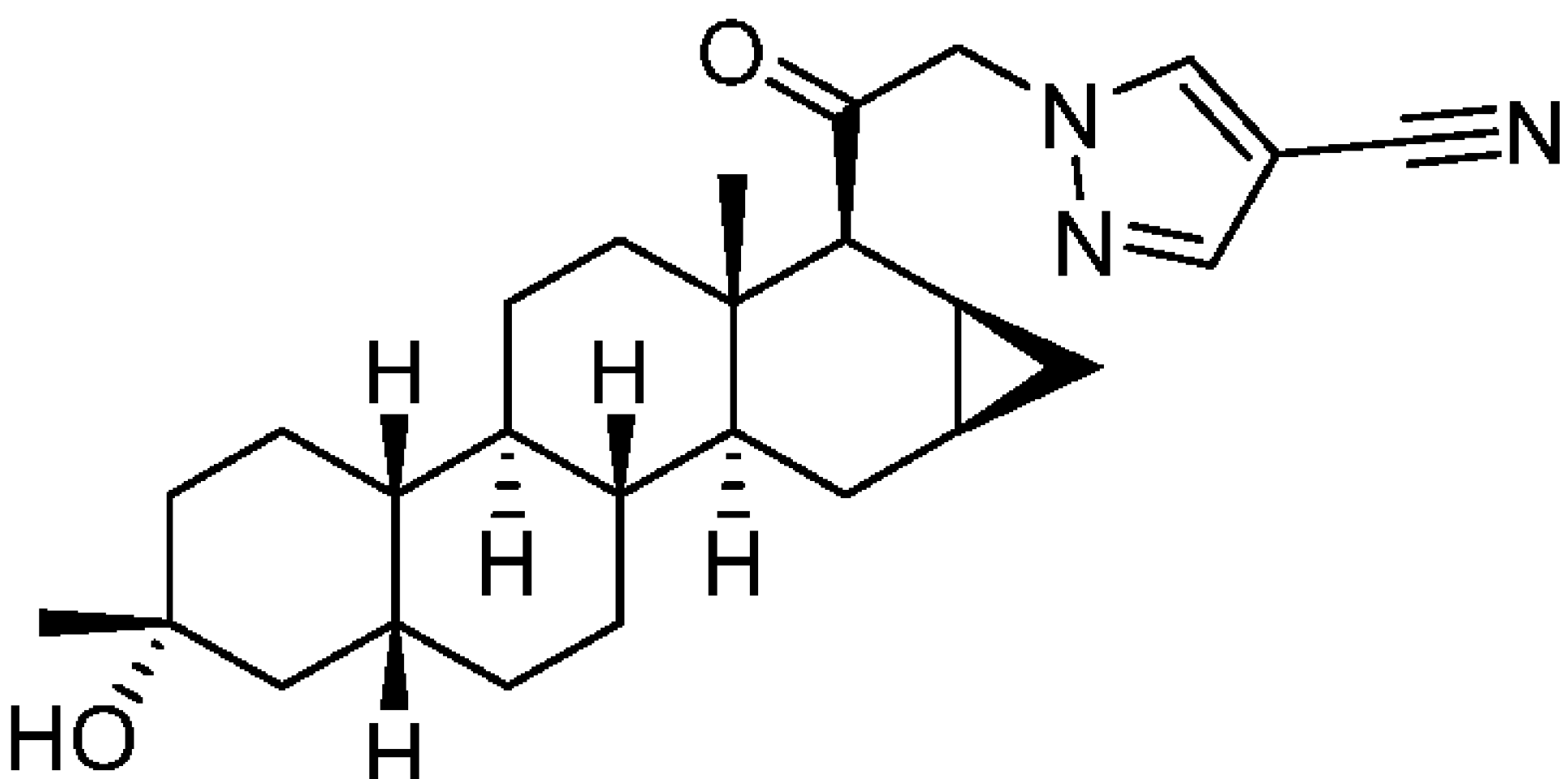
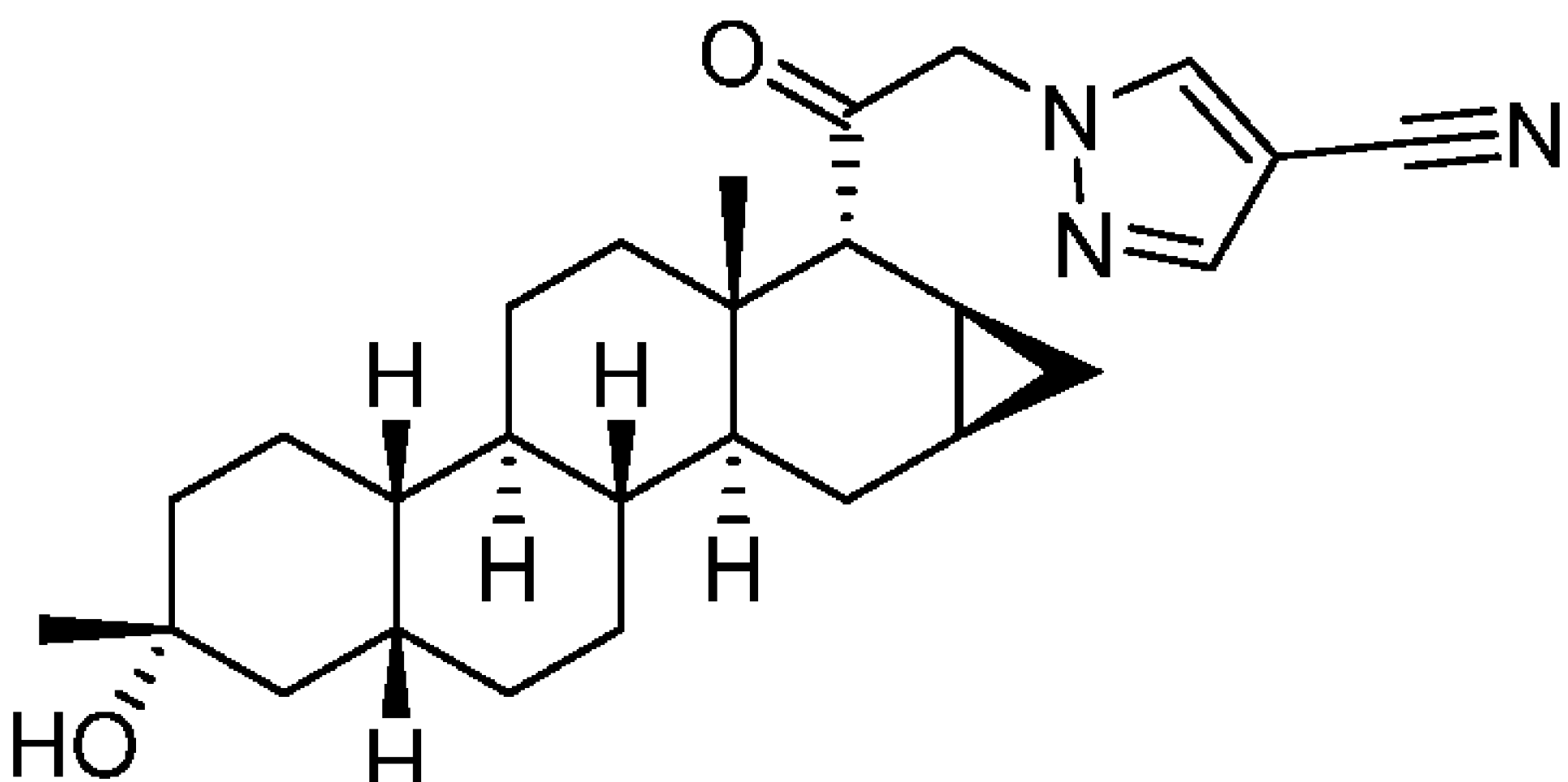
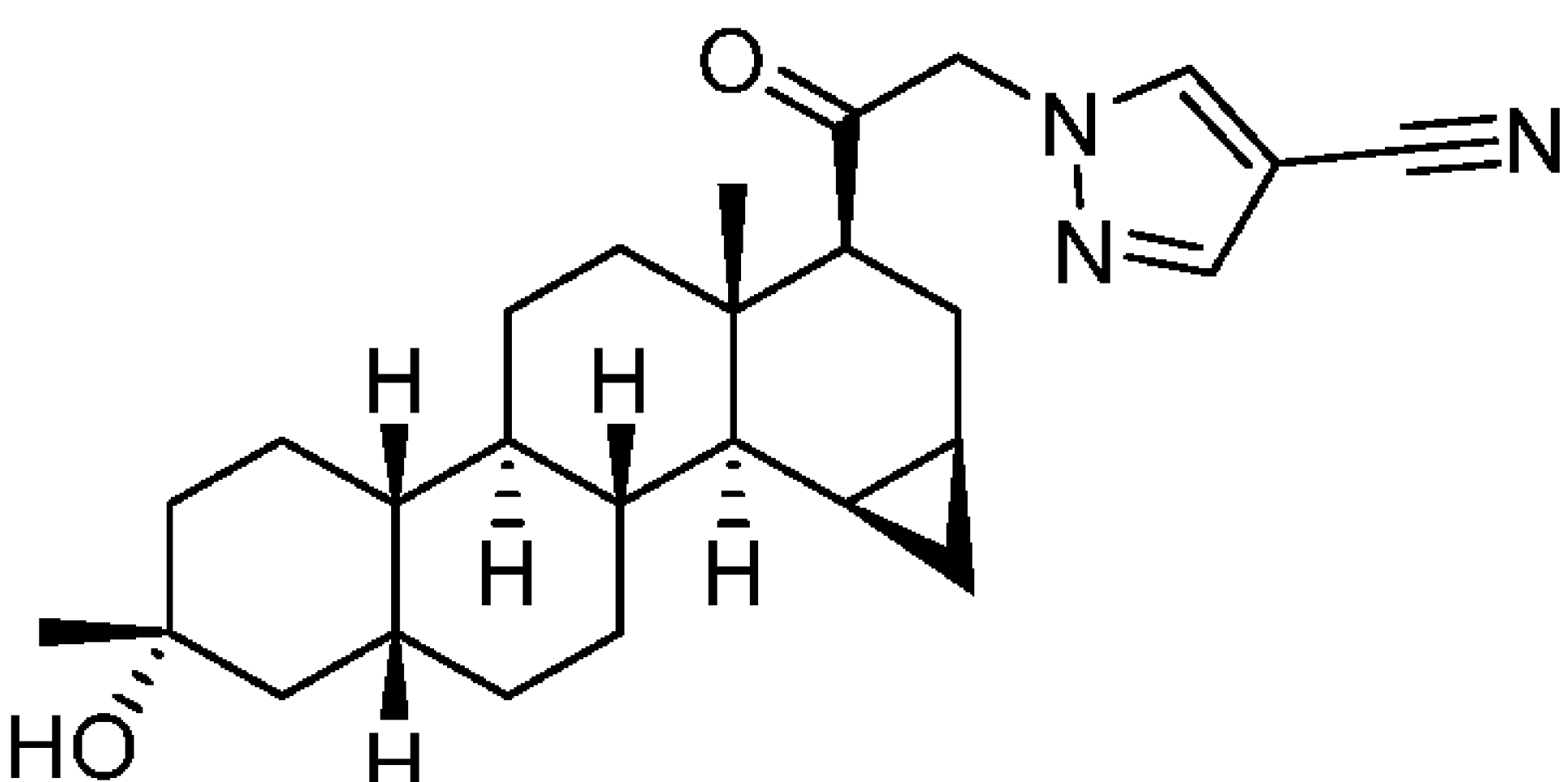
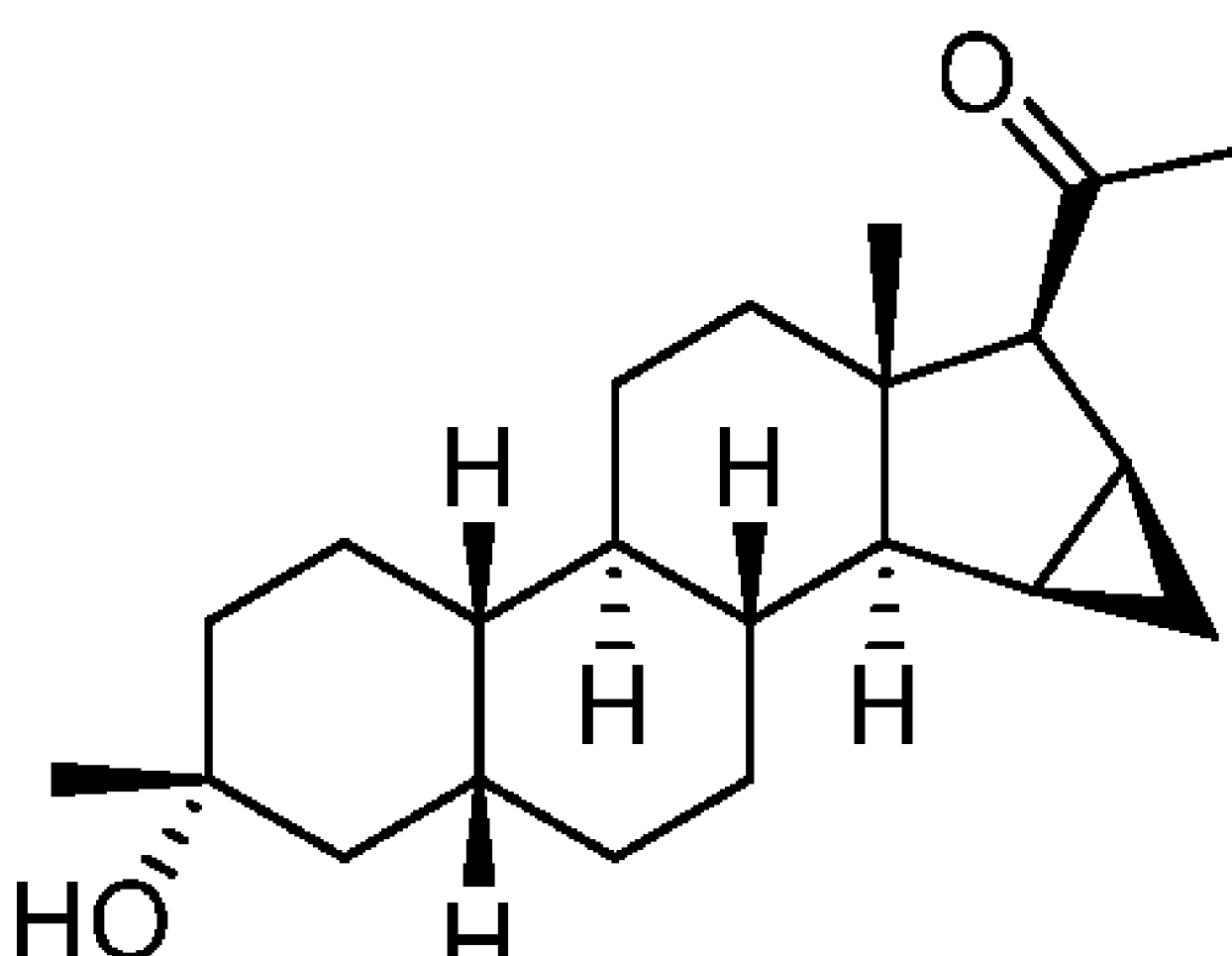


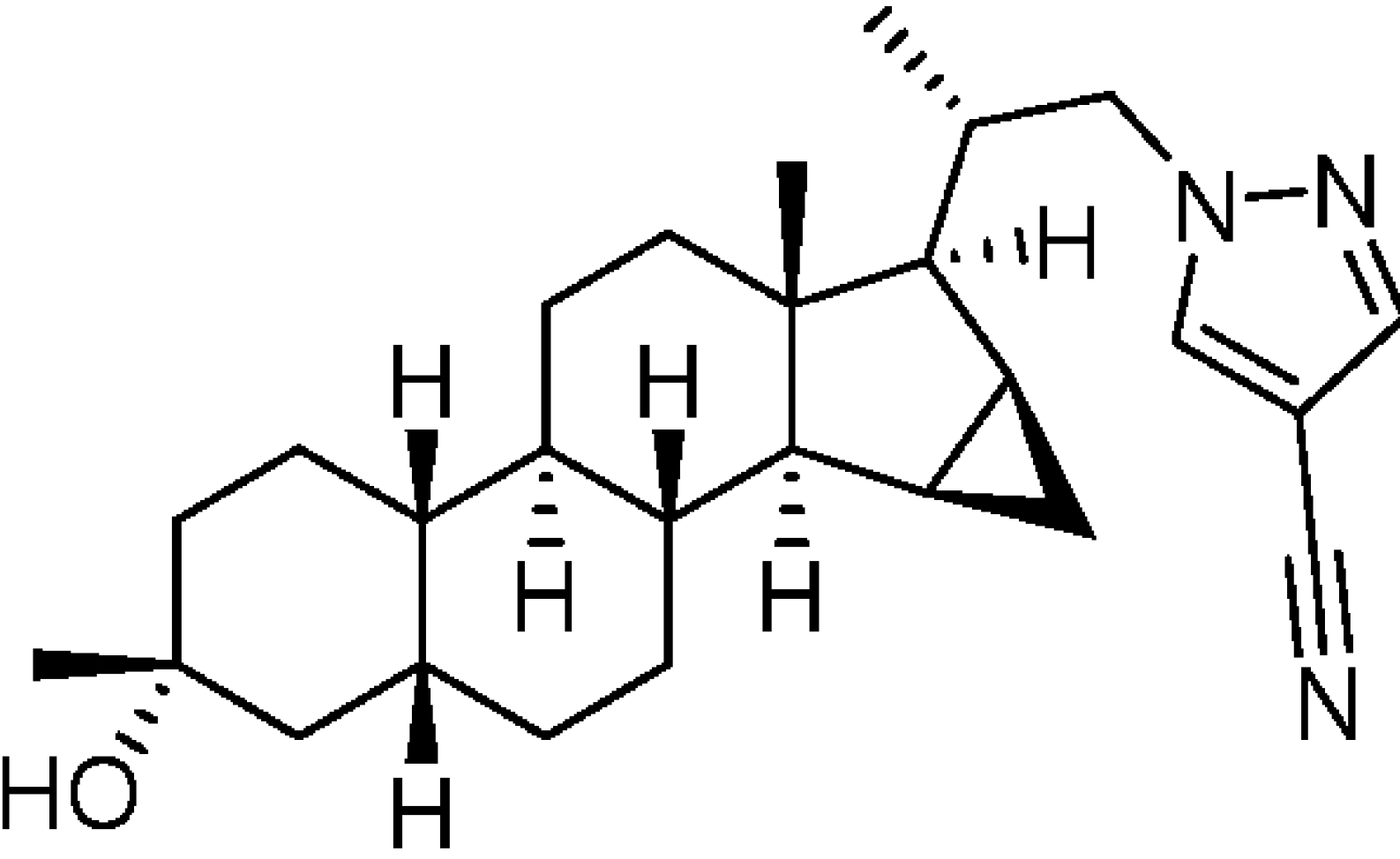
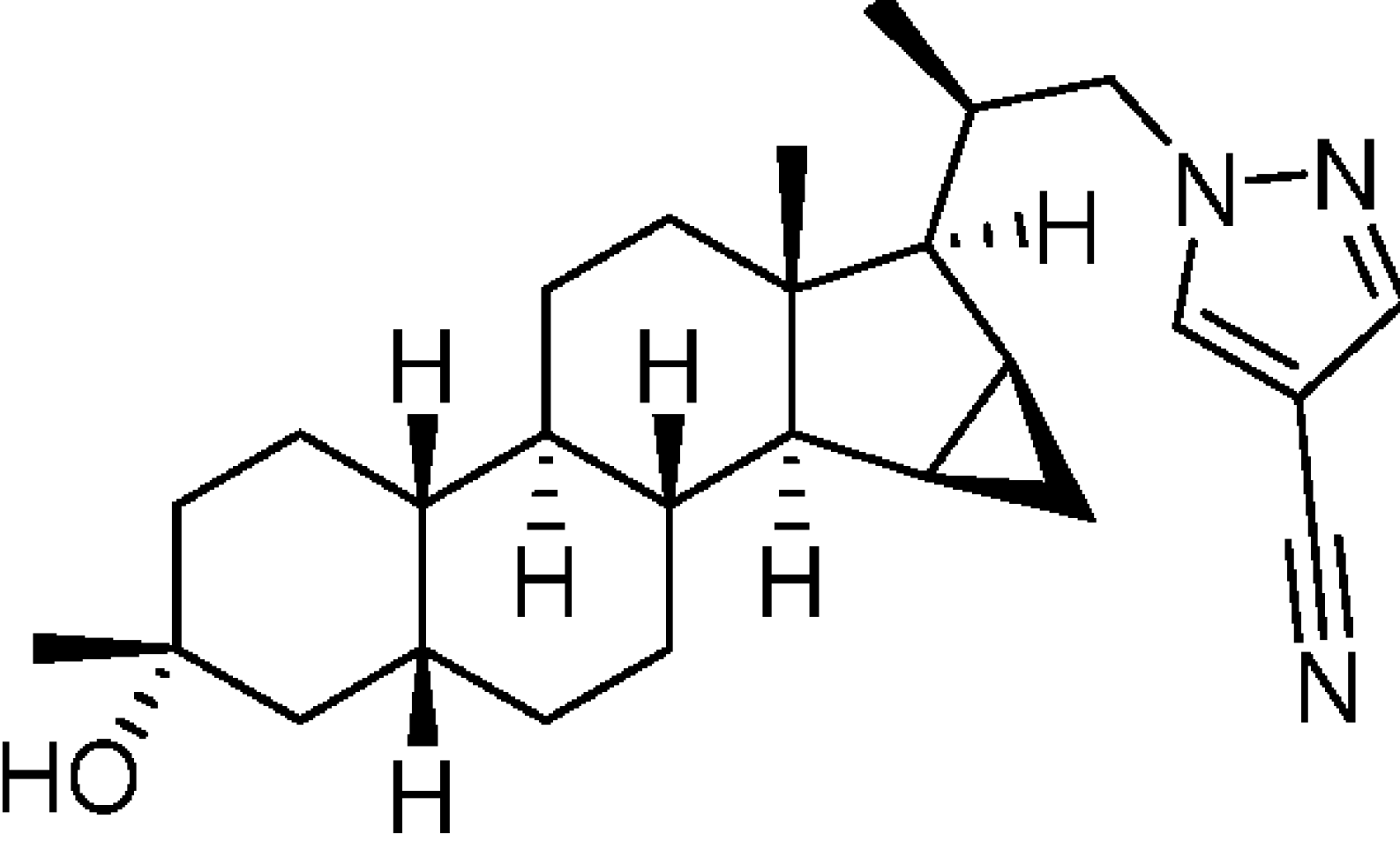
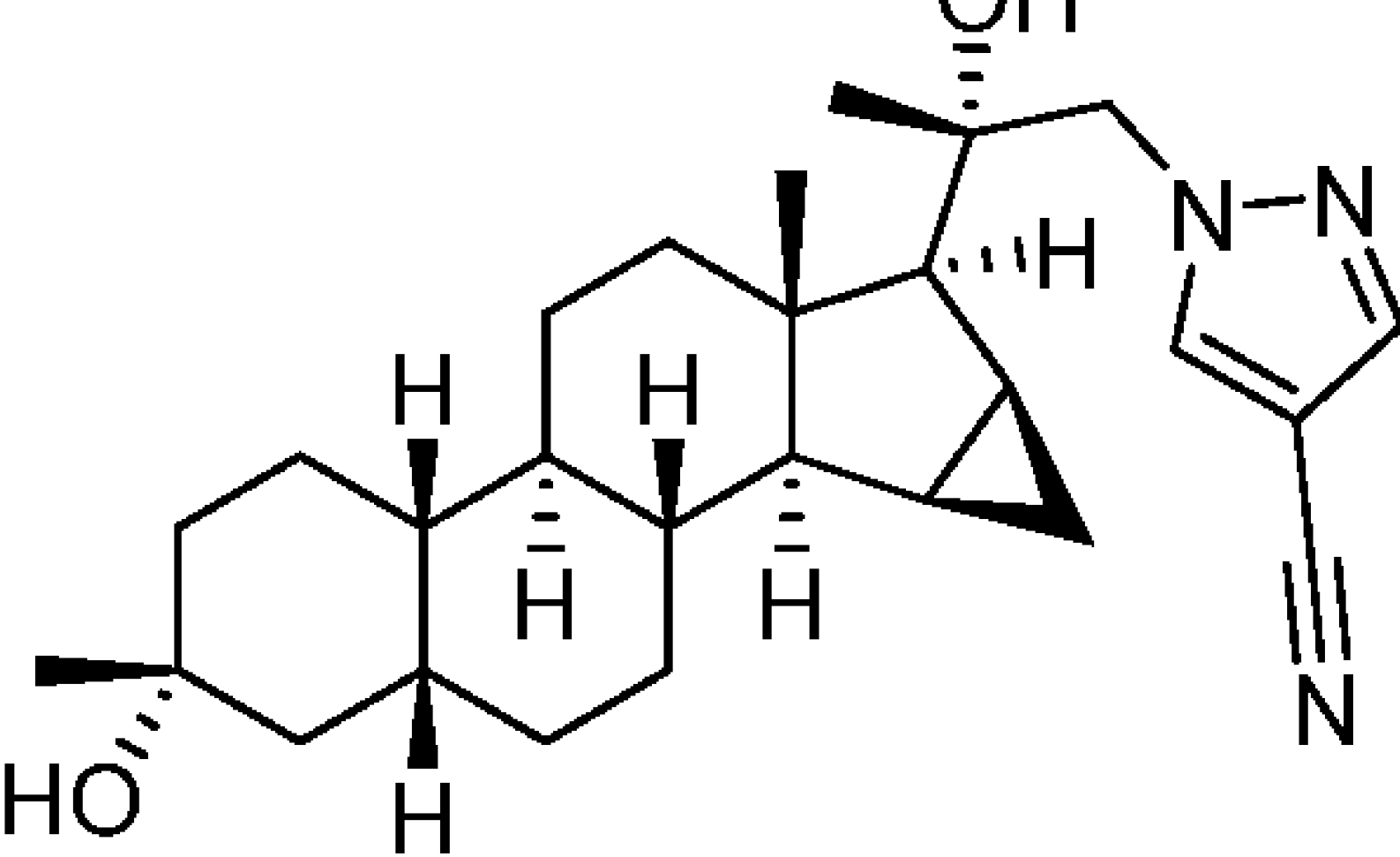
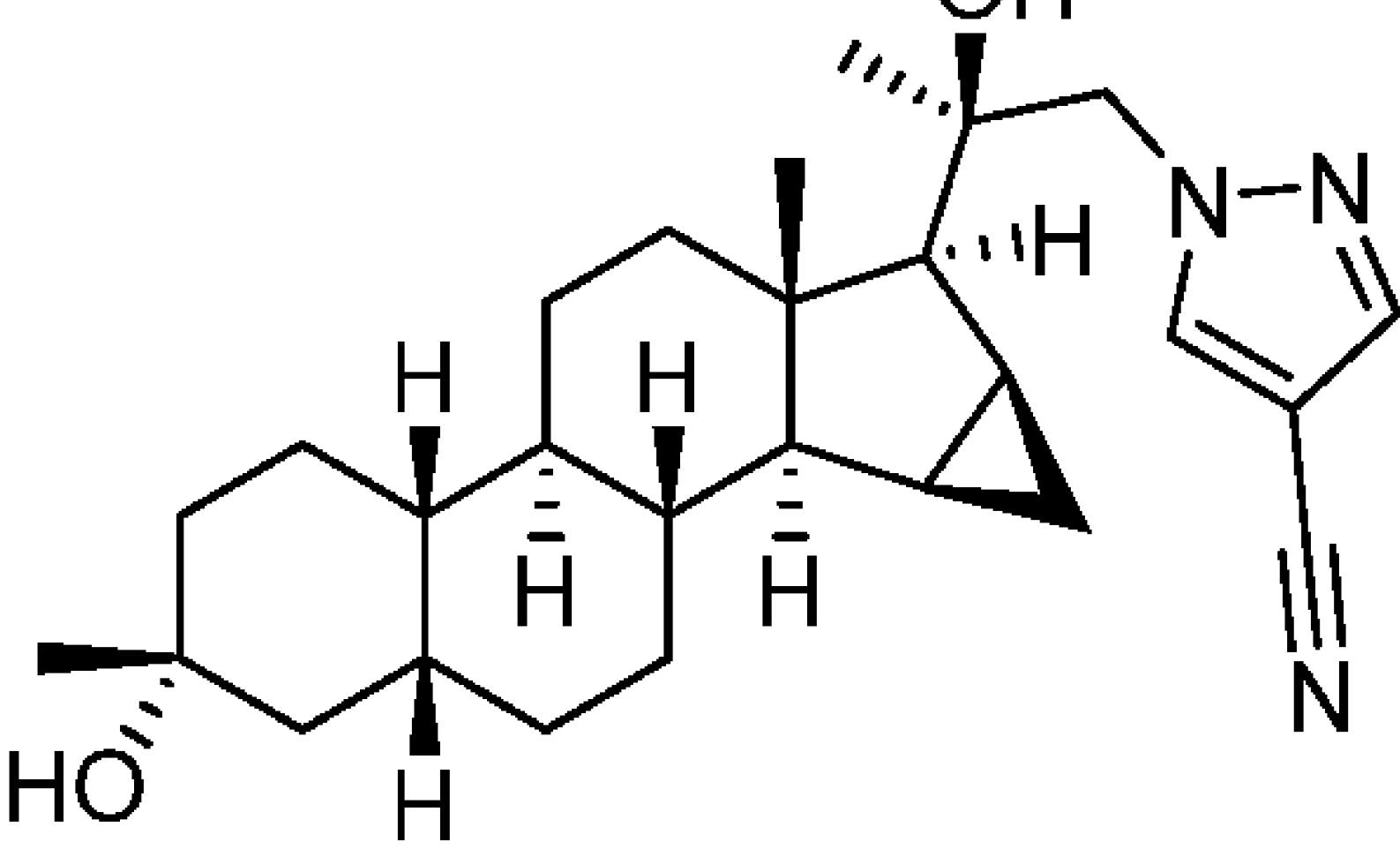
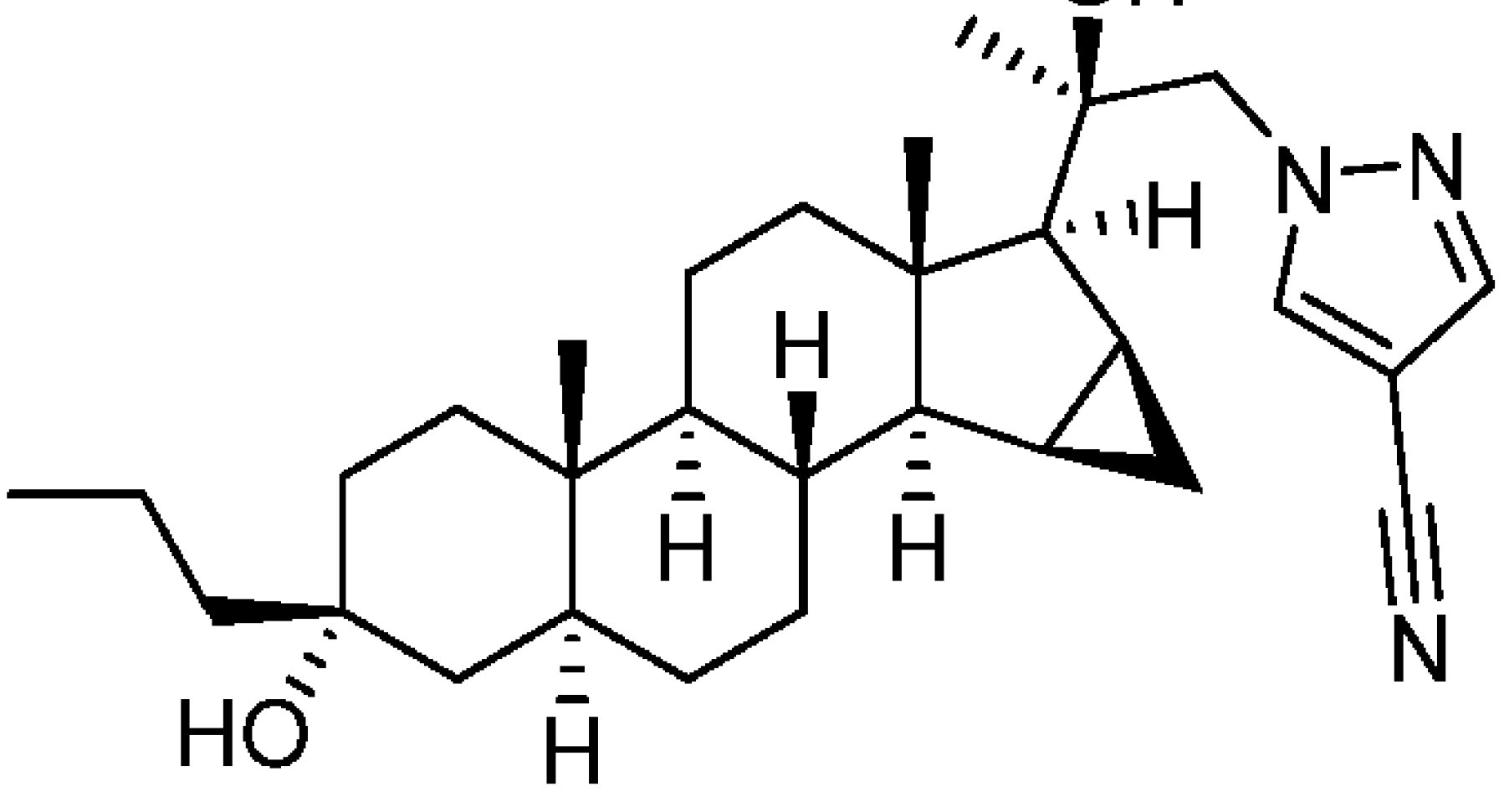
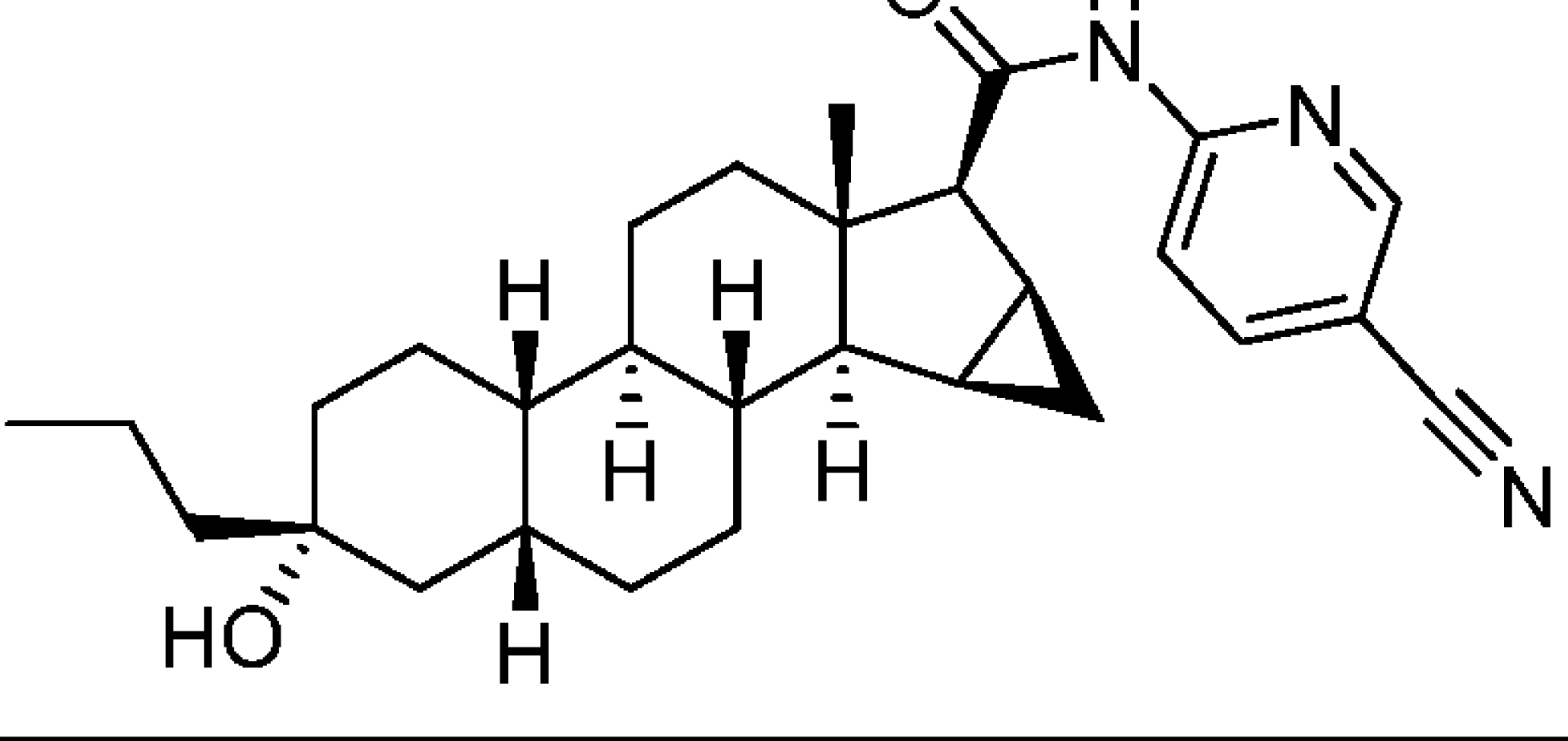


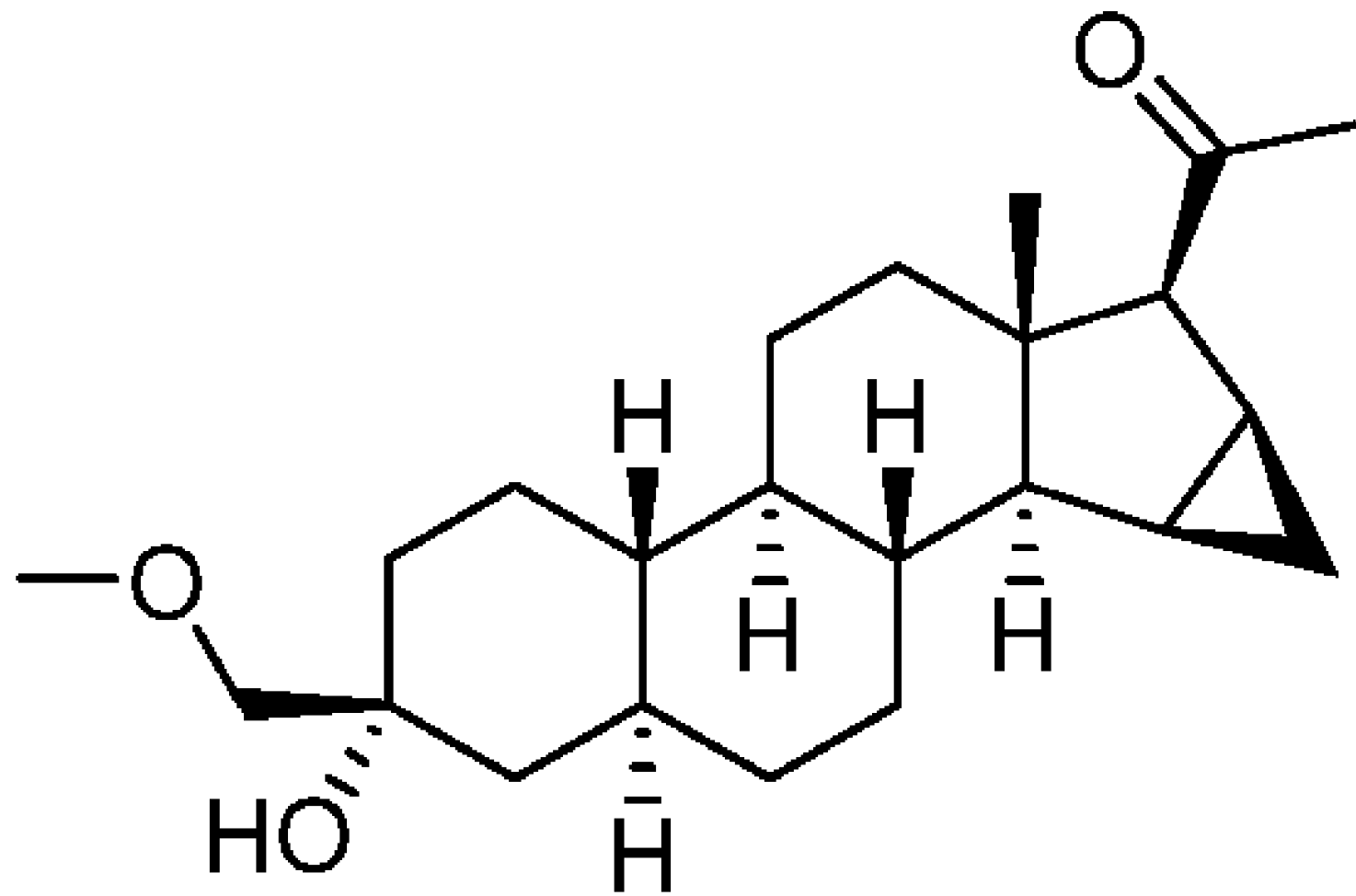
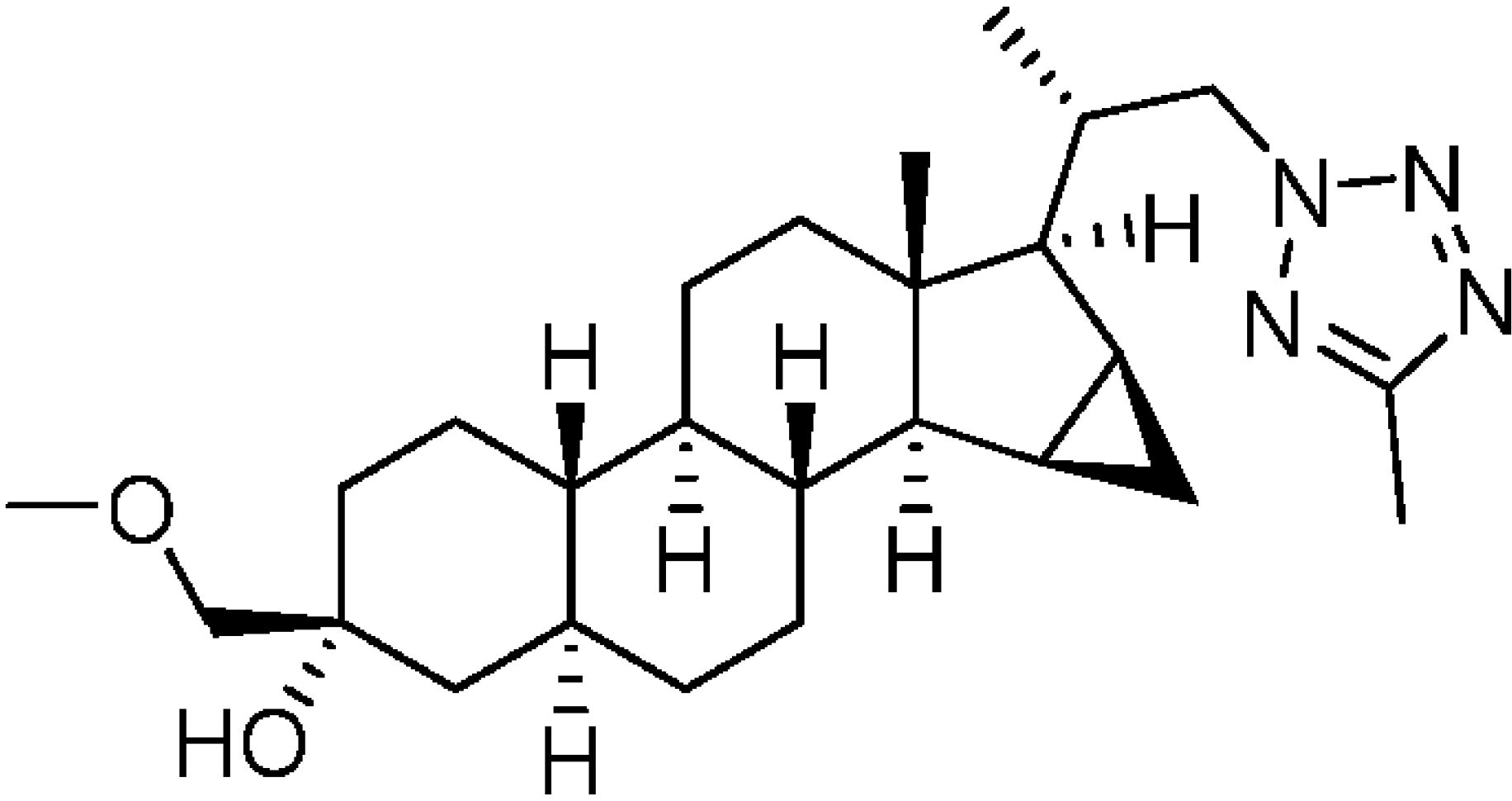
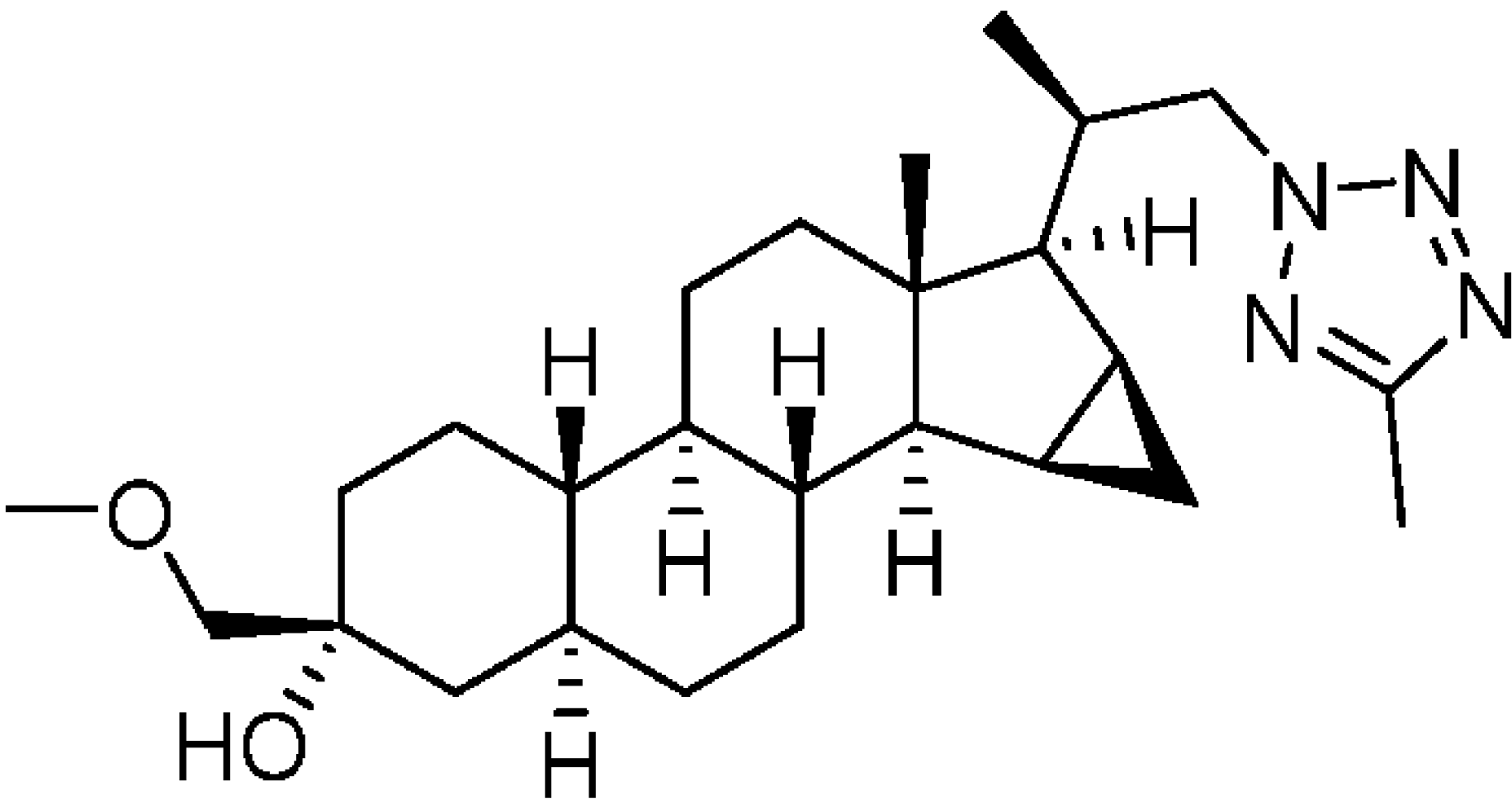
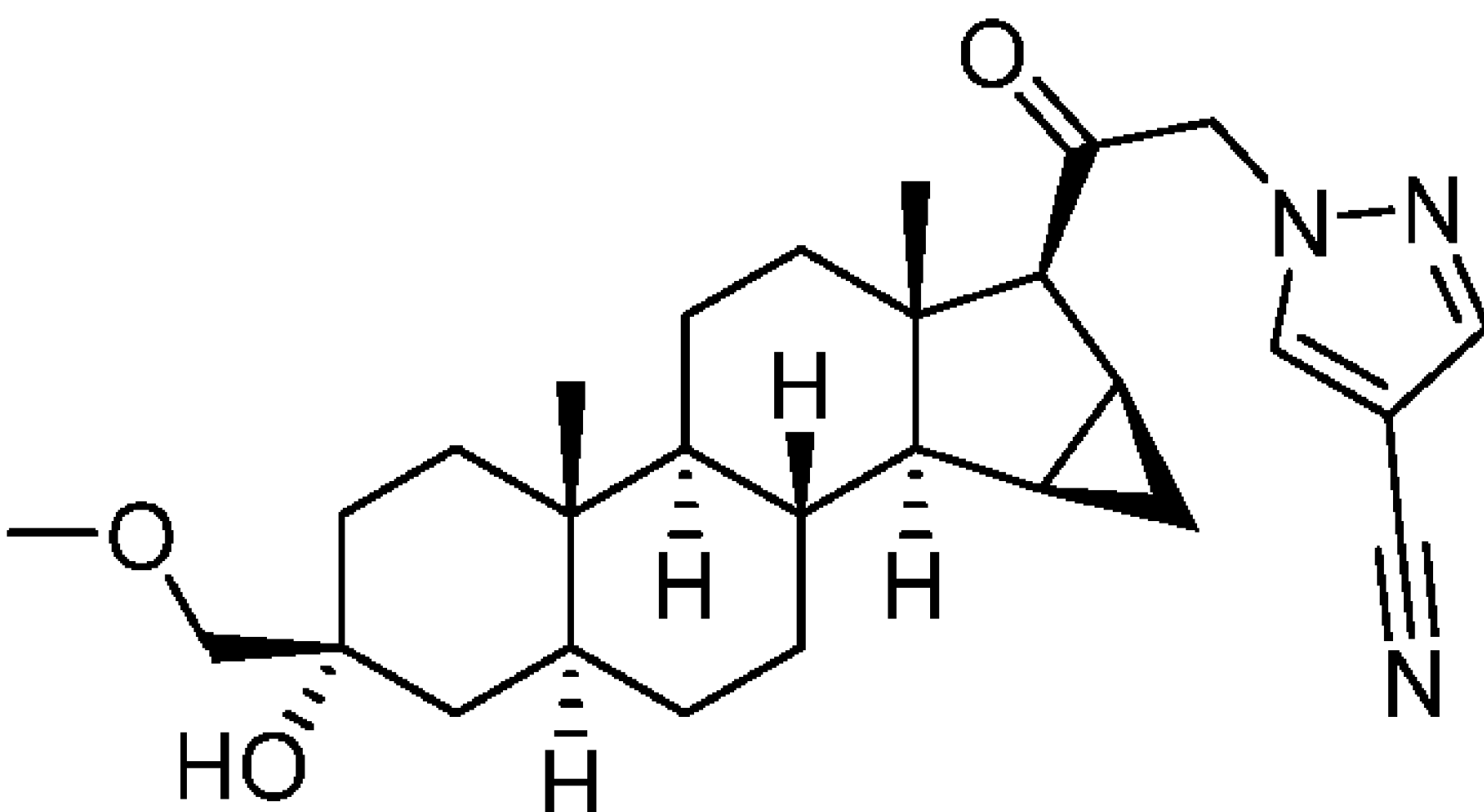
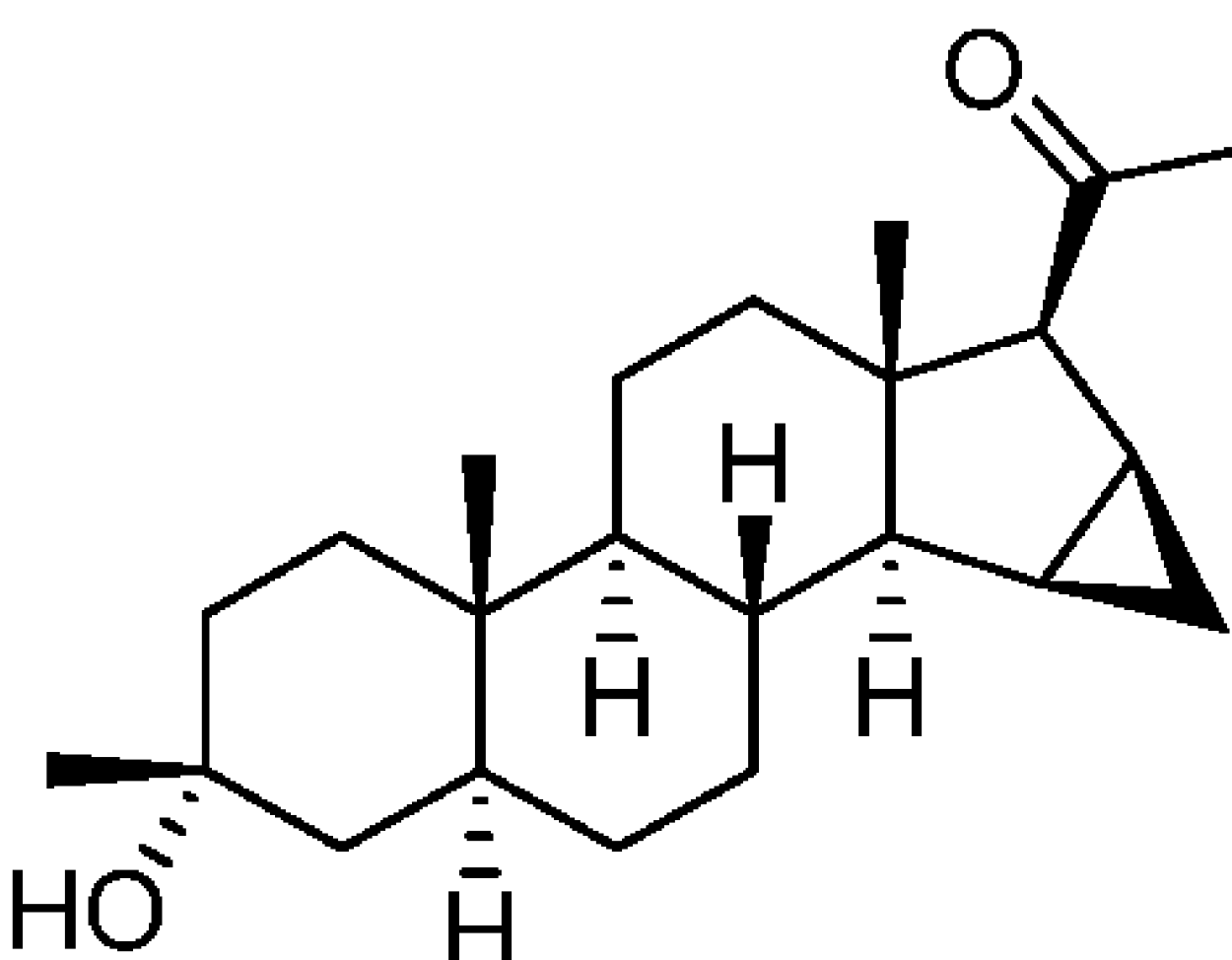
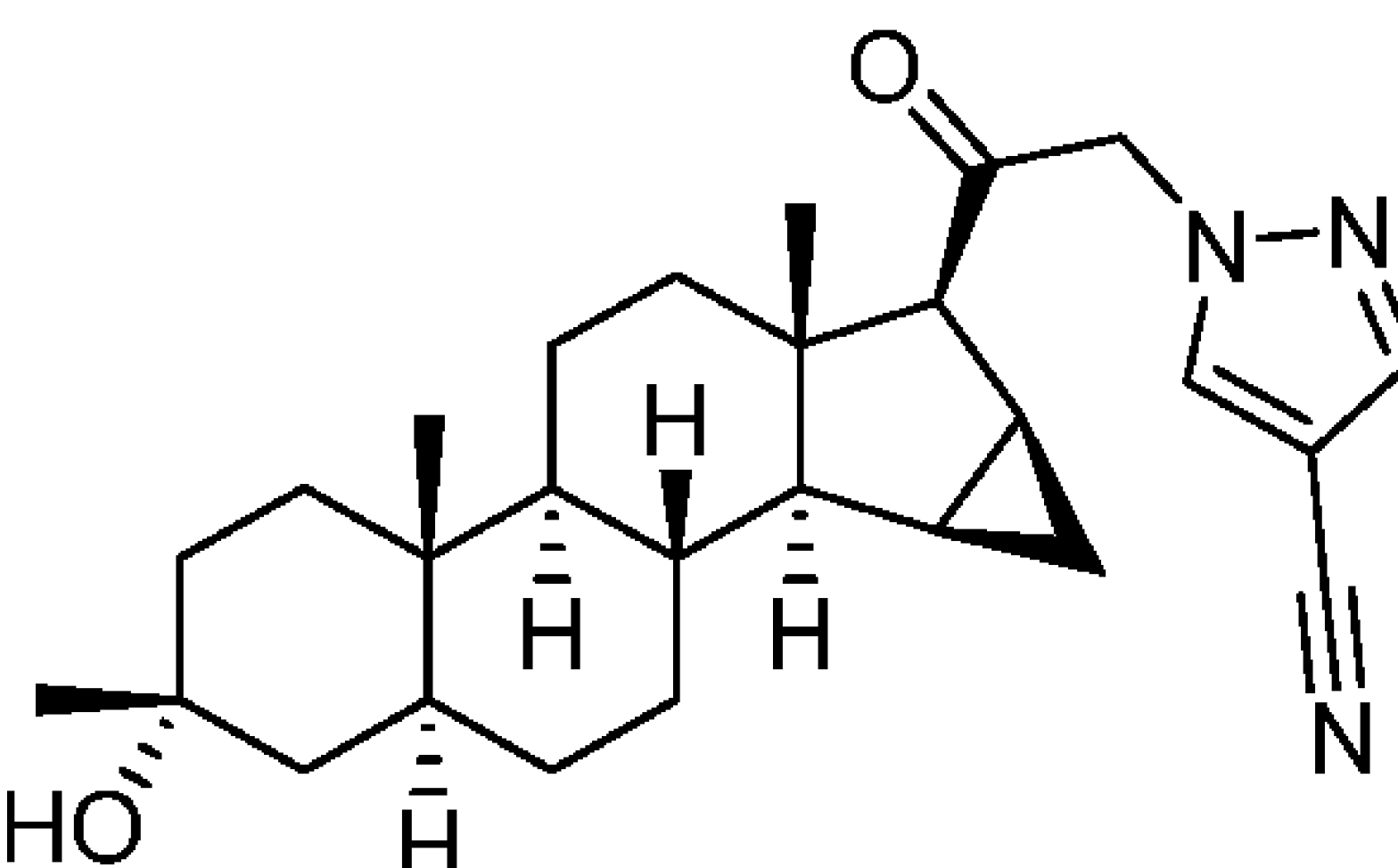
[0527] The above-mentioned synthetic schemes were used to synthesize the compounds in Table 1.

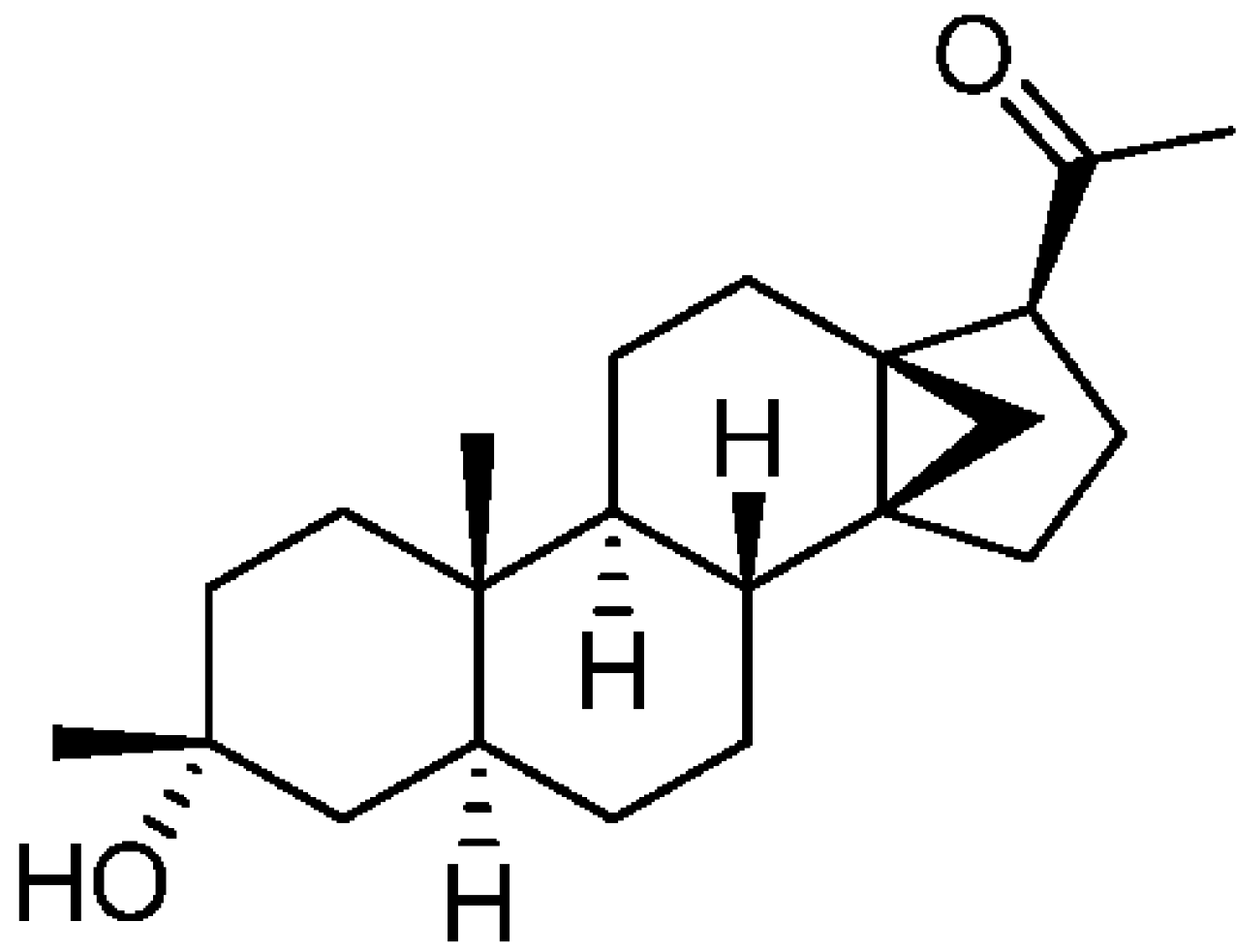
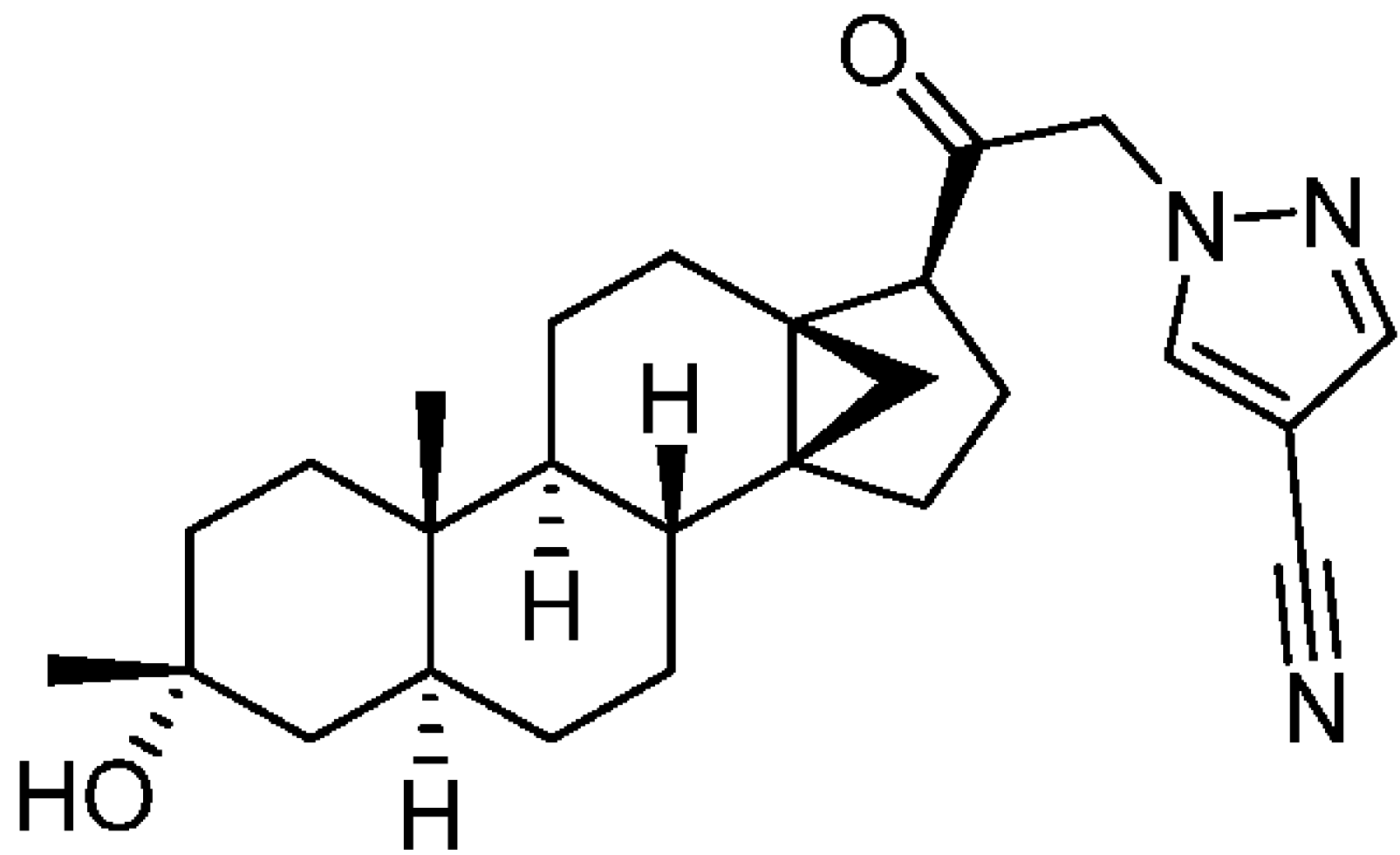
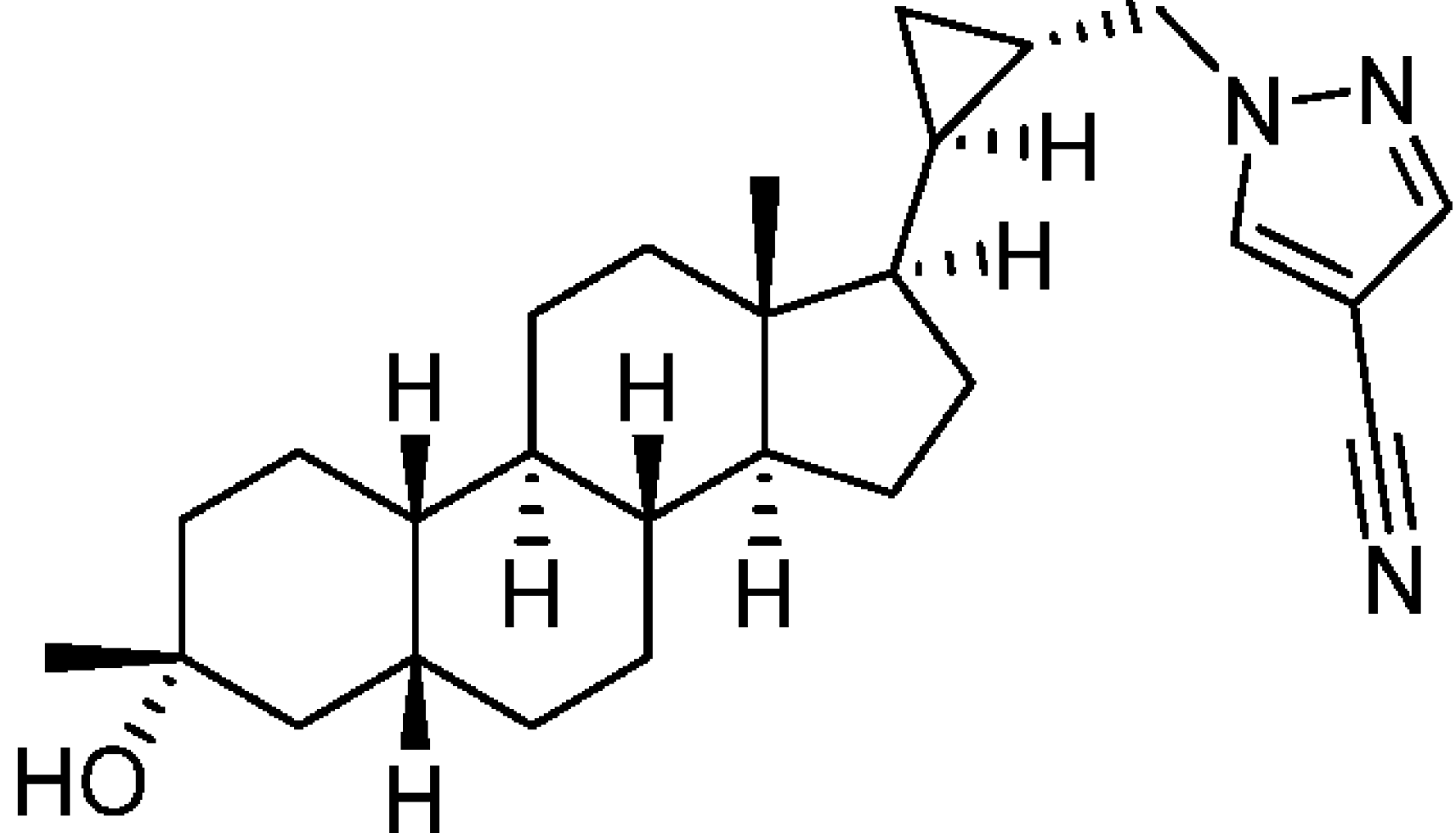
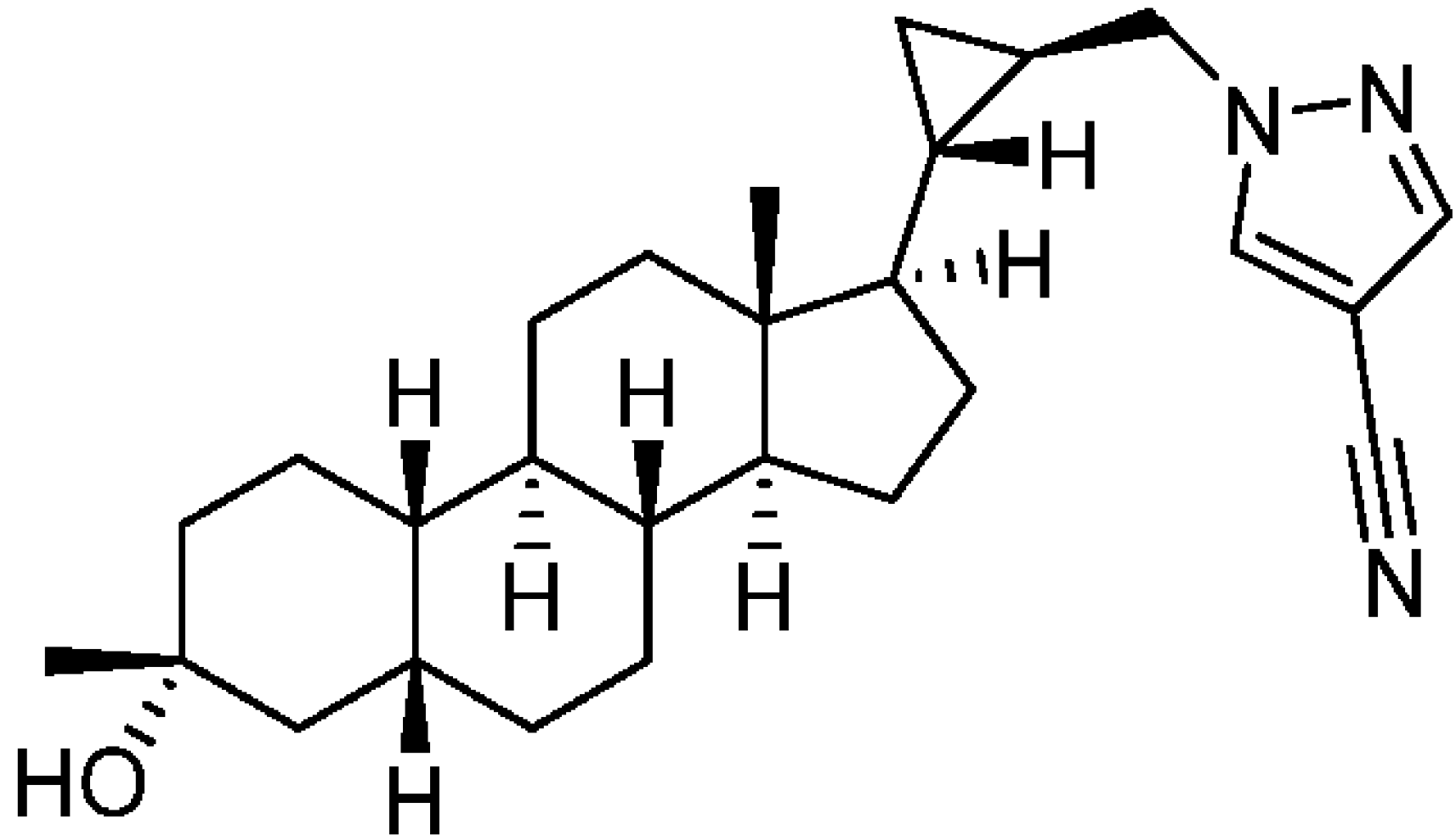
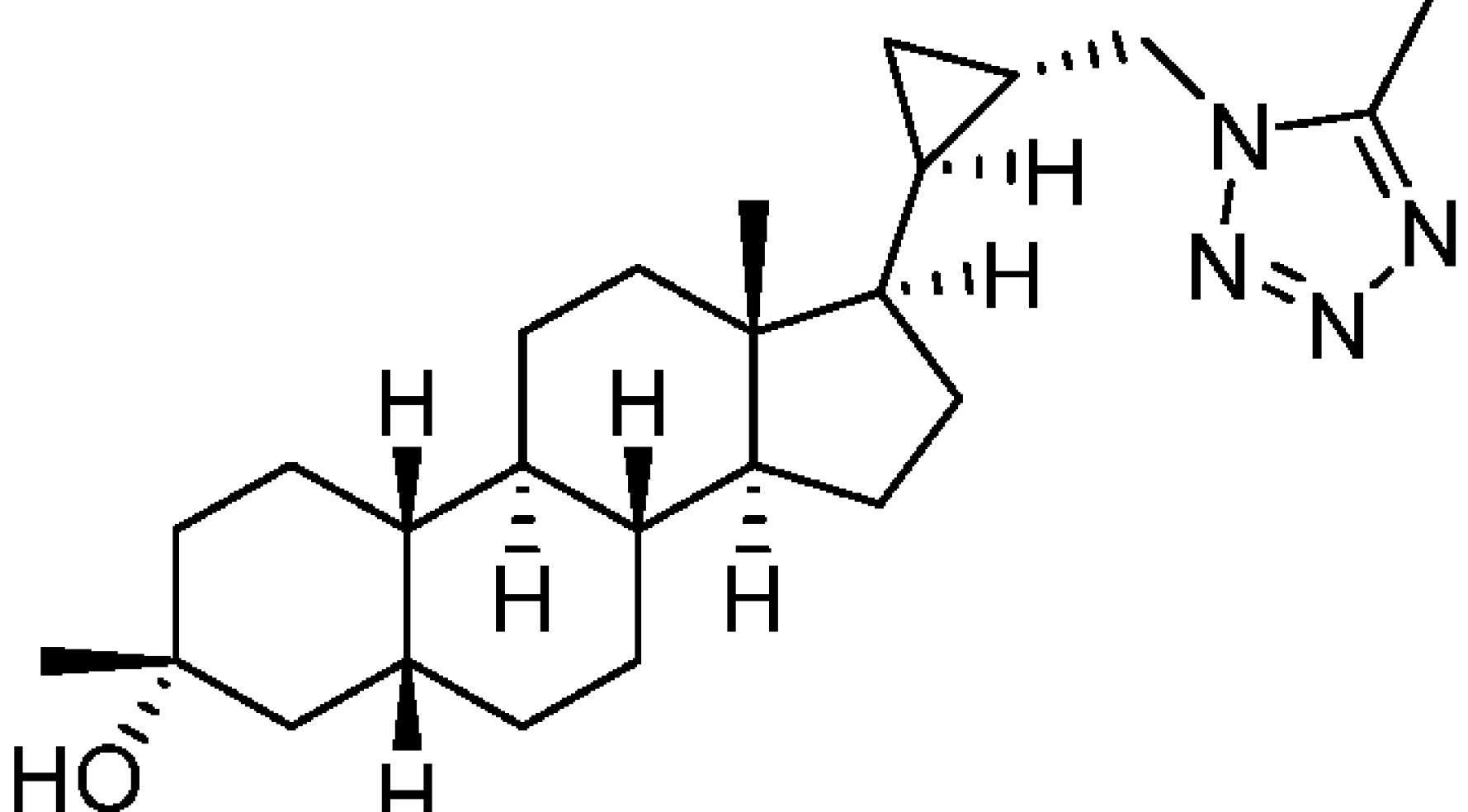
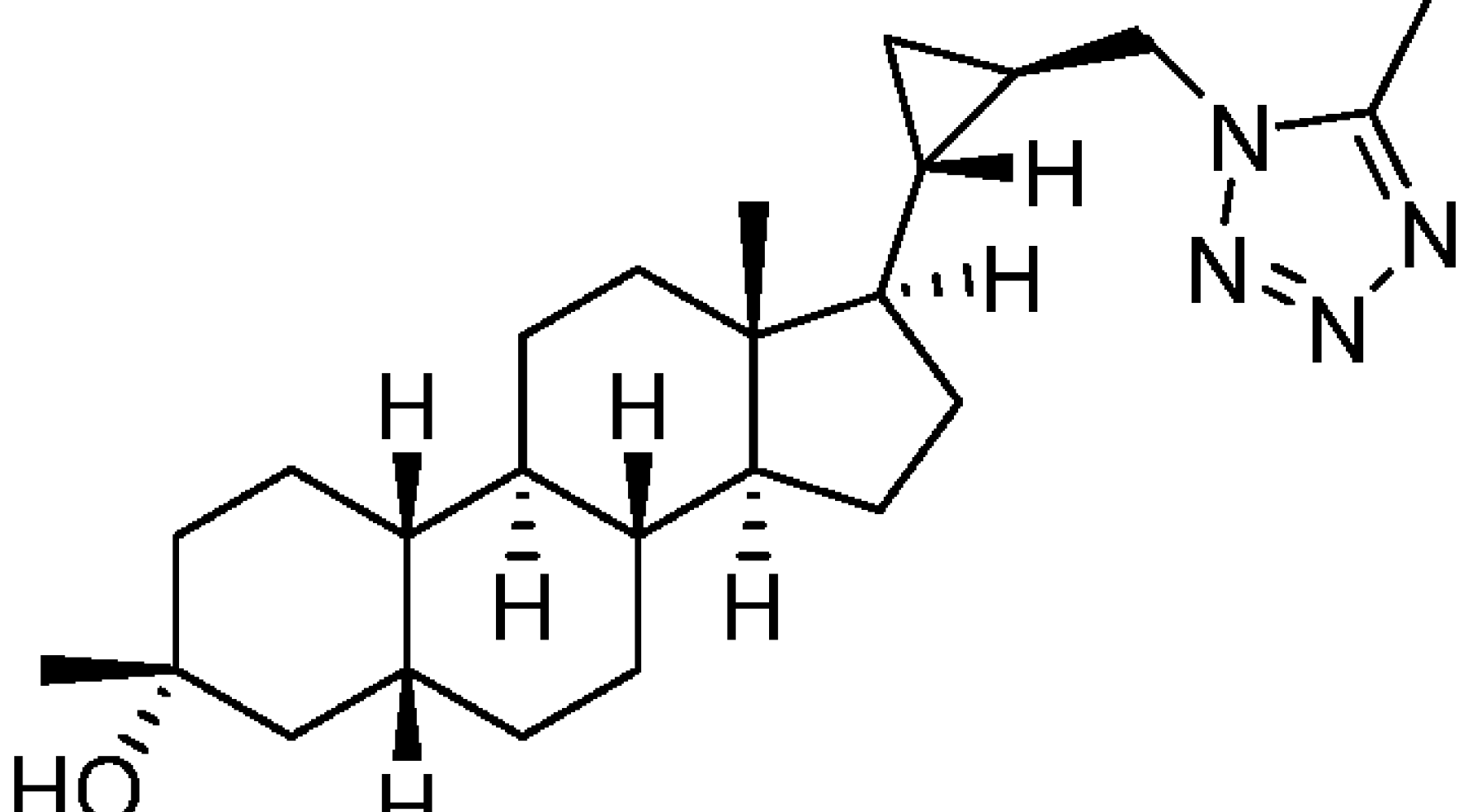
[0528] Table 1: Example compounds of the present invention.

Compd No.	Structure
1	
2	
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Compd No.	Structure
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Compd No.	Structure
10	
11	
12	
13	
14	
15	

Compd No.	Structure
16	
17	
18	
19	
20	
21	

Compd No.	Structure
22	
23	
24	
25	
26	
27	

Compd No.	Structure
28	

[0529] In one aspect, provided herein is a pharmaceutically acceptable salt of a compound described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d)).

[0530] In one aspect, provided herein is a pharmaceutical composition comprising a compound described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B),

(VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d)) 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.

[0531] Compounds of the present invention as described herein act, in certain embodiments, as GABA_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.

[0532] Thus, in an aspect, provided herein is a method of modulating a GABA_A receptor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein.

[0533] 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.

[0534] 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d)).

[0535] In one aspect, the invention includes a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt of a compound described herein, and a pharmaceutically acceptable carrier, vehicle, or excipient.

[0536] III. ALTERNATIVE EMBODIMENTS

[0537] In an alternative embodiment, compounds described herein may also comprise one or more isotopic substitutions. For example, hydrogen may be ^2H (D or deuterium) or ^3H (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.*, ^3H , ^{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.

[0538] A. Pharmaceutical Compositions

[0539] In one aspect, provided herein is a pharmaceutical composition comprising a compound described herein (*e.g.*, a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-

A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII-A1a), (VII-A1b), (VII-A1c), (VII-A1d), (VII-B1a), (VII-B1b), (VII-B1c), or (VII-B1d)) 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.

[0540] 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.

[0541] 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.

[0542] 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.

[0543] 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.

[0544] 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.

[0545] 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.

[0546] 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.

[0547] 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.

[0548] 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.

[0549] 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.

[0550] 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.

[0551] 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.

[0552] 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 or stability of the active

ingredients or formulation. All such known transdermal formulations and ingredients are included within the scope provided herein.

[0553] 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.

[0554] 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.

[0555] 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.

[0556] 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.

[0557] 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.

[0558] 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).

[0559] 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.

[0560] 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 -1,4-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).

[0561] 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.

[0562] 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.

[0563] 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.

[0564] 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.

[0565] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions that 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.

[0566] In one aspect, provided is a kit comprising a composition (e.g., a solid composition) comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d).

[0567] B. Combination Therapy

[0568] A compound or composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-

A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII - A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII - B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII - A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII - B1d), 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.

[0569] 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.

[0570] 1. Selective Serotonin Reuptake Inhibitor (SSRI)

[0571] In some embodiments, the compound or composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c),

(III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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).

[0572] 2. Norepinephrine Reuptake Inhibitor (NERI)

[0573] In some embodiments, the compound or composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-

A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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).

[0574] 3. Antipsychotics

[0575] In some embodiments, the compound or composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d),

(II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII-A1a), (VII-A1b), (VII-A1c), (VII-A1d), (VII-B1a), (VII-B1b), (VII-B1c), or (VII-B1d), 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).

[0576] 4. Cannabinoids

[0577] In some embodiments, the compound or composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-

A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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, Cannabidiolic Acid, Cannabinol, Cannabigerol, Cannabichromene, Tetrahydrocannabivarin, and Cannabidivarin.

[0578] 5. NMDA Receptor Antagonists

[0579] In some embodiments, the compound or composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2),

(VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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.

[0580] 6. GABA_A Receptor Agonists

[0581] In some embodiments, the compound or composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-

A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutically acceptable salt thereof) is administered in combination with GABA receptor agonist(s). GABA receptor agonist is 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, Flurirazepam, 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).

[0582] 7. Cholinesterase Inhibitors

[0583] In some embodiments, the compound or composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-

A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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, Donepezil (Aricept), Tacrine (Cognex), Rivastigmine (Exelon, Exelon Patch), Galantamine (Razadyne, Reminyl), Memantine/Donepezil (Namzaric), Ambenonium (Mytelase), Neostigmine (Bloxiverz), Pyridostigmine (Mestinon Timespan, Regonol), and Galantamine (Razadyne).

[0584] 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-

C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d),

(III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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.

[0585] C. Methods of Use and Treatment

[0586] In an aspect, compounds described herein, *e.g.*, compounds of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-

C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d) 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 (*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.

[0587] 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.

[0588] 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.

[0589] 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.

[0590] 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.

[0591] 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.

[0592] 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.

[0593] 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.

[0594] 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.

[0595] 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.

[0596] 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.

[0597] 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.

[0598] 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.

[0599] 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.

[0600] 1. Neuroendocrine Disorders and Dysfunction

[0601] 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.

[0602] 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 libido, 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.

[0603] 2. Neurodegenerative Diseases and Disorders

[0604] 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 cyoclonus), 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 epilepticus; 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.

[0605] 3. Mood disorders

[0606] 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).

[0607] **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.

[0608] 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.

[0609] 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).

[0610] 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.

[0611] 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.

[0612] 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.

[0613] 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.

[0614] **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.

[0615] **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.

[0616] **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).

[0617] **Double depression** refers to fairly depressed mood (dysthymia) that lasts for at least 2 years and is punctuated by periods of major depression.

[0618] **Depressive Personality Disorder (DPD)** refers to a personality disorder with depressive features.

[0619] **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.

[0620] **Minor depressive disorder** or minor depression refers to a depression in which at least 2 symptoms are present for 2 weeks.

[0621] **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.

[0622] **Depression caused by chronic medical conditions** refers to depression caused by chronic medical conditions such as cancer or chronic pain, chemotherapy, chronic stress.

[0623] **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 psychological 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).

[0624] 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 feeling of worthlessness or hopelessness.

[0625] 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).

[0626] 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.

[0627] 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).

[0628] 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d) (*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).

[0629] 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c),

(III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d)) 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-

C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-

C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII - A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII - B1d). 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII - A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII - B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-

A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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.

[0630] 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-

B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d). 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d). 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-

C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d). 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d). 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-

B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d) (e.g., treatment with a compound described herein, e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-

A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B),

(VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), is no more than 7.

[0631] 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).

[0632] 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).

[0633] 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.

[0634] 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.

[0635] 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.

[0636] 4. Anxiety Disorders

[0637] 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.

[0638] 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.

[0639] 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).

[0640] 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.

[0641] 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.

[0642] 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.

[0643] 5. Women's Health Disorders

[0644] 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).

[0645] 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.

[0646] 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.

[0647] 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).

[0648] 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.

[0649] **Miscarriage** refers to a pregnancy that ends on its own, within the first 20 weeks of gestation.

[0650] **Abortion** refers to the deliberate termination of a pregnancy, which can be performed during the first 28 weeks of pregnancy.

[0651] **Infertility and related disorders** include uterine fibroids, polycystic ovary syndrome, endometriosis, and primary ovarian insufficiency.

[0652] **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.

[0653] **Other disorders and conditions** that affect only women include Turner syndrome, Rett syndrome, and ovarian and cervical cancers.

[0654] **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.

[0655] **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.

[0656] 6. Epilepsy

[0657] The compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b),

(III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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.

[0658] 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 myoclonic 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.

[0659] 7. Epileptogenesis

[0660] 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).

[0661] 8. Status epilepticus (SE)

[0662] 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.

[0663] 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.

[0664] The compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d) 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.

[0665] 9. Seizure

[0666] 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.

[0667] 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.

[0668] 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.

[0669] 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.

[0670] 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."

[0671] 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.

[0672] Clonic seizures are repetitive, rhythmic jerks that involve both sides of the body at the same time.

[0673] Tonic seizures are characterized by stiffening of the muscles.

[0674] Atonic seizures consist of a sudden and general loss of muscle tone, particularly in the arms and legs, which often results in a fall.

[0675] 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.

[0676] 10. Movement Disorders

[0677] 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.

[0678] The methods described herein can be used to treat tremor, for example the compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII-A1a), (VII-A1b), (VII-A1c), (VII-A1d), (VII-B1a), (VII-B1b), (VII-B1c), or (VII-B1d) 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.

[0679] 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).

[0680] 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).

[0681] 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 occur irregularly and often can be relieved by complete rest.

[0682] 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.

[0683] **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.

[0684] **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.

[0685] **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.

[0686] **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.

[0687] **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.

[0688] **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.

[0689] **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.

[0690] **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.

[0691] **Ataxia** refers to the loss of full control of bodily movements, and may affect the fingers, hands, arms, legs, body, speech, and eye movements.

[0692] **Myoclonus and Startle** is a response to a sudden and unexpected stimulus, which can be acoustic, tactile, visual, or vestibular.

[0693] **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.

[0694] **Restless Legs Syndrome** is a neurologic sensorimotor disorder characterized by an overwhelming urge to move the legs when at rest.

[0695] **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.

[0696] **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.

[0697] 11. Anesthesia / Sedation

[0698] 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.

[0699] Sedation is the reduction of irritability or agitation by administration of a pharmacological agent, generally to facilitate a medical procedure or diagnostic procedure.

[0700] Sedation and analgesia include a continuum of states of consciousness ranging from minimal sedation (anxiolysis) to general anesthesia.

[0701] **Minimal sedation** is also 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.

[0702] **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.

[0703] **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.

[0704] **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.

[0705] 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.

[0706] 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.

[0707] 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.

[0708] 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a),

(VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutically acceptable salt thereof).

[0709] 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-

B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII - A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII - B1d), or a pharmaceutically acceptable salt thereof).

[0710] 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d),

(VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutically acceptable salt thereof), wherein the subject has a respiratory condition.

[0711] In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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.

[0712] 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.

[0713] In some embodiments, a compound or pharmaceutical composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a),

(VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutically acceptable salt thereof)

continues after a subject has ended treatment with mechanical ventilation.

[0714] In some embodiments, a compound or pharmaceutical composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-

C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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.

[0715] 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-

C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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.

[0716] 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-

C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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).

[0717] 12. Respiratory condition

[0718] In some embodiments, a subject with a respiratory condition suffers from respiratory distress. In some embodiments, respiratory distress includes acute respiratory distress.

[0719] 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.

[0720] 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.

[0721] 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.

[0722] In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-

A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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.

[0723] In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-

A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-

A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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.

[0724] In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1),

(VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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.

[0725] In some embodiments, administration of a compound or pharmaceutical composition described herein (e.g., a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b), (VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), or a pharmaceutical salt thereof, or a composition comprising a compound of Formula (I), (II), (II-A), (II-B), (II-C), (II-A1), (II-A2), (II-B1), (II-B2), (II-C1), (II-C2), (II-A1a), (II-A1b), (II-A1c), (II-A1d), (II-A2a), (II-A2b), (II-A2c), (II-A2d), (II-B1a), (II-B1b), (II-B1c), (II-B1d), (II-B2a), (II-B2b), (II-B2c), (II-B2d), (II-C1a), (II-C1b), (II-C1c), (II-C1d), (II-C2a), (II-C2b), (II-C2c), (II-C2d), (III), (III-A), (III-B), (III-C), (III-A1), (III-A2), (III-B1), (III-B2), (III-C1), (III-C2), (III-A1a), (III-A1b), (III-A1c), (III-A1d), (III-A2a), (III-A2b), (III-A2c), (III-A2d), (III-B1a), (III-B1b), (III-B1c), (III-B1d), (III-B2a), (III-B2b), (III-B2c), (III-B2d), (III-C1a), (III-C1b), (III-C1c), (III-C1d), (III-C2a), (III-C2b), (III-C2c), (III-C2d), (IV), (IV-A), (IV-A1), (IV-A1a), (IV-A1b), (IV-A1a1), (IV-A1a2), (IV-A1b1), (IV-A1b2), (V), (V-A), (V-A1), (V-A2), (V-A1a), (V-A1b), (V-A2a), (V-A2b), (VI), (VI-A), (VI-B), (VI-A1), (VI-A2), (VI-B1), (VI-B2), (VI-A1a), (VI-A1b), (VI-A1c), (VI-A1d), (VI-B1a), (VI-B1b),

(VI-B1c), (VI-B1d), (VI-A3a), (VI-A3b), (VI-B3a), (VI-B3b), (VII), (VII-A), (VII-B), (VII-A1), (VII-A2), (VII-B1), (VII-B2), (VII -A1a), (VII -A1b), (VII -A1c), (VII -A1d), (VII -B1a), (VII -B1b), (VII -B1c), or (VII -B1d), 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.

[0726] 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.

[0727] 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.

[0728] 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.

[0729] 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, myeloperoxidase 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, Straüssler-Scheinker syndrome, COPD, dry-eye disease, or Sjogren's disease.

[0730] 13. Infections

[0731] 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.

[0732] 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.

[0733] 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.

[0734] 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*.

[0735] IV. EXAMPLES

[0736] 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.

[0737] Materials and Methods

[0738] 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.

[0739] 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.

[0740] 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 neuroactive steroids 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.

[0741] ¹H-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 integrations) of a compound.

[0742] 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

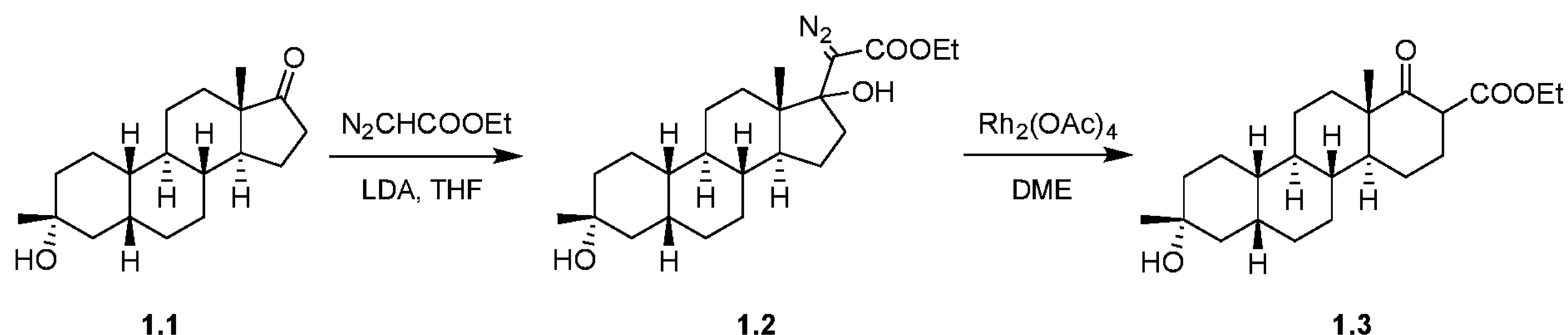
C18 2.1*30mm, 3um; Wavelength: UV 220 nm; Column temperature: 50°C; MS ionization: ESI; Detector: PDA & ELSD.

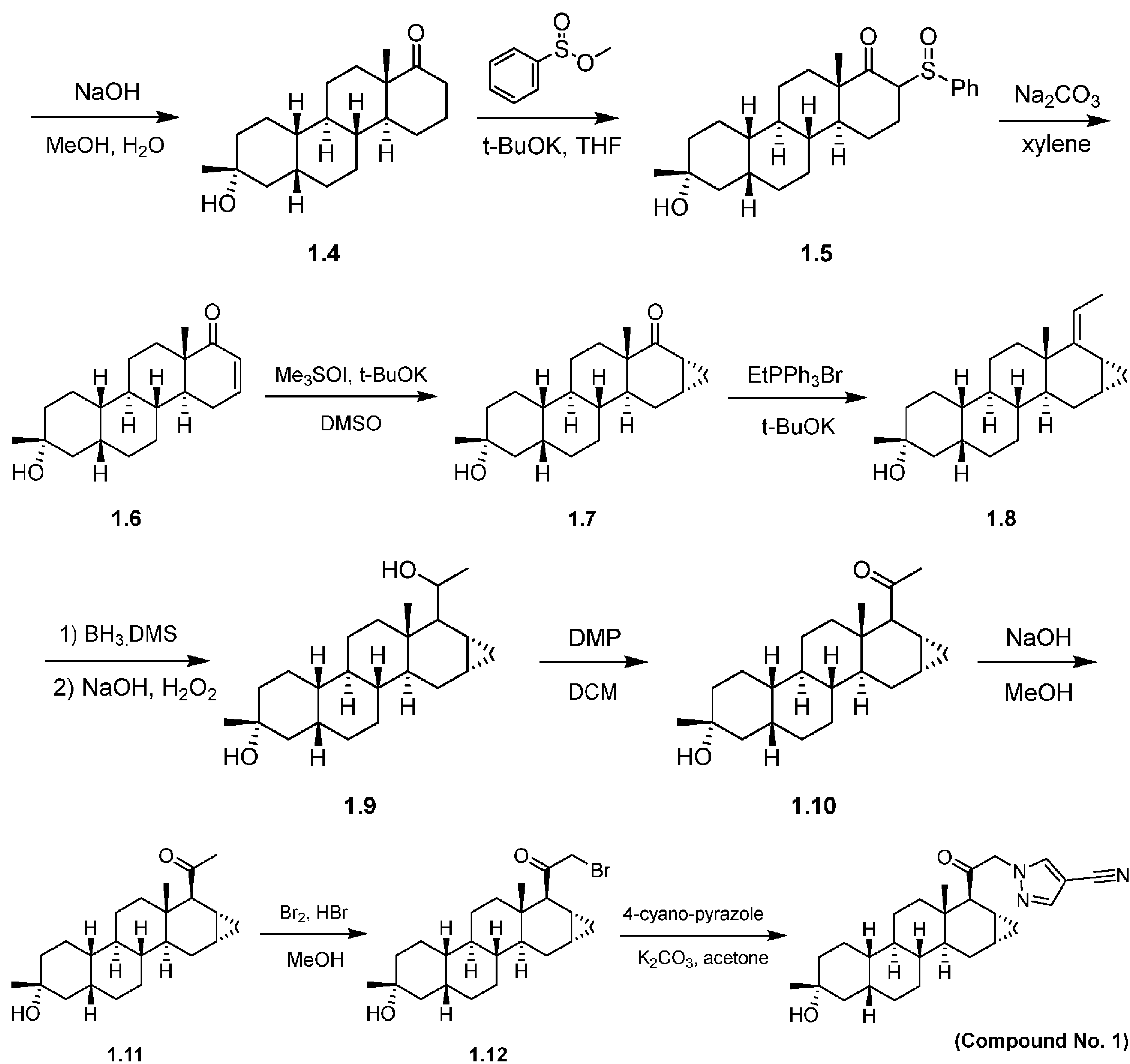
[0743] Abbreviations:

[0744] 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*-Bu₃P)₂: bis(tri-*tert*-butylphosphine)palladium(0); AcCl: acetyl chloride; *i*-PrMgCl: Isopropylmagnesium chloride; TBSCl: *tert*-Butyl(chloro)dimethylsilane; (*i*-PrO)₄Ti: 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; TMSCF₃: (Trifluoromethyl)trimethylsilane; Ts: *p*-toluenesulfonyl; Bu: butyl; Ti(OiPr)₄: tetraisopropoxytitanium; LAH: Lithium Aluminium Hydride; LDA: lithium diisopropylamide; LiOH.H₂O: lithium hydroxide hydrates; MAD: methyl aluminum bis(2,6-di-*t*-butyl-4-methylphenoxide); MeCN: acetonitrile; NBS: N-bromosuccinimide; Na₂SO₄: sodium sulfate; Na₂S₂O₃: 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.

[0745] The composition of each of Compound Nos. 1-28, set forth in the following examples, was verified by mass spectroscopy analysis.

[0746] Example No. 1: Synthesis of 1-(2-((2R,4aS,4bR,6aS,7S,7aR,8aR,9aS,9bR,11aR)-2-hydroxy-2,6a-dimethyloctadecahydro-1H-cyclopropa[b]chrysen-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (Compound No. 1).





[0747] Synthesis of 1.2

[0748] LDA (171 mL, 343 mmol, 2M in THF) was added to a stirred solution of **1.1** (20 g, 68.8 mmol) and ethyl diazoacetate (43.4 g, 343 mmol, 90%) in THF (600 mL) at -70°C. The resulting mixture was stirred at -70°C for 2 hours. Then acetic acid (19.5 mL, 343 mmol) in THF (60 mL) was added and the mixture was warmed to 20°C for 16 hours. Water (300 mL) was added to the mixture. The aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (0~15% of ethyl acetate in petroleum ether) to give **1.2** (25 g, 90%). ¹H NMR (400 MHz, CDCl₃) δ_H 4.75-4.60 (m, 1H), 4.29-4.21 (m, 2H), 2.18-2.08 (m, 1H), 1.91-1.76 (m, 4H), 1.73-1.58 (m, 3H), 1.49-1.36 (m, 6H), 1.34-1.28 (m, 5H), 1.26-1.22 (m, 6H), 1.15-0.97 (m, 5H), 0.90 (s, 3H).

[0749] Synthesis of 1.3

[0750] To a solution of **1.2** (25 g, crude) in DME (300 mL) was added $\text{Rh}_2(\text{OAc})_4$ (680 mg, 1.54 mmol) in one portion at 15°C. After stirring at 15°C for 12 hours, the mixture was treated with H_2O (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic phase was washed with brine (2 x 80 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to provide **1.3** (23.2 g) as crude that was used directly for the next reaction.

[0751] Synthesis of 1.4

[0752] KOH (20.7 g, 369 mmol) was added to a solution of **1.3** (23.2 g, 61.6) in MeOH (300 mL) at 15°C. After stirring at 70°C for 1 hour, the reaction mixture was poured into saturated brine (300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layer was washed with HCl (1M, 200 mL), saturated NaHCO_3 (200 mL), brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to give **1.4** (18.5 g, 99%). $^1\text{HNMR}$ (400 MHz, CDCl_3) δ_{H} 2.67-2.53 (m, 1H), 2.24-2.14 (m, 1H), 2.09-2.03 (m, 1H), 1.93-1.69 (m, 7H), 1.66-1.47 (m, 6H), 1.43-1.31 (m, 5H), 1.31-1.21 (m, 8H), 1.18-0.93 (m, 7H).

[0753] Synthesis of 1.5

[0754] To a solution of t-BuOK (13.5 g, 121 mmol) in THF (370 mL) was added **1.4** (18.5 g, 60.7 mmol) at 25 °C under N_2 . The mixture was stirred at 25 °C for 10 minutes. Then methyl benzenesulfinate (18.9 g, 121 mmol) was added. After stirring at 30°C for 0.5 hour, the mixture was quenched with 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 in vacuum to give **1.5** (26 g, crude). $^1\text{HNMR}$ (400 MHz, CDCl_3) δ_{H} 7.65-7.62 (m, 1H), 7.52-7.43 (m, 4H), 3.75-3.60 (m, 1H), 2.02-1.95 (m, 2H), 1.88-1.65 (m, 6H), 1.64-1.51 (m, 8H), 1.43-1.29 (m, 5H), 1.26-1.22 (m, 5H), 1.04-0.89 (m, 4H).

[0755] Synthesis of 1.6

[0756] To a mixture of **1.5** (26 g, 60.6 mmol) in xylene (300 mL) was added Na_2CO_3 (96.3 g, 909 mol) in portions. After stirring at 140 °C for 12 hours under N_2 , the mixture was filtered and concentrated. The residue was purified by silica gel chromatography (0-30% of ethyl acetate in petroleum ether) to give the **1.6** (12 g, 66%). $^1\text{HNMR}$ (400 MHz, CDCl_3) δ_{H} 6.90-6.78 (m, 1H), 5.91 (dd, $J = 1.6, 10.0$ Hz, 1H), 2.45 (td, $J = 5.2, 19.2$ Hz, 1H), 2.02-1.87 (m, 3H), 1.84-1.73 (m, 3H), 1.66-1.56 (m, 5H), 1.44-1.32 (m, 6H), 1.30-1.24 (m, 5H), 1.21-1.11 (m, 1H), 1.03-0.96 (m, 4H).

[0757] Synthesis of 1.7

[0758] A stirred solution of trimethylsulfoxonium iodide (7.26 g, 33.0 mmol) and t-BuOK (4.07 g, 36.3 mmol) in DMSO (120 mL) was heated at 60°C for 1.0 h under N₂. Compound **1.6** (5.0 g, 16.5 mmol) was added to the reaction mixture and stirred at 25°C for 1 h. The reaction was treated with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic phase was washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum to afford **1.7** (3.4 g, 65%).

¹HNMR(400 MHz, CDCl₃) δ_H 2.17-2.00 (m, 2H), 1.92-1.83 (m, 1H), 1.79-1.71 (m, 3H), 1.68-1.59 (m, 3H), 1.55-1.46 (m, 3H), 1.44-1.36 (m, 3H), 1.35-1.19 (m, 8H), 1.18-1.04 (m, 2H), 1.03-0.91 (m, 6H), 0.81-0.74 (m, 1H).

[0759] Synthesis of 1.8

[0760] To a mixture of PPh₃EtBr (31.7 g, 85.6 mmol) in THF (130 mL) was added t-BuOK (9.6 g, 85.6 mmol) at 15°C under N₂. The resulting mixture was stirred at 40°C for 30 min. Compound **1.7** (3.4 g, 10.7 mmol) was added in portions below 40°C. The reaction mixture was stirred at 80°C for 36 hours. The reaction mixture was quenched with saturated NH₄Cl aqueous (100 mL) at 15°C. Then the organic layer was separated. The aqueous layer was extracted with EtOAc (2×80 mL). The combined organic phase was concentrated under vacuum to give a white solid. The residue was purified by trituration with MeOH/H₂O (1:1, 500 mL) and then purified by flash column (0~12% of ethyl acetate in petroleum ether) to give **1.8** (2.36 g, 67%).

[0761] Synthesis of 1.9

[0762] To a solution of **1.8** (2.36 g, 7.18 mmol) in THF (40 mL) was added BH₃.Me₂S (2.15 mL, 21.5 mmol, 10M) at 0°C. After stirring at 20°C for 12 hours, ethanol (7.52 mL) at 15°C, followed by NaOH aqueous (25.8 mL, 5.0 M) were added to the resulting mixture at 0°C. Hydrogen peroxide (12.9 mL, 10 M) was added dropwise at 0°C to the reaction mixture. The resulting mixture was stirred at 78°C for 1 hour. The mixture was cooled down to 15°C. Saturated aqueous Na₂S₂O₃ (80 mL) was added to the mixture. The aqueous phase was extracted with EtOAc (2×80 mL). The combined organic phase was washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (0~30% of ethyl acetate in petroleum ether) to afford **1.9** (1.6 g, 65%).

[0763] Synthesis of 1.10

[0764] To a solution of **1.9** (1.6 g, 4.61 mmol) in DCM (20 mL) was added Dess-martin reagent (3.9 g, 9.22 mmol) at 20°C. After the mixture was stirred at 20°C for 1 hour, the

mixture was quenched with saturated aqueous NaHCO₃ (30 mL) at 20°C. The DCM phase was separated and washed with saturated aq. NaHCO₃/Na₂S₂O₃ (1:1, 2 x 50 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (0~25% of ethyl acetate in petroleum ether) to give **1.10** (1.3 g, 82%).

[0765] Synthesis of 1.11

[0766] To a solution of **1.10** (100 mg, 0.290 mmol) in MeOH (10 mL) was added NaOH (347 mg, 8.7 mmol) in H₂O (1 mL) under N₂. After stirring at 80°C for 16 hours, the mixture was treated with H₂O (30 mL) and extracted with EtOAc (3 x 40 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (15~25% ethyl acetate in petroleum ether) to give **1.11** (90 mg, 90%). ¹HNMR (400 MHz, CDCl₃) δ_H 2.23 (s, 3H), 2.18-2.15 (m, 1H), 2.02-1.95 (m, 1H), 1.90-1.82 (m, 1H), 1.78-1.74 (m, 2H), 1.68-1.57 (m, 4H), 1.40-1.11 (m, 13H), 0.99-0.85 (m, 8H), 0.71-0.63 (m, 1H), 0.60-0.50 (m, 1H), -0.12 (q, *J* = 5.2 Hz, 1H).

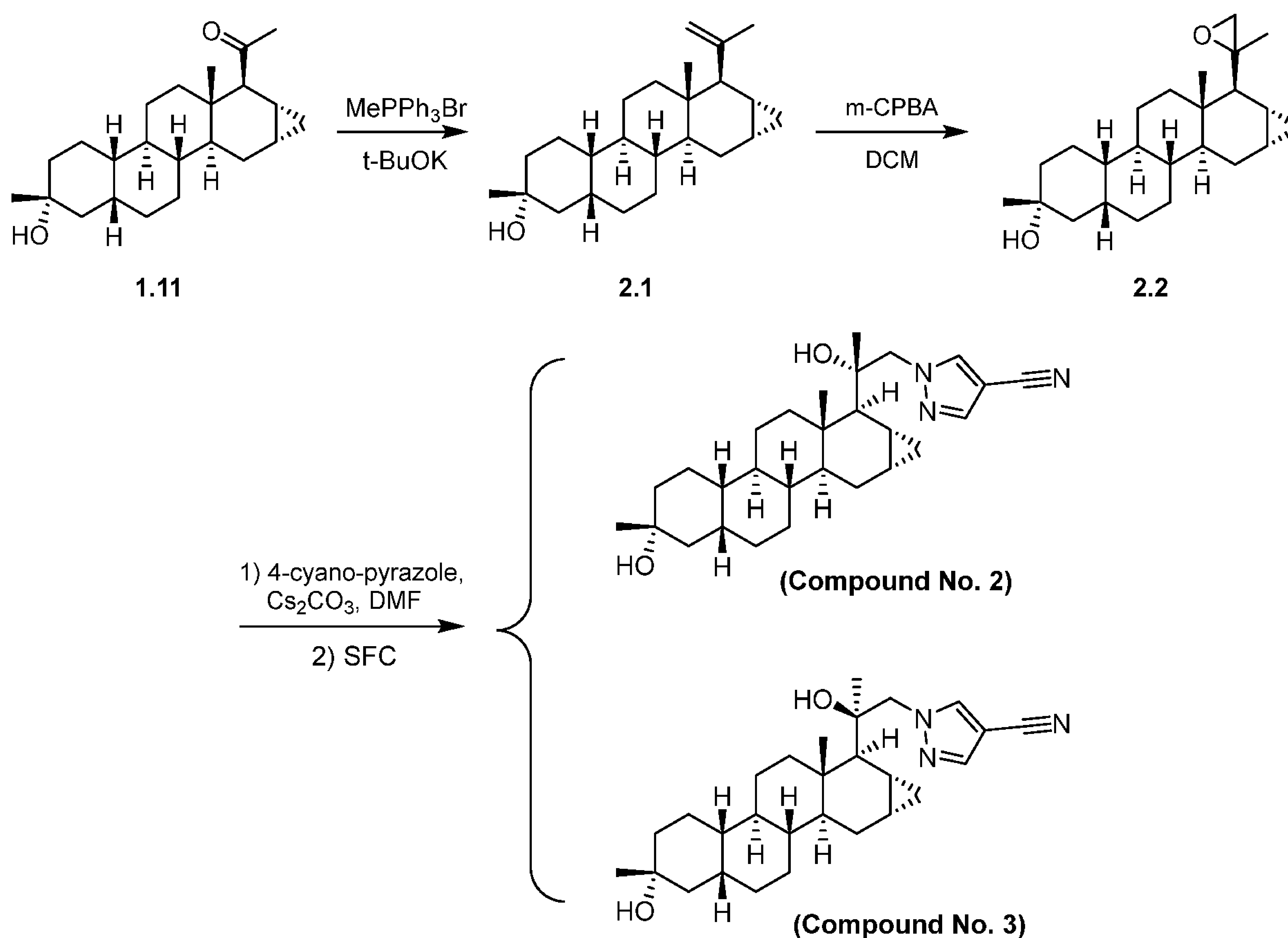
[0767] Synthesis of 1.12

[0768] To a solution of **1.11** (80 mg, 0.23 mmol) in MeOH (5 mL) was added HBr (9.37 mg, 0.046 mmol, 40% in water) and Br₂ (44.5 mg, 0.27 mmol) at 20°C. After stirring at 20°C for 2 h, the mixture was quenched with sat. aq. NaHCO₃ (10 mL), treated with water (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford **1.12** (100 mg) as crude used directly for the next step.

[0769] Synthesis of Compound No. 1

[0770] To a solution of **1.12** (100 mg, 0.23 mmol) in acetone (10 mL) was added 4-cyanopyrazole (32.9 mg, 0.35 mmol) and K₂CO₃ (66.2 mg, 0.47 mmol) at 20°C and stirred for 16 hours. To the reaction mixture was added H₂O (20 mL) at 25°C. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with saturated brine (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered, concentrated and purified by flash column (0-50% of ethyl acetate in petroleum ether) to give **1** (33.8 mg, 33.1 %). ¹HNMR (400 MHz, CDCl₃) δ_H 7.87 (s, 1H), 7.83 (s, 1H), 5.15-5.05 (m, *J* = 1.0 Hz, 2H), 2.14 (d, *J* = 4.4 Hz, 1H), 2.06-1.97 (m, 1H), 1.88-1.81 (m, 1H), 1.79-1.58 (m, 6H), 1.43-1.16 (m, 13H), 1.08-0.86 (m, 8H), 0.79-0.70 (m, 1H), 0.63-0.53 (m, 1H), -0.08 (q, *J* = 4.4 Hz, 1H).

[0771] **Example No. 2: Synthesis of 1-((S)-2-hydroxy-2-((2R,4aS,4bR,6aS,7S,7aR,8aR,9aS,9bR,11aR)-2-hydroxy-2,6a-dimethyloctadecahydro-1H-cyclopropa[b]chrysen-7-yl)propyl)-1H-pyrazole-4-carbonitrile (Compound No. 2) and 1-((S)-2- 1-((R)-2-hydroxy-2-((2R,4aS,4bR,6aS,7S,7aR,8aR,9aS,9bR,11aR)-2-hydroxy-2,6a-dimethyloctadecahydro-1H-cyclopropa[b]chrysen-7-yl)propyl)-1H-pyrazole-4-carbonitrile (Compound No. 3).**



[0772] Synthesis of 2.1

[0773] To a solution of PPh_3MeBr (4.64 g, 13 mmol) in THF (40 mL) was added $t\text{-BuOK}$ (1.45 g, 13 mmol). The reaction mixture was stirred for 0.5 h at 50°C . A solution of **1.11** (450 mg, 1.3 mmol) in THF (5 mL) was added to the reaction at 50°C . After the reaction mixture was stirred for 16 hours at 50°C , the mixture was poured into saturated NH_4Cl (100 mL) and 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 in vacuum. The mixture was purified by flash chromatography (0~25% ethyl acetate in petroleum ether) to get **2.1** (300 mg, 67%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 4.88 (s, 1H), 4.75-4.70 (m, 1H), 2.02-1.94 (m, 1H), 1.91-1.72 (m, 6H), 1.53-1.37 (m, 7H), 1.31-1.19 (m, 9H), 0.95-0.76 (m, 10H), 0.67-0.59 (m, 1H), 0.57-0.48 (m, 1H), -0.14 (q, $J = 4.8$ Hz, 1H).

[0774] Synthesis of 2.2

[0775] To a solution **2.1** (150 mg, 0.43 mmol) in DCM (10 mL), m-CPBA (141 mg, 0.65 mmol, 80%) was added. After stirring at 20°C for 1 h, the mixture was quenched by saturated aq. NaHCO₃ (10 mL) at 20°C. The DCM phase was separated and washed with saturated aq. NaHCO₃/Na₂S₂O₃ (1:1, 2 x 100 mL), brine (10 mL), dried over Na₂SO₄, filtered and concentrated under vacuum to give **2.2** (170 mg). ¹HNMR (400 MHz, CDCl₃) δ_H 2.73-2.66 (m, 2H), 1.99-1.93 (m, 1H), 1.86-1.62 (m, 5H), 1.42-1.34 (m, 5H), 1.33-1.15 (m, 11H), 1.05-0.91 (m, 6H), 0.89-0.65 (m, 6H), 0.50-0.38 (m, 1H), 0.11--0.19 (m, 1H).

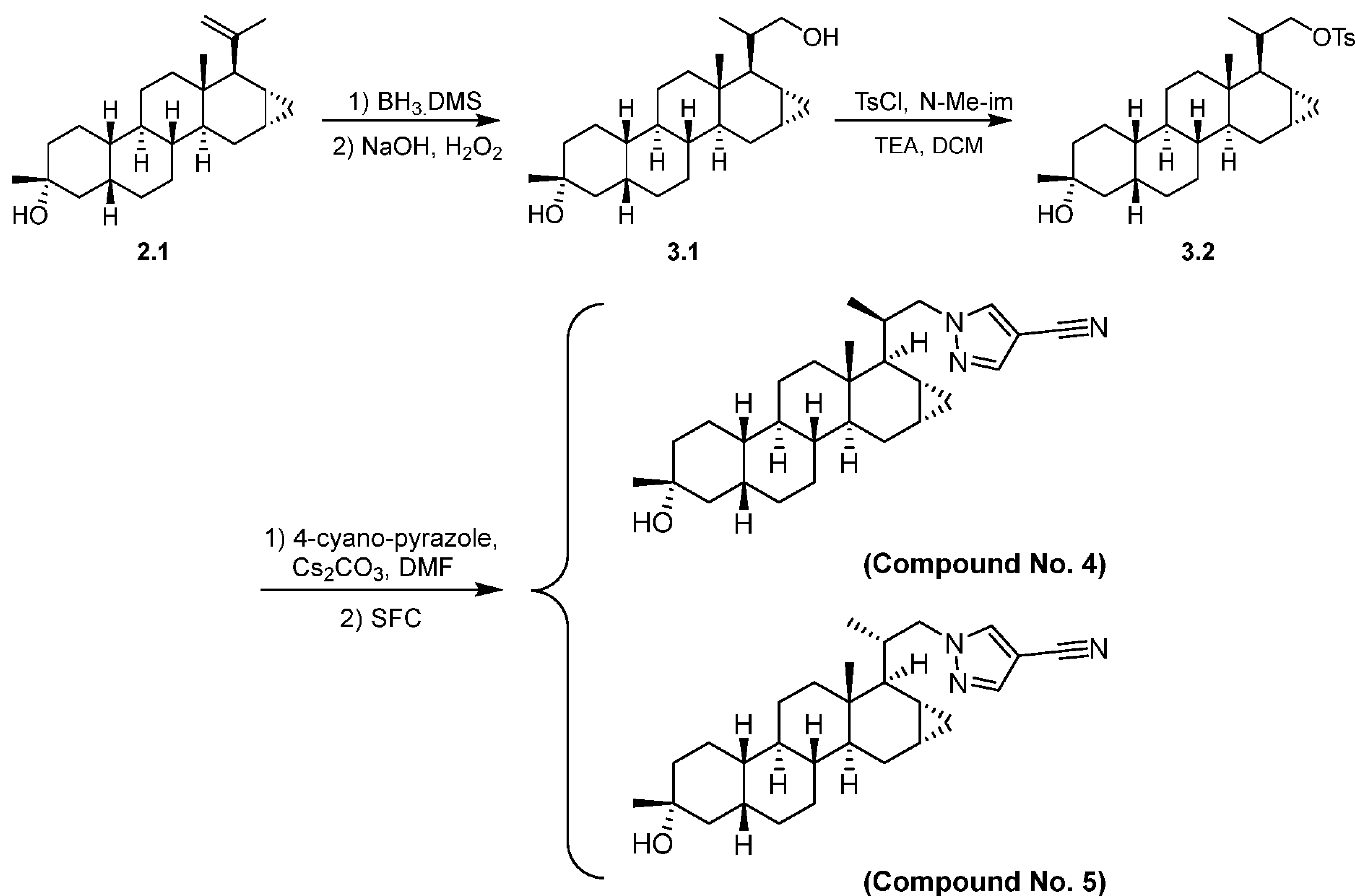
[0776] Synthesis of Compound No. 2 and Compound No. 3

[0777] A solution of **2.2** (200 mg, 0.55 mmol), Cs₂CO₃ (547 mg, 1.67 mmol) and 4-cyano-pyrazole (103 mg, 1.11 mmol) in DMF (10 mL) was stirred at 120°C for 16 hours. The mixture was poured into saturated NH₄Cl (30 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with LiCl (100 mL, 3% in water), brine (2 x 30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (0~40% of ethyl acetate in petroleum ether) to give a mixed product. The residue was purified by SFC (Column: DAICEL CHIRALCEL OD-H (250mm*30mm, 5um); Condition: 0.1%NH₃H₂O EtOH; Begin B: 35%; End B: 35%; FlowRate (ml/min): 60; Injections: 60) to get **Compound No. 2** (7.9 mg, 3%) and **Compound No. 3** (70.3 mg, 28%).

[0778] Compound No. 2: ¹HNMR (400 MHz, CDCl₃) δ_H 7.93 (s, 1H), 7.86 (s, 1H), 4.41 (d, *J* = 13.8 Hz, 1H), 4.17 (d, *J* = 13.8 Hz, 1H), 3.62 (s, 1H), 2.31-2.18 (m, 1H), 1.98-1.91 (m, 1H), 1.89-1.82 (m, 1H), 1.78-1.66 (m, 3H), 1.53-1.36 (m, 5H), 1.31-1.21 (m, 11H), 1.02-0.59 (m, 11H), 0.56-0.47 (m, 1H), 0.44-0.34 (m, 1H), -0.43 (q, *J* = 4.8 Hz, 1H).

[0779] Compound No. 3: ¹HNMR (400 MHz, CDCl₃) δ_H 7.96 (s, 1H), 7.80 (s, 1H), 4.48-4.34 (m, 2H), 2.47 (s, 1H), 2.20-2.11 (m, 1H), 2.04-1.96 (m, 1H), 1.91-1.84 (m, 1H), 1.78-1.66 (m, 3H), 1.56-1.23 (m, 14H), 1.12-1.07 (m, 4H), 1.02 (s, 3H), 0.99-0.52 (m, 8H), -0.09--0.15 (m, 1H).

[0780] **Example No. 3: Synthesis of 1-((R)-2-((2R,4aS,4bR,6aS,7R,7aR,8aR,9aS,9bR,11aR)-2-hydroxy-2,6a-dimethyloctadecahydro-1H-cyclopropa[b]chrysen-7-yl)propyl)-1H-pyrazole-4-carbonitrile (Compound No. 4) and 1-((S)-2-((2R,4aS,4bR,6aS,7R,7aR,8aR,9aS,9bR,11aR)-2-hydroxy-2,6a-dimethyloctadecahydro-1H-cyclopropa[b]chrysen-7-yl)propyl)-1H-pyrazole-4-carbonitrile (Compound No. 5).**



[0781] Synthesis of 3.1

[0782] $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (0.3 mL, 10M, 2.99 mmol) was added to a solution of **2.1** (150 mg, 0.43 mmol) in THF (5 mL) under N_2 . After stirring at 20 °C for 12 hours, the mixture was cooled down to 0°C. Then EtOH (0.771 mL, 13.1 mmol) and NaOH (2.61 mL, 5M, 13.1 mmol) were added to the mixture, followed by dropwise addition of H_2O_2 (1.3 mL, 10M, 13.1 mmol) at 15°C. The mixture was stirred at 70°C for 1 hour. Then the mixture was poured into $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL, sat.) and stirred for 30 mins. The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with saturated brine (50 mL) and dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated to get **3.1** (180 mg, crude).

[0783] Synthesis of 3.2

[0784] To a solution of **2.1** (180 mg, 0.49 mmol) in DCM (5 mL) was added N-methylimidazole (61.4 mg, 0.74 mmol), TEA (206 μL , 1.49 mmol) and TsCl (190 mg, 0.99

mmol). After the mixture stirring at 20°C for 1 h, the mixture was poured into NaHCO₃ (10 mL, saturated). The aqueous phase was extracted with DCM (2 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give **3.2** (200 mg, crude), which was used directly for next step.

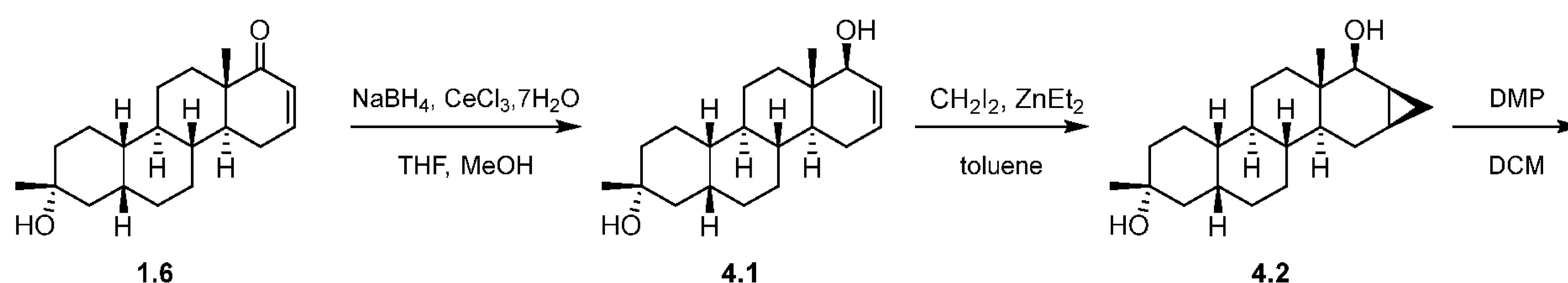
[0785] Synthesis of Compound No. 4 and Compound No. 5

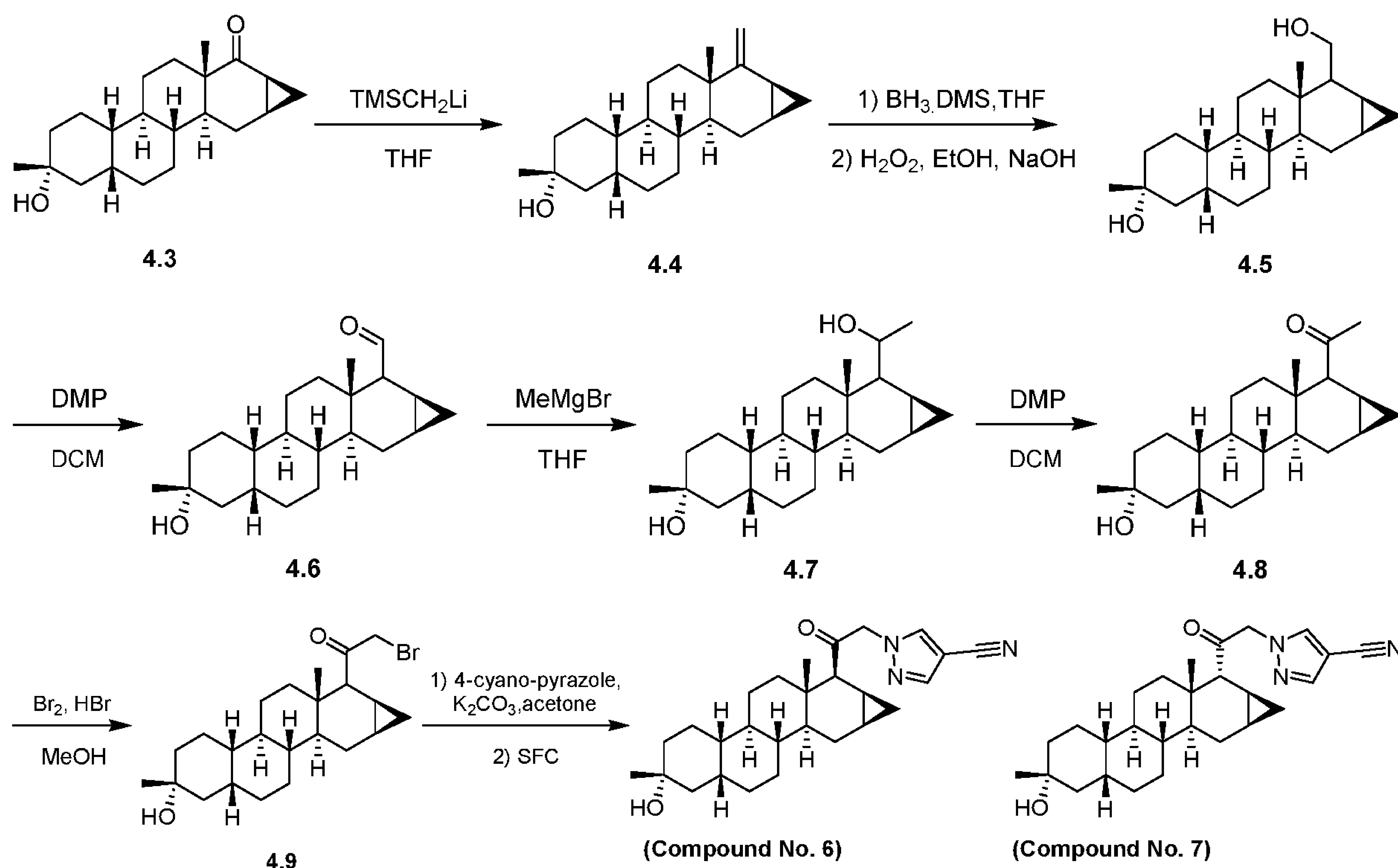
[0786] To a solution of **3.2** (200 mg, 0.38 mmol) in DMF (10 mL) was added 4-cyano-pyrazole (54.2 mg, 0.58 mmol) and Cs₂CO₃ (253 mg, 0.77 mmol). After stirring at 120 °C for 16 hours, the mixture was poured into water (20 mL) and stirred for 5 mins. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with saturated brine (2 x 100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (0-30% of ethyl acetate in petroleum ether). The residue was purified by SFC (Column: DAICEL CHIRALCEL OD-H (250mm*30mm, 5um); Condition: 0.1%NH₃H₂O EtOH; Begin B: 30%; End B: 30%; FlowRate (ml/min): 60; Injections: 60) to give **Compound No. 4** (4 mg, 2%) and **Compound No. 5** (60.4 mg, 36%).

[0787] Compound No. 4: ¹HNMR (400 MHz, CDCl₃) δ_H 7.83 (s, 1H), 7.81 (s, 1H), 4.18-3.96 (m, 2H), 2.76-2.65 (m, 1H), 1.99-1.91 (m, 1H), 1.87-1.80 (m, 1H), 1.76-1.68 (m, 3H), 1.45-1.32 (m, 4H), 1.27-1.07 (m, 9H), 0.99-0.55 (m, 16H), 0.40-0.30 (m, 1H), -0.22--0.36 (m, 1H).

[0788] Compound No. 5: ¹HNMR (400 MHz, CDCl₃) δ_H 7.81 (s, 1H), 7.77 (s, 1H), 4.59-4.48 (m, 1H), 3.94-3.81 (m, 1H), 2.66-2.54 (m, 1H), 2.03-1.84 (m, 3H), 1.76-1.60 (m, 4H), 1.55-1.28 (m, 7H), 1.27-1.03 (m, 7H), 0.98-0.83 (m, 11H), 0.76-0.66 (m, 1H), 0.60-0.48 (m, 2H), -0.10--0.17 (m, 1H).

[0789] Example No. 4: Synthesis of 1-(2-((2R,4aS,4bR,6aS,7S,7aS,8aS,9aS,9bR,11aR)-2-hydroxy-2,6a-dimethyloctadecahydro-1H-cyclopropa[b]chrysen-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (Compound No. 6) and 1-(2-((2R,4aS,4bR,6aS,7R,7aS,8aS,9aS,9bR,11aR)-2-hydroxy-2,6a-dimethyloctadecahydro-1H-cyclopropa[b]chrysen-7-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (Compound No. 7).





[0790] Synthesis of 4.1

[0791] To a solution of **1.6** (1 g, 3.30 mmol) in MeOH (16 mL) and THF (4 mL) was added $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.46 g, 3.96 mmol) at 0°C . After stirring at 0°C for 10 min. NaBH_4 (150 mg, 3.96 mmol) was added. The mixture was stirred at 0°C for 1 h. The mixture was added to NH_4Cl (50 mL) and extracted with DCM (2 x 100 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by flash column (0~50% of ethyl acetate in petroleum ether) to give **4.1** (1.3 g, crude). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 5.77-5.63 (m, 1H), 5.53-5.42 (m, 1H), 3.86 (s, 1H), 2.20-2.08 (m, 1H), 2.01-1.87 (m, 2H), 1.80-1.69 (m, 3H), 1.54-1.48 (m, 3H), 1.44-1.28 (m, 7H), 1.28-1.24 (m, 4H), 1.23-0.89 (m, 6H), 0.79 (s, 3H).

[0792] Synthesis of 4.2

[0793] To a solution of **4.1** (1.7 g, 5.58 mmol) in toluene (20 mL) was added diethylzinc (16.7 mL, 16.7 mmol, 1 M) and diiodomethane (1.34 mL, 16.7 mmol, 3.32 g/mL) at 0°C for 30 min. Then the mixture was stirred 25°C for 16 hours. The mixture was quenched with NH_4Cl (100 mL), extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (0~30% ethyl acetate in petroleum ether) to give **4.1** and **4.2** (1.1 g). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 3.82-3.74 (m, 1H), 2.20-1.60 (m,

7H), 1.57-1.30 (m, 5H), 1.28-1.26 (m, 3H), 1.26-1.22 (m, 4H), 1.22-0.79 (m, 9H), 0.69 (s, 3H), 0.60-0.53 (m, 1H), 0.48-0.40 (m, 1H).

[0794] Synthesis of 4.3

[0795] To a solution of **4.2** (1.05 g, 3.29 mmol) in DCM (15 mL) was added Dess-martin (2.78 g, 6.58 mmol) at 25 °C. After stirring at 25 °C for 10 min. The mixture was quenched by saturated NaHCO₃/Na₂S₂O₃ aqueous (1:1, 150mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give **4.3** (1.4 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 2.50-2.40 (m, 1H), 2.32-2.20 (m, 2H), 2.05-1.70 (m, 9H), 1.45-1.30 (m, 5H), 1.28-1.25 (m, 6H), 1.09-0.96 (m, 6H), 0.92 (s, 3H).

[0796] Synthesis of 4.4

[0797] To a solution of **4.3** (700 mg, 2.21 mmol) in THF (5 mL) was added TMSCH₂Li (22.0 mL, 11.0 mmol, 0.5 M) at -30°C. After stirring for 16 hours at 25°C. The mixture was poured into saturated NH₄Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with saturated brine (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column (0~20% of ethyl acetate in petroleum ether) to give **4.4** (420 mg, 60 %). ¹H NMR (400 MHz, CDCl₃) δ_H 4.96-4.92 (m, 1H), 4.87-4.84 (m, 1H), 2.25-2.17 (m, 1H), 1.98-1.86 (m, 3H), 1.82-1.58 (m, 5H), 1.53-1.32 (m, 8H), 1.27-1.24 (m, 7H), 0.90-0.88 (m, 2H), 0.84 (s, 3H), 0.82-0.73 (m, 2H), 0.57-0.51 (m, 1H).

[0798] Synthesis of 4.5

[0799] BH₃·Me₂S (1.32 mL, 10M, 13.2 mmol) was added to a solution of **4.4** (420 mg, 1.33 mmol) in THF (8 mL) under N₂. The reaction mixture was stirred at 20°C for 12 hours. The mixture was cooled down to 0°C. Then, EtOH (4.70 mL, 79.8 mmol) and NaOH (15.9 mL, 5M, 79.8 mmol) were added to the mixture, followed by dropwise addition of H₂O₂ (7.97 mL, 10M, 79.8 mmol) at 15°C. After stirring at 70°C for 1 hour, the mixture was poured into Na₂S₂O₃ (30 mL, sat.) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (0 ~70% ethyl acetate in petroleum ether) to give **4.5** (120 mg, 39 %).

[0800] Synthesis of 4.6

[0801] To a solution of **4.5** (180 mg, 0.541 mmol) in DCM (5 mL) was added DMP (457 mg, 1.08 mmol) at 25°C. After stirring at 25°C for 10 min, the mixture was poured into NaHCO₃/

Na₂S₂O₃ (20 mL, 1:1) and extracted with DCM (2 x 10 mL). The combined organic phase was washed with NaHCO₃/Na₂S₂O₃ (1:1, 2 x 10 mL, sat.), brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give **4.6** (175 mg, crude).

[0802] Synthesis of 4.7

[0803] To a solution of MeMgBr (573 µL, 1.72 mmol) was added **4.6** (190 mg, 0.575 mmol) in THF (2 mL) at 0°C. The reaction mixture was stirred at 25°C for 1 h. The mixture was poured into NH₄Cl (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered, concentrated in vacuum and purified by flash chromatography (0~30% of ethyl acetate in petroleum ether) to give **4.7** (130 mg, 65 %).

[0804] Synthesis of 4.8

[0805] To a solution of **4.7** (100 mg, 0.289 mmol) in DCM (10 mL) was added DMP (244 mg, 0.577 mmol) at 25°C. The mixture was stirred at 25°C for 1 h. The mixture was poured into NaHCO₃/Na₂S₂O₃ (20 mL, 1:1) and extracted with DCM (2 x 10 mL). The combined organic phase was washed with NaHCO₃/Na₂S₂O₃ (1:1, 2 x 10 mL, sat.), brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated to give **4.8** (125 mg, crude).

[0806] Synthesis of 4.9

[0807] To a solution of **4.8** (130 mg, 0.377 mmol) in methanol (3 mL) was added HBr (40%, 76.2 mg, 0.377 mmol) and Br₂ (66.3 mg, 0.415 mmol) dropwise at 25 °C and stirred for 1 h. NaHCO₃ (10 ml, sat. aq.) was added to the reaction mixture at 25 °C. The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give **4.9** (130 mg, crude).

[0808] Synthesis of Compound No. 6 and Compound No. 7

[0809] A solution of **4.9** (130 mg, 0.30 mmol), K₂CO₃ (171 mg, 1.22 mmol) and 4-cyano-pyrazole (57.1 mg, 0.61 mmol) in acetone (5 mL) was stirred at 25°C for 16 hours. The mixture was poured into saturated H₂O (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with saturated brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by flash chromatography (10~15% ethyl acetate in petroleum ether) to give **Compound No. 7** (30 mg, 22 %) and **Compound No. 6** (45 mg, 34 %). **Compound No. 7** (30 mg) was further purified by HPLC (Column: Phenomenex Gemini-NX C¹⁸ 75*30mm*3um; Condition: water (0.225%FA)-ACN; Begin B: 60; End B: 90; Gradient Time (min): 7; 100%B Hold Time

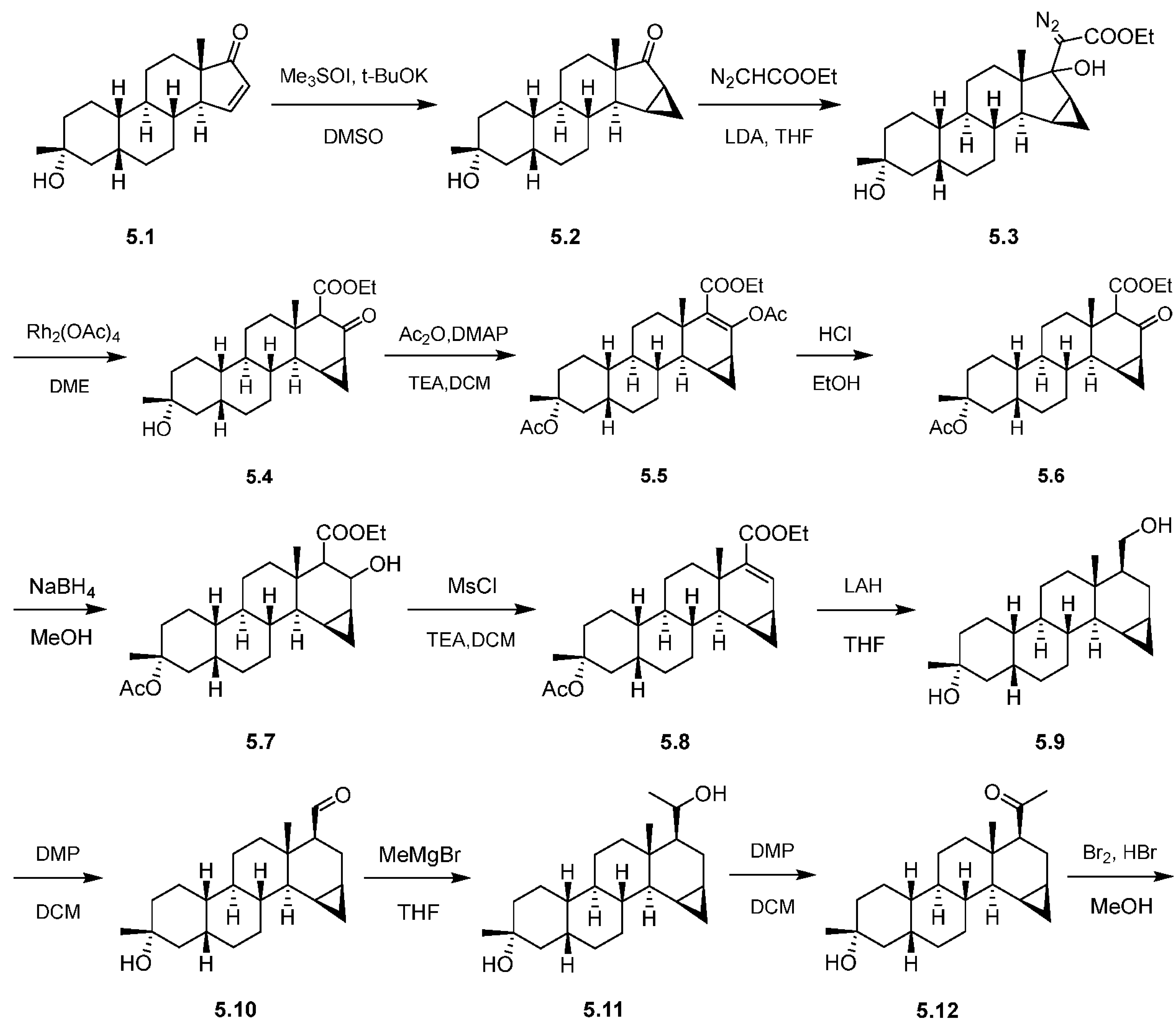
(min) 2; Flow Rate (ml/min): 30; Injections: 4) and lyophilized to give **7** (3.8 mg, 13 %).

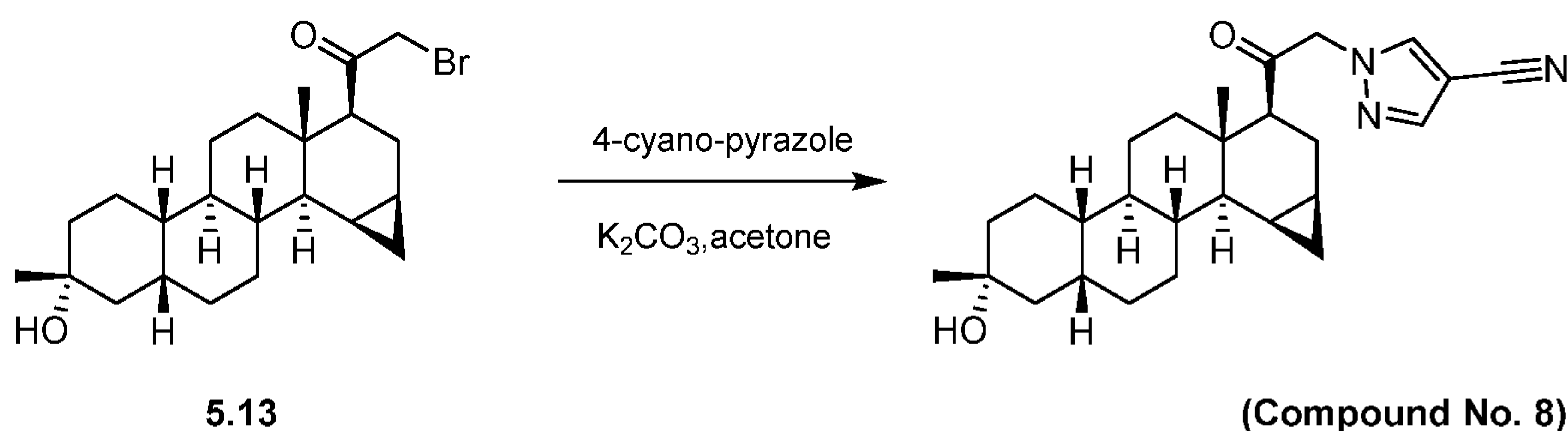
Compound **6** (45 mg, 0.103 mmol) was lyophilized to give **6** (25.6 mg, 57 %).

[0810] Compound No. 6: ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.86 (s, 1H), 7.83 (s, 1H), 5.29-5.23 (m, 2H), 2.84-2.73 (m, 1H), 2.29-2.16 (m, 1H), 1.91-1.74 (m, 4H), 1.45-1.29 (m, 9H), 1.26 (s, 3H), 1.21-1.15 (m, 2H), 1.03-0.87 (m, 7H), 0.83 (s, 3H), 0.79-0.65 (m, 3H).

[0811] Compound No. 7: ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.91 (s, 1H), 7.84 (s, 1H), 5.16 (d, $J = 18.0$ Hz, 1H), 5.03 (d, $J = 18.0$ Hz, 1H), 2.87 (s, 1H), 2.37-2.20 (m, 1H), 1.86-1.58 (m, 7H), 1.40-1.26 (m, 8H), 1.24 (s, 3H), 1.21-0.92 (m, 6H), 0.88 (s, 3H), 0.77-0.62 (m, 3H), 0.51-0.45 (m, 1H).

[0812] Example No. 5: Synthesis of 1-(2-((1S,2aR,3aR,3bS,3cR,5aR,7R,9aS,9bR,11aS)-7-hydroxy-7,11a-dimethyloctadecahydro-1H-cyclopropa[c]chrysen-1-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (Compound No. 8).





[0813] Synthesis of 5.2

[0814] To a stirred solution of trimethylsulfoxonium iodide (56.3 g, 256 mmol) in DMSO (800 mL) was added t-BuOK (31.5 g, 281 mmol). After stirring at 60°C for 1 h under N₂, **5.1** (37 g, 128 mmol) was added and stirred at 25°C for 2 hours. The reaction was treated with water (500 mL) and extracted with EtOAc (2 x 500 mL). The combined organic phase was washed with brine (500 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by column (0-20% of ethyl acetate in petroleum ether) to give **5.2** (20 g, 52%). ¹H NMR (400 MHz, CDCl₃) δ_H 2.04-2.00 (m, 1H), 1.96-1.90 (m, 1H), 1.85-1.70 (m, 6H), 1.65-1.55 (m, 4H), 1.42-1.26 (m, 12H), 1.14-1.03 (m, 2H), 0.95 (s, 3H), 0.90-0.82 (m, 1H).

[0815] Synthesis of 5.3

[0816] An LDA solution (82.5 mL, 2M, 165 mmol) was added to a stirred solution of **5.2** (10 g, 33 mmol) and ethyl diazoacetate (17.3 mL, 165 mmol) in THF (500 mL) at -70°C. After stirring at -70°C for 3 h, acetic acid (9.42 mL, 165 mmol) in THF (10 mL) was added, then the mixture was warmed up to 20°C and stirred for 16 hrs. Water (500 mL) was added to the reaction mixture and combined with another batch from **5.2** (10 g) to be extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with saturated brine (500 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (0~30% of ethyl acetate in petroleum ether) to give **5.3** (20 g).

[0817] Synthesis of 5.4

[0818] To a solution of **5.3** (20 g, 48 mmol) in DME (300 mL) was added Rh₂(OAc)₄ (530 mg, 1.2 mmol). After stirring at 20°C for 12 hours, H₂O (100 mL) was added to the mixture and extracted with EtOAc (2 x 60 mL). The combined organic phase was washed with brine (2 x 30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (0-40% of ethyl acetate in petroleum ether) to give **5.4** (9 g, 48%). ¹H NMR (400 MHz, CDCl₃) δ_H 4.24-4.15 (m, 2H), 3.07 (s, 1H), 1.90-1.61 (m, 9H), 1.51-1.31 (m, 10H), 1.30-1.25 (m, 8H), 1.17-1.10 (m, 1H), 1.06-0.98 (m, 4H), 0.93-0.85 (m, 1H).

[0819] Synthesis of 5.5

[0820] To a solution of **5.4** (9 g, 23.1 mmol) and DMAP (2.82 g, 23.1 mmol) in DCM (100 mL) was added dropwise TEA (4.66 g, 46.2 mmol) and Ac₂O (7.07 g, 69.3 mmol) at 20°C. After stirring at 20°C for 16 hours, the mixture was poured into ice-water (50 mL) and extracted with DCM (2 x 100 mL). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give **5.5** (10 g, crude).

[0821] Synthesis of 5.6

[0822] HCl (5 mL, in 50 mL EtOH) was added to a solution of **5.5** (10 g, 21.1 mmol) in THF (50 mL). The mixture was stirred at 20°C for 48 then pour over NaHCO₃ (50 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (2 x 30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column (0~30% of ethyl acetate in petroleum ether) to give **5.6** (3.6 g, 40%). ¹H NMR (400 MHz, CDCl₃) δ_H 4.19 (q, *J* = 7.2 Hz, 2H), 3.07 (s, 1H), 1.99 (s, 3H), 1.92-1.60 (m, 12H), 1.53-1.30 (m, 8H), 1.29-1.10 (m, 6H), 1.06-0.87 (m, 6H).

[0823] Synthesis of 5.7

[0824] To a solution of **5.6** (0.5 g, 1.28 mmol) in MeOH/THF (5 mL/5 mL) was added NaBH₄ (96.8 mg, 2.56 mmol) at 25°C. After stirring at 25°C for 1 h, the reaction mixture was quenched with saturated aq. NH₄Cl (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under vacuum to give **5.7** (500 mg, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 4.65 (dd, *J* = 4.0, 8.8 Hz, 1H), 4.19-4.10 (m, 2H), 3.65 (s, 1H), 2.11 (d, *J* = 4.0 Hz, 1H), 2.07-1.96 (m, 5H), 1.90-1.58 (m, 10H), 1.53-1.38 (m, 6H), 1.30-1.23 (m, 7H), 1.13-1.03 (m, 5H), 0.92-0.85 (m, 1H), 0.48-0.40 (m, 1H).

[0825] Synthesis of 5.8

[0826] To a solution of **5.7** (600 mg, 1.38 mmol) in DCM (20 mL) was added TEA (2.77 g, 27.5 mmol) and 1-methyl-1H-imidazole (5 mL) at 20°C. The reaction mixture was cooled down to 0°C. Then, MsCl (1.17 g, 10.3 mmol) in DCM (10 mL) was added. After stirring at 20°C for 16 hours, the reaction mixture was quenched with water (50 mL) and extracted with DCM (2 x 50 mL). The combined organic phase was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by flash column (0~20% of ethyl acetate in petroleum ether) to give **5.8** (500 mg, 87%). ¹H NMR (400 MHz, CDCl₃) δ_H 7.05 (d, *J* = 5.8 Hz, 1H), 4.18-4.09 (m, 2H), 2.33-2.28 (m, 1H), 2.99-1.94 (m, 4H),

1.88-1.58 (m, 10H), 1.56-1.33 (m, 10H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.18-1.10 (m, 5H), 0.91-0.86 (m, 2H).

[0827] Synthesis of 5.9

[0828] To a solution of LiAlH_4 (100 mg, 2.63 mmol) in THF (5 mL) was added **5.8** (200 mg, 0.482 mmol) in THF (5 mL) under N_2 . The mixture was stirred at 25°C for 1 h. Then H_2O (0.1 mL) in THF (2 mL), 10% NaOH aq. (0.1 mL) and H_2O (0.3 mL) were added. The mixture was filtered and concentrated. The residue was combined with another reaction of **5.9** (200 mg) to be purified by flash chromatography (0~60% of ethyl acetate in petroleum ether) to give **5.9** (250 mg, crude). Crude **5.9** (50 mg) was purified by prep-HPLC (Column: Xtimate C18 150*40mm*5um; Condition: water(0.225%FA)-ACN; Begin B: 52; End B: 92; Gradient Time(min): 10; 100%B Hold Time(min): 5; FlowRate(mL/min): 30; Injections: 3) to give **5.9** (8 mg, 16%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 3.79 (dd, $J = 4.0, 10.4$ Hz, 1H), 3.24 (dd, $J = 8.0, 10.8$ Hz, 1H), 2.25-2.11 (m, 1H), 1.90-1.30 (m, 19H), 1.27 (s, 3H), 1.18-0.76 (m, 6H), 0.68 (s, 3H), 0.36-0.23 (m, 2H).

[0829] Synthesis of 5.10

[0830] To a solution of **5.9** (200 mg, 0.60 mmol) in DCM (5 mL) was added DMP (508 mg, 1.2 mmol) at 25°C. After stirring at 25°C for 10 min, the mixture was poured into $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ (50 mL, 1:1) and extracted with DCM (2 x 50 mL). The combined organic phase was washed with $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ (1:1, 2 x 50 mL, sat.), brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to give **5.10** (200 mg, crude).

[0831] Synthesis of 5.11

[0832] To a solution of MeMgBr (1 mL, 3 mmol) in THF (5 mL) was added **5.10** (250 mg, 0.75 mmol) in THF (5 mL) at 0°C. After stirring at 25°C for 1 h, the mixture was poured into NH_4Cl (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL), dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by flash column (0~50% of ethyl acetate in petroleum ether) to give **5.11** (150 mg, crude).

[0833] Synthesis of 5.12

[0834] To a solution of **5.11** (100 mg, 0.28 mmol) in DCM (5 mL) was added DMP (244 mg, 0.57 mmol) at 25°C. After stirring at 25°C for 10 min, the reaction mixture was poured into $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ (30 mL, 1:1) and extracted with DCM (2 x 30 mL). The combined organic phase was washed with $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ (1:1, 2 x 30 mL, sat.), brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was combined with another batch

from **5.12** (50 mg) to be purified by flash column (0~15% of ethyl acetate in petroleum ether) to give **5.12** (100 mg, 67%).

[0835] Synthesis of 5.13

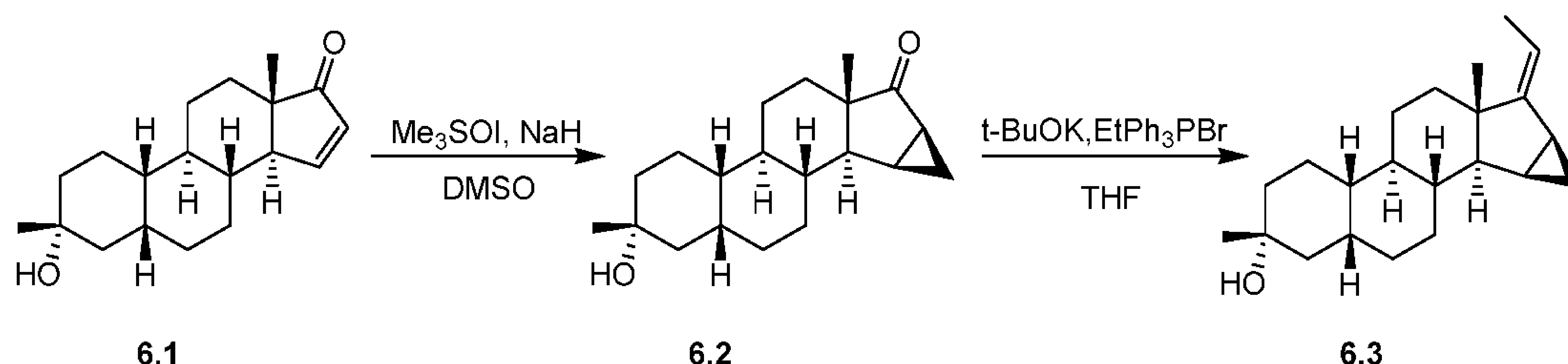
[0836] To a solution of **5.12** (100 mg, 0.29 mmol) in MeOH (5 ml) was added HBr (11.7 mg, 0.058 mmol, 40% in water) and Br₂ (74.1 mg, 0.46 mmol) at 25°C. After stirring at 25°C for 2 hrs, the reaction mixture was quenched with sat. aq NaHCO₃ (10 mL), treated with water (20 mL), extracted with EtOAc (2 x 30 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, concentrated in vacuum to afford **5.13** (100 mg) as crude to use directly for the next step.

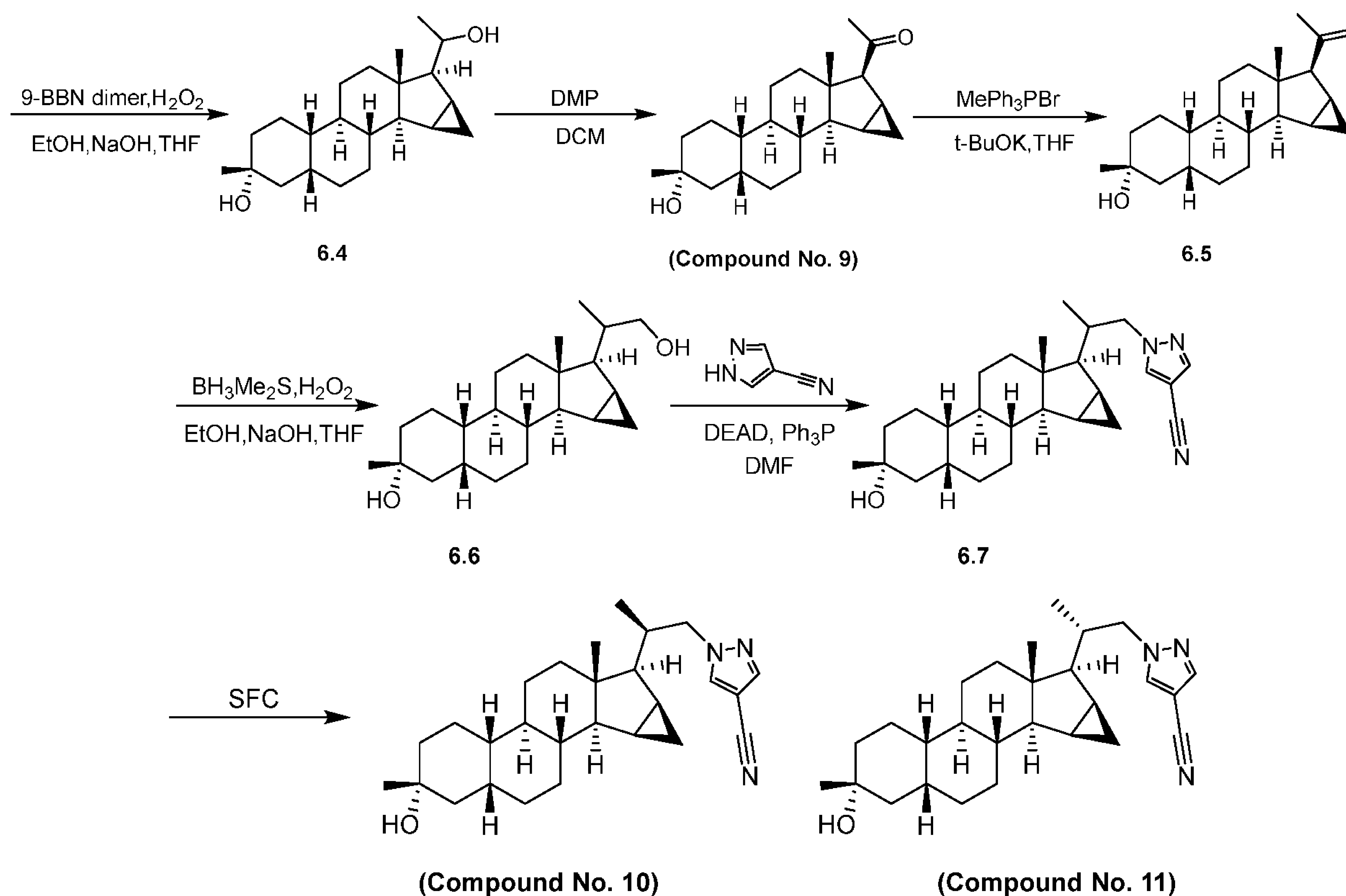
[0837] Synthesis of Compound No. 8

[0838] To a solution of **8.13** (100 mg, 0.23 mmol) in acetone (5 mL) was added 4-cyano-pyrazole (43.9 mg, 0.47 mmol) and K₂CO₃ (66.2 mg, 0.47 mmol) at 25°C and stirred for 16 hours. The reaction mixture was poured into H₂O (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (0-50% of ethyl acetate in petroleum ether) and lyophilized to give **Compound No. 8** (25 mg, 25 %).

¹H NMR (400 MHz, CDCl₃) δ_H 7.81 (s, 2H), 5.06-4.92 (m, 2H), 2.42-2.33 (dd, *J* = 4.8, 12.4 Hz, 1H), 2.02-1.63 (m, 7H), 1.53-1.39 (m, 8H), 1.37-1.25 (m, 4H), 1.35-1.25 (m, 2H), 1.24-0.93 (m, 5H), 0.91-0.80 (m, 4H), 0.47-0.38 (m, 2H).

[0839] Example No. 6: Synthesis of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethanone (Compound No. 9), 1-((R)-2-((2R,4aS,4bR,6aS,7R,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)propyl)-1H-pyrazole-4-carbonitrile (Compound No. 10), and 1-((S)-2-((2R,4aS,4bR,6aS,7R,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)propyl)-1H-pyrazole-4-carbonitrile (Compound No. 11).





[0840] Synthesis of 6.2

[0841] To a stirred solution of trimethylsulfoxonium iodide (455 mg, 2.07 mmol) in DMSO (20 mL) and THF (20 mL) was added NaH (82.6 mg, 2.07 mmol, 60 % in mineral oil) and stirred at 0°C for 1 h under N₂. A solution of **6.1** (500 mg, 1.73 mmol) in DMSO (10 mL) was added to the resulting mixture at 0°C and stirred at 25°C for 16 hrs. The reaction mixture was treated with water (50 mL). The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with water (2 x 100 mL), brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by column (0-20% of ethyl acetate in petroleum ether) to give **6.2** (360 mg, 69%). ¹H NMR (400 MHz, CDCl₃) δ_H 2.05-1.98 (m, 1H), 1.96-1.91 (m, 1H), 1.87-1.65 (m, 8H), 1.61-1.53 (m, 4H), 1.47-1.22 (m, 11H), 1.12-1.02 (m, 2H), 0.96 (s, 3H).

[0842] Synthesis of 6.3

[0843] To a solution of PPh₃EtBr (11.0 g, 29.7 mmol) in THF (100 mL) was added t-BuOK (3.33 g, 29.7 mmol). After the reaction mixture was stirred for 0.5 h at 40°C, a solution of **6.2** (1.80 g, 5.95 mmol) in THF (20 mL) was added into the reaction at 40°C. The reaction mixture was stirred for 12 hours at 40°C. The mixture was poured into saturated NH₄Cl (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with saturated brine (2 x 100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in

vacuum. The mixture was purified by silica gel chromatography (0-10% ethyl acetate in petroleum ether) to get **6.3** (1.20 g, 64.1 %). ¹H NMR (400 MHz, DMSO) δ_H 5.35 (q, *J*=6.8 Hz, 1H), 2.15-2.09 (m, 1H), 1.86-1.63 (m, 11H), 1.44-1.22 (m, 14H), 1.17-1.06 (m, 1H), 0.99 (s, 3H), 0.93-0.82 (m, 2H), 0.49-0.40 (m, 1H).

[0844] Synthesis of 6.4

[0845] The solution of **6.3** (1.30 g, 4.13 mmol) in THF (20 mL) was added 9-BBN dimer (1.99 g, 8.26 mmol) under N₂. After the reaction mixture was stirred at 60°C under N₂ for 2 h, the resulting mixture was cooled down to 0°C. EtOH (2.83 mL, 49.5 mmol), NaOH (9.9 mL, aqueous 5M, 49.5 mmol) was added to the mixture. Then H₂O₂ (4.95 mL, 10M, 49.5 mmol) was added dropwise at 15°C. The mixture was stirred at 60°C for 2 hour. Then the mixture was cooled and poured into Na₂S₂O₃ (200 mL, sat.) and stirred for 30 mins. The aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layer was washed with saturated brine (2 x 100 mL), dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated to get **6.4** (1.60 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 3.87-3.76 (m, 1H), 2.43-2.37 (m, 2H), 1.84-1.70 (m, 7H), 1.45-1.35 (m, 7H), 1.26-1.25 (m, 6H), 1.20-1.10 (m, 4H), 0.92-0.80 (m, 4H), 0.79-0.76 (m, 1H), 0.74 (s, 3H), 0.24-0.14 (m, 1H).

[0846] Synthesis of Compound No. 9

[0847] To a solution of **5.4** (1.60 g, 4.81 mmol) in DCM (20 mL) was added Dess-martin (4.08 g, 9.62 mmol). After the reaction mixture was stirred at 40°C for 30 mins, the mixture was quenched by saturated NaHCO₃ aqueous (30 mL), the DCM phase was separated and washed with saturated NaHCO₃/Na₂S₂O₃ aqueous (1:1, 2 x 30 mL), brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column (0~20% of ethyl acetate in petroleum ether) to give **Compound No. 9** (1.10 g, 69.6%). 40.0 mg of **Compound No. 9** was triturated from MeCN (2 mL) to get **Compound No. 9** (25.6 mg). ¹H NMR (400 MHz, CDCl₃) δ_H 2.74 (d, *J*=4.4 Hz, 1H), 2.21 (s, 3H), 1.96-1.63 (m, 8H), 1.51-1.19 (m, 16H), 1.12-1.00 (m, 1H), 0.89-0.82 (m, 1H), 0.72 (s, 3H), 0.46-0.33 (m, 1H).

[0848] Synthesis of 6.5

[0849] To a solution of PPh₃MeBr (4.32 g, 12.1 mmol) in THF (20 mL) was added t-BuOK (1.35 mg, 12.1 mmol). The reaction mixture was stirred for 0.5h at 60°C. A solution of **Compound No. 1** (800 mg, 2.42 mmol) in THF (20 mL) was added to the reaction at 60°C. After the reaction mixture was stirred for 12 hours at 60°C, the mixture was poured into saturated NH₄Cl (300 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with saturated brine (2 x 100 mL), dried over anhydrous Na₂SO₄, filtered

and concentrated in vacuum. The mixture was purified by silica gel chromatography (0-15% ethyl acetate in petroleum ether) to get **6.5** (600 mg, 75.4%) ¹H NMR (400 MHz, CDCl₃) δ_H 5.12-5.08 (m, 1H), 4.87-4.82 (m, 1H), 2.42-2.36 (m, 1H), 1.90-1.60 (m, 12H), 1.52-1.35 (m, 5H), 1.29-0.98 (m, 11H), 0.69-0.65 (m, 1H), 0.64 (s, 3H), 0.28-0.20 (m, 1H).

[0850] Synthesis of 6.6

[0851] The solution of **6.5** (400 mg, 1.21 mmol) in THF (10 mL) was added BH₃.Me₂S (0.5 mL, 10M, 5 mmol) under N₂, the reaction mixture was stirred at 25°C under N₂ for 12 h. The reaction mixture was cooled down to 0°C. Then EtOH (1.38 mL, 24.2 mmol) and NaOH (4.84 mL, 5M, 24.2 mmol) were added to the mixture. Afterwards H₂O₂ (2.42 mL, 10M, 24.2 mmol) was added dropwise at 15°C. After the mixture was stirred at 60°C for 2 hour, the mixture was cooled and poured into Na₂S₂O₃ (100 mL, sat.) and stirred for 30 mins. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated to get **6.6** (400 mg, crude), which was used directly for the next step.

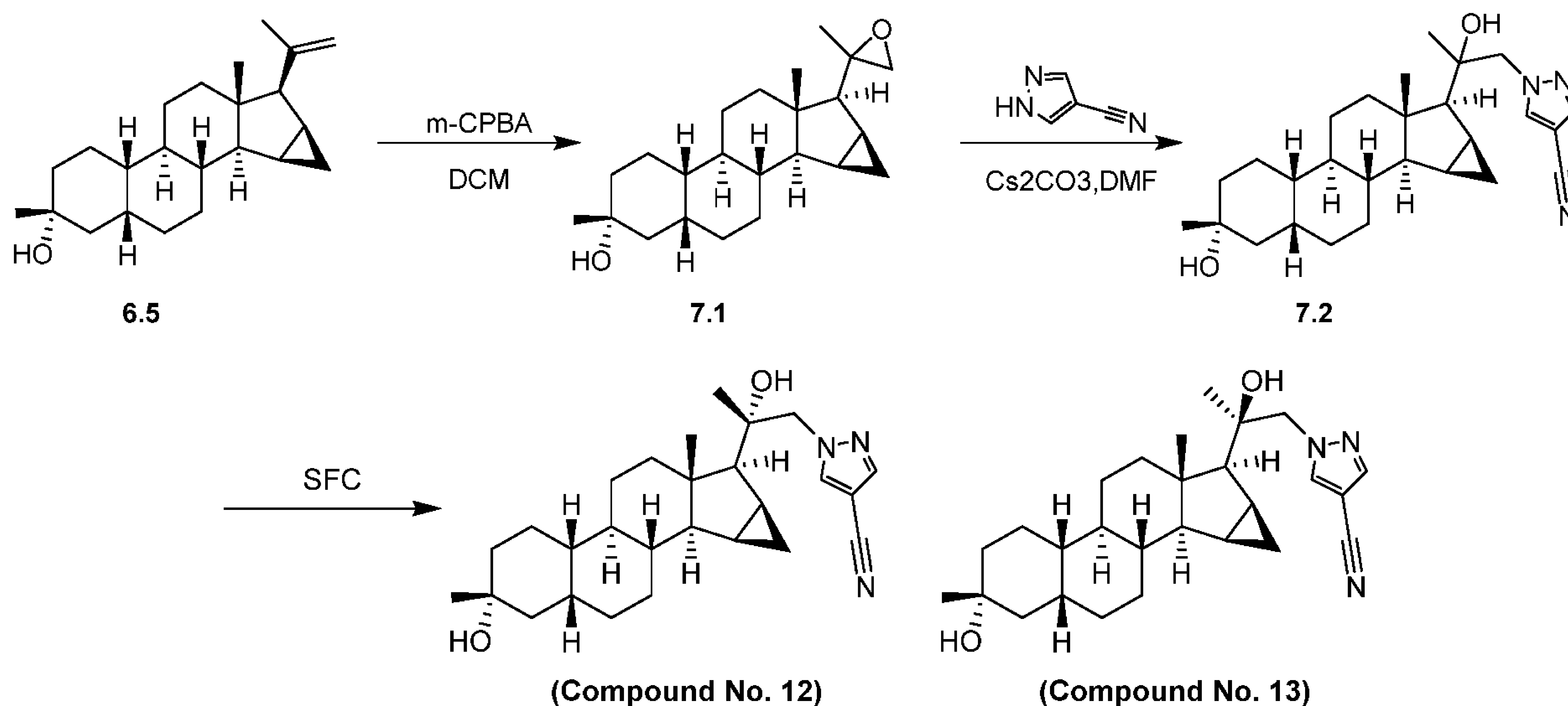
[0852] Synthesis of Compound No. 10 and Compound No. 11

[0853] To a solution of **6.6** (400 mg, 1.15 mmol) and 1H-pyrazole-4-carbonitrile (214 mg, 2.3 mmol) in DMF (10 mL) was added Ph₃P (1.2 g, 4.6 mmol), DEAD (0.801 g, 4.6 mmol), the mixture was stirred at 25°C for 2 hours. The mixture poured into ice-water (30 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column (0~40% of ethyl acetate in petroleum ether) to give **6.7** (400 mg, impure). The residue was combined with another 100 mg of **6.7** to be purified by SFC (Column: DAICEL CHIRALCEL OD-H(250mm*30mm,5um); Condition: 0.1%NH₃H₂O ETOH; Begin B: 35%; End B:35%; Flow Rate (ml/min): 60; Injections: 140) to get **Compound No. 10** (24.1 mg, 4.03%, peak 3, Rt = 3.551 min) and **Compound No. 11** (83.4 mg, 13.9%, peak 4, Rt = 4.095 min).

[0854] Compound No. 10: ¹H NMR (400 MHz, CDCl₃) δ_H 7.83-7.76 (m, 2H), 4.60-4.50 (m, 1H), 4.02-3.88 (m, 1H), 2.26-2.14 (m, 1H), 1.85-1.65 (m, 7H), 1.44-1.30 (m, 7H), 1.28-1.06 (m, 12H), 0.79 (t, *J*=3.2 Hz, 6H), 0.72-0.68 (m, 1H), 0.22-0.14 (m, 1H).

[0855] Compound No. 11: ¹H NMR (400 MHz, CDCl₃) δ_H 7.88-7.72 (m, 2H), 4.41-4.33 (m, 1H), 3.76-3.67 (m, 1H), 2.33-2.21 (m, 1H), 1.86-1.57 (m, 9H), 1.42-1.08 (m, 17H), 0.92-0.88 (m, 6H), 0.69-0.64 (m, 1H), 0.19-0.11 (m, 1H).

[0856] Example No. 7: Synthesis of 1-((S)-2-hydroxy-2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)propyl)-1H-pyrazole-4-carbonitrile (Compound No. 12) and 1-((R)-2-hydroxy-2-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-2-hydroxy-2,6a-dimethyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)propyl)-1H-pyrazole-4-carbonitrile (Compound No. 13)



[0857] Synthesis of 7.1

[0858] m-CPBA (147 mg, 0.6847 mmol, 80%) was added to a solution of **6.5** (150 mg, 0.456 mmol) in DCM (5 mL). After the mixture was stirred at 20°C for 0.5 h, the mixture was quenched by saturated NaHCO₃ aqueous (10 mL) at 20°C. The DCM phase was separated and washed with saturated NaHCO₃/Na₂S₂O₃ aqueous (1:1, 2 x 10 mL), brine (10 mL), dried over Na₂SO₄, filtered and concentrated under vacuum to give **7.1** (150 mg, crude). ¹H NMR (400 MHz, DMSO) δ_H 3.26 (d, *J*=5.2 Hz, 1H), 2.59 (d, *J*=5.2 Hz, 1H), 2.26 (d, *J*=3.6 Hz, 1H), 1.87-1.62 (m, 7H), 1.41-1.35 (m, 7H), 1.31-1.25 (m, 8H), 1.21-1.00 (m, 6H), 0.80 (s, 3H), 0.64-0.57 (m, 1H), 0.18-0.10 (m, 1H).

[0859] Synthesis of Compound No. 12 and Compound No. 13

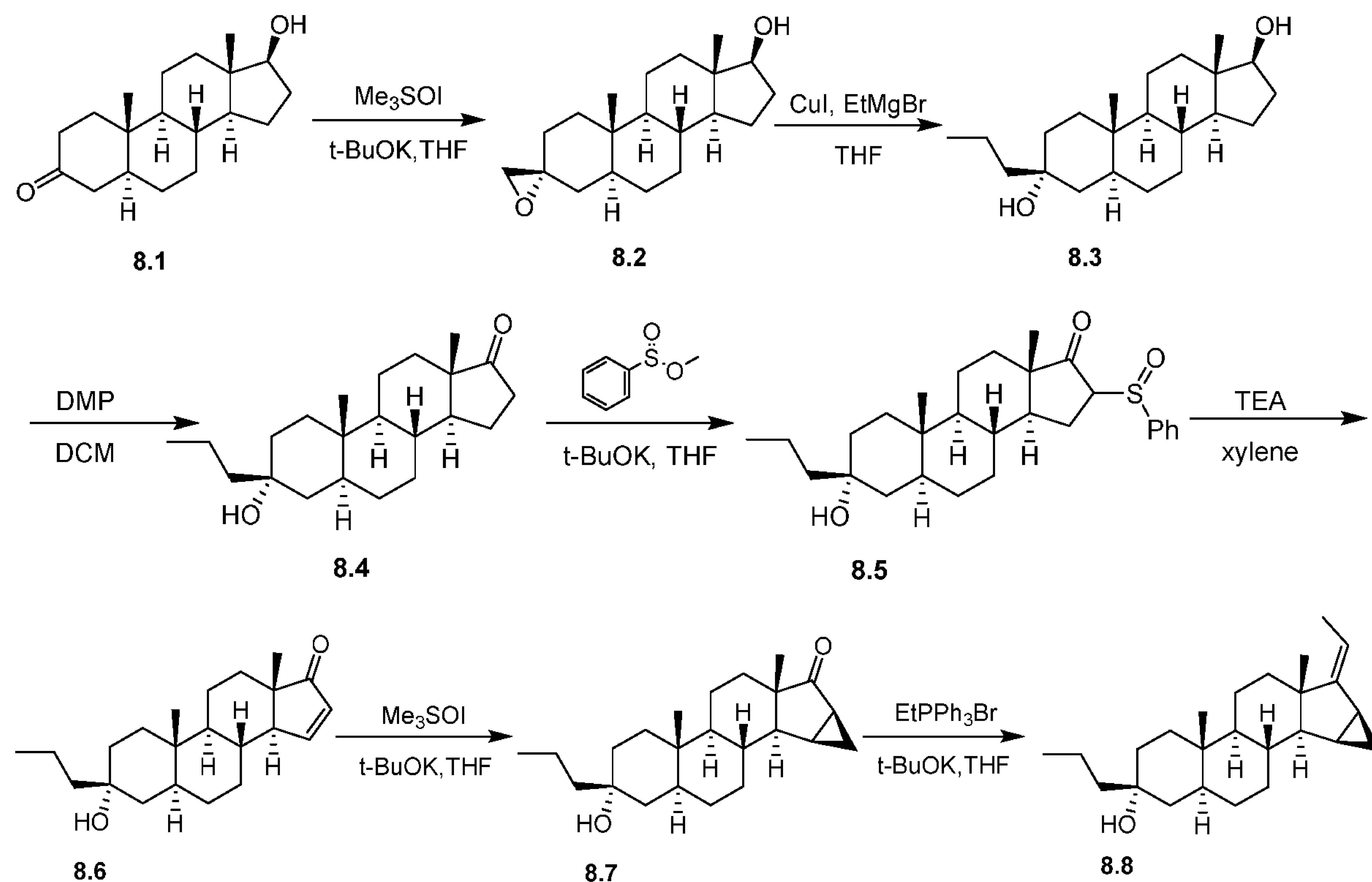
[0860] A solution of **7.1** (150 mg, 0.435 mmol), Cs₂CO₃ (426 mg, 1.3 mmol) and 1H-pyrazole-4-carbonitrile (81.0 mg, 0.871 mmol) in DMF (10 mL) was stirred at 120°C for 16 hours. The reaction mixture was poured into saturated NH₄Cl (30 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with LiCl (100 mL, 3% in water), saturated brine (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was combined with another solution of crude **7.2** to be purified

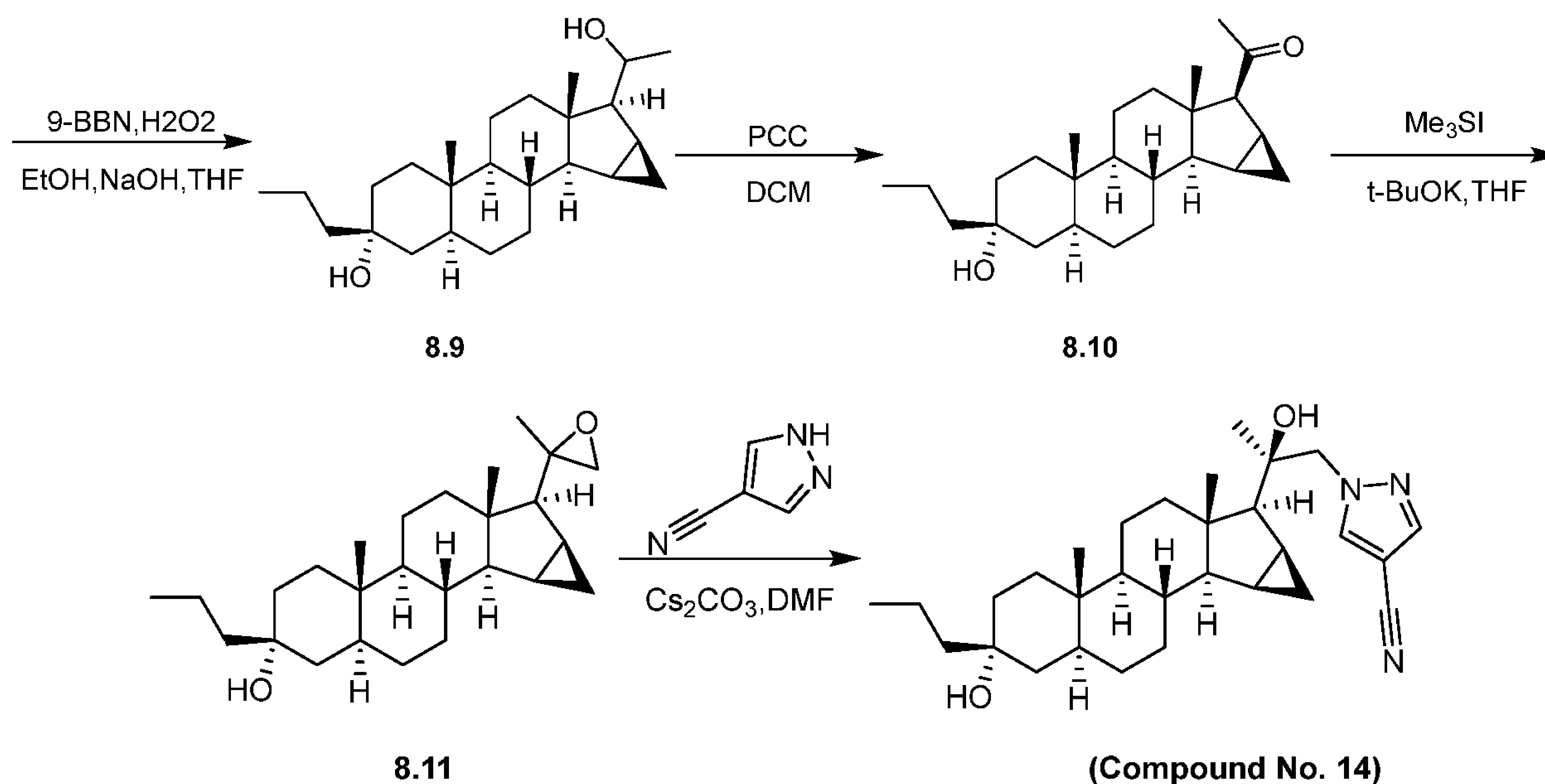
by silica gel chromatography (0~40% of ethyl acetate in petroleum ether) to afford **7.2** (120 mg, crude). The residue was purified by SFC (Column: DAICEL CHIRALCEL OJ-H (250mm*30mm, 5um); Condition: 0.1%NH₃H₂O ETOH; Begin B: 20%; End B: 20%; Flow Rate (ml/min): 60; Injections: 110) to get **Compound No. 12** (68.6 mg, 57.6%, peak 1, Rt = 2.771 min) and **Compound No. 13** (9.20 mg, peak 2, Rt = 2.889 min).

[0861] Compound No. 12: ¹H NMR (400 MHz, CDCl₃) δ_H 7.99 (s, 1H), 7.81 (s, 1H), 4.43 (d, *J*=14.0 Hz, 1H), 4.24 (d, *J*=13.6 Hz, 1H), 2.55 (s, 1H), 1.89-1.56 (m, 10H), 1.42-1.17 (m, 16H), 1.15 (s, 3H), 1.05 (s, 3H), 0.93-0.86 (m, 1H), 0.35-0.26 (m, 1H).

[0862] Compound No. 13: ¹H NMR (400 MHz, CDCl₃) 7.97 (s, 1H), 7.81 (s, 1H), 4.29 (q, *J*=14.0 Hz, 2H), 2.61 (s, 1H), 1.93-1.64 (m, 9H), 1.41-1.20 (s, 15H), 1.14 (s, 3H), 1.10-1.03 (m, 2H), 1.00 (s, 3H), 0.92-0.88 (m, 1H), 0.38-0.30 (m, 1H).

[0863] Example No. 8: Synthesis of 1-((R)-2-hydroxy-2-((2R,4aS,4bS,6aS,7S,7aS,8aR,8bS,8cR,10aS)-2-hydroxy-4a,6a-dimethyl-2-propyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)propyl)-1H-pyrazole-4-carbonitrile (Compound No. 14)





[0864] Synthesis of 8.2

[0865] A suspension of trimethylsulfoxonium iodide (60.2 g, 274 mmol) and t-BuOK (30.6 g, 274 mmol) in THF (1000 mL) was heated at 60°C for 1 h under N₂. Compound **8.1** (40.0 g, 137 mmol) was added to the reaction mixture and stirred at 25°C for 1 h. The reaction was treated with water (1000 mL), extracted with EtOAc (2 x 1000 mL). The combined organic phase was washed with brine (1000 mL), dried over anhydrous Na₂SO₄, filtered, concentrated in vacuum to afford **8.2** (35.0 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 3.65-3.60 (m, 1H), 2.70-2.50 (m, 2H), 2.21-2.00 (m, 2H), 1.82-1.75 (m, 3H), 1.74-1.48 (m, 6H), 1.47-1.00 (m, 10H), 0.99-0.80 (m, 4H), 0.79-0.72 (m, 4H).

[0866] Synthesis of 8.3

[0867] To a solution of **8.2** (35.0 g, 114 mmol) in THF (350 mL) was added CuI (12.9 g, 68.4 mmol) in one portion and then EtMgBr (76 mL, 3 M, 228 mmol) dropwise at 0°C. The reaction mixture was stirred at 0°C for 1 h. The mixture was poured into water (350 mL), extracted with EtOAc (2 x 350 mL). The combined organic phase was washed with brine (350 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give **8.3** (35.0 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 3.76-3.52 (m, 1H), 1.80-1.70 (m, 1H), 1.69-1.50 (m, 6H), 1.49-1.30 (m, 13H), 1.29-1.20 (m, 7H), 1.13-0.82 (m, 4H), 0.80-0.70 (m, 6H).

[0868] Synthesis of 8.4

[0869] To a solution of **8.3** (35.0 g, 104 mmol) in DCM (350 mL) was added Dess-martin reagent (88.1 g, 208 mmol) at 20°C. The reaction mixture was stirred at 20°C for 15 mins. The mixture was poured into saturated NaHCO₃/Na₂S₂O₃ aqueous (1:1, 400 mL). The aqueous phase was extracted with EtOAc (3 x 400 mL). The combined organic phase was

washed with saturated brine (2 x 400 mL), dried over anhydrous Na₂SO₄, filtered, concentrated and purified by flash column (0~15% of ethyl acetate in petroleum ether) to give **8.4** (29.8 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 2.47-2.03 (m, 1H), 2.15-2.00 (m, 1H), 1.99-1.80 (m, 1H), 1.79-1.75 (m, 2H), 1.74-1.70 (m, 1H), 1.68-1.48 (m, 5H), 1.46-1.25 (m, 10H), 0.99-0.80 (m, 9H), 0.79-0.76 (m, 3H), 0.75 (s, 3H).

[0870] Synthesis of **8.5**

[0871] To a solution of t-BuOK (6.72 g, 60 mmol) in THF (100 mL) was added **8.4** (10.0 g, 30 mmol) at 15°C under N₂. After stirring at 15°C for 10 mins, methyl benzenesulfinate (9.37 g, 60 mmol) was added and stirred at 30°C for 0.5 h. The mixture was quenched with H₂O (100 mL), extracted with EtOAc (2 x 100 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give **8.5** (12.0 g, crude).

[0872] Synthesis of **8.6**

[0873] To a mixture of **8.5** (12.0 g, 27.1 mmol) in xylene (120 mL) was added TEA (20 mL) in portions at 25°C. The reaction mixture was stirred at 125°C for 12 hours under N₂. The mixture was filtered, concentrated and purified by silica gel chromatography (0~30% of ethyl acetate in petroleum ether) to give **8.6** (6.00 g, 70%). ¹H NMR (400 MHz, CDCl₃) δ_H 7.58-7.50 (m, 1H), 6.10-5.97 (m, 1H), 2.36-2.26 (m, 2H), 2.01-1.90 (m, 7H), 1.89-1.43 (m, 6H), 1.42-1.00 (m, 9H), 0.99-0.80 (m, 5H), 0.79-0.75 (m, 3H).

[0874] Synthesis of **8.7**

[0875] To a stirring solution of trimethylsulfoxonium iodide (996 mg, 4.53 mmol) in THF (15 mL) was added NaH (180 mg, 4.53 mmol, 60% in oil) and **8.6** (1.00 g, 3.02 mmol) at 0°C under N₂. The resulting mixture was stirred at 25°C for 2 hours. The reaction was treated with water (10 mL) and extracted with EtOAc (2 x 15 mL). The combined organic phase was washed with water (2 x 15 mL), brine (15 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum to give **8.7** (1.15 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 2.63-2.56 (m, 4H), 2.00-1.80 (m, 6H), 1.79-1.43 (m, 10H), 1.42-1.00 (m, 9H), 0.99-0.80 (m, 4H), 0.79-0.75 (m, 3H).

[0876] Synthesis of **8.8**

[0877] To a mixture of EtPPh₃Br (2.46 g, 6.66 mmol) in THF (15 mL) was added t-BuOK (745 mg, 6.66 mmol) at 25°C under N₂. After stirring at 50°C for 30 mins, **8.7** (1.15 g, 3.33 mmol) was added in portions below 50°C. The reaction mixture was stirred at 50°C for 1 hour. The reaction mixture was quenched with 10% NH₄Cl aqueous (10 mL) at 25°C. The THF layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined

organic phase was dried over Na₂SO₄, filtered, concentrated and purified by column chromatography on silica gel (0%~10% ethyl acetate in petroleum ether) to give **8.8** (760 mg, 64.4%). ¹H NMR (400 MHz, CDCl₃) δ_H 3.67-3.52 (m, 1H), 2.00-1.75 (m, 4H), 1.74-1.43 (m, 10H), 1.42-1.00 (m, 9H), 0.99-0.80 (m, 4H), 0.79-0.70 (m, 6H), 0.78-0.72 (m, 6H).

[0878] Synthesis of 8.9

[0879] To a solution of **8.8** (760 mg, 2.13 mmol) in THF (8 mL) was added 9-BBN (1.03 g, 4.26 mmol). After stirring at 50°C for 1 h under N₂, NaOH aqueous (1.27 g, 6.37 mL, 31.9 mmol) was added to the resulting mixture at 0°C. Hydrogen peroxide (3.18 mL, 10 M, 31.9 mmol) was added dropwise at 0°C. The reaction mixture was stirred at 80°C for 1 h. The mixture was cooled down to 15°C, quenched with Na₂S₂SO₄ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated, which was purified by column chromatography on silica gel (0~45% of ethyl acetate in petroleum ether) to give **8.9** (200 mg, 40.1%). ¹H NMR (400 MHz, CDCl₃) δ_H 3.85-3.74 (m, 1H), 1.98-1.75 (m, 2H), 1.70-1.43 (m, 10H), 1.42-1.00 (m, 12H), 0.99-0.80 (m, 4H), 0.79-0.70 (m, 6H), 0.78-0.73 (m, 6H), 0.22-0.16 (m, 1H).

[0880] Synthesis of 8.10

[0881] To a solution of **8.9** (200 mg, 0.53 mmol) in DCM (4 mL) at 0°C was added silica gel (200 mg) and PCC (172 mg, 0.80 mmol). After stirring at 10°C for 3 h, the resulting mixture was filtered through a pad of silica gel and the filter cake was washed with DCM (10 mL). The filtrate was concentrated and purified by column chromatography on silica gel (0%~10% of ethyl acetate in petroleum ether) to give **8.10** (160 mg, 81%). ¹H NMR (400 MHz, CDCl₃) δ_H 2.75-2.70 (m, 1H), 2.20 (s, 3H), 1.95-1.80 (m, 2H), 1.75-1.65 (m, 1H), 1.60-1.40 (m, 9H), 1.39-1.30 (m, 11H), 1.29-1.05 (m, 2H), 1.00-0.80 (m, 4H), 0.78-0.73 (m, 6H), 0.43-0.36 (m, 1H).

[0882] Synthesis of 8.11

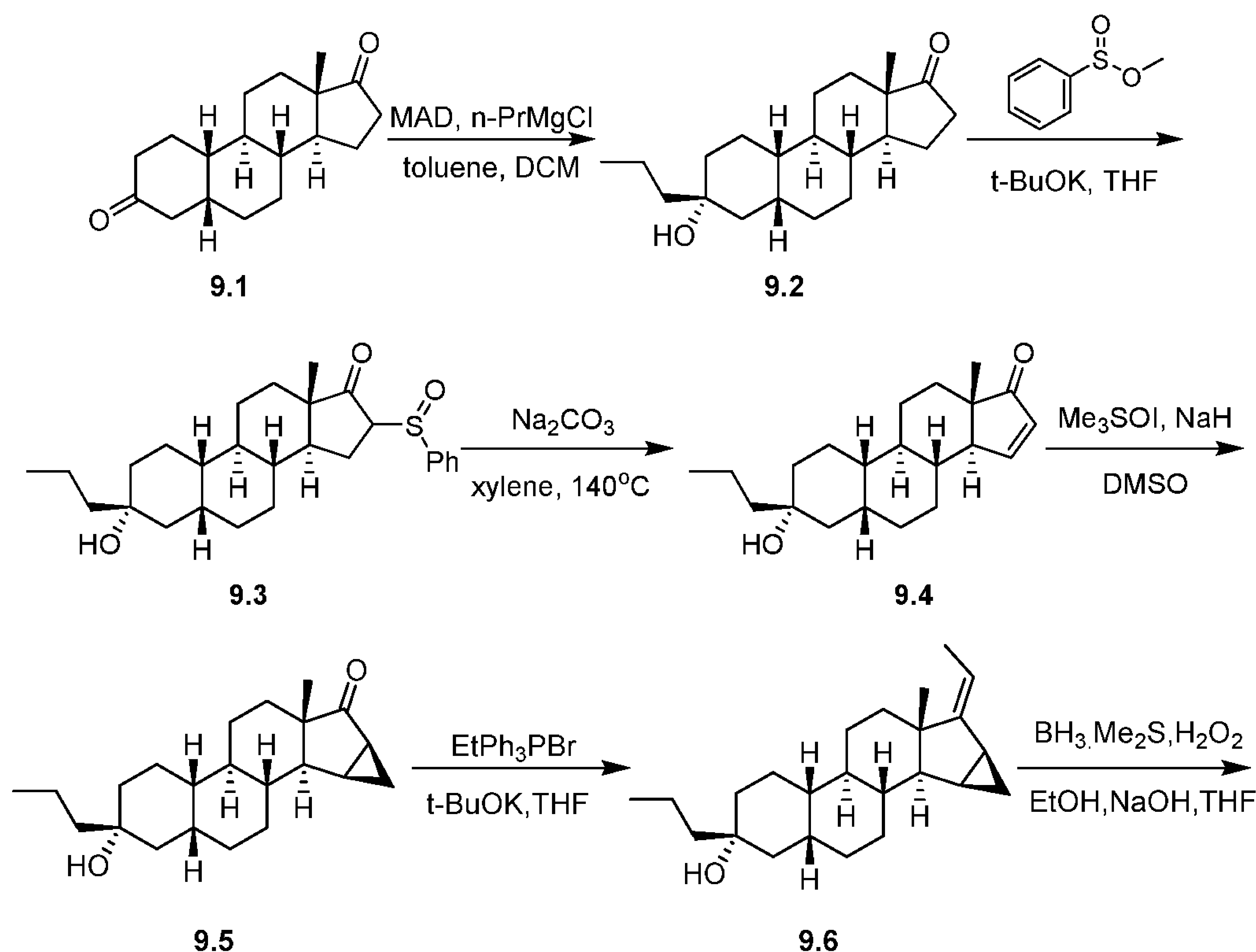
[0883] To a stirring solution of Me₃SI (164 mg, 0.81 mmol) in THF (4 mL) was added t-BuOK (90.1 mg, 0.81 mmol) at 0°C for 1.0 h under N₂. The resulting mixture was added to a solution of **8.10** (150 mg, 0.40 mmol) at 0°C and stirred at 25°C for 16 h. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (2 x 6 mL). The combined organic phase was washed with water (2 x 6 mL), brine (6 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum to give **8.11** (150 mg). ¹H NMR (400 MHz, CDCl₃) δ_H 3.27-3.25 (m, 1H), 2.89-2.78 (m, 2H), 2.65-2.60 (m, 1H), 2.51-2.49

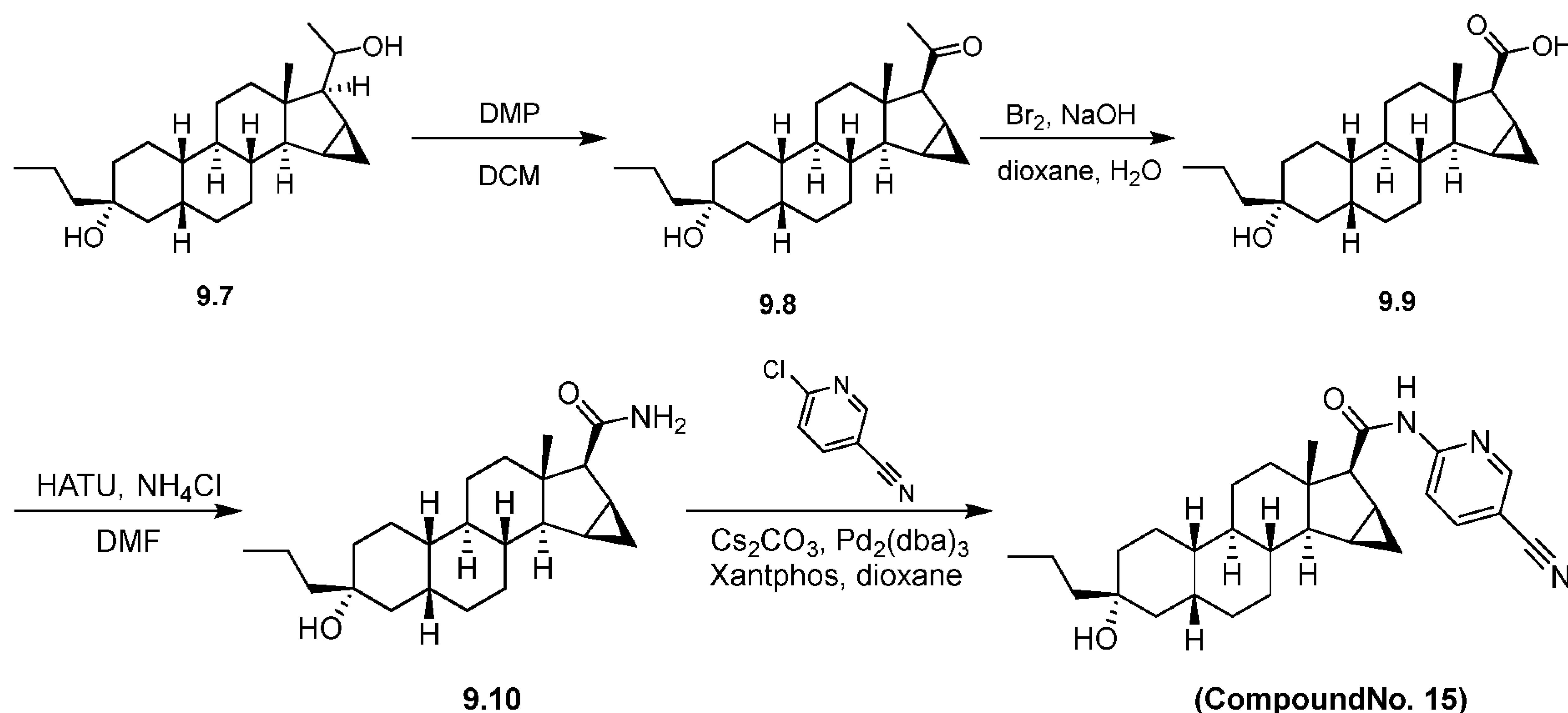
(m, 2H), 2.00-1.98 (m, 2H), 1.97-1.80 (m, 2H), 1.77-1.40 (m, 13H), 1.19-1.08 (m, 6H), 1.07-1.00 (m, 4H), 0.99-0.74 (m, 4H), 0.73-0.50 (m, 2H), 0.18-0.12 (m, 3H).

[0884] Synthesis of Compound No. 14

[0885] To a solution of **8.11** (150 mg, 0.39 mmol) in DMF (3 mL) was added 4-cyanopyrazole (72.1 mg, 0.78 mmol) and Cs₂CO₃ (377 mg, 1.16 mmol) at 25°C. After stirring at 120°C for 16 hours under N₂, the reaction mixture was diluted with water (5 x 5 mL) and washed with EtOAc (3 x 5 mL). The combined organic layer was concentrated and purified by flash column (0~30% of ethyl acetate in petroleum ether) to give **Compound No. 14** (110 mg, crude), which was purified by SFC (DAICEL CHIRALCEL OD-H (250mm*30mm,5um), Condition:0.1% NH₃H₂O ETOH, Begin B:40%, End B:40%, FlowRate (ml/min):70, Injections:80) to afford **6** (33.5 mg, 31%). ¹H NMR (400 MHz, CDCl₃) δ_H 7.97 (s, 1H), 7.80 (s, 1H), 4.35-4.22 (m, 2H), 2.60 (s, 1H), 2.00-1.75 (m, 3H), 1.60-1.45 (m, 9H), 1.44-1.20 (m, 9H), 1.19-1.08 (m, 6H), 1.07-1.00 (m, 4H), 0.99-0.74 (m, 4H), 0.73-0.50 (m, 4H), 0.36-0.31 (m, 1H).

[0886] Example No. 9: Synthesis of (2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aR)-N-(5-cyanopyridin-2-yl)-2-hydroxy-6a-methyl-2-propyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthrene-7-carboxamide (Compound No. 15).





[0887] Synthesis of 9.2

[0888] To a solution of BHT (200 g, 908 mmol) in toluene (600 mL) under nitrogen at 0°C in three-necked flask (3000 mL) was added dropwise trimethylaluminum (227 mL, 2 M in toluene, 453 mmol). The mixture was stirred at 25°C for 1 h and used directly as a solution of MAD. A solution of **9.1** (50.0 g, 182 mmol) in DCM (300 mL) was added dropwise at -70°C under nitrogen to the MAD solution (218 g in toluene, 454 mmol). After stirring at -70°C for 1 h under N₂, n-PrMgCl (121 mL, 3M in ethyl ether, 364 mmol) was added dropwise at -70°C and stirred at for another 2 hours. The reaction mixture was slowly poured into saturated aqueous citric acid (1000 mL) at below 10°C. The aqueous phase was extracted with DCM (2 x 500 mL). The combined organic phase was washed with brine (1000 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was triturated from PE (1500 mL) at 25°C to give **9.2** (110 g, crude). The residue was purified by flash column (5-12% of ethyl acetate in petroleum ether) to give **9.2** (28.0 g). ¹H NMR (400 MHz, CDCl₃) δ_H 2.65-2.54 (m, 1H), 2.50-2.39 (m, 1H), 2.31-2.03 (m, 3H), 2.02-1.88 (m, 2H), 1.87-1.60 (m, 2H), 1.56-1.46 (m, 6H), 1.36 (br dd, *J* = 4.4, 12.2 Hz, 8H), 1.26-1.18 (m, 2H), 1.16-1.02 (m, 2H), 0.97-0.91 (m, 4H), 0.88 (s, 3H).

[0889] Synthesis of 9.3

[0890] To a solution of t-BuOK (7.02 g, 62.6 mmol) in THF (400 mL) was added **9.2** (10.0 g, 31.3 mmol) at 25°C under N₂. After stirring at 25°C for 10 mins, methyl benzenesulfinate (9.77 g, 62.6 mmol) was added. After stirring at 30°C for 0.5 hours, the mixture was quenched with H₂O (200 mL) and extracted with EtOAc (3 x 200 mL). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated in vacuum to give **9.3** (20.0 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 7.77-7.46 (m, 6H), 3.26 (dd, *J* = 8.4, 10.0 Hz, 1H), 2.44-2.10

(m, 1H), 1.80 (br d, $J = 13.2$ Hz, 3H), 1.68-1.43 (m, 7H), 1.68-1.43 (m, 7H), 1.42-1.23 (m, 7H), 1.21-0.96 (m, 3H), 0.96-0.90 (m, 3H).

[0891] Synthesis of 9.4

[0892] To a mixture of **9.3** (20.0 g, 45.1 mmol) in xylene (200 mL) was added Na_2CO_3 (71.6 g, 676 mmol) in portions. After stirring at 140°C for 12 hrs under N_2 , the mixture was filtered and concentrated, the residue was purified by column (0-15% of ethyl acetate in petroleum ether) to give **9.4** (4.50 g). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 7.53 (dd, $J = 1.2, 6.0$ Hz, 1H), 6.03 (dd, $J = 3.2, 6.0$ Hz, 1H), 2.38 (br d, $J = 7.8$ Hz, 1H), 1.85 (d, $J = 3.6$ Hz, 4H), 1.78-1.66 (m, 3H), 1.56 (d, $J = 16.4$ Hz, 7H), 1.41-1.21 (m, 9H), 1.08 (s, 3H), 0.95 (t, $J = 7.2$ Hz, 3H).

[0893] Synthesis of 9.5

[0894] To a solution of Me_3SOI (3.32 g, 15.1 mmol) in 50 ml DMSO was added NaH (362 mg, 15.1 mmol) at 25°C under N_2 . After stirring at 25°C for 1 hour, **9.4** (4.00 g, 12.6 mmol) in 10 ml DMSO was added to the mixture. After stirring at 25°C for 3 hours, the mixture was poured into water (100 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. The mixture was purified by flash column (0-30% of ethyl acetate in petroleum ether) to give **9.5** (2.60 g, 63%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 2.08-1.99 (m, 1H), 1.99-1.89 (m, 1H), 1.73 (br d, $J = 13.6$ Hz, 7H), 1.66-1.45 (m, 8H), 1.44-1.22 (m, 10H), 1.16-1.02 (m, 2H), 0.96 (s, 3H), 0.95-0.91 (m, 2H).

[0895] Synthesis of 9.6

[0896] To a suspension of Ph_3PEtBr (8.72 g, 23.5 mmol) in anhydrous THF (60 mL) was added $t\text{-BuOK}$ (2.63 g, 23.5 mmol) at 25°C under N_2 . After stirring at 55°C for 30 mins, a solution of **9.5** (2.60 g, 7.86 mmol) in anhydrous THF (20 mL) was added dropwise. After stirred at 25°C for 16 hrs, the mixture was cooled and poured into ice-water (100 mL) stirred for 10 mins. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with brine (2 x 200 mL), filtered and concentrated, The mixture was purified by flash column (0-20% of ethyl acetate in petroleum ether) to give **9.6** (2.30 g, 86%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 5.35 (q, $J = 7.2$ Hz, 1H), 2.19-2.09 (m, 1H), 1.91-1.73 (m, 5H), 1.69 (d, $J = 7.2$ Hz, 4H), 1.51-1.30 (m, 11H), 1.27 (br t, $J = 7.2$ Hz, 5H), 1.19-1.02 (m, 2H), 1.00 (s, 3H), 0.94 (t, $J = 7.2$ Hz, 5H), 0.44 (dt, $J = 5.4, 8.1$ Hz, 1H).

[0897] Synthesis of 9.7

[0898] The solution of **9.6** (2.80 g, 8.17 mmol) in THF (60 mL) was added $\text{BH}_3\cdot\text{THF}$ (24.5 mL, 1 M, 24.5 mmol) under N_2 . After stirring at 25°C under N_2 for 2 hours, the mixture was

cooled to 0°C. Ethanol (7.11 mL, 122 mmol) and NaOH (24.4 mL, 5 M, 122 mmol) were added to the reaction mixture. Then, H₂O₂ (12.1 mL, 30%, 122 mmol) was added dropwise at 0°C. The mixture was stirred at 50°C for 2 hours. Saturated aqueous Na₂S₂O₃ (200 mL) was added and the mixture was stirred at 0°C for another 1 hour. The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine (2 x 200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give **9.7** (2.10 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 3.93-3.73 (m, 1H), 1.87-1.63 (m, 5H), 1.63-1.42 (m, 6H), 1.41-1.29 (m, 9H), 1.25 (br d, *J* = 6.4 Hz, 10H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 1H), 0.75 (s, 4H), 0.26-0.14 (m, 1H).

[0899] Synthesis of 9.8

[0900] The solution of **9.7** (2.80 g, 7.76 mmol) in DCM (80 mL) was added DMP (6.57 g, 15.5 mmol) under N₂. After stirring at 25°C under N₂ for 2 hours, saturated aqueous NaHCO₃ (100 mL) and saturated aqueous Na₂S₂O₃ (100 mL) were added to the mixture. The aqueous phase was extracted with DCM (2 x 100 mL). The combined organic phase was washed with brine (2 x 200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column (0~15% of ethyl acetate in petroleum ether) to give **9.8** (2.10 g, 76%). ¹H NMR (400 MHz, CDCl₃) δ_H 2.75 (d, *J* = 4.0 Hz, 1H), 2.21 (s, 3H), 2.01-1.89 (m, 1H), 1.87-1.63 (m, 4H), 1.62-1.45 (m, 6H), 1.44-1.33 (m, 8H), 1.33-1.17 (m, 6H), 1.13-0.99 (m, 1H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.89-0.83 (m, 1H), 0.73 (s, 3H), 0.50-0.32 (m, 1H).

[0901] Synthesis of 9.9

[0902] Liquid bromine (0.127 mL, 399 mg, 2.50 mmol) was added slowly to a vigorously stirred aqueous sodium hydroxide solution (3.34 mL, 8.36 mmol, 2.5 M) at 0°C. After stirring at 25°C for 30 mins, the mixture was added slowly to a stirred solution of **9.8** (300 mg, 0.837 mmol) in dioxane (10 mL). The homogeneous yellow solution became colorless slowly and a white precipitate was formed. After stirring at 25°C for 16 hours, the remaining oxidizing reagent was quenched with NaHCO₃ aqueous (20 mL). The reaction mixture was extracted with EtOAc (2 x 20 mL), washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated to afford **9.9** (360 mg, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 3.72 (s, 1H), 2.80 (d, *J* = 4.4 Hz, 1H), 2.01-1.90 (m, 1H), 1.88-1.60 (m, 5H), 1.59-1.44 (m, 5H), 1.43-1.19 (m, 13H), 1.18-0.99 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 4H), 0.83 (s, 3H), 0.45-0.32 (m, 1H).

[0903] Synthesis of 9.10

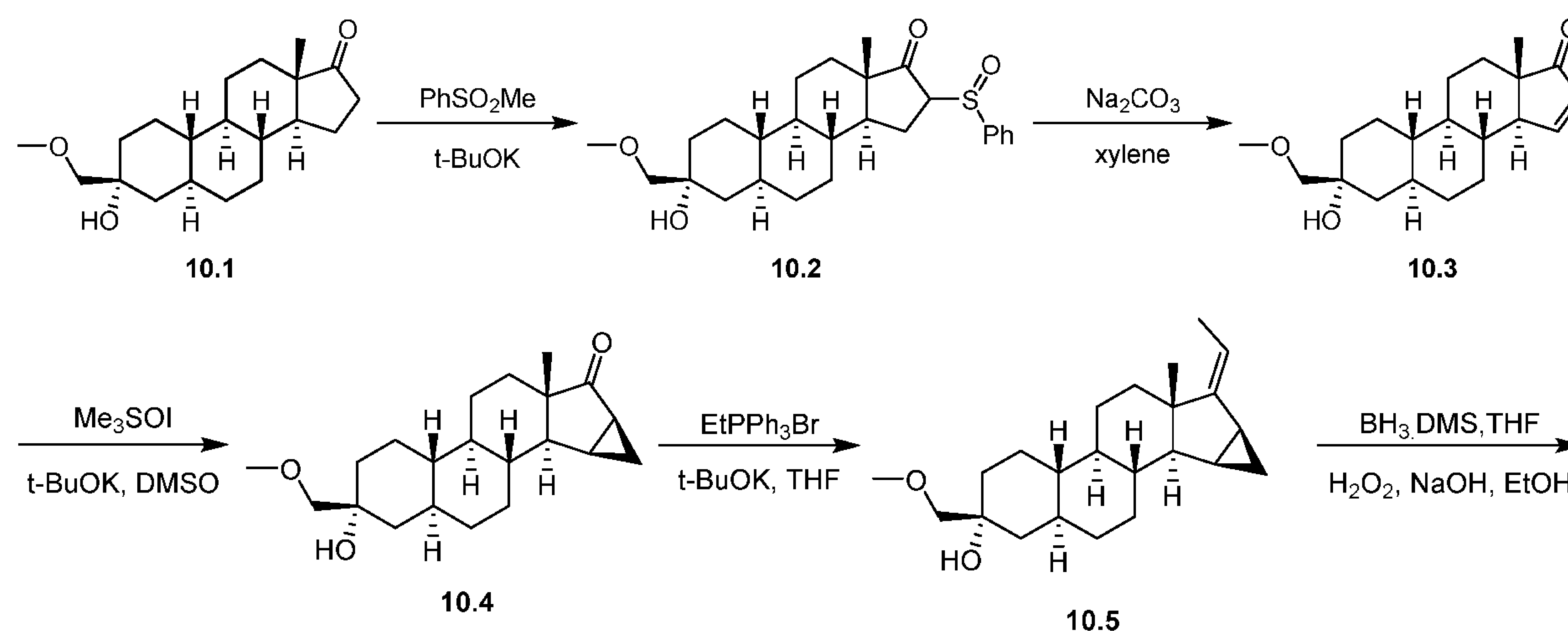
[0904] To a solution of **9.9** (360 mg, 0.998 mmol) in DMF (6 mL) was added HATU (756 mg, 1.99 mmol) and DIPEA (515 mg, 3.99 mmol). After stirring for 20 mins at 25°C, NH₄Cl

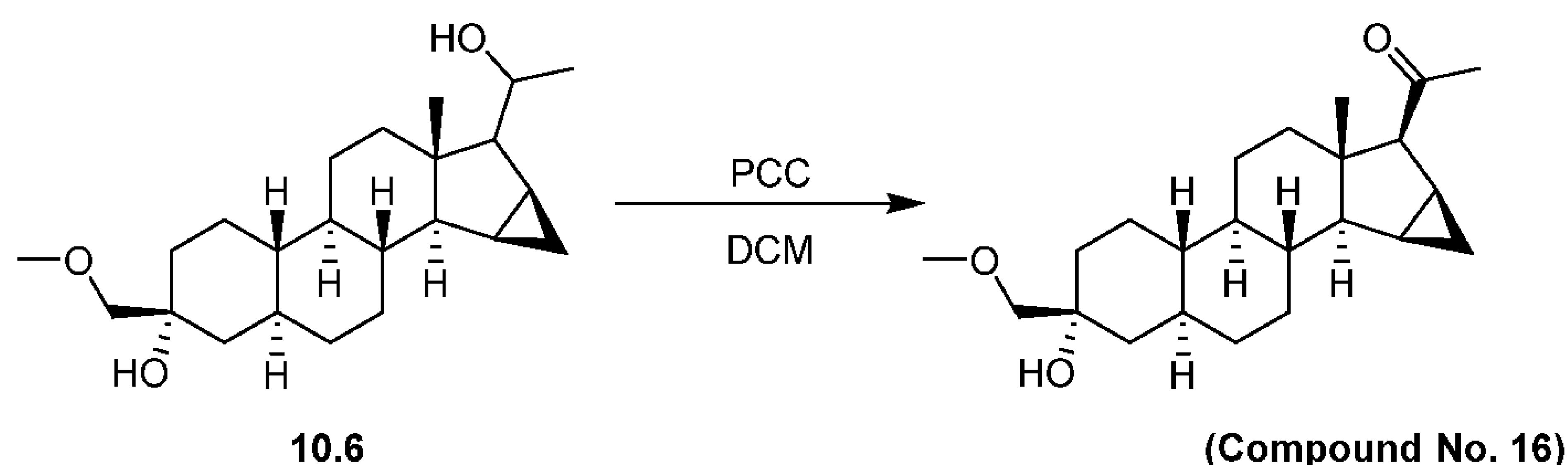
(213 mg, 3.99 mmol) was added. After stirred for 16 hours at 25°C, the reaction mixture was poured into water (20 mL) and extracted with EtOAc (2 x 10 mL), washed with water (2 x 50 mL) and brine (100 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column (30-100% of ethyl acetate in petroleum ether) to afford **9.10** (240 mg, 67%). ¹H NMR (400 MHz, CDCl₃) δ_H 6.16 (br s, 1H), 5.43 (br s, 1H), 2.66 (d, *J* = 4.4 Hz, 1H), 2.04-1.95 (m, 1H), 1.89-1.62 (m, 4H), 1.58-1.43 (m, 5H), 1.42-1.17 (m, 14H), 1.15-1.02 (m, 1H), 0.94 (t, *J* = 7.2 Hz, 5H), 0.81 (s, 3H), 0.53-0.29 (m, 1H).

[0905] Synthesis of Compound No. 15

[0906] To a mixture of 6-chloropyridine-3-carbonitrile (92.4 mg, 0.667 mmol), **7.10** (120 mg, 0.334 mmol), Xantphos (19.3 mg, 0.033 mmol) and Cs₂CO₃ (377 mg, 1.16 mmol) in dioxane (3 mL) was sparged with nitrogen for 2 mins, then Pd₂(dba)₃ (30.5 mg, 0.033 mmol) was added. After stirring at 115°C for 16 h, the mixture was filtered through a pad of silica gel, washed with EtOAc (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column (0-30% of ethyl acetate in petroleum ether) to give **Compound No. 15** (60.0 mg, crude), which was triturated from MeCN (10 ml) at 25°C to give **Compound No. 15** (49.3 mg, 82%). ¹H NMR (400 MHz, CDCl₃) δ_H 8.81 (s, 1H), 8.57 (d, *J* = 1.6 Hz, 1H), 8.44 (d, *J* = 8.8 Hz, 1H), 7.95 (dd, *J* = 2.4, 8.7 Hz, 1H), 2.86 (d, *J* = 4.4 Hz, 1H), 2.04-1.96 (m, 1H), 1.90-1.76 (m, 4H), 1.74-1.65 (m, 3H), 1.55-1.35 (m, 12H), 1.35-1.22 (m, 5H), 1.13-1.03 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.80 (s, 3H), 0.66-0.56 (m, 1H).

[0907] **Example No. 10: Synthesis of 1-((2R,4aS,4bR,6aS,7S,7aS,8aR,8bR,8cR,10aS)-2-hydroxy-2-(methoxymethyl)-6a-methyloctadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-7-yl)ethanone (Compound No. 16).**





[0908] Synthesis of 10.2

[0909] To a solution of t-BuOK (3.50 g, 31.2 mmol) in THF (50 mL) was added **10.1** (5.00 g, 15.6 mmol) at 25°C under N₂. The mixture was stirred at 25°C for 10 min. Then methyl benzenesulfinate (4.87 g, 31.2 mmol) was added. The mixture was stirred at 30 °C for 0.5 hour. The mixture was quenched by H₂O (50 mL) and extracted with EtOAc (3 x 50 mL). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated in vacuum to give **10.2** (5.90 g, crude).

[0910] Synthesis of 10.3

[0911] To a mixture of **10.2** (5.90 g, 13.2 mmol) in xylene (50 mL) was added Na₂CO₃ (20.9 g, 198 mol) in portions at 25°C. The reaction mixture was stirred at 145°C for 16 hrs under N₂. The mixture was filtered and concentrated. The mixture was purified by silica gel chromatography (0-30% of ethyl acetate in petroleum ether) to give the product **10.3** (2.00 g, 48 %). ¹H NMR (400 MHz, CDCl₃) δ_H 7.56-7.49 (m, 1H), 6.05-5.98 (m, 1H), 3.39 (s, 3H), 3.19 (s, 2H), 2.36-2.28 (m, 1H), 2.05-2.00 (m, 1H), 1.98-1.62 (m, 7H), 1.55-1.11 (m, 8H), 1.07 (s, 3H), 1.05-0.79 (m, 3H).

[0912] Synthesis of 10.4

[0913] A stirred solution of trimethylsulfoxonium iodide (2.75 g, 12.5 mmol) and t-BuOK (1.54 g, 13.8 mmol) in DMSO (20 mL) was heated at 60°C for 1.0 hour under N₂. **10.3** (2.00 g, 6.28 mmol) was added to the reaction mixture and stirred at 25°C for 1 hour. The reaction was treated with water (30 mL), extracted with EtOAc (2 x 30 mL). The combined organic phase was washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The mixture was filtered, concentrated and purified by combi-flash (15-30% of ethyl acetate in petroleum ether) to give **10.4** (1.00 g, 48.0 %). ¹H NMR (400 MHz, CDCl₃) δ_H 3.32 (s, 3H), 3.12 (s, 2H), 1.94-1.75 (m, 4H), 1.68-1.51 (m, 8H), 1.46-1.36 (m, 1H), 1.30-1.20 (m, 2H), 1.17-0.92 (m, 7H), 0.89 (s, 3H), 0.81-0.65 (m, 2H).

[0914] Synthesis of 10.5

[0915] To a mixture of EtPPh₃Br (3.56 g, 9.60 mmol) in THF (12 mL) was added t-BuOK (1.07 g, 9.60 mmol) at 25 °C under N₂. The resulting mixture was stirred at 40°C for 30 min. **10.4** (0.40 g, 1.20 mmol) was added in portions below 40°C. The reaction mixture was stirred at 40°C for 16 hour to give a yellow suspension. The reaction mixture was quenched with 10% NH₄Cl aqueous (40 mL) at 25°C. The aqueous was extracted with EtOAc (2 x 40 mL). The combined organic phase was separated, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column (0~35% of ethyl acetate in petroleum ether) to give **10.5** (0.40 g, 97 %).

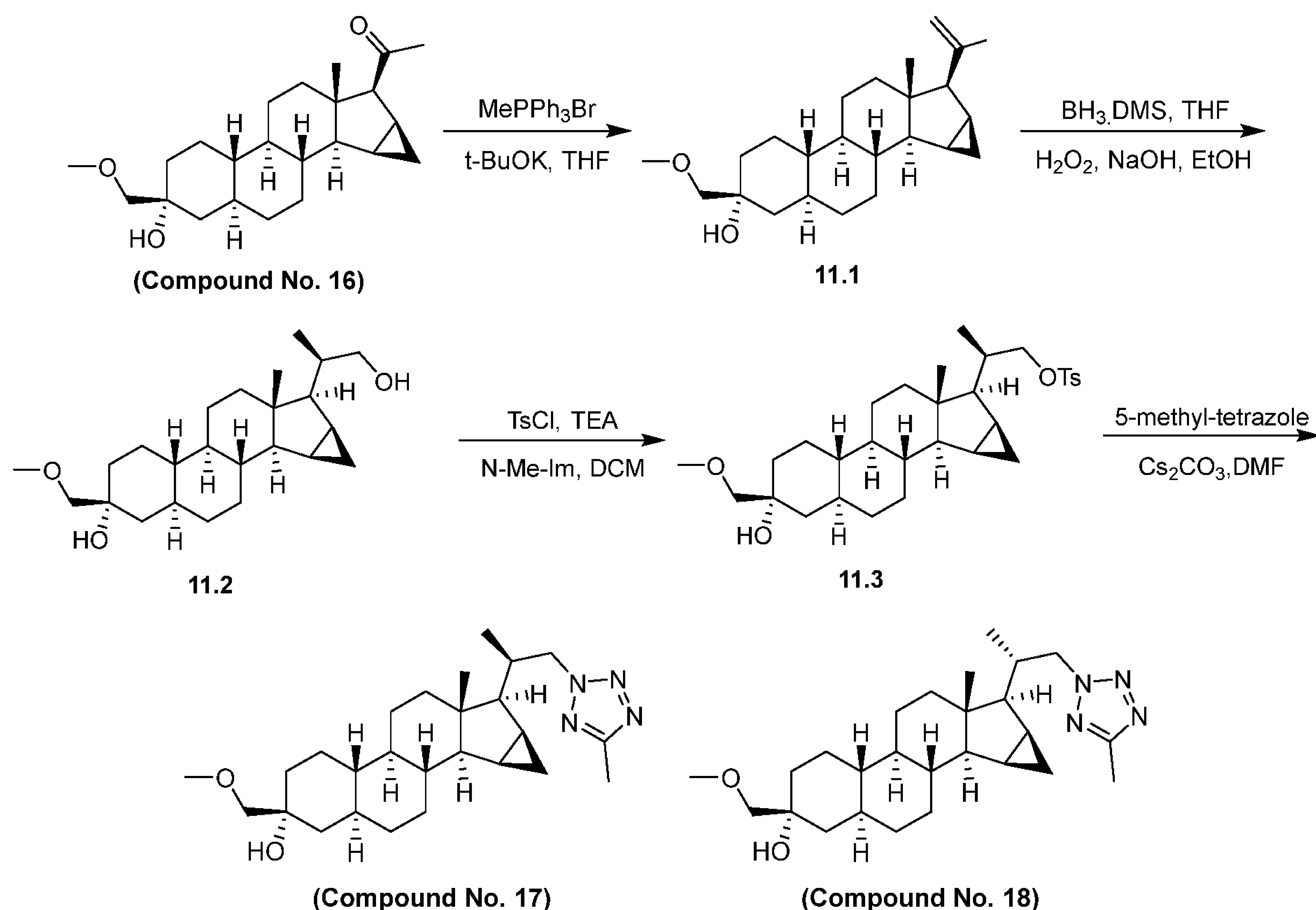
[0916] Synthesis of 10.6

[0917] To a solution of **10.5** (1.00 g, 2.90 mmol) in THF (120 mL) was added BH₃.Me₂S (1.44 mL, 10 M, 14.4 mmol) at 0°C under N₂. The mixture was stirred at 25°C for 16 hours. Ethanol (1.70 ml, 28.9 mmol), NaOH (5.77 mL, 5M aq., 28.9 mmol) and H₂O₂ (4.34 mL, 10 M, 43.4 mmol) were added dropwise to the mixture. The resulting mixture was stirred at 60 °C for 1 hour. The mixture was quenched with Na₂S₂O₃ (20 mL). The mixture was concentrated and filtered. The solid was washed with EA (20 mL), dried over Na₂SO₄, filtered and concentrated to give **10.6** (1.00 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 3.87-3.77 (m, 1H), 3.38 (s, 3H), 3.18 (s, 2H), 2.05-1.86 (m, 2H), 1.58-1.39 (m, 3H), 1.31-1.08 (m, 16H), 1.06-0.81 (m, 5H), 0.80-0.65 (m, 5H), 0.26-0.13 (m, 1H).

[0918] Synthesis of Compound No. 16

[0919] To a mixture of **8.6** (800 mg, 0.551 mmol) in DCM (20 mL) was added silica gel (1.42 g) and PCC (1.42 g, 6.60 mmol). The reaction mixture was stirred at 25°C for 1h. PE (10 mL) was added to the reaction mixture. The mixture was filtered and washed with DCM (2 x 20 mL). The residue was purified by flash column (15~30% of ethyl acetate in petroleum ether) to give **Compound No. 16** (500 mg, 63%). ¹H NMR (400 MHz, CDCl₃) δ_H 3.39 (s, 3H), 3.19 (s, 2H), 2.76-2.72 (m, 1H), 2.20 (s, 3H), 2.01 (s, 1H), 1.95-1.87 (m, 2H), 1.77-1.60 (m, 5H), 1.46-0.97 (m, 13H), 0.88-0.76 (m, 2H), 0.72 (s, 3H), 0.45-0.35 (m, 1H)

[0920] Example No. 11: Synthesis of (2R,4aS,4bR,6aS,7R,7aS,8aR,8bR,8cR,10aS)-2-(methoxymethyl)-6a-methyl-7-((S)-1-(5-methyl-2H-tetrazol-2-yl)propan-2-yl)octadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-2-ol (Compound No. 17) & (2R,4aS,4bR,6aS,7R,7aS,8aR,8bR,8cR,10aS)-2-(methoxymethyl)-6a-methyl-7-((R)-1-(5-methyl-2H-tetrazol-2-yl)propan-2-yl)octadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-2-ol (Compound No. 18).



[0921] Synthesis of 11.1

[0922] To a mixture of MePPh_3Br (1.92 g, 5.40 mmol) in THF (8 mL) was added $t\text{-BuOK}$ (605 mg, 5.40 mmol) at 25°C under N_2 . The resulting mixture was stirred at 40°C for 30 min. Compound No. 16 (0.65 g, 1.80 mmol) was added in portions at 55°C . The reaction mixture was stirred at 55°C for 16 hour to give a yellow suspension. The reaction mixture was quenched with 10% NH_4Cl aqueous (40 mL) at 25°C . The aqueous was extracted with EtOAc (2 x 40 mL). The combined organic phase was separated, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column (0~35% of ethyl acetate in petroleum ether) to give 11.1 (1.00 g, crude). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 5.10 (s, 1H), 4.84 (s, 1H), 3.39 (s, 3H), 3.19 (s, 2H), 2.42-2.37 (m, 1H), 2.04-1.87 (m, 2H), 1.74 (s, 3H), 1.73-1.41 (m, 7H), 1.29-0.98 (m, 11H), 0.81-0.66 (m, 3H), 0.64 (s, 3H), 0.29-0.20 (m, 1H).

[0923] Synthesis of 11.2

[0924] To a solution of **11.1** (1.00 g, 2.78 mmol) in THF (10 mL) was added $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (1.11 mL, 10 M, 11.1 mmol) at 25°C under N_2 . The mixture was stirred at 25°C for 16 hours. Ethanol (1.96 mL, 33.3 mmol), NaOH (6.65 mL, 5M aq., 33.3 mmol) and H_2O_2 (4.17 mL, 10 M, 41.7 mmol) were added dropwise. The resulting mixture was stirred at 60°C for 1 hour. The mixture was quenched with $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL). The mixture was concentrated and filtered. The solid was washed with EA (200 mL) dried over Na_2SO_4 , filtered and concentrated to give **11.2** (0.52 g, 50 %). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 3.76-3.66 (m, 1H), 3.45-3.30 (m, 4H), 3.18 (s, 2H), 2.01-1.42 (m, 13H), 1.29-1.17 (m, 5H), 1.14 (m, 3H), 1.12-0.99 (m, 5H), 0.76 (s, 3H), 0.74-0.68 (m, 2H), 0.64-0.58 (m, 1H), 0.14-0.08 (m, 1H).

[0925] Synthesis of 11.3

[0926] To a solution of **11.2** (0.52 g, 1.38 mmol) in DCM (10 mL) was added N-methylimidazole (226 mg, 2.76 mmol), TEA (535 μL , 4.14 mmol) and TsCl (394 mg, 2.07 mmol). The mixture was stirred at 25°C for 1 h. The mixture was poured into NaHCO_3 (20 mL, saturated) and washed with 1M HCl (20 mL). The aqueous phase was extracted with DCM (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered to give **11.3** (0.71 g, 97 %). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 7.83-7.74 (m, 2H), 7.38-7.30 (m, 2H), 4.14-4.05 (m, 1H), 3.78-3.70 (m, 1H), 3.38 (s, 3H), 3.18 (s, 2H), 2.44 (s, 3H), 2.04-1.62 (m, 7H), 1.57-1.11 (m, 10H), 1.08-1.06 (m, 3H), 1.05-0.80 (m, 5H), 0.76-0.61 (m, 5H), 0.59-0.51 (m, 1H), 0.13-0.01 (m, 1H).

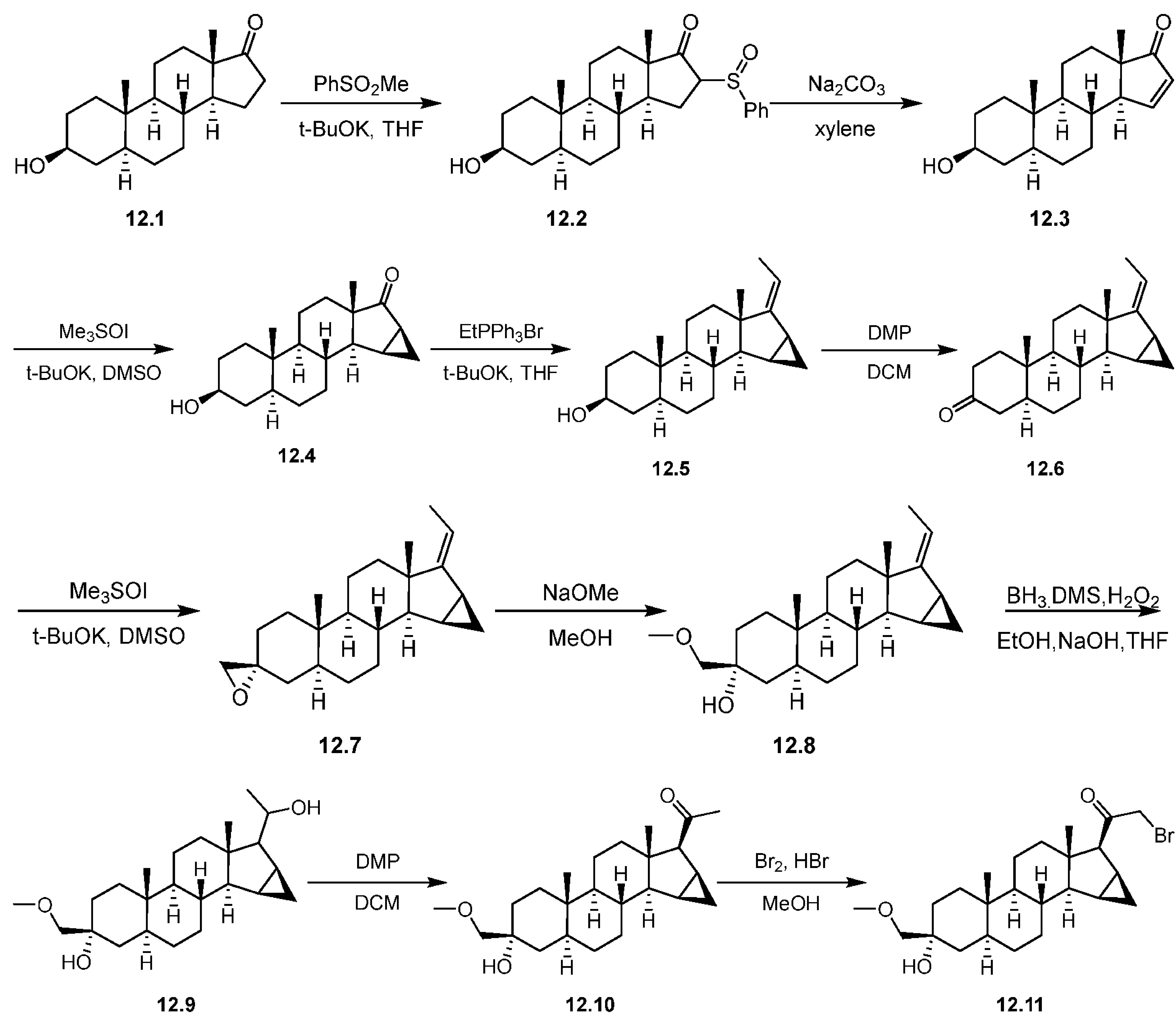
[0927] Synthesis of Compound No. 17 and Compound No. 18

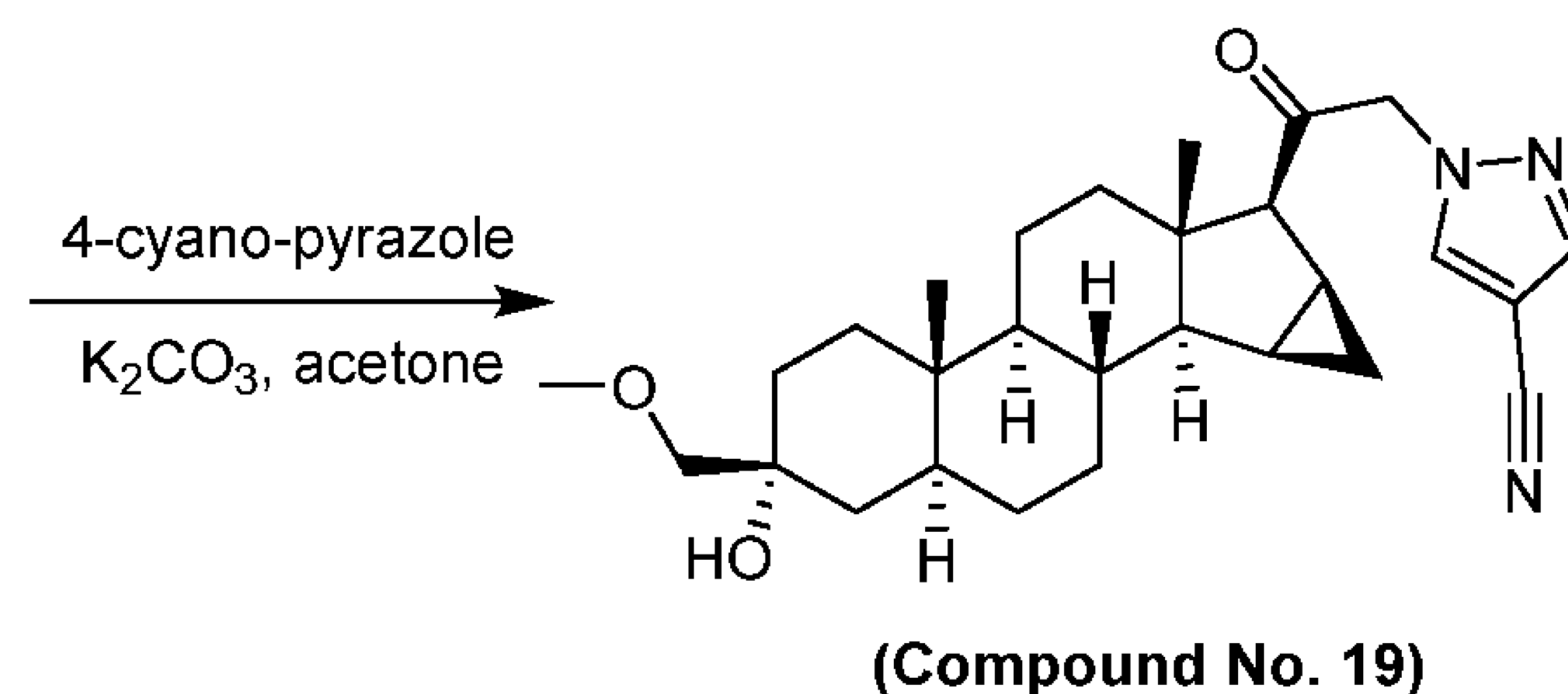
[0928] A solution of **11.3** (0.30 g, 0.56 mmol), Cs_2CO_3 (736 mg, 2.262 mmol) and 5-methyltetrazole (95.0 mg, 1.13 mmol) in DMF (5 mL) was stirred at 100°C for 16 hours. The mixture was added into saturated H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with saturated brine (2 x 20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by flash chromatography (10~30% ethyl acetate in petroleum ether) to give **Compound No. 18** (75.0 mg, 30 %) and SFC (1st run: Column: DAICEL CHIRALCEL OD-H (250mm*30mm, 5 μm); Condition: 0.1% $\text{NH}_3\text{H}_2\text{O}$ ETOH; Begin B: 30%; End B: 30%; FlowRate (ml/min): 70; Injections: 60. 2nd run: Column: DAICEL CHIRALPAK AD(250mm*30mm, 10 μm); Condition: 0.1% $\text{NH}_3\text{H}_2\text{O}$ ETOH; Begin B: 40%; End B: 40%; FlowRate(ml/min): 70; Injections: 60) and lyophilized to give **Compound No. 18** (29.5 mg, 12%) and **Compound No. 17** (3.20 mg, 1.3%).

[0929] **Compound No. 17:** ^1H NMR (400 MHz, CDCl_3) δ_{H} 4.88-4.75 (m, 1H), 4.59-4.44 (m, 1H), 3.39 (s, 3H), 3.18 (s, 2H), 2.55 (s, 3H), 2.38-2.28 (m, 1H), 1.93-1.86 (m, 1H), 1.74-1.65 (m, 6H), 1.49-1.38 (m, 1H), 1.32-0.96 (m, 13H), 0.83 (d, $J = 6.4$ Hz, 3H), 0.79 (s, 3H), 0.75-0.68 (m, 3H), 0.21-0.14 (m, 1H).

[0930] **Compound No. 18:** ^1H NMR (400 MHz, CDCl_3) δ_{H} 4.70-4.59 (m, 1H), 4.35-4.18 (m, 1H), 3.39 (s, 3H), 3.19 (s, 2H), 2.54 (s, 3H), 2.44-2.30 (m, 1H), 2.04-1.58 (m, 10H), 1.49-1.42 (m, 1H), 1.27-0.99 (m, 10H), 0.93 (d, $J = 6.4$ Hz, 3H), 0.91 (s, 3H), 0.79-0.65 (m, 3H), 0.20-0.09 (m, 1H).

[0931] **Example No. 12: Synthesis of (2R,4aS,4bR,6aS,7R,7aS,8aR,8bR,8cR,10aS)-2-(methoxymethyl)-6a-methyl-7-((S)-1-(5-methyl-2H-tetrazol-2-yl)propan-2-yl)octadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-2-ol (Compound No. 19).**





[0932] Synthesis of 12.2

[0933] To a solution of t-BuOK (19.3 g, 172 mmol) in THF (500 mL) was added **12.1** (25.0 g, 86.0 mmol) at 15°C under N₂. The mixture was stirred at 15°C for 10 minutes. Then methyl benzenesulfinate (26.8 g, 172 mmol) was added. The mixture was stirred at 30°C for 0.5 hour. The mixture was quenched with H₂O (300 mL) and extracted with EtOAc (2 x 200 mL). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated in vacuum to give **12.2** (45.0 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 7.64-7.56 (m, 2H), 7.55-7.44 (m, 3H), 3.65-3.50 (m, 1H), 3.50-3.20 (m, 1H), 1.90-1.61 (m, 8H), 1.52-1.17 (m, 10H), 1.16-1.02 (m, 2H), 0.95-0.87 (m, 3H), 0.82-0.77 (m, 3H), 0.74-0.55 (m, 1H).

[0934] Synthesis of 12.3

[0935] To a mixture of **12.2** (45.0 g, 108 mmol) in xylene (450 mL) was added Na₂CO₃ (170 g, 1.61 mol) in portions. The reaction mixture was stirred at 125 °C for 12 hours under N₂. The mixture was filtered, concentrated and purified by flash column (0-30% of ethyl acetate in petroleum ether /DCM (1/1)) to give **12.3** (18.8 g, 48%). ¹H NMR (400 MHz, CDCl₃) δ_H 7.51 (dd, *J* = 0.8, 6.0 Hz, 1H), 6.05-5.97 (dd, *J* = 3.2, 6.0 Hz, 1H), 3.66-3.57 (m, 1H), 2.32-2.20 (m, 1H), 2.05-1.94 (m, 1H), 1.90-1.54 (m, 8H), 1.53-1.23 (m, 7H), 1.05 (s, 3H), 1.02-0.94 (m, 1H), 0.87 (s, 3H), 0.83-0.75 (m, 1H).

[0936] Synthesis of 12.4

[0937] A stirred solution of trimethylsulfoxonium iodide (28.6 g, 130 mmol) and t-BuOK (16.0 g, 143 mmol) in DMSO (450 mL) was heated at 60°C for 1.0 h under N₂. Compound **12.3** (18.8 g, 65.1 mmol) was added to the reaction mixture and stirred at 25°C for 1 hour. The reaction was treated with water (300 mL), then it was extracted with EtOAc (2 x 300 mL). The combined organic phase was washed with water (2 x 200 mL), brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum to afford **12.4** (23.3 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 3.67-3.52 (m, 1H), 1.97-1.58 (m, 10H), 1.40-1.29 (m, 5H), 1.20-0.99 (m, 6H), 0.94 (s, 3H), 0.84-0.75 (m, 5H).

[0938] Synthesis of 12.5

[0939] To a mixture of MePPh₃Br (78.3 g, 211 mmol) in THF (200 mL) was added t-BuOK (23.6 g, 211 mmol) at 25°C under N₂. The resulting mixture was stirred at 50°C for 30 minutes. Compound **12.4** (21.3 g, 70.4 mmol) was added in portions below 50°C. The reaction mixture was stirred at 50°C for 16 hours. The reaction mixture was quenched with 10% aqueous NH₄Cl (300 mL) at 15°C. The aqueous was extracted with EtOAc (200 mL x 3). The combined organic phase was washed with brine (200 mL x 2), dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was triturated from MeOH (780 mL) at 25°C and purified by flash chromatography (0~25% of ethyl acetate in petroleum ether) to give **12.5** (5.81 g, 26%). ¹H NMR (400 MHz, CDCl₃) δH 5.35 (q, J = 7.2 Hz, 1H), 3.65-3.54 (m, 1H), 2.17-2.06 (m, 1H), 1.95-1.71 (m, 4H), 1.71-1.66 (m, 4H), 1.65-1.60 (m, 2H), 1.44-1.24 (m, 9H), 1.02-0.97 (m, 4H), 0.96-0.86 (m, 2H), 0.85-0.79 (m, 4H), 0.78-0.65 (m, 1H), 0.50-0.39 (m, 1H).

[0940] Synthesis of 12.6

[0941] To a solution of **12.5** (4.46 g, 14.1 mmol) in DCM (45 mL) was added DMP (5.47 g, 28.2 mmol). After stirring at 25°C for 2 hours. The reaction mixture was quenched with saturated NaHCO₃ solution (100 mL) and sat. Na₂S₂O₃ (50 mL). After stirring at 25°C for 15 minutes, the organic phase was separated, washed with sat. NaHCO₃ (60 mL) and sat. Na₂S₂O₃ (30 mL), dried over anhydrous Na₂SO₄, filtered, concentrated to give **12.6** (4.30 g, crude). ¹H NMR (400 MHz, CDCl₃) δH 5.35 (q, J = 7.2 Hz, 1H), 2.46-2.06 (m, 5H), 2.01-1.93 (m, 2H), 1.83-1.71 (m, 2H), 1.70-1.67 (m, 3H), 1.54-1.31 (m, 5H), 1.20-1.07 (m, 2H), 1.06-0.97 (m, 7H), 0.95-0.78 (m, 4H), 0.51-0.41 (m, 1H).

[0942] Synthesis of 12.7

[0943] A stirred solution of trimethylsulfoxonium iodide (5.63 g, 25.6 mmol) and t-BuOK (3.15 g, 28.1 mmol) in DMSO (100 mL) was heated at 60°C for 1.0 hour under N₂. Compound **12.6** (4.00 g, 12.8 mmol) was added to the reaction mixture and stirred at 25°C for 1 hour. The reaction mixture was treated with water (200 mL), then extracted with EtOAc (2 x 150 mL). The combined organic phase was washed with water (2 x 100 mL), brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum to afford **12.7** (9.00 g, crude). ¹H NMR (400 MHz, CDCl₃) δH 5.39-5.23 (m, 1H), 1.96-1.68 (m, 6H), 1.65 (d, J = 7.2 Hz, 3H), 1.63-1.26 (m, 10H), 1.19-0.99 (m, 5H), 0.96 (s, 3H), 0.94-0.86 (m, 2H), 0.84 (s, 3H), 0.46-0.37 (m, 1H).

[0944] Synthesis of 12.8

[0945] Metal sodium (6.32 g, 275 mmol) was added to MeOH (180 mL) in portions. After stirring at 20 °C for 1 hour, a solution of **12.7** (9.00 g, 27.5 mmol) in THF (40 mL) was added to the mixture at 25°C. The resulting mixture was stirred at 60°C for 24 hours. The mixture was poured into H₂O (200 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with NH₄Cl aqueous (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give **12.8** (5.10 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 5.39-5.29 (m, 1H), 3.38 (s, 3H), 3.18 (s, 2H), 1.94-1.74 (m, 3H), 1.67 (d, *J* = 7.2 Hz, 3H), 1.64-1.05 (m, 15H), 0.97 (s, 3H), 0.93-0.80 (m, 4H), 0.77 (s, 3H), 0.48-0.37 (m, 1H).

[0946] Synthesis of 12.9

[0947] To a solution of **12.8** (5.10 g, 66.9 mmol) in THF (50 mL) was added BH₃·Me₂S (2.83 mL, 10 M, 28.4 mmol) at 25°C. The mixture was stirred at 25°C for 16 hours. To the resulting mixture was added ethanol (4.96 mL, 85.2 mmol) at 25°C. Then NaOH aqueous (17.0 mL, 5 M, 85.2 mmol) was added dropwise at 25°C followed by H₂O₂ (8.52 mL, 10 M, 85.2 mmol). After the addition, the mixture was stirred at 70°C for 1 hour. The mixture was extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with saturated brine (2 x 80 mL), dried over anhydrous Na₂SO₄. The combined organic phase was concentrated under vacuum to give **12.9** (6.08 g, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 3.89-3.73 (m, 1H), 3.38 (s, 3H), 3.17 (s, 2H), 1.95-1.87 (m, 1H), 1.78-1.41 (m, 7H), 1.37-1.26 (m, 8H), 1.25-1.21 (m, 4H), 1.20-1.07 (m, 4H), 0.91-0.80 (m, 3H), 0.78-0.70 (m, 6H), 0.24-0.13 (m, 1H).

[0948] Synthesis of 12.10

[0949] To a solution of **12.9** (3.08 g, 8.17 mmol) in DCM (30 mL) was added DMP (3.16 g, 16.3 mmol). After stirring at 25°C for 1 hour, the reaction mixture was washed with saturated NaHCO₃ solution (50 mL) and sat. Na₂S₂O₃ (50 mL) twice, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (0~45% of ethyl acetate in petroleum ether) to give **12.10** (3.00 g). ¹H NMR (400 MHz, CDCl₃) δ_H 3.38 (s, 3H), 3.18 (s, 2H), 2.73 (d, *J* = 4.0 Hz, 1H), 2.25-2.09 (m, 3H), 1.98-1.85 (m, 2H), 1.74-1.60 (m, 2H), 1.57-0.97 (m, 14H), 0.81-0.92 (m, 2H), 0.76 (s, 3H), 0.70 (s, 3H), 0.30-0.45 (m, 1H).

[0950] Synthesis of 12.11

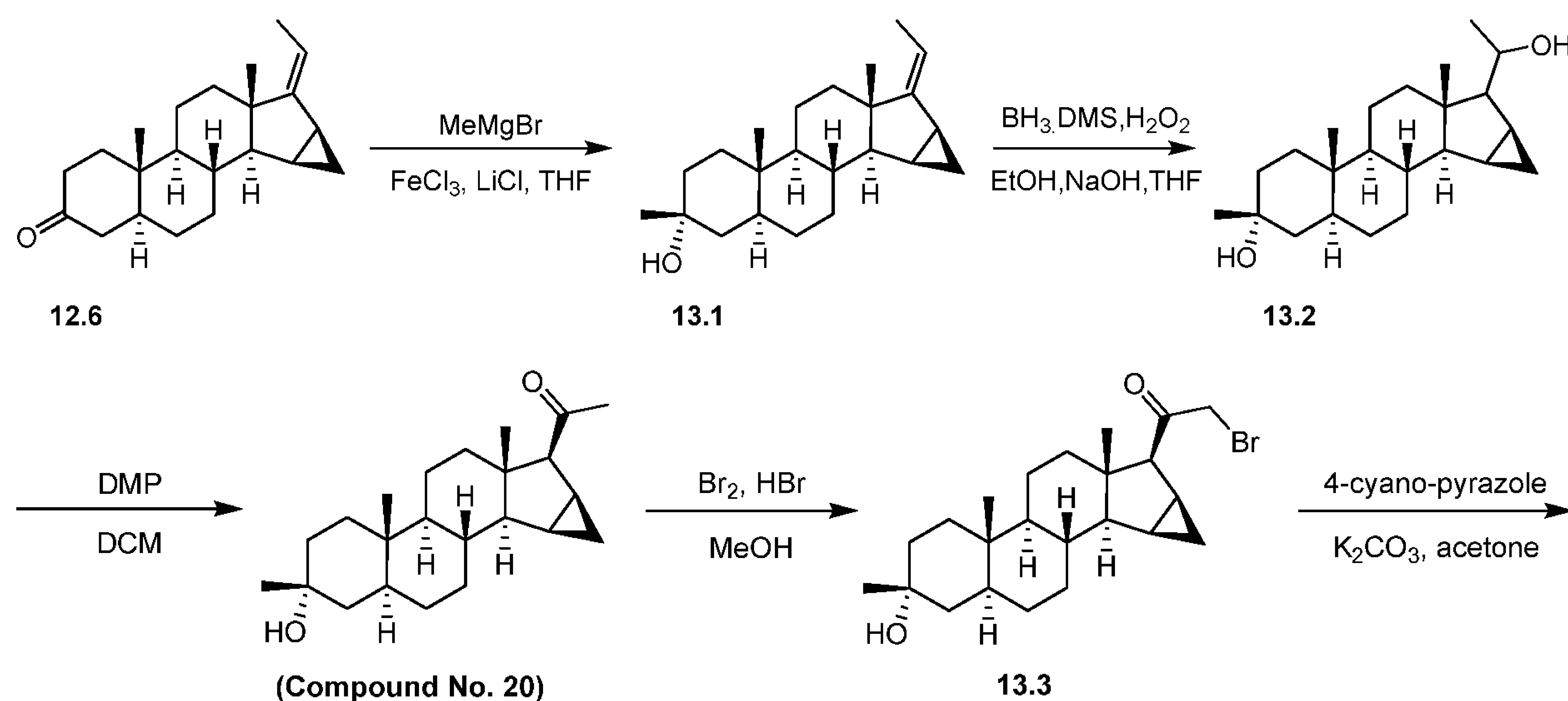
[0951] To a mixture of **12.10** (0.20 g, 0.533 mmol) in MeOH (5 mL) was added HBr (8.50 mg, 0.106 mmol, 40% aq.) and Br₂ (93.6 mg, 0.586 mmol) at 20°C. The reaction mixture was

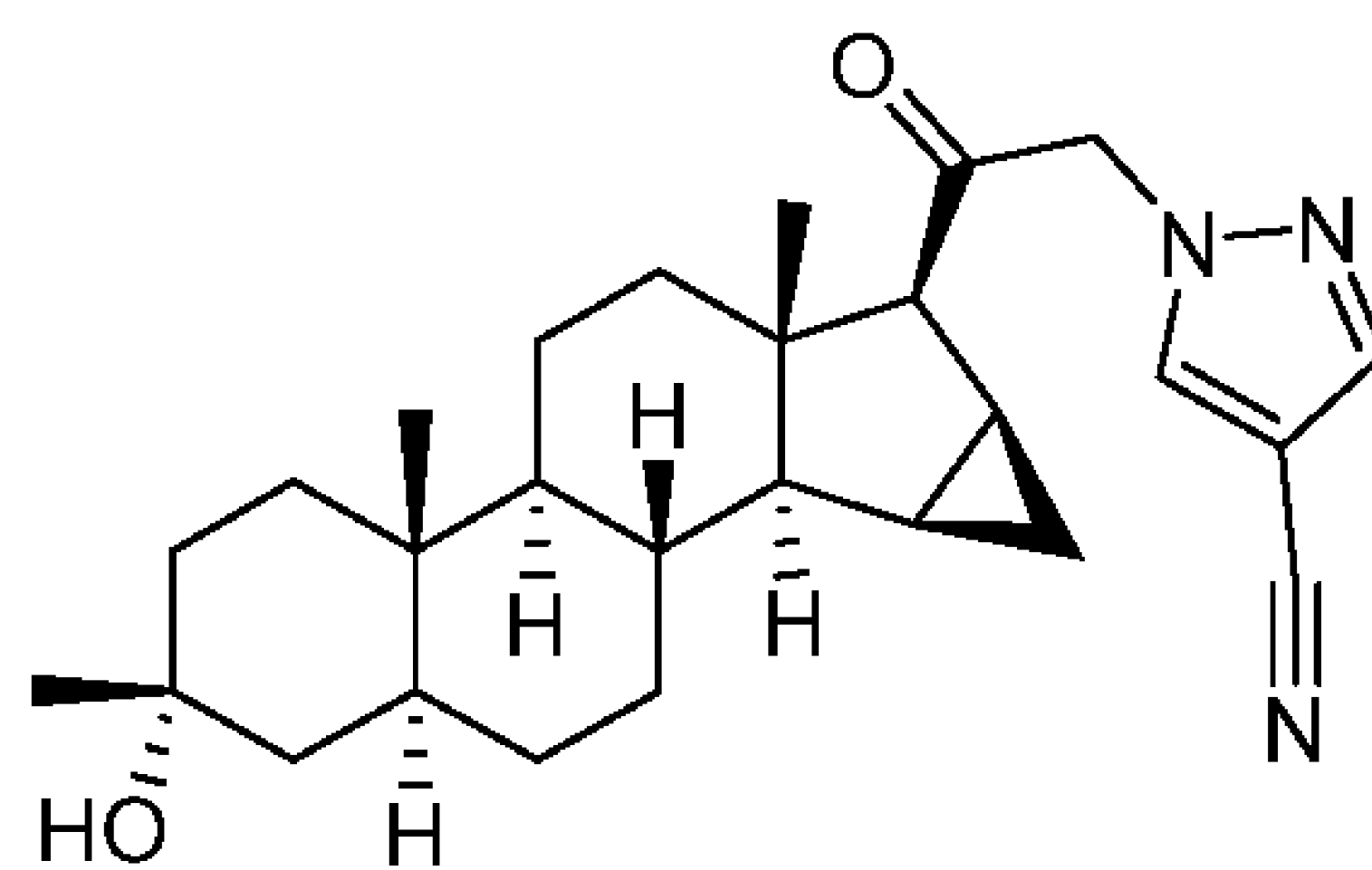
stirred at 25°C for 2 hours. The mixture was added NaHCO₃/Na₂S₂O₃ (20 mL, 1:1). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with saturated brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give **12.11** (0.20 g, crude).

[0952] Synthesis of Compound No. 19

[0953] To a solution of **12.11** (0.20 g, 0.441 mmol) in acetone (5 mL) was added 4-cyano-pyrazole (82.1 mg, 0.882 mmol) and K₂CO₃ (123 mg, 0.882 mmol) at 25 °C and stirred for 16 hours. To the reaction mixture was added H₂O (10 ml) at 25 °C. The aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with saturated brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered, concentrated, purified by flash chromatography (0-50% of ethyl acetate in petroleum ether) and SFC (column: DAICEL CHIRALCEL OD (250mm*30mm, 10um); Mobile phase: A: CO₂ B: 0.1%NH₃H₂O ETOH; gradient: from 40% to 40% of B, Flow Rate (mL/min): 80) and triturated from PE (5 mL) at 25°C to give **Compound No. 19** (120 mg, 58%). ¹H NMR (400 MHz, CDCl₃) δ_H 7.87 (s, 1H), 7.82 (s, 1H), 5.22-5.12 (m, 2H), 3.39 (s, 3H), 3.18 (s, 2H), 2.82 (d, *J* = 2.4 Hz, 1H), 1.95-1.89 (m, 2H), 1.78-1.64 (m, 2H), 1.51-0.80 (m, 18H), 0.76 (s, 6H), 0.51-0.45 (m, 1H).

[0954] Example No. 13: Synthesis of (2R,4aS,4bR,6aS,7R,7aS,8aR,8bR,8cR,10aS)-2-(methoxymethyl)-6a-methyl-7-((R)-1-(5-methyl-2H-tetrazol-2-yl)propan-2-yl)octadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-2-ol (Compound No. 20) and (2R,4aS,4bR,6aS,7R,7aS,8aR,8bR,8cR,10aS)-2-(methoxymethyl)-6a-methyl-7-((R)-1-(5-methyl-2H-tetrazol-2-yl)propan-2-yl)octadecahydrocyclopropa[4,5]cyclopenta[1,2-a]phenanthren-2-ol (Compound No. 21).





(Compound No. 21)

[0955] Synthesis of 13.1

[0956] A suspension of LiCl (852 mg, 20.1 mmol, anhydrous) in THF (30 mL, anhydrous) was stirred at 10°C for 30 mins under N₂. Then FeCl₃ (1.70 g, 10.5 mmol, anhydrous) was added at 10°C. The mixture was cooled down to -30°C. MeMgBr (12.7 mL, 38.4 mmol, 3M in diethyl ether) was added dropwise to the mixture at -30°C. The resulting mixture was stirred at -30°C for 10 mins. Then **12.6** (1.00 g, 3.20 mmol) in THF (10 mL, anhydrous) was added at -30°C. The mixture was stirred at -15°C for 4 hours. Citric acid (30 mL, 20% aq.) was added to the mixture. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with saturated brine (2 x 30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by flash chromatography (0~30% ethyl acetate in petroleum ether) to give **13.1** (850 mg, 81 %). ¹H NMR (400 MHz, CDCl₃) δ_H 5.35 (q, *J* = 6.8 Hz, 1H), 2.15-2.09 (m, 1H), 1.93-1.88 (m, 1H), 1.81-1.71 (m, 2H), 1.70-1.67 (m, 3H), 1.52-1.44 (m, 6H), 1.32-1.23 (m, 7H), 1.21-1.19 (m, 4H), 0.98 (s, 3H), 0.92-0.83 (m, 3H), 0.80-0.75 (m, 4H), 0.48-0.41 (m, 1H).

[0957] Synthesis of 13.2

[0958] BH₃·Me₂S (684 μL, 10M, 6.84 mmol) was added under N₂ to a solution of **13.1** (750 mg, 2.28 mmol) in THF (5 mL). The reaction mixture was stirred at 20°C under N₂ for 12 hours. EtOH (2.41 mL, 41.0 mmol) and NaOH (8.20 mL, 5M, 41.0 mmol) were added to the mixture. Then H₂O₂ (4.10 mL, 10M, 41.0 mmol) was added dropwise at 15°C. The mixture was stirred at 70°C for 1 hour. Then the mixture was poured into Na₂S₂O₃ (50 mL, sat.) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with saturated brine (2 x 30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column (0 ~45% ethyl acetate in petroleum ether) to give **13.2** (690 mg, 87 %).

[0959] Synthesis of Compound No. 20

[0960] To a solution of **13.2** (300 mg, 0.86 mmol) in DCM (10 mL) was added Dess-martin reagent (733 mg, 1.73 mmol) at 25°C. The reaction mixture was stirred at 25°C for 10 min. The mixture was quenched with saturated NaHCO₃/Na₂S₂O₃ aqueous (1:1, 20 mL). The

mixture combined with another batch of **13.2** (300 mg) and extracted with DCM (3 x 50 mL), washed with brine (2 x 15 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by flash column (0-30% of ethyl acetate in petroleum ether) to give **Compound No. 20** (600 mg). The residue (30.0 mg) was re-crystallized from MeCN (8 mL) to give **Compound No. 20** (7.00 mg, 23 %). ¹H NMR (400 MHz, CDCl₃) δ_H 2.73 (d, *J* = 4.0 Hz, 1H), 2.20 (s, 3H), 1.97-1.87 (m, 2H), 1.73-1.66 (m, 1H), 1.62-1.57 (m, 1H), 1.53-1.22 (m, 14H), 1.20 (s, 3H), 1.18-1.11 (m, 2H), 0.88-0.81 (m, 2H), 0.76 (s, 3H), 0.71 (s, 3H), 0.43-0.34 (m, 1H).

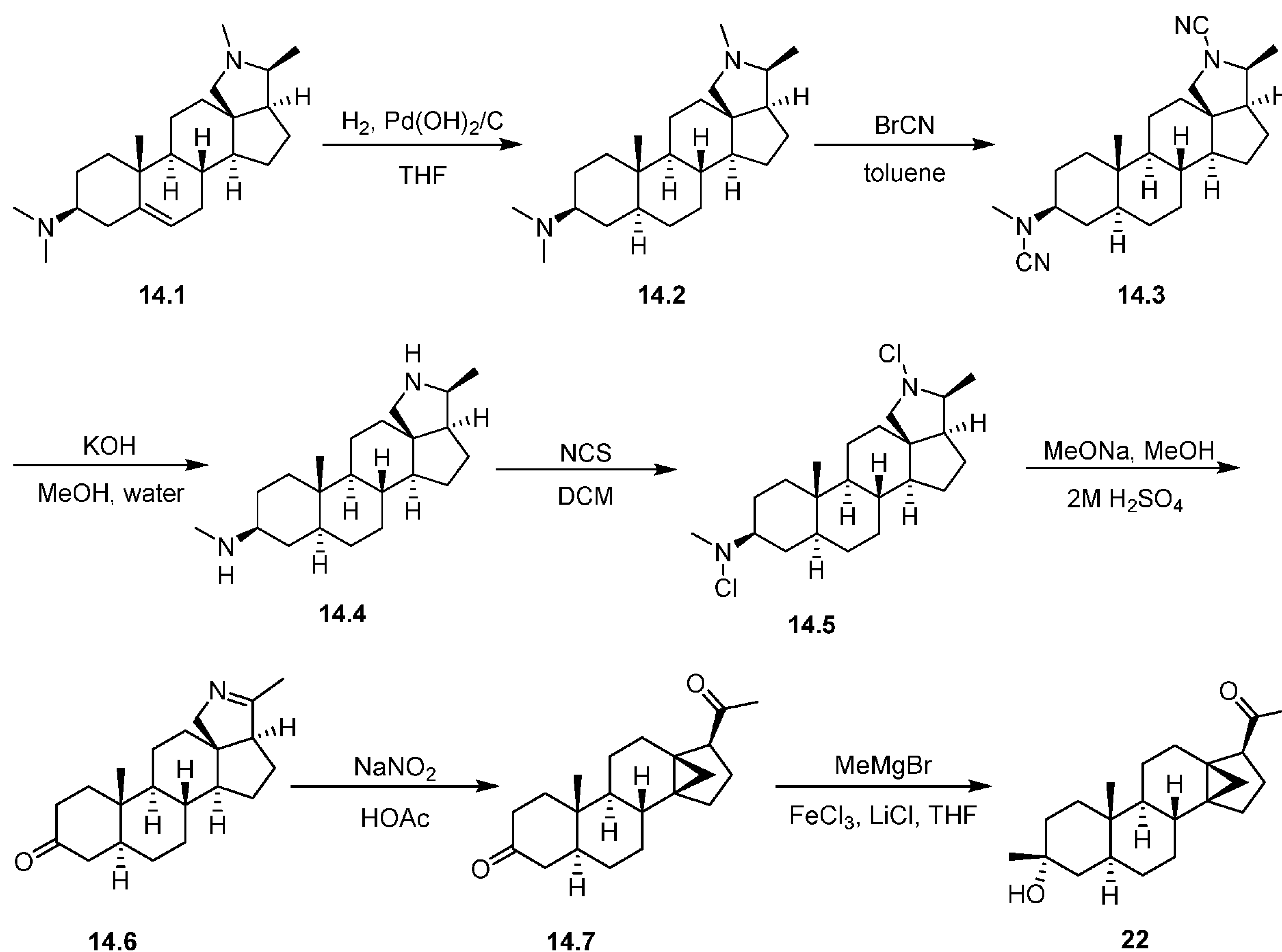
[0961] Synthesis of 13.3

[0962] To a mixture of **Compound No. 20** (150 mg, 0.43 mmol) in MeOH (3 mL) was added HBr (7.03 mg, 0.087 mmol, 40% aq.) and Br₂ (83.4 mg, 0.52 mmol) at 20°C. The reaction mixture was stirred at 25 °C for 1 h. NaHCO₃ (20 mL) was added to the mixture. The aqueous phase was extracted with EA (3 x 30 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give **13.3** (200 mg). ¹H NMR (400 MHz, CDCl₃) δ_H 4.15-4.05 (m, 2H), 2.99 (d, *J* = 4.4 Hz, 1H), 1.94-1.86 (m, 2H), 1.74-1.69 (m, 1H), 1.49-1.44 (m, 2H), 1.39-1.24 (m, 11H), 1.22-1.19 (m, 4H), 1.17-1.06 (m, 2H), 0.96-0.78 (m, 3H), 0.76 (s, 3H), 0.71 (s, 3H), 0.47-0.39 (m, 1H).

[0963] Synthesis of Compound No. 21

[0964] To a solution of **13.1** (200 mg, 0.47 mmol) in acetone (5 mL) was added 1H-pyrazole-4-carbonitrile (87.8 mg, 0.94 mmol) and K₂CO₃ (132 mg, 0.94 mmol) at 25°C and stirred for 16 hours. To the reaction mixture was added H₂O (20 ml) at 25°C. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with saturated brine (2 x 50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column (0-50% of EtOAc in PE) and re-crystallized from MeCN (10 mL) to give **Compound No. 21** (45.6 mg, 22%). ¹H NMR (400 MHz, CDCl₃) δ_H 7.87 (s, 1H), 7.82 (s, 1H), 5.26-5.11 (m, 2H), 2.82 (d, *J* = 2.8 Hz, 1H), 1.99-1.86 (m, 2H), 1.80-1.71 (m, 1H), 1.65-1.57 (m, 2H), 1.53-1.23 (m, 13H), 1.21 (s, 3H), 1.19-1.11 (m, 2H), 1.01-0.95 (m, 1H), 0.89-0.81 (m, 1H), 0.77 (s, 6H), 0.5-0.44 (m, 1H).

[0965] **Example No. 14: Synthesis of 1-((3R,5S,8R,9S,10S,13S,14S,17S)-3-hydroxy-3,10-dimethyltetradecahydro-1H-13,14-methanocyclopenta[a]phenanthren-17-yl)ethanone (Compound No. 22).**



[0966] **Synthesis of 14.2**

[0967] To a solution of **14.1** (9.50 g, 26.6 mmol) in THF (200 mL) was added $\text{Pd}(\text{OH})_2/\text{C}$ (4.00 g, 10%, dry). The mixture was stirred at 25°C under H_2 balloon (15 psi) for 16 hrs. The mixture was filtered through a pad of celite and the solid was washed with THF (3 x 50 mL). The combined filtrate was concentrated to give **14.2** (9.00 g, 94%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 2.95 (d, $J = 10.0$ Hz, 1H), 2.40-2.32 (m, 1H), 2.26 (s, 6H), 2.19 (s, 3H), 2.16-2.07 (m, 1H), 1.83-1.56 (m, 9H), 1.48-1.05 (m, 11H), 1.02 (d, $J = 6.4$ Hz, 3H), 0.99-0.88 (m, 3H), 0.71 (s, 3H), 0.69-0.58 (m, 1H).

[0968] **Synthesis of 14.3**

[0969] To a solution of **14.2** (9.00 g, 25.0 mmol) in toluene (800 mL) was added a solution of BrCN (13.2 g, 125 mmol) in toluene (100 mL). The mixture was stirred at 80°C for 1 h. The resulting mixture was quenched with aq. Na_2CO_3 (500 mL, 20%). The organic layer was separated, dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by flash chromatography (15~30% ethyl acetate in petroleum ether) to give **14.3** (7.90 g,

83%). **¹H NMR** (400 MHz, CDCl₃) δ_H 3.78-3.69 (m, 1H), 3.18 (d, *J* = 10.0 Hz, 1H), 3.05 (d, *J* = 10.0 Hz, 1H), 2.84 (s, 3H), 2.78-2.66 (m, 1H), 1.96-1.61 (m, 9H), 1.57-1.37 (m, 2H), 1.35-1.19 (m, 8H), 1.16-0.87 (m, 6H), 0.75 (s, 3H), 0.72-0.64 (m, 1H). **LC-ELSD/MS:** purity=92%, MS ESI calcd. for C₂₄H₃₇N₄ [M+H]⁺ 381.3, found 381.3.

[0970] Synthesis of 14.4

[0971] To a solution of **14.3** (7.90 g, 20.7 mmol) in MeOH (700 mL) was added a solution KOH (160 g, 2.8 mol) in water (120 mL). The mixture was refluxed at 77°C for 48 h. Water (800 mL) was added to the mixture and concentrated. The residue was extracted with DCM (3 x 200 mL). The combined organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated to give **14.4** (6.60 g, 96%). **¹H NMR** (400 MHz, CDCl₃) δ_H 3.25-3.15 (m, 1H), 2.77 (d, *J* = 11.6 Hz, 1H), 2.53 (d, *J* = 12.0 Hz, 1H), 2.41 (s, 3H), 2.38-2.27 (m, 1H), 1.87-1.39 (m, 12H), 1.36-1.12 (m, 7H), 1.09 (d, *J* = 6.4 Hz, 3H), 1.06-0.88 (m, 5H), 0.71 (s, 3H), 0.69-0.60 (m, 1H). **LC-ELSD/MS:** purity=97%, MS ESI calcd. for C₁₁H₂₀N [M+2H]⁺⁺/2 166.2, found 166.2; calcd. for C₂₂H₃₉N₂ [M+H]⁺ 331.3, found 331.3.

[0972] Synthesis of 14.5

[0973] To a solution of **14.4** (6.60 g, 19.9 mmol) in DCM (800 mL) was added NCS (6.63 g, 49.7 mmol) under N₂. The mixture was stirred at 25°C for 1 h. The mixture was concentrated in vacuum below 35°C to give intermediate **14.5** (15.0 g, crude). **LC-ELSD/MS:** purity=96%, MS ESI calcd. for C₂₂H₃₇Cl₂N₂ [M+H]⁺ 399.2, found 399.1.

[0974] Synthesis of 14.6

[0975] Intermediate **14.5** (15.0 g) was dissolved in THF/MeOH (80 mL/20 mL) and added to a MeONa/MeOH solution (10.0 g Na dissolved in 1000 mL MeOH) under N₂ and stirred at 65°C for 1 h. The mixture was concentrated in vacuum. To the residue was added H₂SO₄ (1000 mL, 2M) at 0°C and the mixture was stirred at 25°C for 16 h. The mixture was basified with NH₃·H₂O (400 mL, conc. 14M) and the mixture was extracted with DCM (2 x 300 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column (10~40% ethyl acetate in petroleum ether, 1% TEA added) to give **14.6** (5.50 g, 88%). **¹H NMR** (400 MHz, CDCl₃) δ_H 3.60-3.52 (m, 1H), 3.46-3.38 (m, 1H), 2.58-2.48 (m, 2H), 2.45-2.22 (m, 3H), 2.12-2.00 (m, 2H), 1.98 (s, 3H), 1.83-1.48 (m, 7H), 1.42-1.18 (m, 6H), 1.11-1.01 (m, 2H), 0.99 (s, 3H), 0.73-0.85 (m, 1H). **LC-ELSD/MS:** purity=95%, MS ESI calcd. for C₂₁H₃₂NO [M+H]⁺ 314.2, found 314.2.

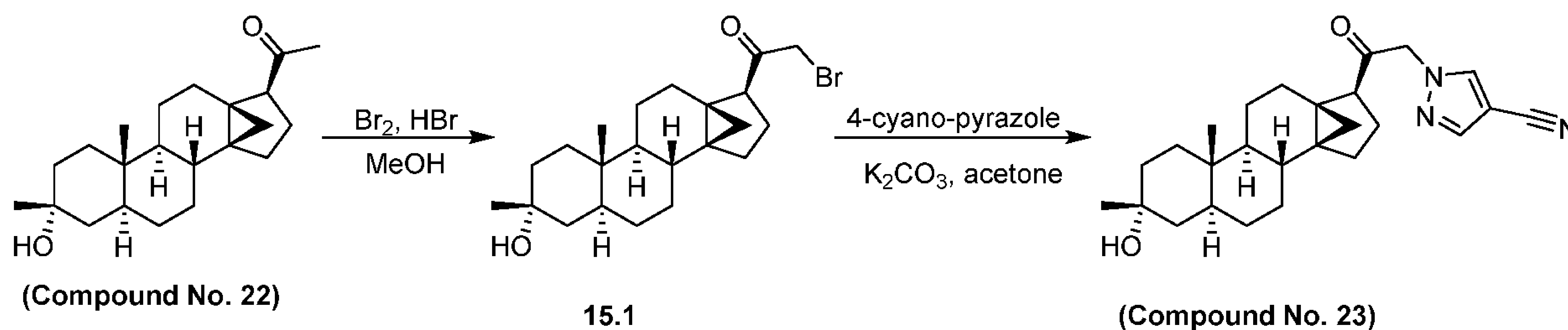
[0976] Synthesis of 14.7

[0977] To a solution of **14.6** (5.50 g, 17.5 mmol) in AcOH (500 mL) and water (100 mL) was added dropwise NaNO₂ (12.0 g, 175 mmol, in 50 mL water) at 5°C. The mixture was stirred at 10°C for 2 h. To the mixture was added water (1000 mL) and extracted with DCM (3 x 250 mL). The combined organic layer was washed with NaHCO₃ (1000 mL, sat.), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column (10~16% ethyl acetate in petroleum ether) to give **14.7** (1.88 g, 34%). A portion (100 mg) of the product was recrystallized from MeCN/water (20 ml, 1:1) to give **14.7** (54.0 mg). ¹H NMR (400 MHz, CDCl₃) δ_H 2.77 (dd, *J* = 8.0, 11.2 Hz, 1H), 2.43-2.14 (m, 7H), 2.12-1.99 (m, 2H), 1.96-1.62 (m, 7H), 1.56-1.23 (m, 6H), 0.94-0.81 (m, 4H), 0.76 (d, *J* = 5.2 Hz, 1H), 0.70-0.59 (m, 1H), 0.21 (d, *J* = 5.2 Hz, 1H). LC-ELSD/MS: purity>99%, MS ESI calcd. for C₂₁H₃₁O₂ [M+H]⁺ 315.2, found 315.2.

[0978] Synthesis of Compound No. 22

[0979] A suspension of LiCl (254 mg, 6.0 mmol, anhydrous) in THF (20 mL, anhydrous) was stirred at 10°C for 30 mins under N₂. Then FeCl₃ (509 mg, 3.14 mmol, anhydrous) was added at 10°C. The mixture was cooled to -30°C. To the mixture was added dropwise MeMgBr (3.80 mL, 3M in ether, 11.4 mmol) at -30°C. The resulting mixture was stirred at -30°C for 10 mins. Compound **14.7** (300 mg, 0.95 mmol) in THF (5 mL) was added at -30°C. The reaction mixture was stirred at -15°C for 1 hour. To the mixture was added citric acid (30 mL, 10% aq.). The mixture was extracted with EtOAc (2 x 20 mL). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column (10~20% ethyl acetate in petroleum ether) twice and lyophilized to give **22** (160 mg, 51%). ¹H NMR (400 MHz, CDCl₃) δ_H 2.75 (dd, *J* = 8.0, 11.2 Hz, 1H), 2.18-2.08 (m, 4H), 1.92-1.72 (m, 3H), 1.69-1.57 (m, 3H), 1.55-1.12 (m, 16H), 0.83-0.58 (m, 6H), 0.17 (d, *J* = 5.2 Hz, 1H). LC-ELSD/MS: purity>99%, MS ESI calcd. for C₂₂H₃₄O₂ [M+H-H₂O]⁺ 313.2, found 313.2.

[0980] **Example No. 15: Synthesis of 1-(2-((3R,5S,8R,9S,10S,13S,14S,17S)-3-hydroxy-3,10-dimethyltetradecahydro-1H-13,14-methanocyclopenta[a]phenanthren-17-yl)-2-oxoethyl)-1H-pyrazole-4-carbonitrile (Compound No. 2).**



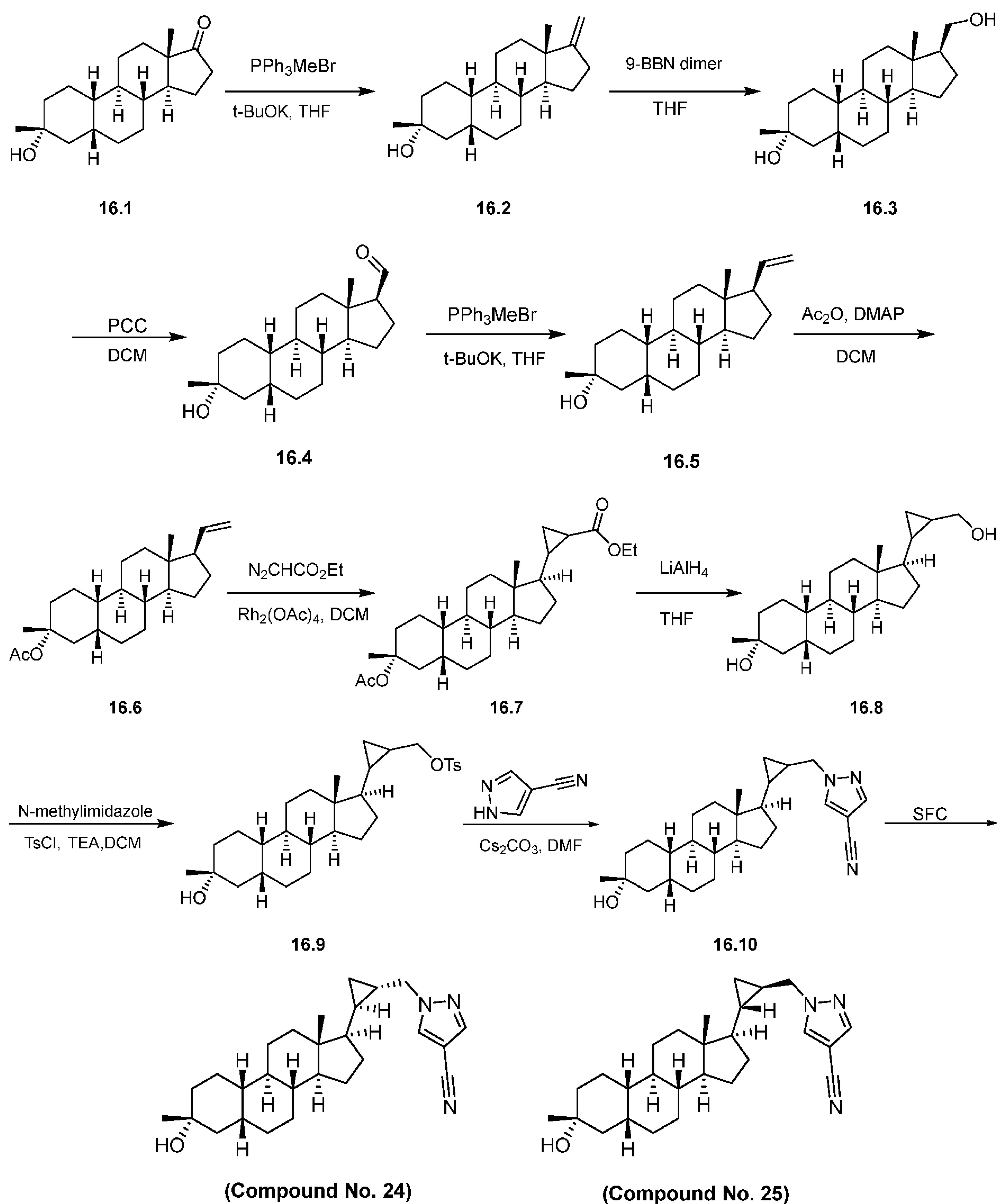
[0981] **Synthesis of 15.1**

[0982] To a solution of **Compound No. 22** (105 mg, 0.32 mmol) in MeOH (4 mL) was added HBr (6.4 mg, 40% aq, 0.03 mmol) and Br₂ (55.8 mg, 0.35 mmol). The mixture was stirred at 20°C for 1 h. To the mixture was added NaHCO₃ (5 mL, sat. aq.) and extracted with EtOAc (2 x 10 mL). The combined organic layer was separated, dried over Na₂SO₄, filter and concentrated to give **15.1** (130 mg, crude). ¹H NMR (400 MHz, CDCl₃) δ_H 4.00 (s, 2H), 3.08 (dd, *J* = 7.6, 10.8 Hz, 1H), 2.25-2.05 (m, 2H), 1.90-1.10 (m, 18H), 0.80-0.65 (m, 6H), 0.62 (s, 3H), 0.19 (d, *J* = 5.6 Hz, 1H).

[0983] **Synthesis of Compound No. 23**

[0984] To a solution of **15.1** (130 mg, 0.32 mmol) in acetone (2 mL) was added K₂CO₃ (131 mg, 0.95 mmol) and 4-cyano-pyrazole (35.4 mg, 0.38 mmol). The mixture was stirred at 25°C for 16 h. To the mixture was added water (10 mL) and extracted with EtOAc (10 mL). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column (30~50% ethyl acetate in petroleum ether), re-crystallized from MeCN/water (20 mL, 1:1) and lyophilized to give **23** (42.6 mg, 32%). ¹H NMR (400 MHz, CDCl₃) δ_H 7.87 (s, 1H), 7.82 (s, 1H), 5.12 (d, *J* = 18.0 Hz, 1H), 5.04 (d, *J* = 18.0 Hz, 1H), 2.87 (dd, *J* = 8.0, 11.6 Hz, 1H), 2.23-2.15 (m, 1H), 1.94-1.79 (m, 3H), 1.76-1.57 (m, 4H), 1.51-1.10 (m, 15H), 0.83-0.73 (m, 2H), 0.71-0.59 (m, 4H), 0.25 (d, *J* = 5.2 Hz, 1H). **LC-ELSD/MS:** purity > 99%, MS ESI calcd. for C₂₆H₃₅N₃O₂ [M+H-H₂O]⁺ 404.3, found 404.3.

[0985] Example No. 16: Synthesis of 1-(((1S,2R)-2-((3R,5R,8R,9R,10S,13S,14S,17R)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)cyclopropyl)methyl)-1H-pyrazole-4-carbonitrile (Compound No. 24) and 1-(((1R,2S)-2-((3R,5R,8R,9R,10S,13S,14S,17R)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)cyclopropyl)methyl)-1H-pyrazole-4-carbonitrile (Compound No. 25).



[0986] Synthesis of 16.2

[0987] To a mixture of PPh_3MeBr (24.5 g, 68.8 mmol) in THF (100 ml) was added $t\text{-BuOK}$ (7.70 g, 68.8 mmol) at 15°C under N_2 . The resulting mixture was stirred at 50 °C for 60 min. **16.1** (10 g, 34.4 mmol) was added in portions below 50°C. After stirring at 50 °C for 16 hours, the reaction mixture was quenched with 10% NH_4Cl aqueous (100 ml) and extracted with EtOAc (2 x 100 ml). The combined organic phase was concentrated under vacuum. The residue was re-crystallized from (MeOH/ H_2O =1/1 (350 ml)) at 25°C to give **16.2** (13 g). ^1H NMR (400 MHz, CDCl_3) δ_{H} 4.64 - 4.62 (m, 1H), 4.62 - 4.58 (m, 1H), 2.56 - 2.38 (m, 1H), 2.31 - 2.17 (m, 1H), 1.93 - 1.58 (m, 8H), 1.54 - 1.36 (m, 6H), 1.35 - 1.24 (m, 7H), 1.15 - 1.03 (m, 4H), 0.78 (s, 3H).

[0988] Synthesis of 16.3

[0989] To a solution of **16.2** (13 g, 45.0 mmol) in THF (250 ml) was added 9-BBN dimer (21.7 g, 90.0 mmol) and the mixture was stirred at 15°C for 16 hours. To the mixture was added dropwise EtOH (31 ml, 540 mmol) followed by NaOH (21.6 g in 108 ml water, 5 M, 540 mmol) and H_2O_2 (54 ml, 10 M, 540 mmol). The mixture was stirred at 78°C for 1 h. The mixture was quenched by $\text{Na}_2\text{S}_2\text{SO}_3$ (250 ml, 10%) and extracted with EtOAc (2 x 200 ml). The organic layer was separated, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash column (0-40% of ethyl acetate in petroleum ether) to give **16.3** (22 g). ^1H NMR (400 MHz, CDCl_3) δ_{H} 3.75 - 3.66 (m, 1H), 3.59 - 3.48 (m, 1H), 1.84 - 1.76 (m, 5H), 1.65 - 1.63 (m, 3H), 1.48 - 1.43 (m, 6H), 1.33 - 1.24 (m, 8H), 1.22 - 0.96 (m, 7H), 0.64 (s, 3H).

[0990] Synthesis of 16.4

[0991] To a solution of **16.3** (22 g, 71.7 mmol) in DCM (300 ml) at 0°C was added silica gel (30.7 g) and PCC (30.7 g, 143 mmol). The mixture was stirred at 10°C for 4 hours. PE (150 ml) was added to the reaction mixture. The resulting mixture was filtered through a pad of silica gel and the filter cake was washed with DCM (3x200 ml). The residue was filtered and concentrated in vacuum to give product. The crude product was purified by silica gel chromatography (0-25% of ethyl acetate in petroleum ether) to give **16.4** (8 g). ^1H NMR (400 MHz, CDCl_3) δ_{H} 9.76 (d, $J=2.1$ Hz, 1H), 2.33 - 2.27 (m, 1H), 2.01 - 1.99 (m, 1H), 1.83 - 1.73 (m, 7H), 1.48 - 1.31 (m, 10H), 1.26 (s, 3H), 1.23 - 0.99 (m, 6H), 0.75 (s, 3H).

[0992] Synthesis of 16.5

[0993] To a mixture of PPh_3MeBr (18.7 g, 52.4 mmol) in THF (75 ml) was added $t\text{-BuOK}$ (5.86 g, 52.4 mmol) at 15°C under N_2 . The resulting mixture was stirred at 50°C for 60 min.

Compound **16.4** (8 g, 26.2 mmol) was added in portions below 50°C. After stirring at 50 °C for 6 hours, the reaction mixture was quenched with 10% NH₄Cl aqueous (80 ml) and extracted with EtOAc (2 x 80 ml). The combined organic phase was concentrated under vacuum. The residue was re-crystallized from (MeOH: H₂O=1:1 (261 ml)) at 25 °C to give **16.5** (8 g). ¹H NMR (400 MHz, CDCl₃) δ_H 5.82 - 5.69 (m, 1H), 4.98 (s, 1H), 4.96 - 4.89 (m, 1H), 1.96 (q, *J*=8.9 Hz, 1H), 1.90 - 1.62 (m, 8H), 1.54 - 1.28 (m, 9H), 1.26 (s, 3H), 1.24 - 0.95 (m, 7H), 0.59 (s, 3H).

[0994] Synthesis of 16.6

[0995] To a solution of **16.5** (1.1 g, 3.63 mmol) in DCM (15 ml) was added DMAP (442 mg, 3.63 mmol) and acetyl acetate (1.47g, 1.36ml, 14.5 mmol). After stirring at 25°C for 16 hours, the residue was poured into ice-water (50 ml) and extracted with DCM (2 x 50 ml). The combined organic phase was washed with saturated brine (2 x 100 ml), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column (0~2% of ethyl acetate in petroleum ether) to give **16.6** (1.1 g, 88%). ¹H NMR (400 MHz, CDCl₃) δ_H 5.82-5.60 (m, 1H), 4.98 (s, 1H), 4.96-4.93 (m, 1H), 1.98 (s, 5H), 1.87 - 1.73 (m, 5H), 1.70 - 1.59 (m, 5H), 1.55 - 1.54 (m, 3H), 1.51 - 1.23 (m, 6H), 1.16 - 0.97 (m, 6H), 0.59 (s, 3H).

[0996] Synthesis of 16.7

[0997] To a solution of **16.6** (370 mg, 1.07 mmol) and rhodium (II) acetate dimer (2.36 mg, 0.005 mmol) in refluxing DCM (5 ml) was added dropwise a solution of ethyl diazoacetate (670 mg, 5.88 mmol) in DCM (10 ml). After stirring at 45°C for 1 hour and then at 20°C for 16 hours, the residue was poured into water (50 ml) and extracted with DCM (2 x 50 ml). The combined organic phase was washed with brine (2 x 50 ml), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column (0~0.5% of ethyl acetate in petroleum ether) to give **16.7** (410 mg, 89.1%). ¹H NMR (400 MHz, CDCl₃) δ_H 4.19 - 4.04 (m, 2H), 2.03 - 1.90 (m, 4H), 1.89 - 1.57 (m, 10H), 1.54 (s, 3H), 1.49 - 1.19 (m, 11H), 1.18 - 0.83 (m, 8H), 0.80 - 0.60 (m, 4H).

[0998] Synthesis of 16.8

[0999] To a solution of LiAlH₄ (36.1 mg, 0.95 mmol) in THF (10 ml) was added **1.7** (410 mg, 0.95 mmol) in THF (5 ml) under N₂. After stirring at 20°C for 1 h, the mixture was added H₂O (0.5 ml) in THF (10 ml), 10% NaOH aq. (0.5 ml) and H₂O (1.5 ml). The mixture was filtered, concentrated and purified by flash column (0~45% of ethyl acetate in petroleum ether) two times to give **16.8** (29.6 mg, 9.0%). ¹H NMR (400 MHz, CDCl₃) δ_H 3.59 - 3.35

(m, 2H), 1.90 - 1.75 (m, 5H), 1.65 - 1.60 (m, 2H), 1.49 - 1.33 (m, 7H), 1.26 (m, 6H), 1.19 - 0.87 (m, 7H), 0.72 (d, $J=2.40$ Hz, 4H), 0.53 - 0.21 (m, 3H). **LC-ELSD/MS** purity>99%; MS ESI calcd. for $C_{23}H_{38}O_2$ $[M-2H_2O+H]^+$ 311.2, found 311.2.

[01000] Synthesis of 16.9

[01001] To a solution of **16.8** (700 mg, 2.01 mmol) in DCM (30 mL) was added N-methylimidazole (247 mg, 3.01 mmol), TEA (2.21 ml, 16.0 mmol) and TsCl (1.53 g, 8.04 mmol). After stirring at 15°C for 6 hours, the mixture was poured into water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with water (2 x 100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to **16.9** (1 g). **^1H NMR** (400 MHz, $CDCl_3$) δ_H 7.78 (m, 2 H) 7.33 (m, 2 H) 3.14 - 3.30 (m, 2 H) 2.44 (s, 3 H) 1.62 - 1.72 (m, 8 H) 1.33 - 1.40 (m, 10 H) 0.91 - 1.07 (m, 10 H) 0.66 (s, 3 H) 0.27 - 0.52 (m, 4 H).

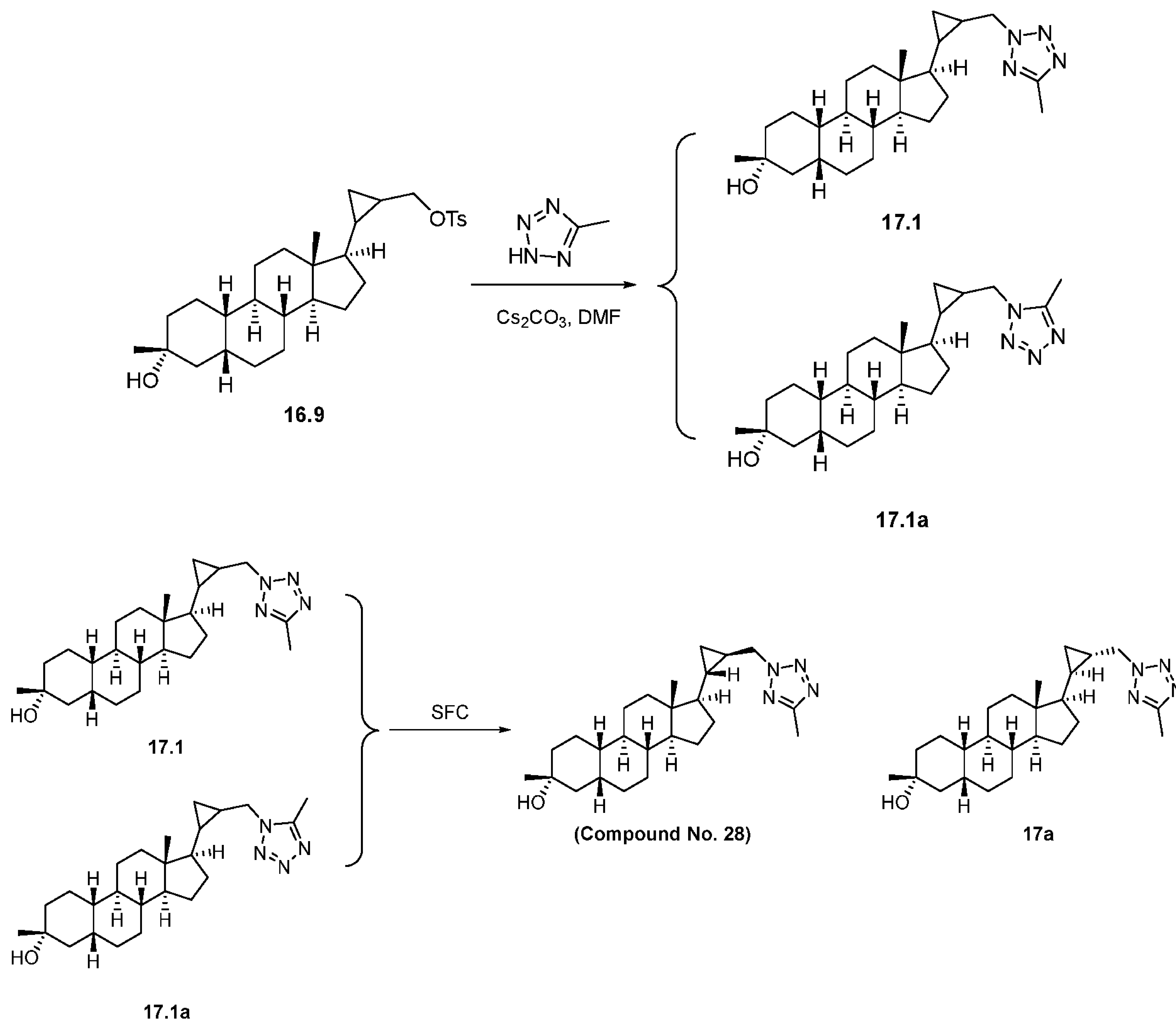
[01002] Synthesis of Compound No. 24 and Compound No. 25

[01003] To a solution of **16.9** (1 g, 1.99 mmol) in DMF (30 ml) was added Cs_2CO_3 (1.30 g, 3.98 mmol) and 4-cyano-pyrazole (370 mg, 3.98 mmol). After stirring at 80°C for 16 hours. The mixture was diluted with EtOAc (2 x 60 ml) and washed with water (100 ml), LiCl (5%, 100 ml aq.), dried over Na_2SO_4 and filtered. The residue was purified by flash column (0~20% ethyl acetate in petroleum ether) and separated by SFC (column: Chiralpak AD-3 50 μ m 4.6mm I.D., 3 μ m); Mobilephase: A: CO_2 B: ethanol (0.05% DEA); gradient: Isocratic: 40% B, FlowRate (ml/min): 4)) to give **Compound No. 24** (97.5 mg, 24%) and **Compound No. 25** (136.3 mg, 33%).

[01004] Compound No. 24: **^1H NMR** (400 MHz, $CDCl_3$) δ_H 7.86 (s, 1 H) 7.79 (s, 1 H) 4.02 (m, 2 H) 1.44 - 1.87 (m, 11 H) 1.35 - 1.40 (m, 6 H) 1.25 (s, 3 H) 0.87 - 1.13 (m, 8 H) 0.61 - 0.69 (m, 2 H) 0.59 (s, 3 H) 0.36 - 0.50 (m, 2 H). **LC-ELSD/MS** purity>99%, analytic SFC: 100% de ; MS ESI calcd. for $C_{27}H_{39}N_3O$ $[M+H-H_2O]^+$ 404.3, found 404.3.

[01005] Compound No. 25: **^1H NMR** (400 MHz, $CDCl_3$) δ_H 7.90 (s, 1 H) 7.79 (s, 1 H) 4.10 (dd, $J=14.00, 6.80$ Hz, 1 H) 3.93 (dd, $J=14.00, 7.60$ Hz, 1 H) 1.63 - 1.91 (m, 7 H) 1.28 - 1.58 (m, 10 H) 1.25 (s, 3 H) 0.92 - 1.22 (m, 8 H) 0.70 (s, 3 H) 0.49 - 0.68 (m, 4 H). **LC-ELSD/MS** purity>99%, MS ESI calcd. for $C_{27}H_{39}N_3O$ $[M+H-H_2O]^+$ 404.3, found 404.3.

[01006] Example No. 17: Synthesis of (3R,5R,8R,9R,10S,13S,14S,17R)-3,13-dimethyl-17-((1S,2R)-2-((5-methyl-2H-tetrazol-2-yl)methyl)cyclopropyl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (Compound No. 28) and (3R,5R,8R,9R,10S,13S,14S,17R)-3,13-dimethyl-17-((1R,2S)-2-((5-methyl-2H-tetrazol-2-yl)methyl)cyclopropyl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (17a)



[01007] Synthesis of 17.1 and 17.1a

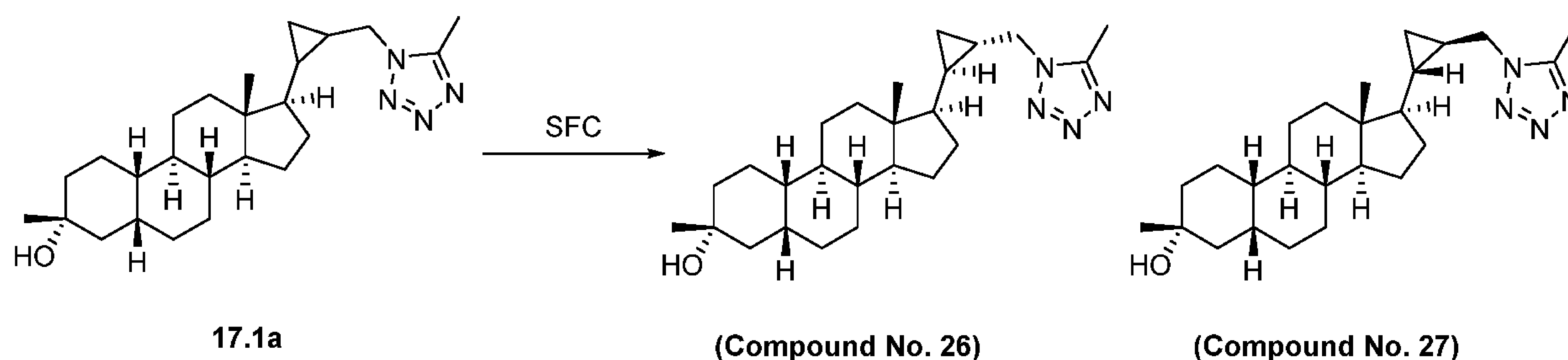
[01008] To a solution of 16.9 (390 mg, 0.79 mmol) in DMF (12 mL) was added Cs₂CO₃ (508 mg, 1.55 mmol) and 5-methyl-2H-1,2,3,4-tetrazole (130 mg, 1.55 mmol). After stirring at 80°C for 16 hours. The mixture was diluted with EtOAc (2 x 60 mL) and washed with water (100 mL), LiCl (5%, 100 mL aq.), dried over Na₂SO₄, filtered and purified by flash column (0~60% ethyl acetate in petroleum ether) to give 17.1 (76 mg, mixture) and 17.1a (55 mg, mixture). 17.1 (76 mg, 0.184 mmol) was separated by SFC (column: Chiralpak AD-3 50; 4.6mm I.D., 3µm Mobile phase: A: CO₂ B: ethanol (0.05% DEA); gradient: Isocratic:

40% B, FlowRate (ml/min): 4)) to give **Compound No. 28** (40 mg, 53%) and **2a** (20 mg, 26%).

[01009] Compound No. 28: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 4.48 (dd, $J=13.60$, 6.80 Hz, 1 H) 4.30 (dd, $J=13.60$, 7.60 Hz, 1 H) 2.53 (s, 3 H) 1.75 - 1.91 (m, 4 H) 1.60 - 1.66 (m, 2 H) 1.27 - 1.57 (m, 9 H) 1.25 (s, 4 H) 1.14 - 1.24 (m, 2 H) 0.91 - 1.12 (m, 7 H) 0.68 (s, 5 H) 0.56 - 0.63 (m, 1 H) 0.47 - 0.56 (m, 1 H). **LC-ELSD/MS** purity>99%, analytic SFC: 100% de ; MS ESI calcd. for $\text{C}_{25}\text{H}_{40}\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$ 413.3, found 413.3.

[01010] 17a: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 4.55 (dd, $J=13.60$, 7.20 Hz, 1 H) 4.26 (dd, $J=14.00$, 8.40 Hz, 1 H) 2.53 (s, 3 H) 1.68 - 1.89 (m, 4 H) 1.59 - 1.64 (m, 1 H) 1.51 - 1.57 (m, 2 H) 1.27 - 1.47 (m, 9 H) 1.25 (s, 3 H) 0.80 - 1.23 (m, 9 H) 0.68 - 0.78 (m, 1 H) 0.54 (s, 5 H) 0.35 - 0.44 (m, 1 H). **LC-ELSD/MS** purity>99%, analytic SFC: 100% de ; MS ESI calcd. for $\text{C}_{25}\text{H}_{40}\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$ 413.3, found 413.3.

[01011] Example No. 18: Synthesis of (3R,5R,8R,9R,10S,13S,14S,17R)-3,13-dimethyl-17-((1R,2S)-2-((5-methyl-1H-tetrazol-1-yl)methyl)cyclopropyl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (Compound No. 26) & (3R,5R,8R,9R,10S,13S,14S,17R)-3,13-dimethyl-17-((1S,2R)-2-((5-methyl-1H-tetrazol-1-yl)methyl)cyclopropyl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (Compound No. 27)



[01012] Synthesis of Compound No. 26 and Compound No. 27

[01013] 17.1a (40 mg) was separated by SFC (Column: DAICEL CHIRALCEL OJ-H (250mm*30mm, 5um); Condition: 0.1% $\text{NH}_3\text{H}_2\text{O}$ ETOH; Begin B: 20%; End B: 20%) to give **Compound No. 26** (4.4 mg, 11%) and **Compound No. 27** (13.7 mg, 34%).

[01014] Compound No. 26: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 4.24 (dd, $J=14.40$, 6.40 Hz, 1 H) 4.07 (dd, $J=14.40$, 8.00 Hz, 1 H) 2.58 (s, 3 H) 1.57 - 1.85 (m, 6 H) 1.27 - 1.47 (m, 9 H) 1.25 (s, 3 H) 0.84 - 1.23 (m, 10 H) 0.60 - 0.76 (m, 2 H) 0.57 (s, 3 H) 0.40 - 0.55 (m, 2 H). **LC-ELSD/MS** purity>99%, analytic SFC: 100% de ; MS ESI calcd. for $\text{C}_{25}\text{H}_{40}\text{N}_4\text{O}$ $[\text{M} - \text{H}_2\text{O} + \text{H}]^+$ 395.3, found 395.3.

[01015] Compound No. 27: ^1H NMR (400 MHz, CDCl_3) δ_{H} 4.22 (dd, $J=14.40$, 7.20 Hz, 1 H) 4.08 (dd, $J=14.40$, 8.00 Hz, 1 H) 2.58 (s, 3 H) 1.58 - 1.87 (m, 7 H) 1.27 - 1.55 (m, 9 H) 1.25 (s, 3 H) 0.92 - 1.23 (m, 9 H) 0.68 (s, 7 H). **LC-ELSD/MS** purity >99%, analytic SFC: 100% de ; MS ESI calcd. for $\text{C}_{25}\text{H}_{40}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 413.3, found 413.3.

[01016] Example 19: Assays

[01017] Steroid Inhibition of TBPS Binding

[01018] $[\text{}^{35}\text{S}]$ -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).

[01019] 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 $[\text{}^{35}\text{S}]$ -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.

[01020] Various compounds are or can be screened to determine their potential as modulators of [³⁵S]-TBPS binding *in vitro*. These assays are or can be performed in accordance with the above.

[01021] In Table 2 below, A indicates a TBPS IC₅₀ (μM) < 0.1 μM, B indicates a TBPS IC₅₀ (μM) of 0.1 μM to < 1.0 μM, and C indicates a TBPS IC₅₀ (μM) of ≥ 1.0 μM.

[01022] Table 2: TBPS Assay Data.

Compound No.	TBPS IC ₅₀
1	A
2	A
3	A
4	A
5	A
6	A
7	C
8	A
9	A
10	A
11	A
12	A
13	A
14	C
15	A
16	A
17	B
18	B
19	A
20	—
21	—
22	B
23	A
24	A
25	A
26	A
27	B
28	A

EQUIVALENTS AND SCOPE

[01023] 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.

[01024] 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 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.

[01025] 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.

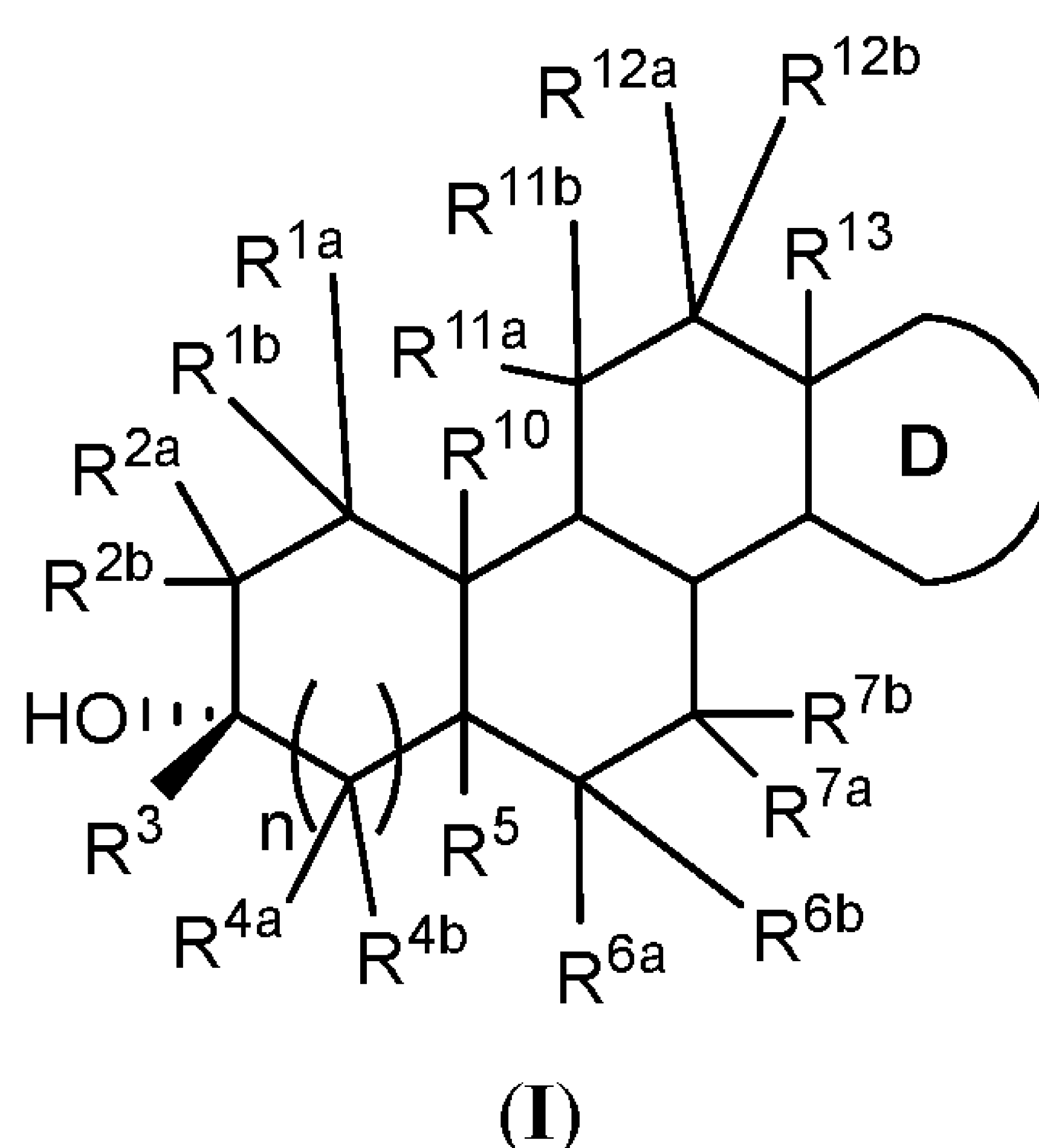
Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

OTHER EMBODIMENTS

[01026] 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.

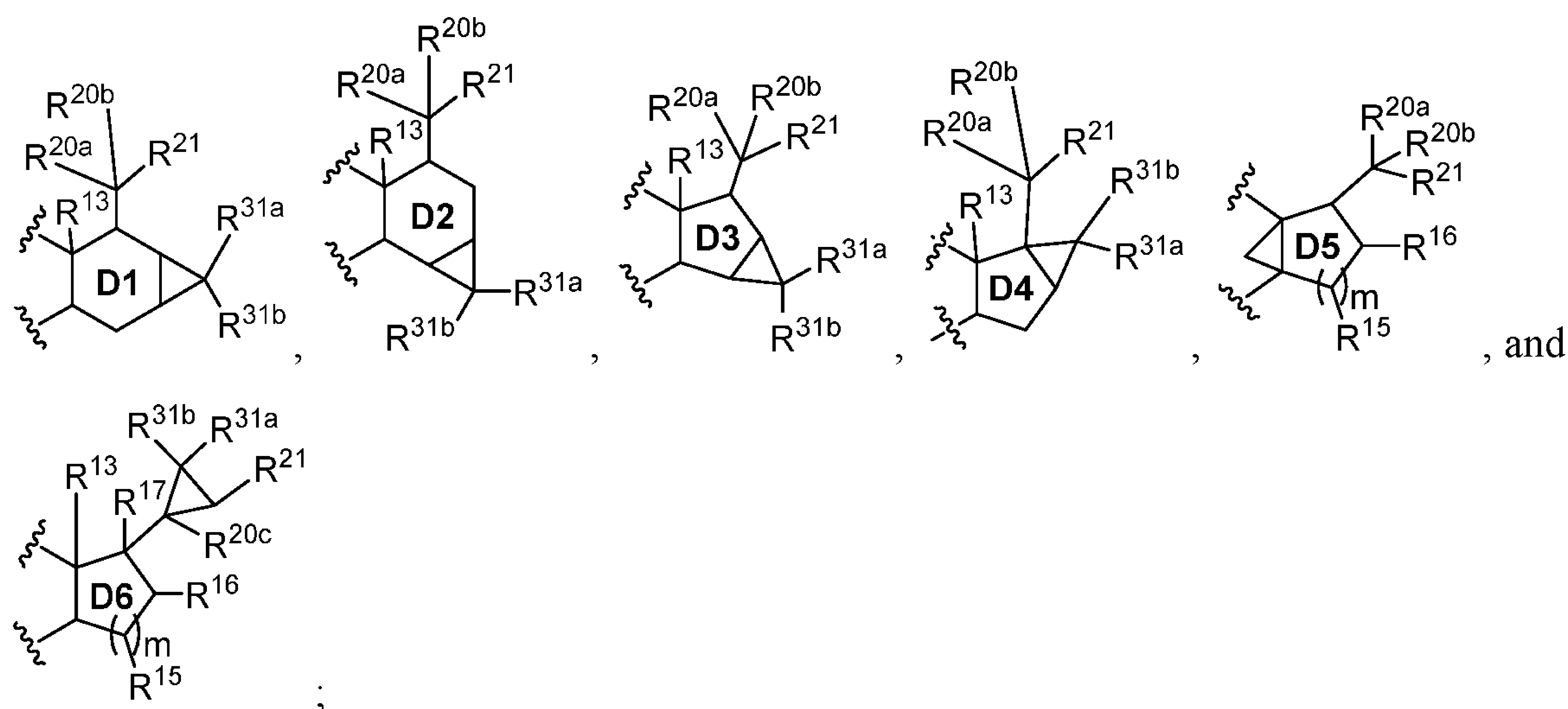
WHAT IS CLAIMED IS:

1. A compound of Formula (I)



or a pharmaceutically acceptable salt thereof, wherein

Ring D is selected from



Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , R^{20a} , R^{20b} , R^{20c} , and R^{21} , is $-L^A-R^{30}$;

Each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -;

Each R^{30} is independently selected from R' , $-OH$, halo, $-CN$, $-NO_2$, and $-CF_3$;

Each R' is independently selected from –H, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₁₋₆ alkyl-O-C₁₋₆ alkyl, and an optionally substituted 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, or

R^{1a} and R^{1b} taken together form oxo, or
 R^{2a} and R^{2b} taken together form oxo, or
 R^{4a} and R^{4b} taken together form oxo, or
 R^{6a} and R^{6b} taken together form oxo, or
 R^{7a} and R^{7b} taken together form oxo, or
 R^{11a} and R^{11b} taken together form oxo, or
 R^{12a} and R^{12b} taken together form oxo, or
 R^{20a} and R^{20b} taken together form oxo;

Each of R⁵ and R^{20c} is independently selected from –H and optionally substituted C₁₋₆ alkyl;

R¹⁰ is –H, optionally substituted C₁₋₆ alkyl, or optionally substituted C₁₋₆ alkyl-O-C₁₋₆ alkyl;

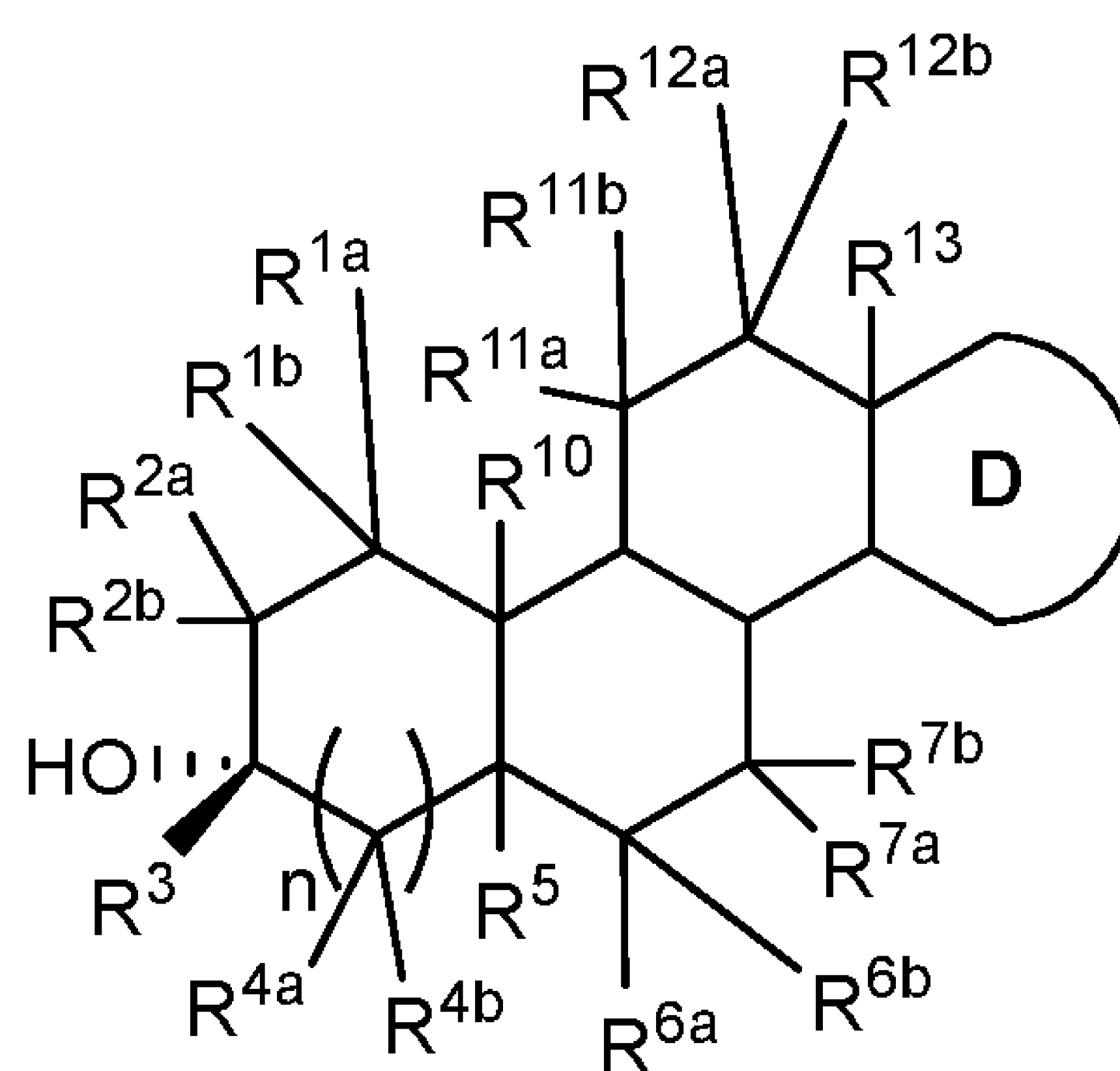
Each of R^{31a} and R^{31b} is independently selected from –H, halo, C₁₋₆ alkyl, and –OR³², wherein R³² is –H, C₁₋₆ alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S;

m is 1 or 2; and

n is 0, 1, or 2,

provided that when one of R^{31a} and R^{31b} is –OR³², the other of R^{31a} and R^{31b} is –H.

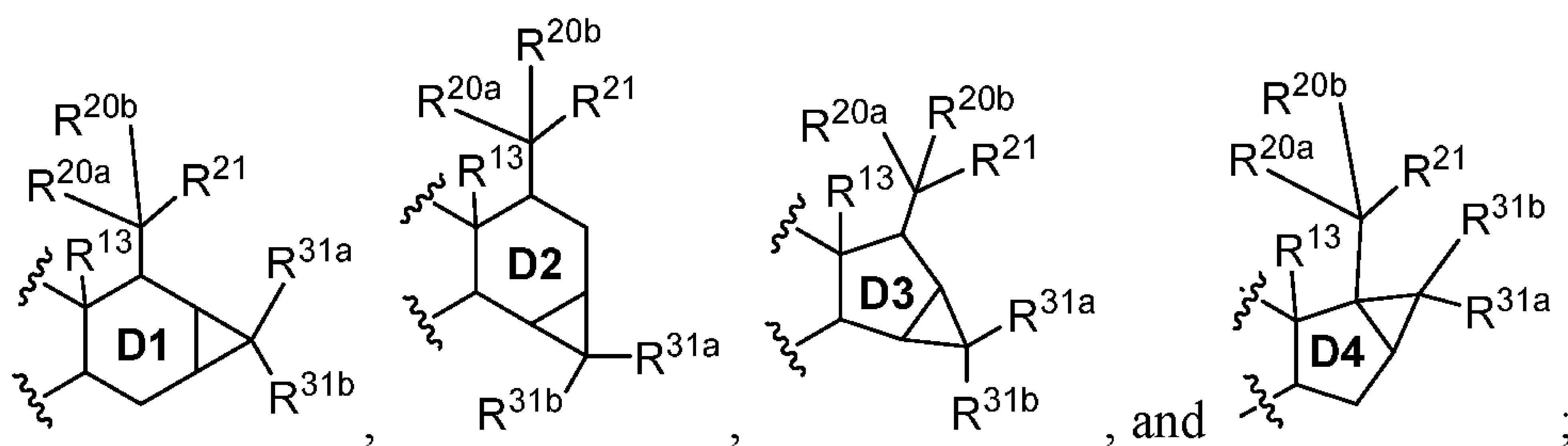
2. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound of Formula (I) is a compound of Formula (II)



(II)

or a pharmaceutically acceptable salt thereof, wherein

Ring D is a fused bicyclic ring selected from



Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{20a} , R^{20b} , and R^{21} is $-L^A-R^{30}$;

Each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -;

R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$;

Each R' is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$, or

R^{1a} and R^{1b} taken together form oxo, or

R^{2a} and R^{2b} taken together form oxo, or

R^{4a} and R^{4b} taken together form oxo, or
R^{6a} and R^{6b} taken together form oxo, or
R^{7a} and R^{7b} taken together form oxo, or
R^{11a} and R^{11b} taken together form oxo, or
R^{12a} and R^{12b} taken together form oxo, or
R^{20a} and R^{20b} taken together form oxo;

R⁵ is -H or C₁₋₆ alkyl;

R¹⁰ is -H or optionally substituted C₁₋₆ alkyl;

R¹³ is -H or optionally substituted C₁₋₆ alkyl;

Each of R^{31a} and R^{31b} is independently selected from -H, halo, C₁₋₆ alkyl, and -OR³²,
wherein R³² is -H, C₁₋₆ alkyl, or a 3-6-membered saturated, partially unsaturated, or fully
unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S;
and

n is 0, 1, or 2,

provided that when one of R^{31a} and R^{31b} is -OR³², the other of R^{31a} and R^{31b} is -H.

3. The compound or pharmaceutically acceptable salt of claim 2, wherein R³ is -H, C₁₋₆ alkyl optionally substituted with R', -N(R')₂, or -O-R'.

4. The compound or pharmaceutically acceptable salt of claim 2 or claim 3, wherein R³ is -H or C₁₋₆ alkyl optionally substituted with R'.

5. The compound or pharmaceutically acceptable salt of any one of claims 2-4, wherein R³ is -H, -CH₃, -CH₂-CH₂-CH₃, or -CH₂-O-CH₃.

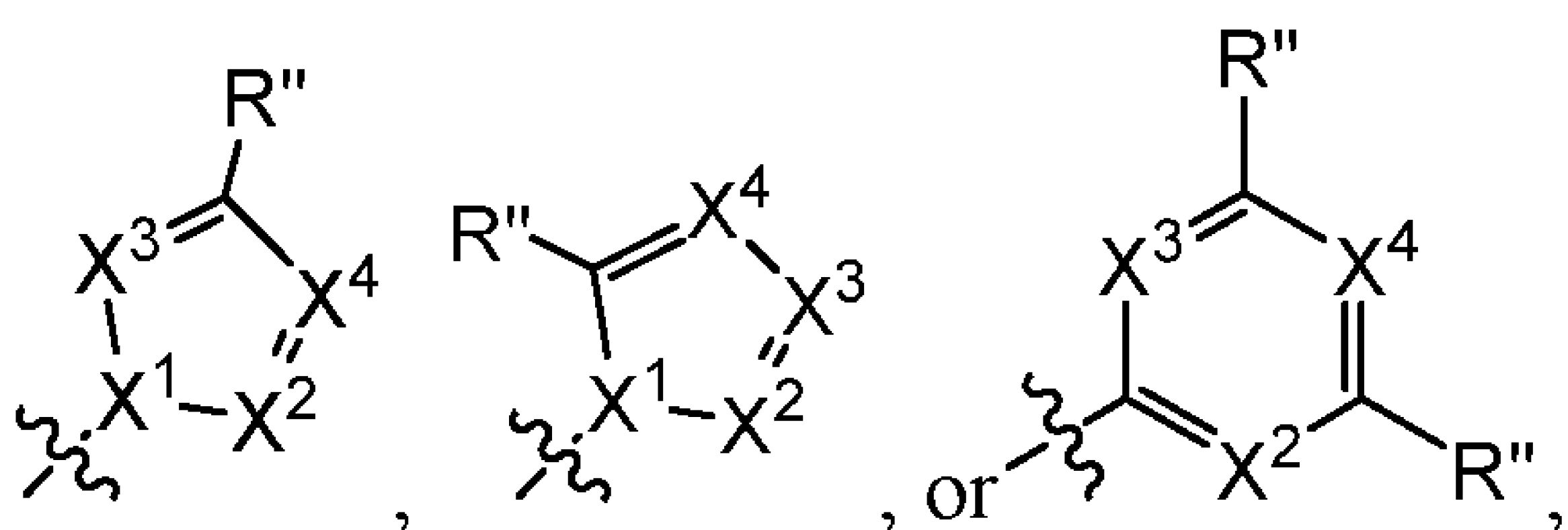
6. The compound or pharmaceutically acceptable salt of any one of claims 2-5, wherein R¹³ is -H, C₁₋₆ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl.

7. The compound or pharmaceutically acceptable salt of any one of claims 2-6, wherein R¹³ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl.

8. The compound or pharmaceutically acceptable salt of any one of claims 2-7, wherein R^{13} is -H, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl.
9. The compound or pharmaceutically acceptable salt of any one of claims 2-8, wherein R^{13} is methyl.
10. The compound or pharmaceutically acceptable salt of any one of claims 2-9, wherein each of R^{20a} and R^{20b} are independently selected from -H, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo.
11. The compound or pharmaceutically acceptable salt of any one of claims 2-10, wherein each of R^{20a} and R^{20b} are independently selected from -H, C_{1-6} alkyl, $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo.
12. The compound or pharmaceutically acceptable salt of any one of claims 2-11, wherein R^{20a} and R^{20b} taken together form oxo.
13. The compound or pharmaceutically acceptable salt of any one of claims 2-12, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, or $-NH-$; and R^{30} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and $-C(CH_3)_3$.
14. The compound or pharmaceutically acceptable salt of any one of claims 2-13, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, or $-NH-$; and R^{30} is a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and $-C(CH_3)_3$.

15. The compound or pharmaceutically acceptable salt of any one of claims 2-14, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond or $-\text{CH}_2-$; and R^{30} is a 5-6-membered partially unsaturated or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-2 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$.

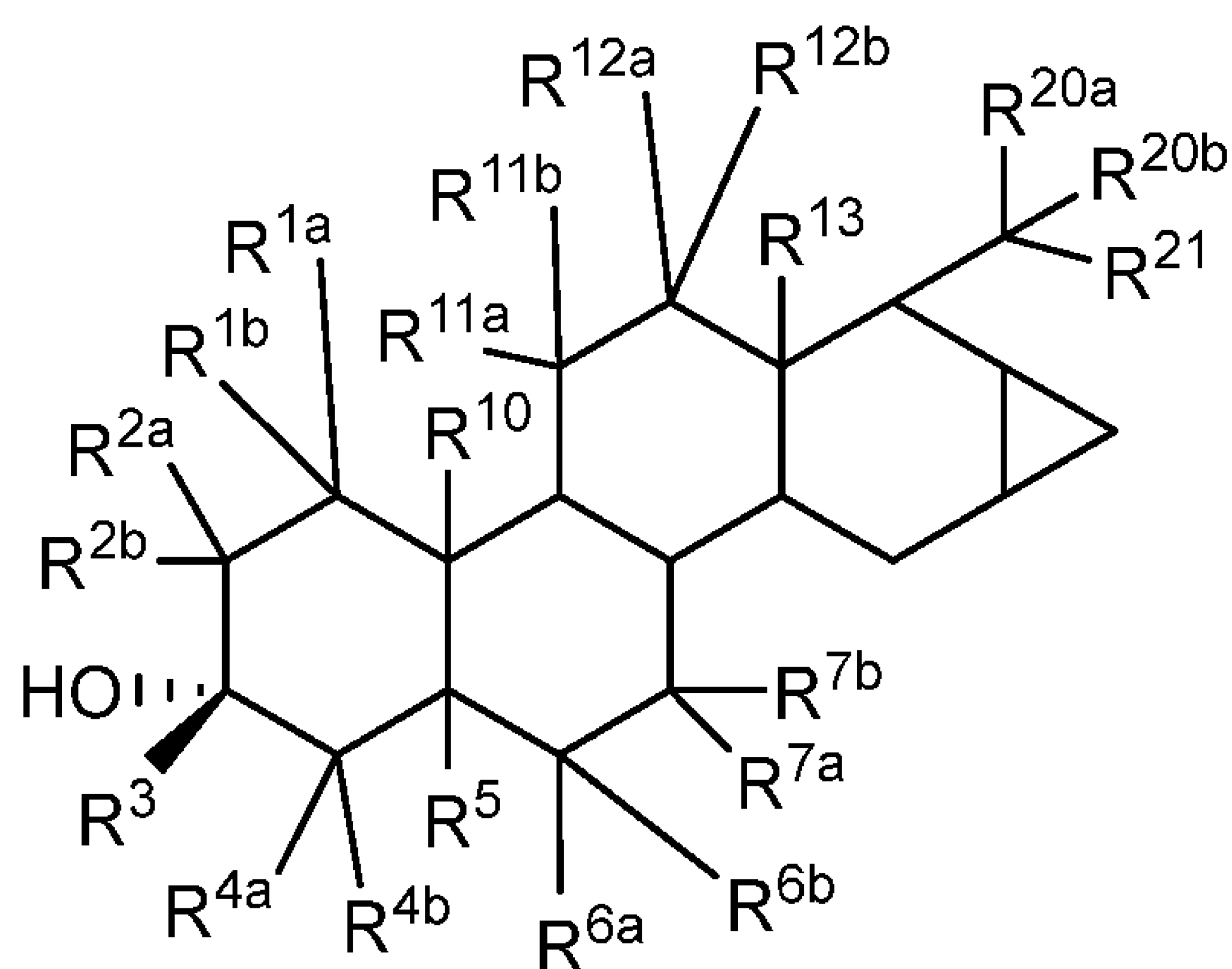
16. The compound or pharmaceutically acceptable salt of any one of claims 2-15, wherein

R^{21} is $-L^A-R^{30}$; L^A is a bond or $-\text{CH}_2-$; and R^{30} is , wherein

each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that

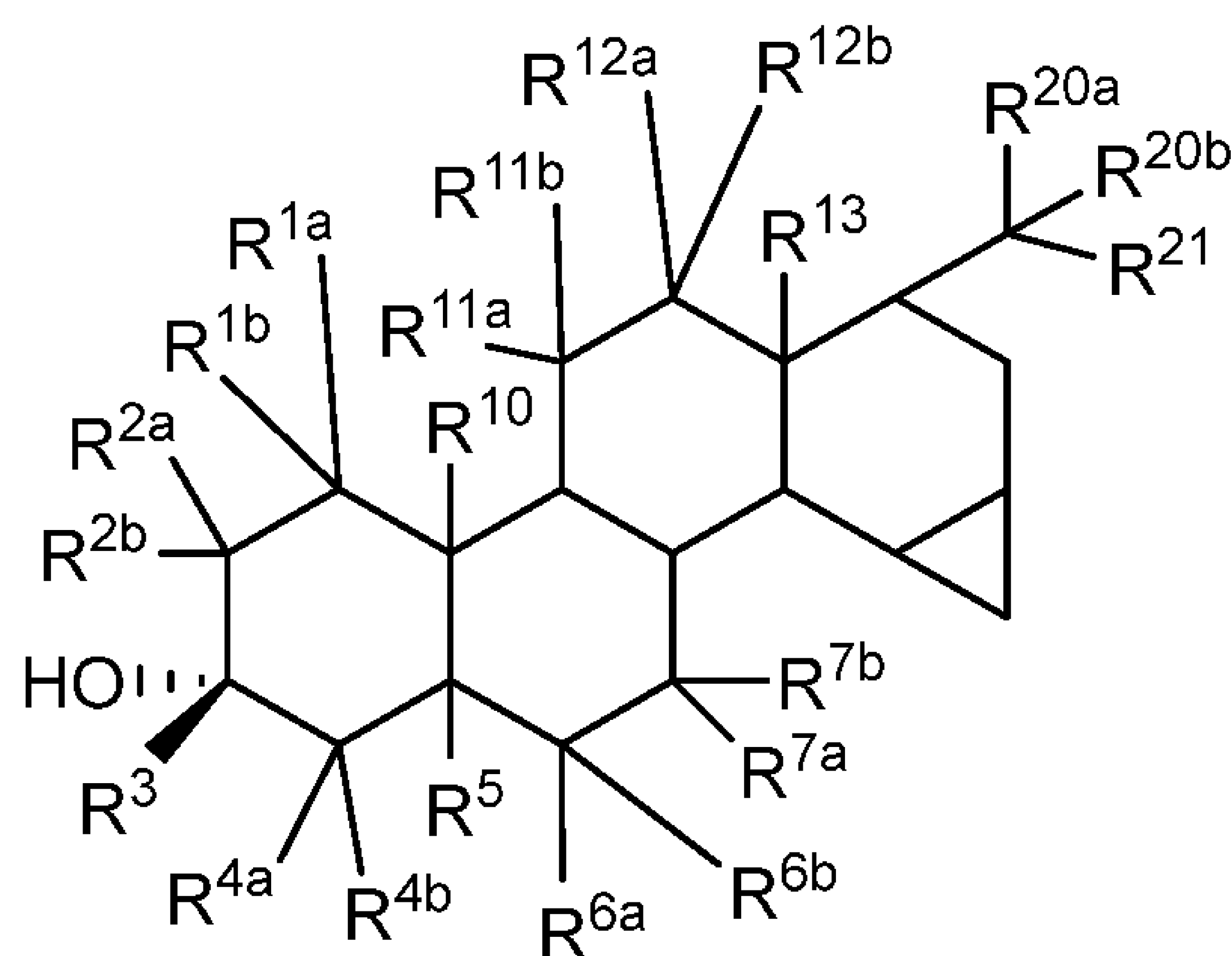
- (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and
- (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$.

17. The compound or pharmaceutically acceptable salt of claim 2, wherein the compound of Formula (II) is a compound of Formula (II-A) or (II-B)



(II-A)

or



(II-B)

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{20a} , R^{20b} , and R^{21} is $-L^A-R^{30}$;

Each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

Each R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$;

Each R' is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$, or

R^{20a} and R^{20b} taken together form oxo;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$ or optionally substituted C_{1-3} alkyl; and

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl.

18. The compound or pharmaceutically acceptable salt of claim 17, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl;

R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-3} alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-CH_2OH$, C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

R^{21} is $-L^A-R^{30}$;

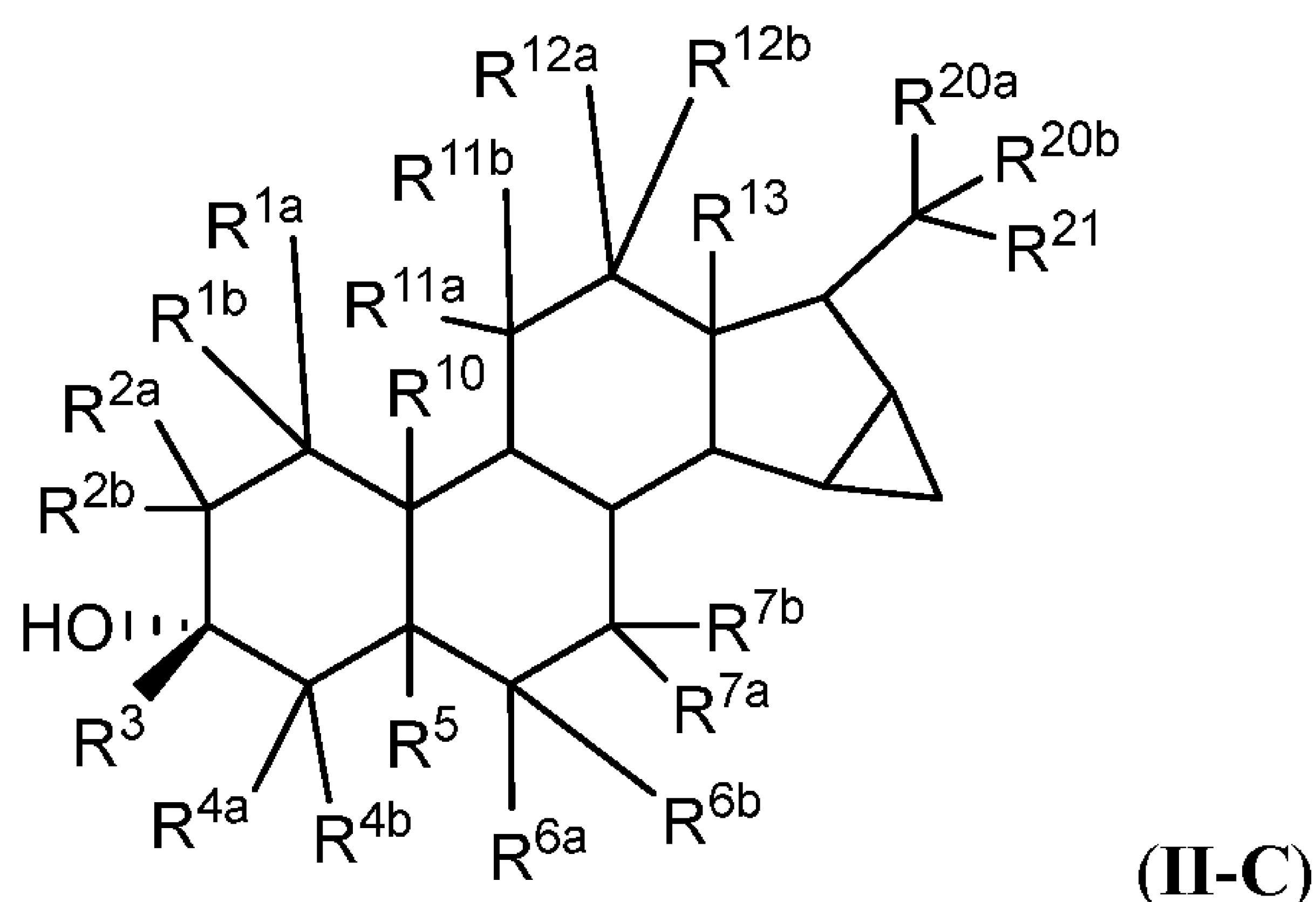
L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -,

$-\text{NR}'\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})_2\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2-$, $-\text{C}(\text{O})\text{NR}'\text{NR}'-$, $-\text{NR}'\text{C}(\text{O})\text{NR}'-$, $-\text{OC}(\text{O})\text{NR}'-$, $-\text{NR}'\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2\text{NR}'-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2-$;

R^{30} is independently selected from R' , halo, $-\text{CN}$, $-\text{NO}_2$, and $-\text{CF}_3$;

Each R' is independently selected from $-\text{H}$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, and $-\text{CH}_3$.

19. The compound or pharmaceutically acceptable salt of claim 2, wherein the compound of Formula (II) is a compound of Formula (II-C)



or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{20a} , R^{20b} , and R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$;

Each L^{A} is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^{A} are optionally and independently replaced by $-\text{NR}'-$, $-\text{S}-$, $-\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}'-$, $-\text{NR}'\text{C}(\text{O})-$, $-\text{NR}'\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})_2\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2-$, $-\text{C}(\text{O})\text{NR}'\text{NR}'-$, $-\text{NR}'\text{C}(\text{O})\text{NR}'-$, $-\text{OC}(\text{O})\text{NR}'-$, $-\text{NR}'\text{NR}'-$, $-\text{NR}'\text{S}(\text{O})_2\text{NR}'-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2-$;

Each R^{30} is independently selected from R' , halo, $-\text{CN}$, $-\text{NO}_2$, and $-\text{CF}_3$;

Each R' is independently selected from $-\text{H}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl,

or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃, or

R^{20a} and R^{20b} taken together form oxo;

R⁵ is -H or C₁₋₆ alkyl;

R¹⁰ is -H or optionally substituted C₁₋₃ alkyl; and

R¹³ is -H or optionally substituted C₁₋₃ alkyl.

20. The compound or pharmaceutically acceptable salt of claim 19, wherein each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from -H or C₁₋₆ alkyl,

R³ is -H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl;

R⁵ is -H or C₁₋₃ alkyl;

R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl;

R¹³ is -H or optionally substituted C₁₋₃ alkyl;

Each of R^{20a} and R^{20b} is independently selected from -H, -OH, -C₁₋₅ alkyl-OH, C₁₋₆ alkyl, and -NH₂, or R^{20a} and R^{20b} taken together form oxo;

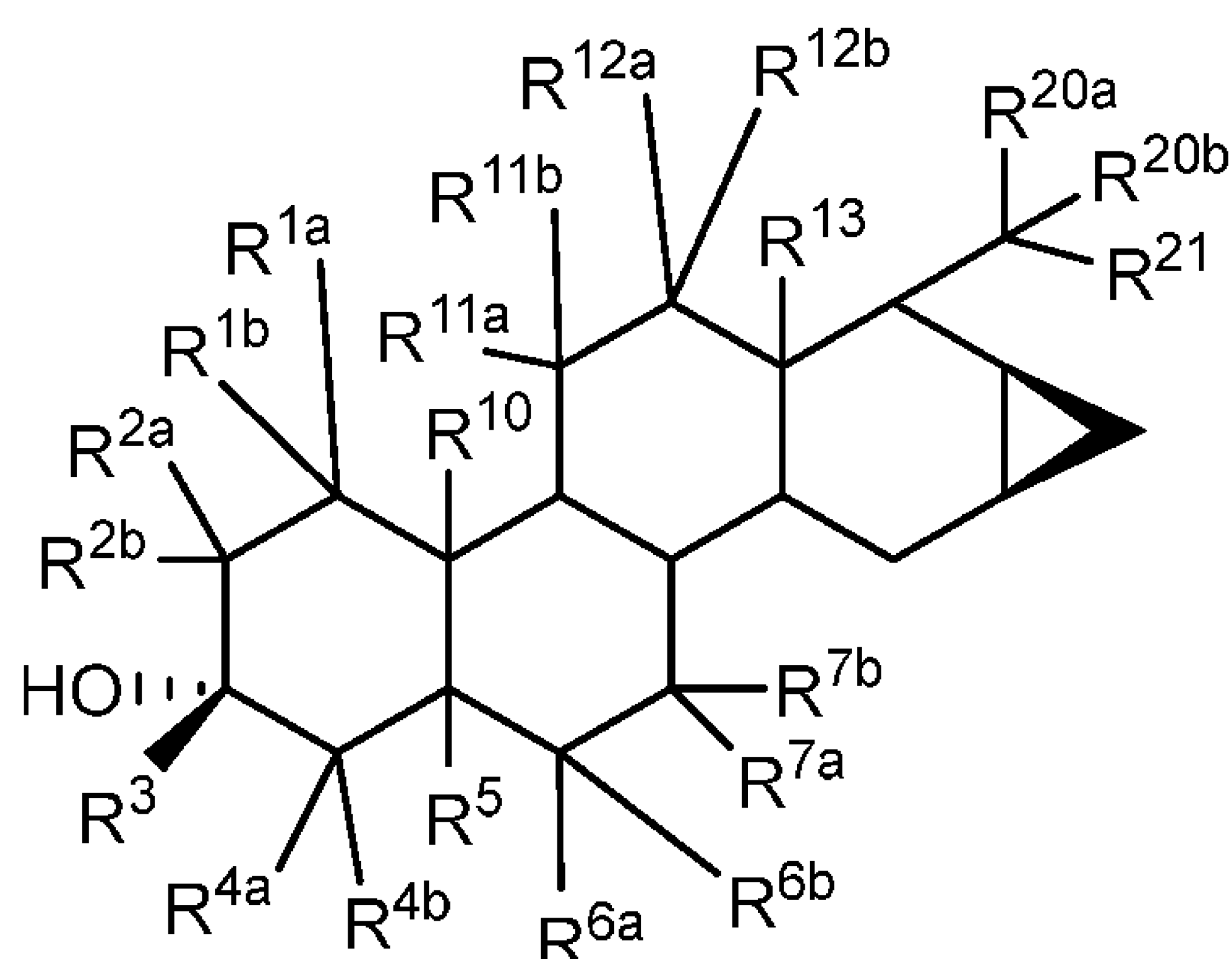
R²¹ is -L^A-R³⁰;

L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by -NR'-, -S-, -O-, -OC(O)-, -C(O)O-, -C(O)-, -C(O)C(O)-, -C(O)NR'-, -NR'C(O)-, -NR'C(O)O-, -S(O)₂NR'-, -NR'S(O)₂-, -C(O)NR'NR'-, -NR'C(O)NR'-, -OC(O)NR'-, -NR'NR'-, -NR'S(O)₂NR'-, -S(O)-, or -S(O)₂-;

R³⁰ is selected from R', halo, -CN, -NO₂, and -CF₃; and

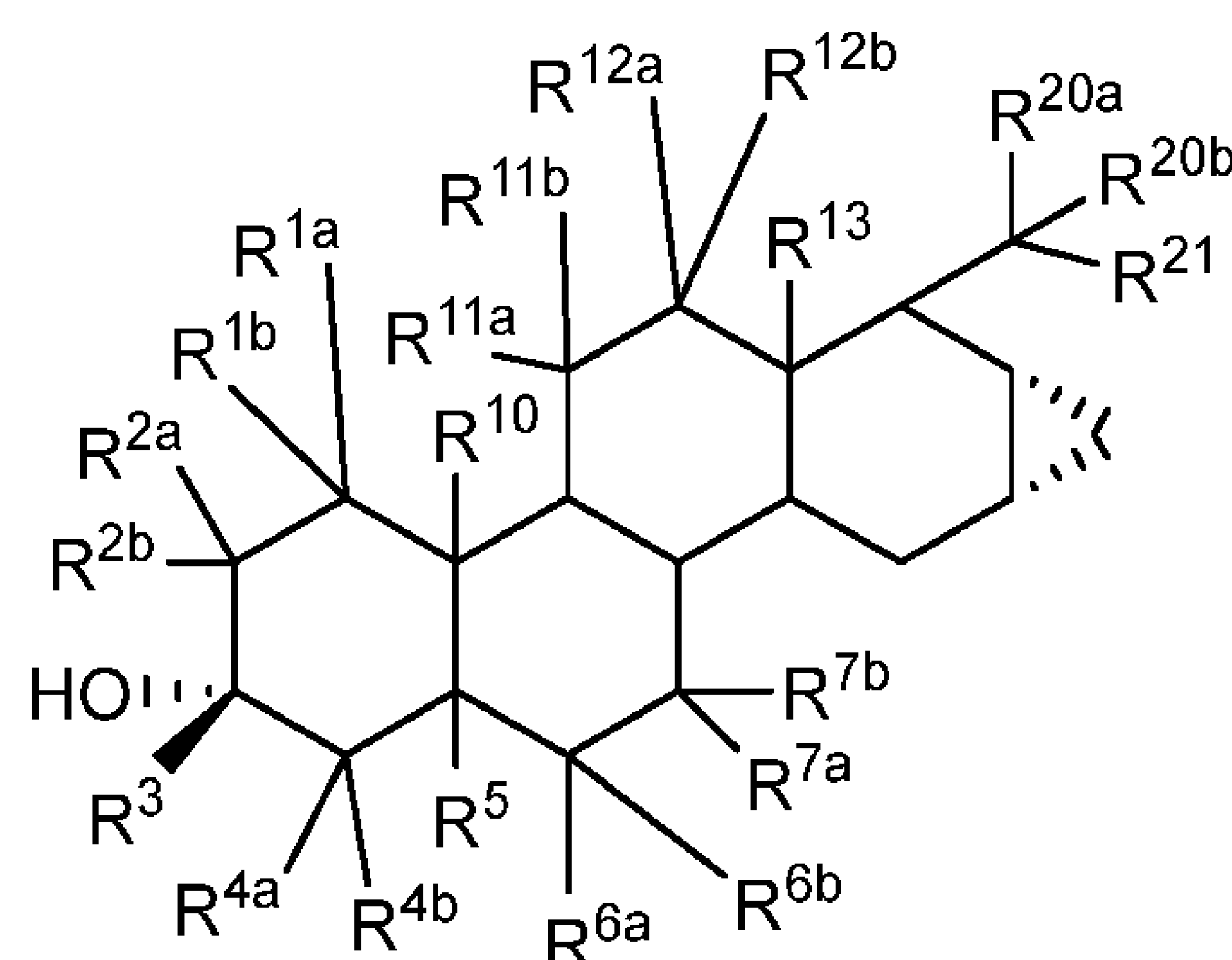
Each R' is independently selected from -H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

21. The compound or pharmaceutically acceptable salt of claim 17 or claim 18, wherein the compound of Formula (II-A) is a compound of Formula (II-A1) or (II-A2)



(II-A1)

or



(II-A2),

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl,

R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

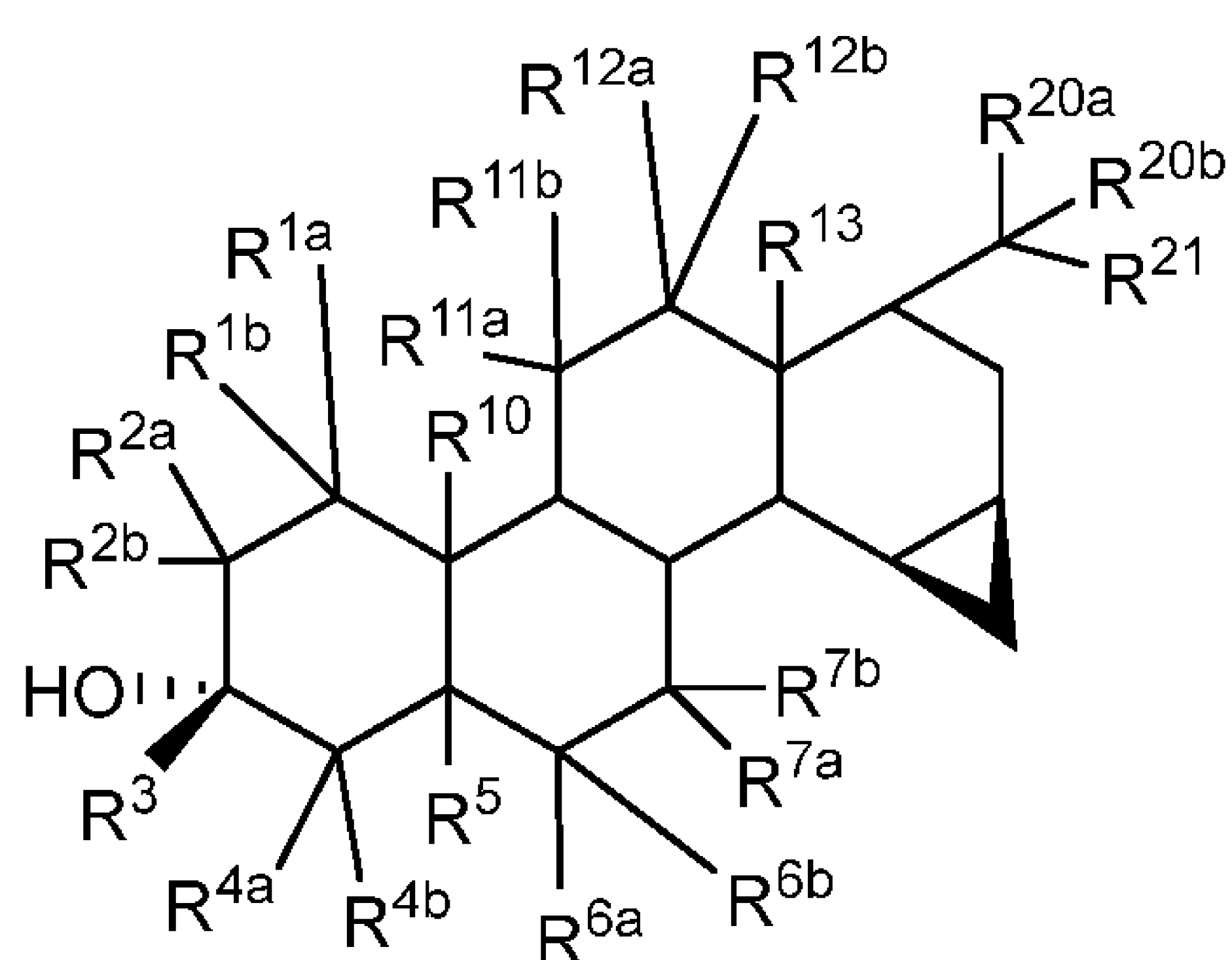
R^{21} is $-L^A-R^{30}$,

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and

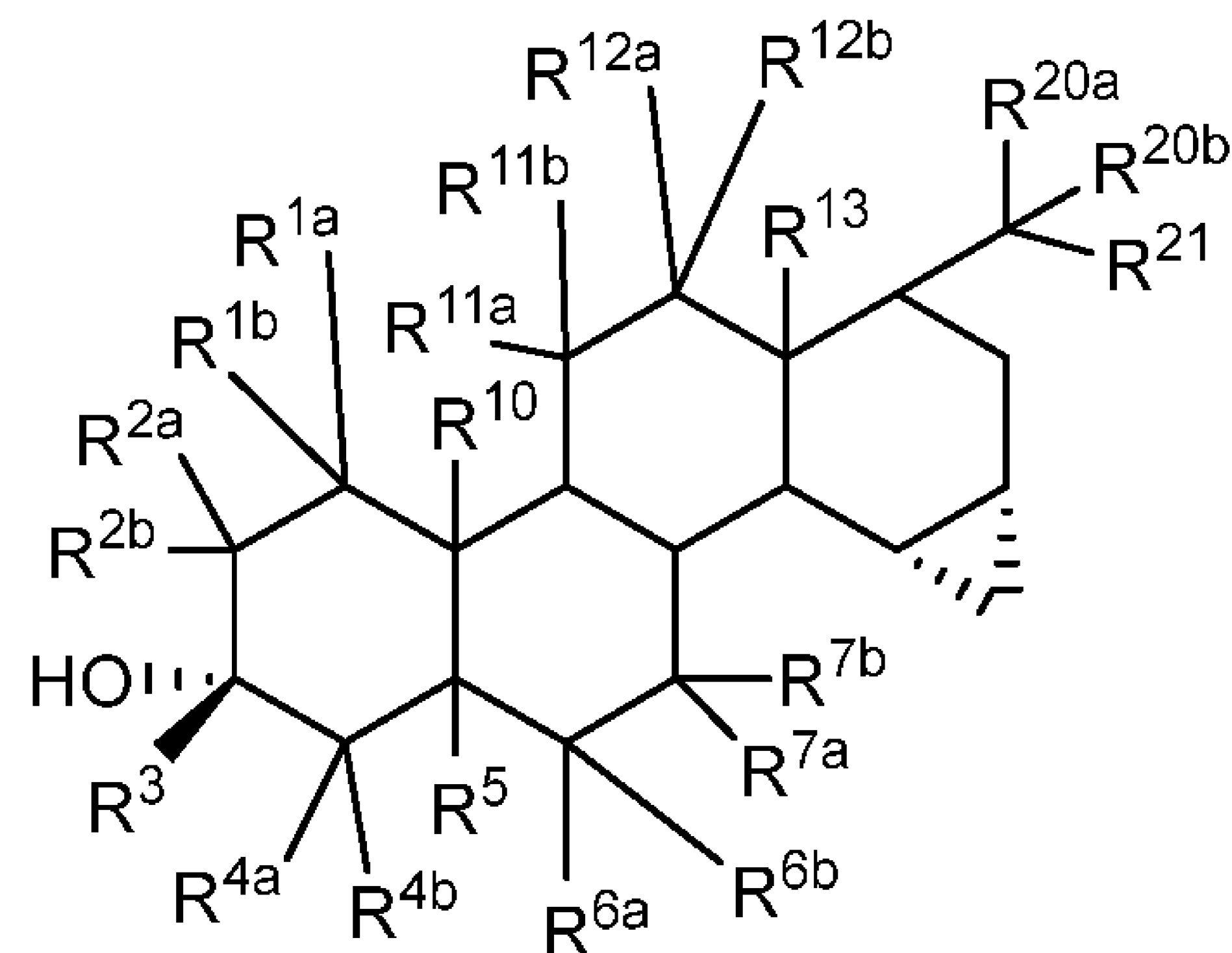
Each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or $-CH_3$.

22. The compound or pharmaceutically acceptable salt of claim 17 or claim 18, wherein the compound of Formula (II-B) is a compound of Formula (II-B1) or (II-B2)



(II-B1)

or



(II-B2),

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl,

R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

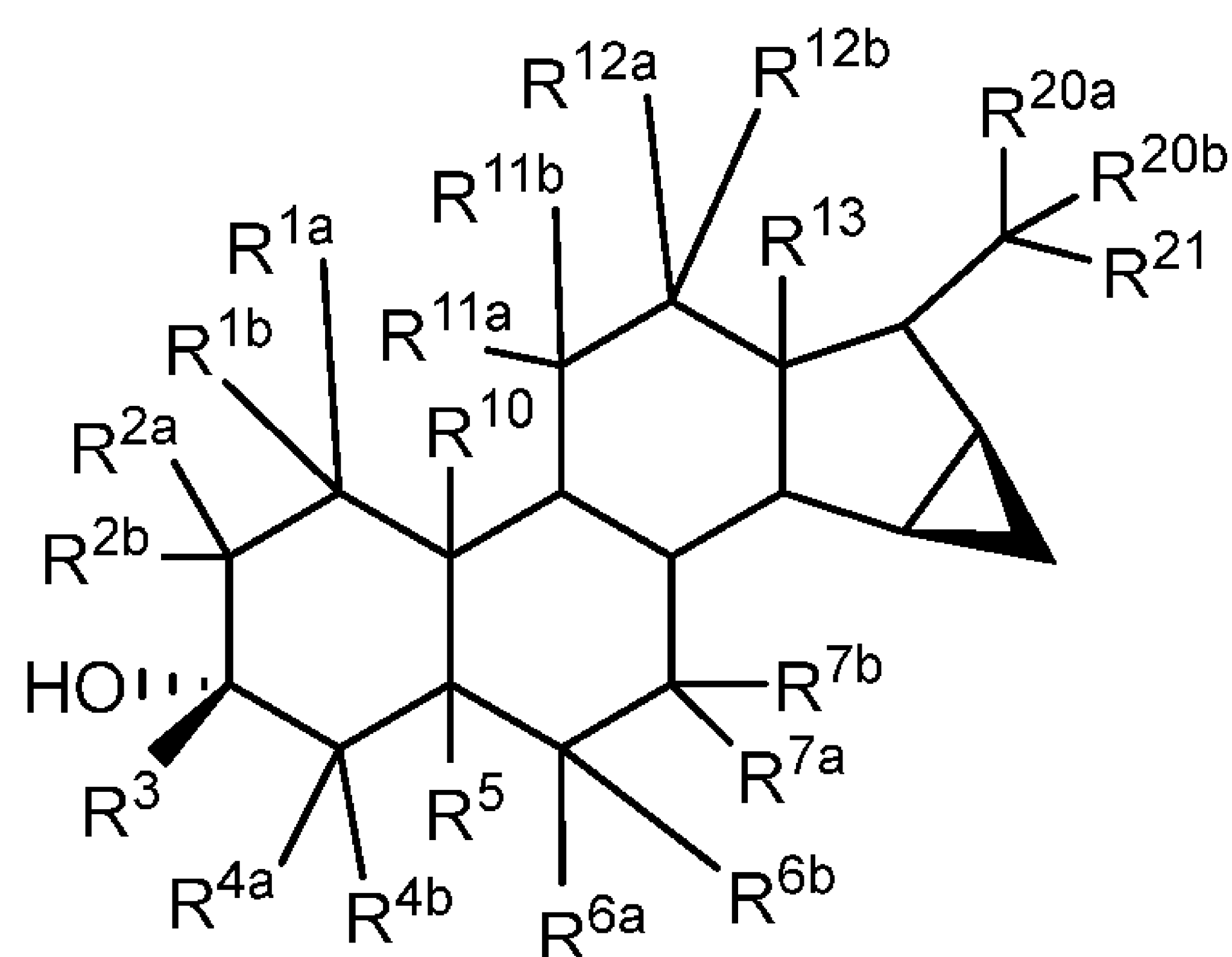
R^{21} is $-L^A-R^{30}$,

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and

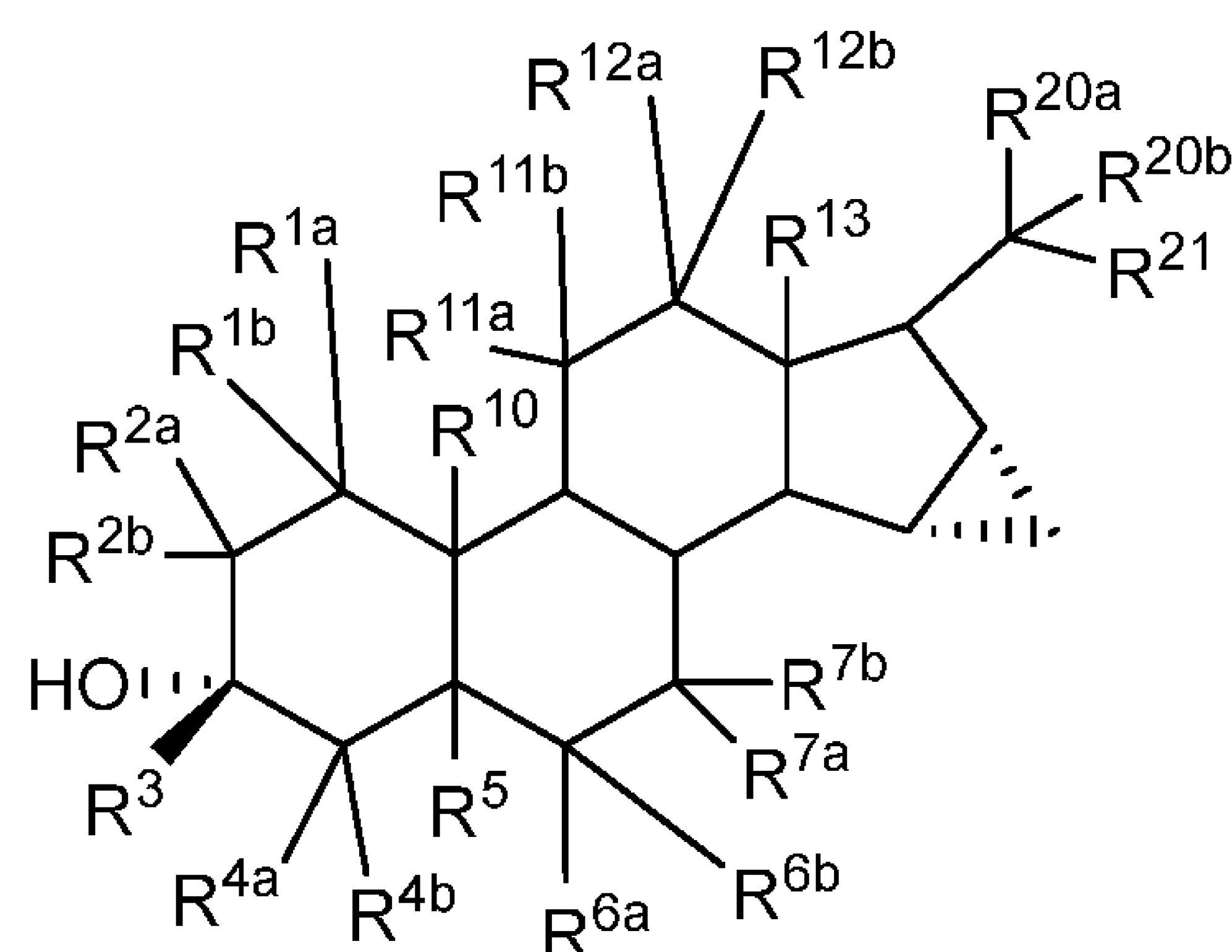
Each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

23. The compound or pharmaceutically acceptable salt of claim 19 or claim 20, wherein the compound of Formula (II-C) is a compound of Formula (II-C1) or (II-C2)



(II-C1)

or



(II-C2),

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ or C_{1-6} alkyl,

R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

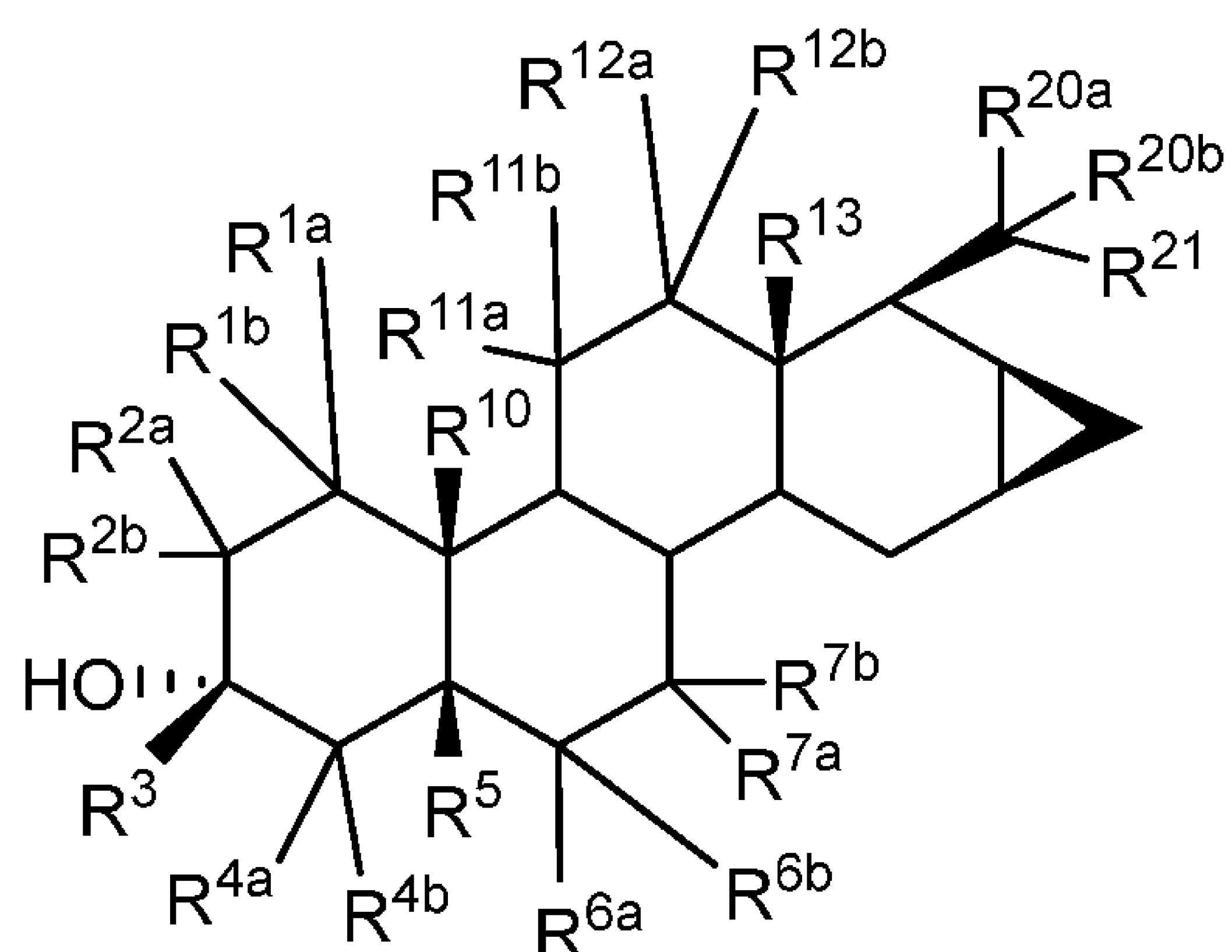
R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

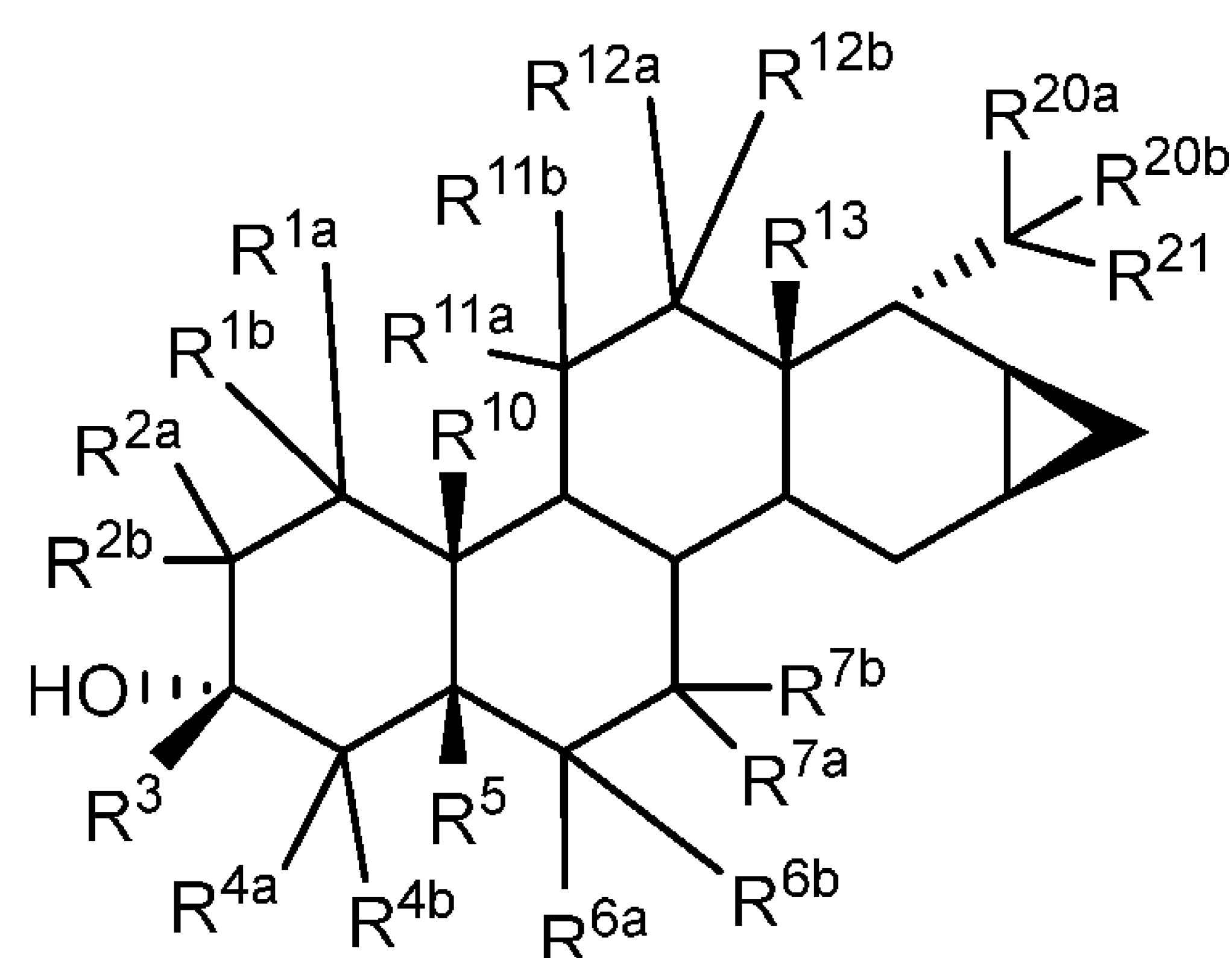
R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and

Each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

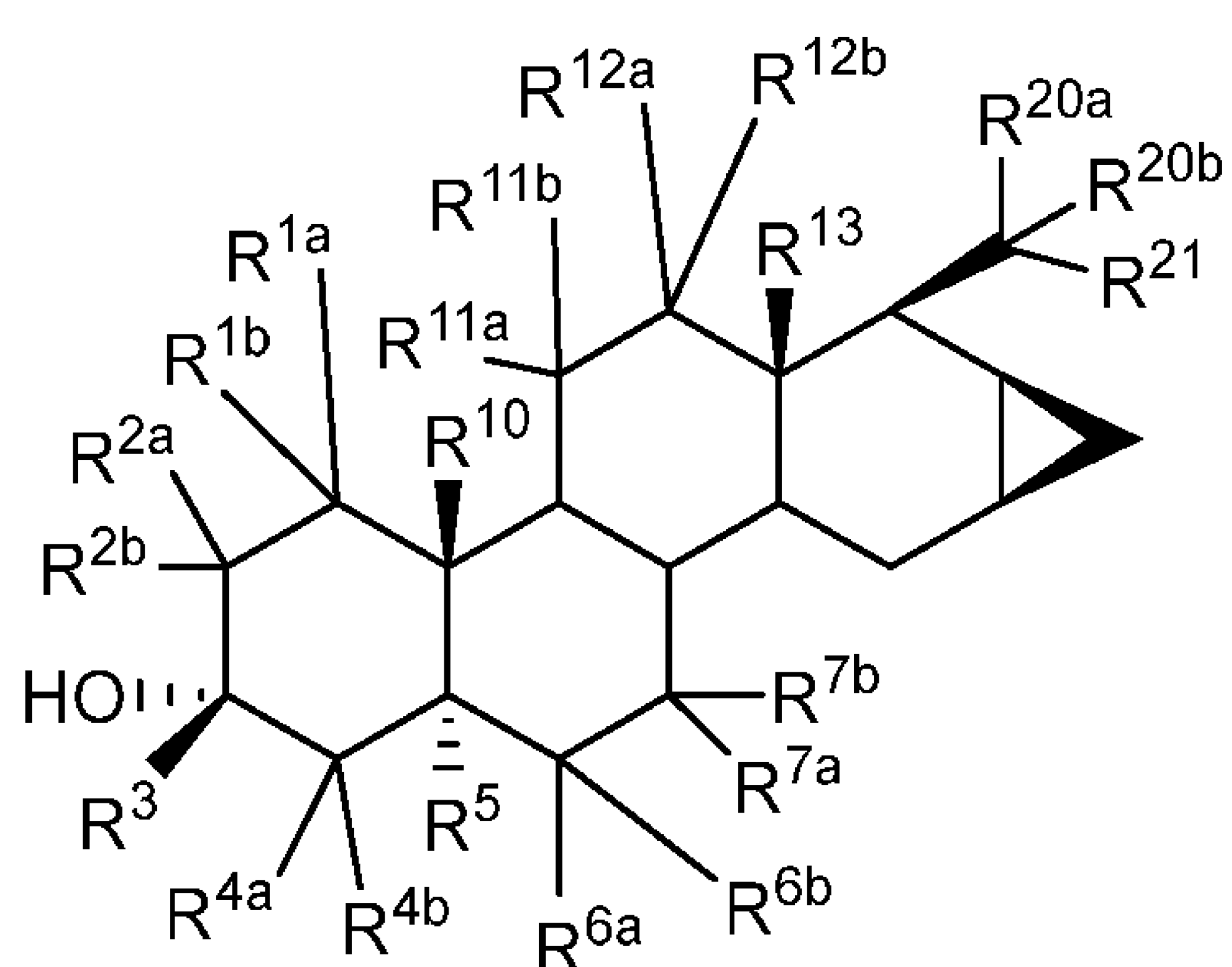
24. The compound or pharmaceutically acceptable salt of claim 21, wherein the compound of Formula (II-A1) is a compound of Formula (II-A1a), (II-A1b), (II-A1c), or (II-A1d)



(II-A1a),

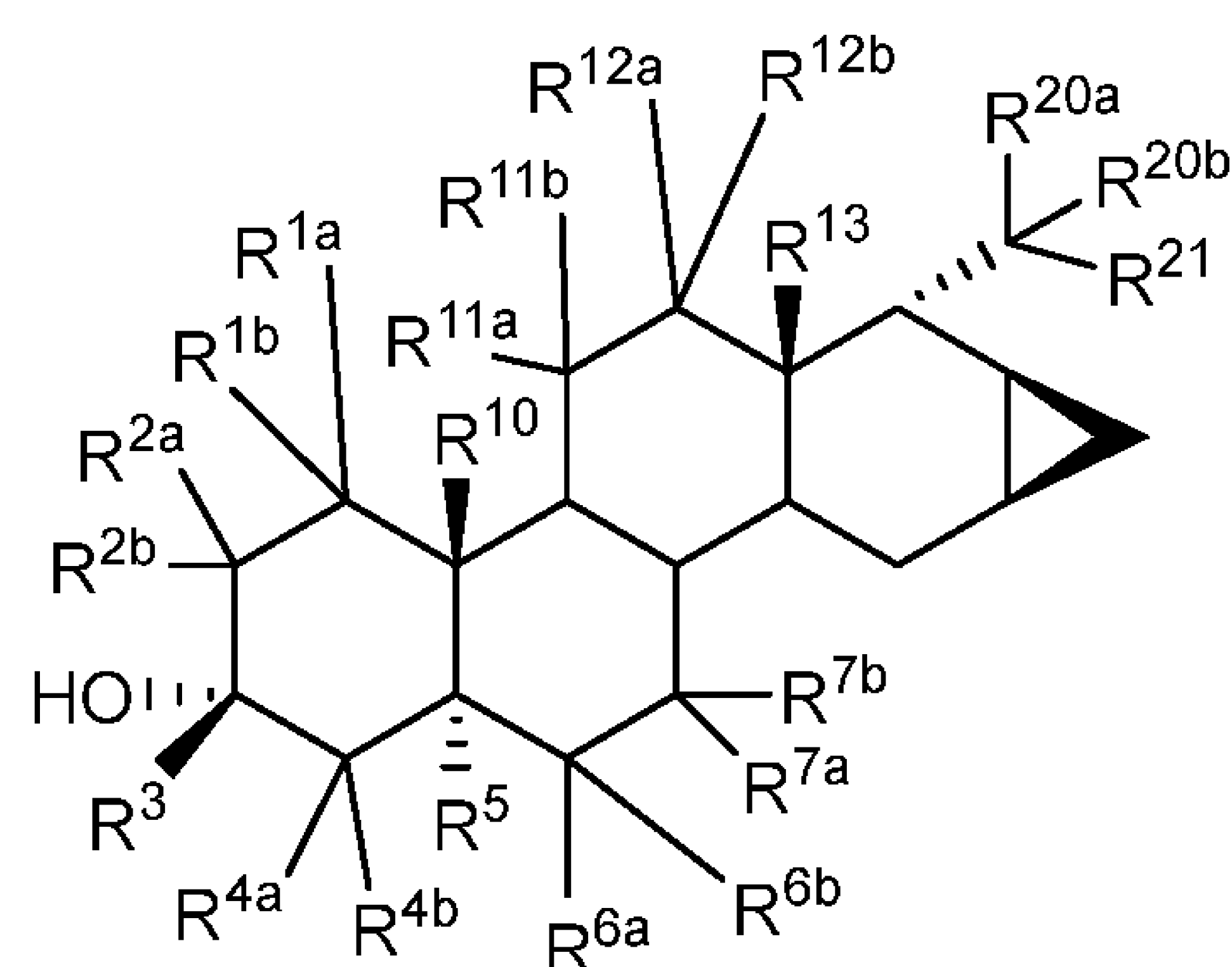


(II-A1b),



(II-A1c),

or



(II-A1d),

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl,

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

R^{21} is $-L^A-R^{30}$;

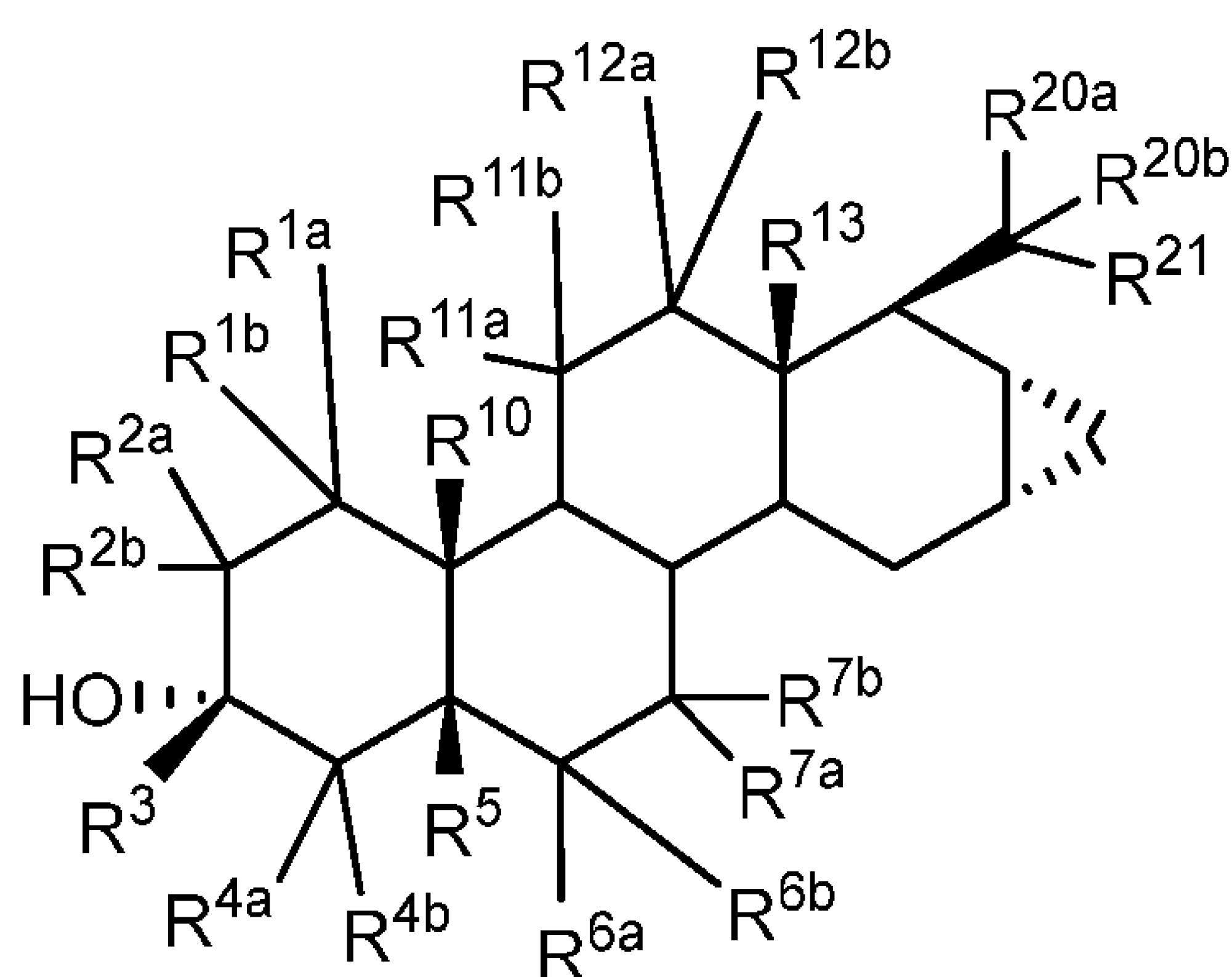
L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -,

–NR'C(O)O–, –S(O)₂NR'–, –NR'S(O)₂–, –C(O)NR'NR'–, –NR'C(O)NR'–, –OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, –S(O)–, or –S(O)₂–;

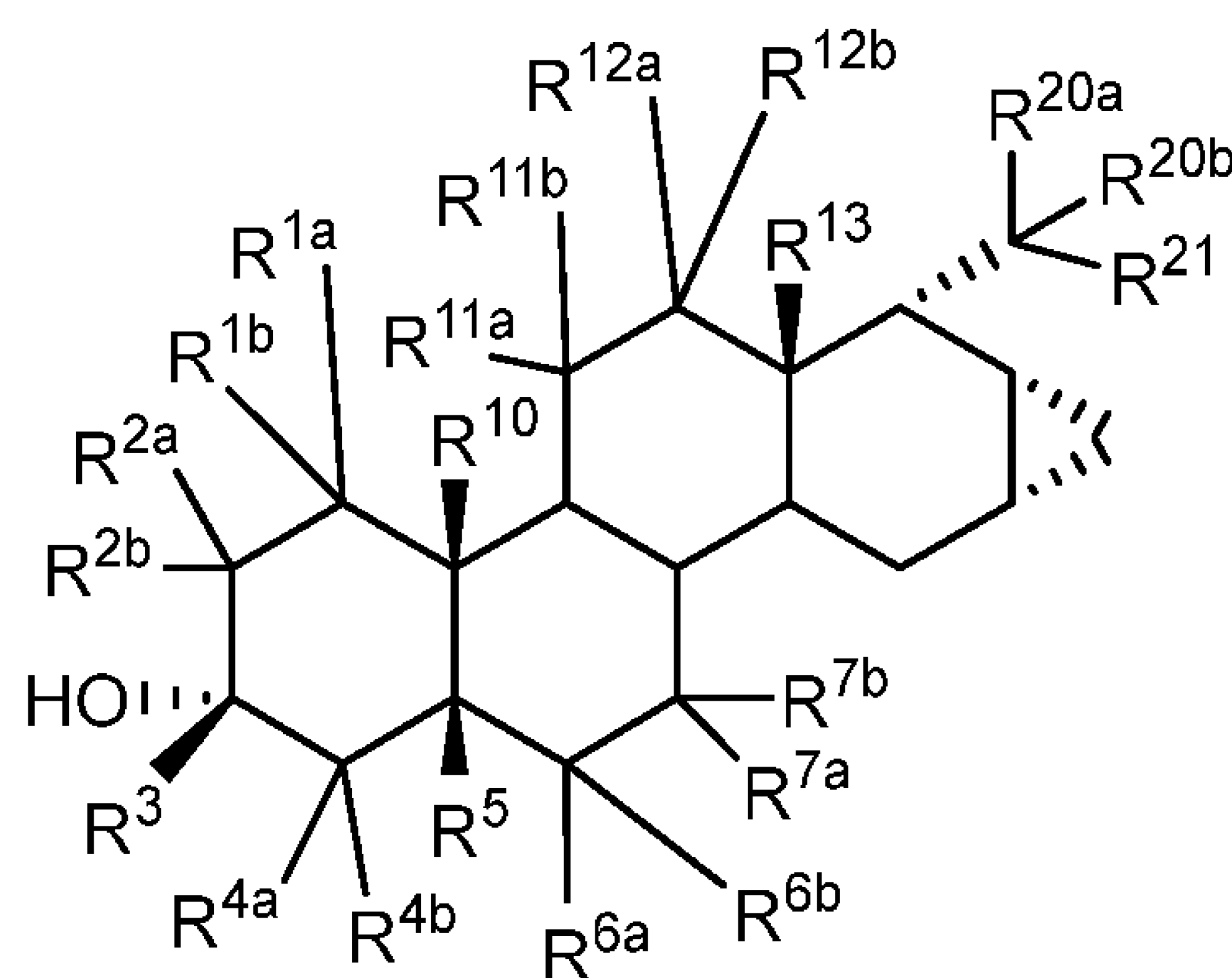
R³⁰ is selected from R', halo, –CN, –NO₂, and –CF₃; and

Each R' is independently selected from –H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, and –CH₃.

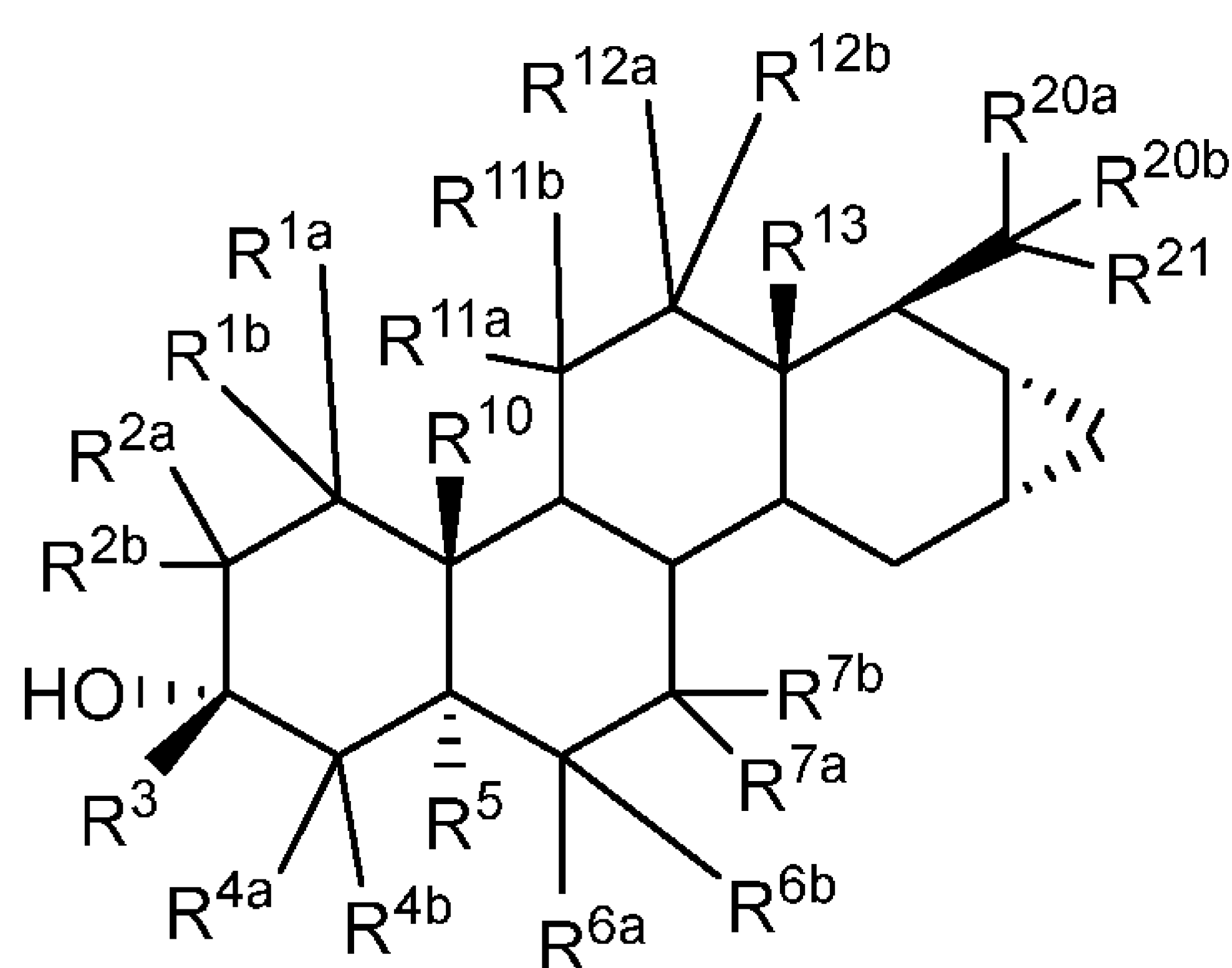
25. The compound or pharmaceutically acceptable salt of claim 21, wherein the compound of Formula (II-A2) is a compound of Formula (II-A2a), (II-A2b), (II-A2c) or (II-A2d)



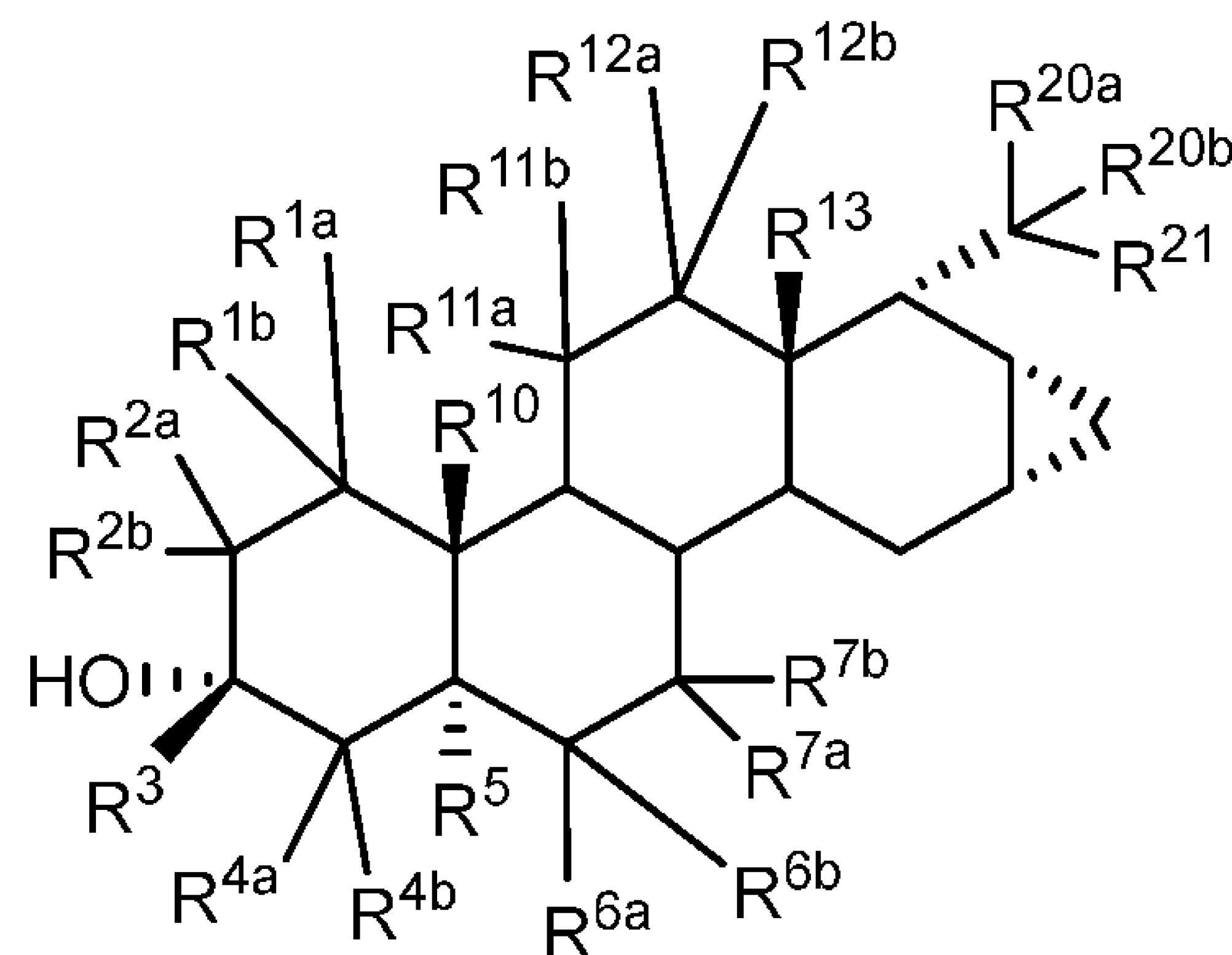
(II-A2a),



(II-A2b),



(II-A2c),



(II-A2d),

or

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from –H and C₁₋₆ alkyl,

R³ is –H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

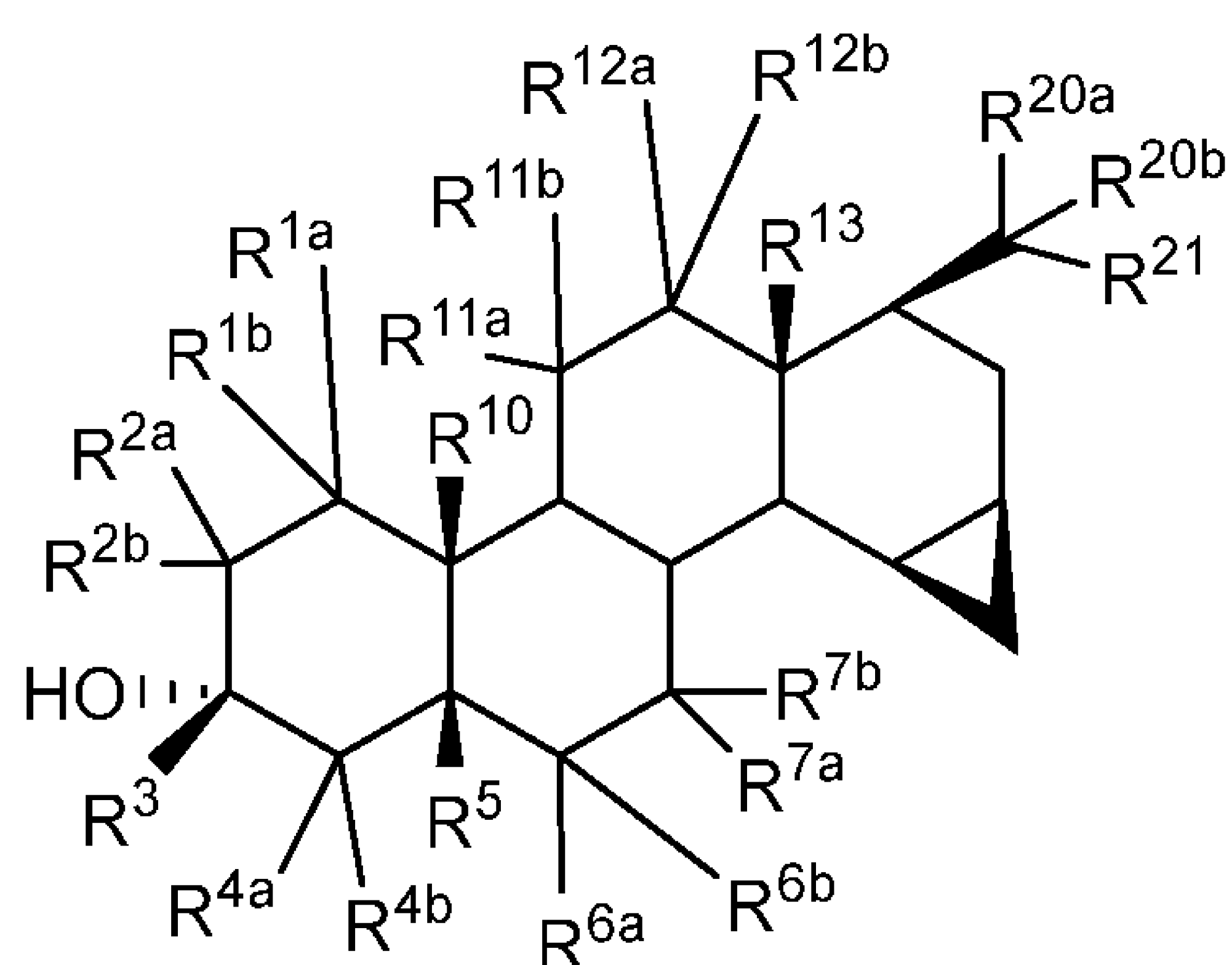
R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

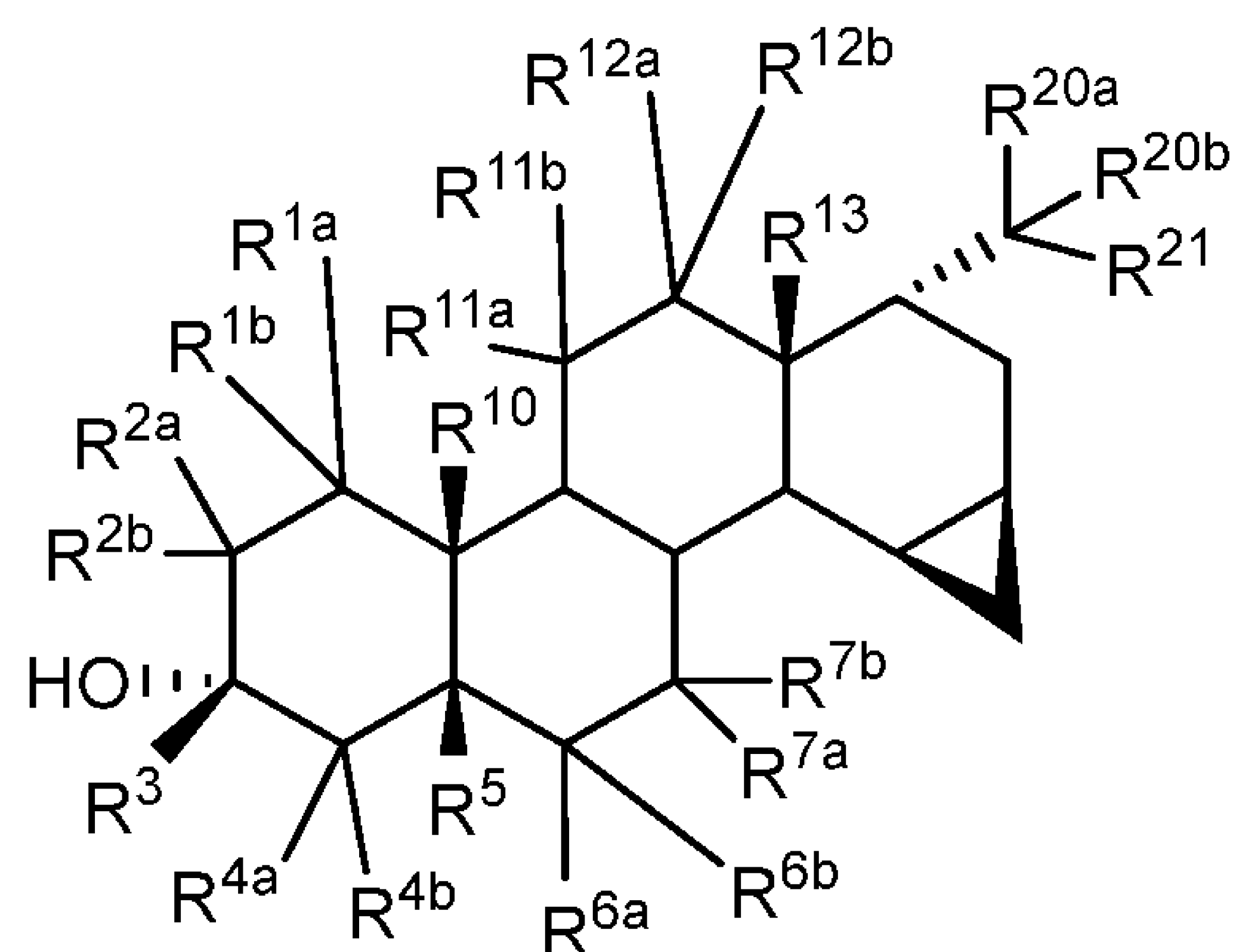
R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and

Each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or $-CH_3$.

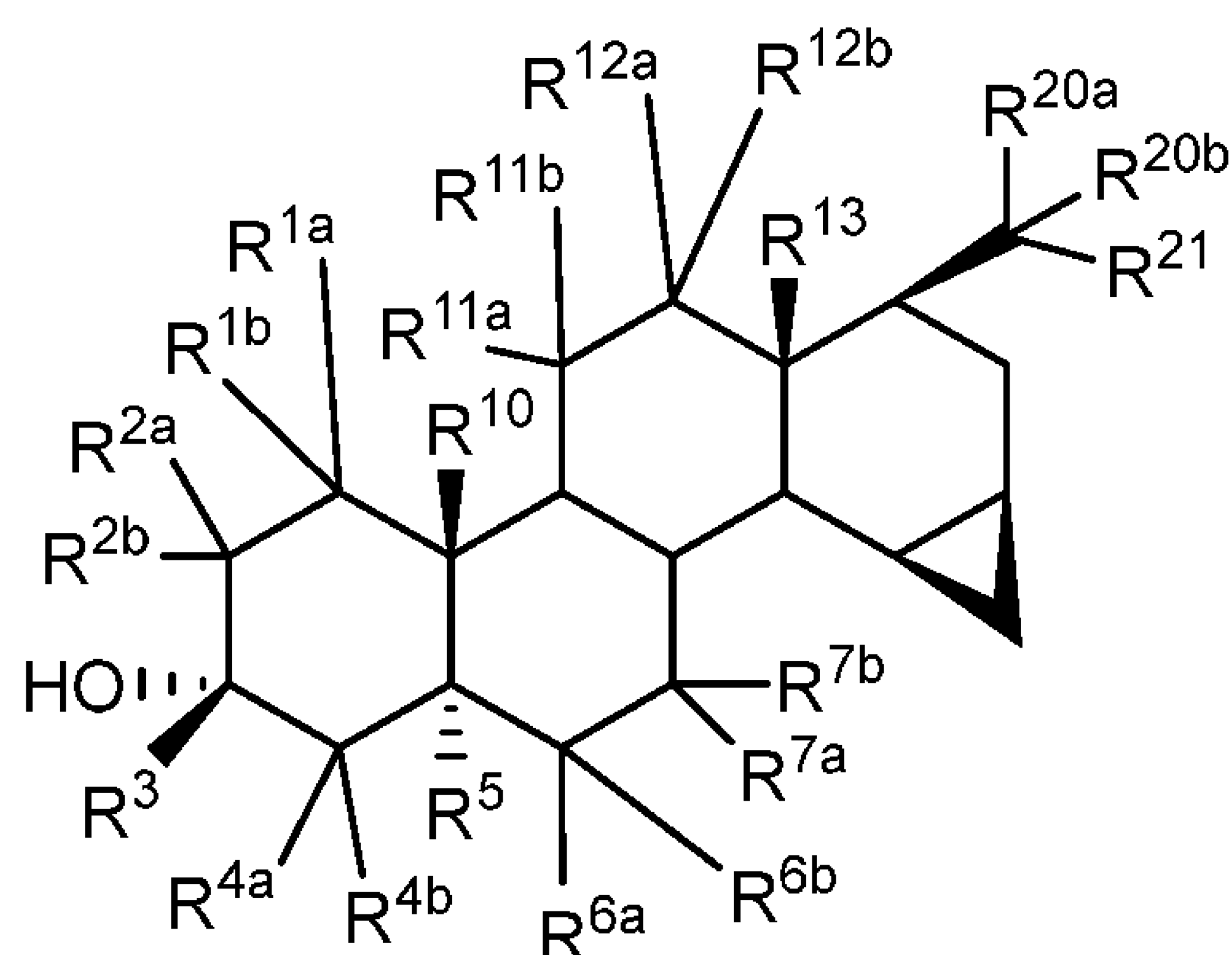
26. The compound or pharmaceutically acceptable salt of claim 22, wherein the compound of Formula (II-B1) is a compound of Formula (II-B1a), (II-B1b), (II-B1c), or (II-B1d)



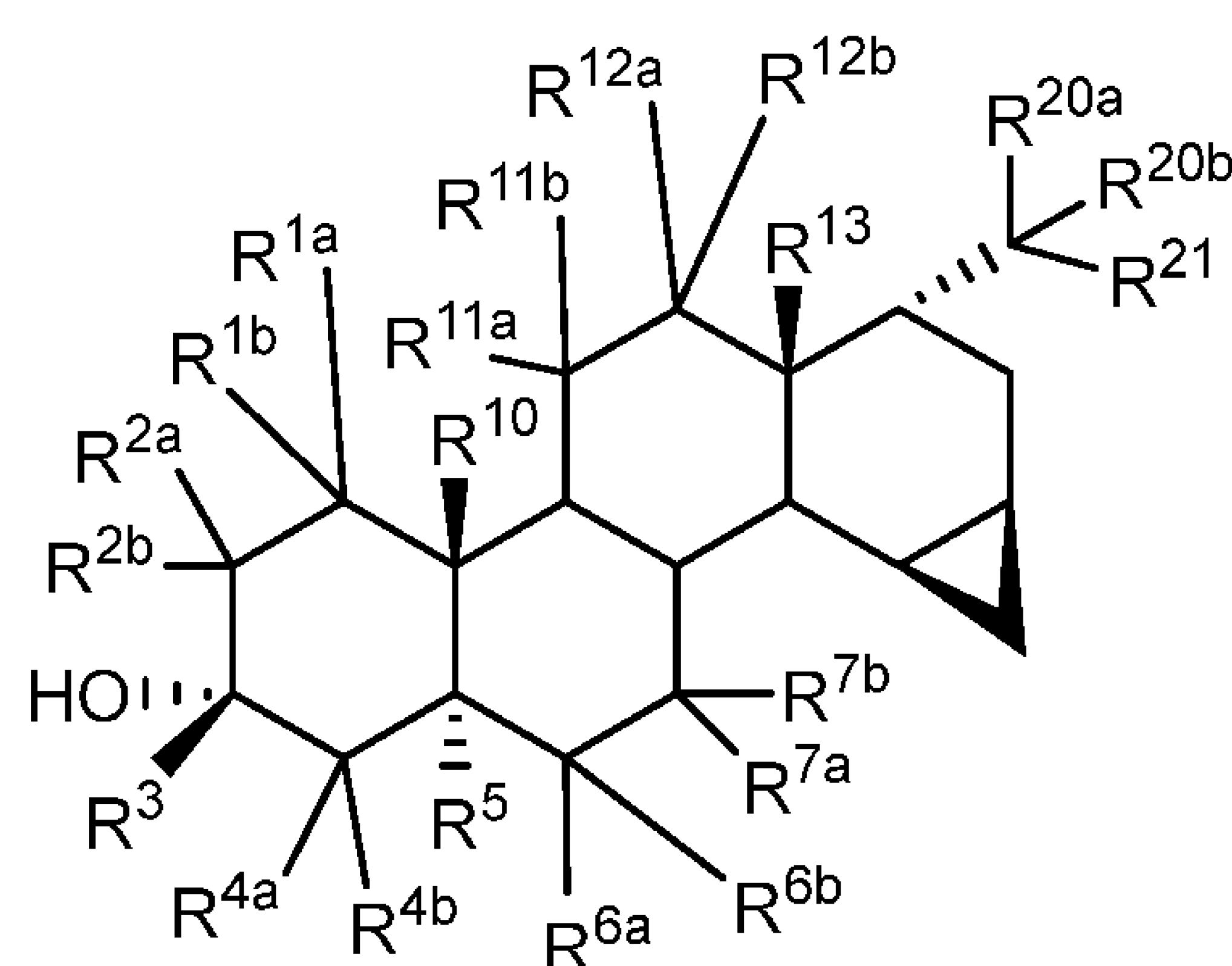
(II-B1a),



(II-B1b),



(II-B1c),



(II-B1d),

or

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ or C_{1-6} alkyl,

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

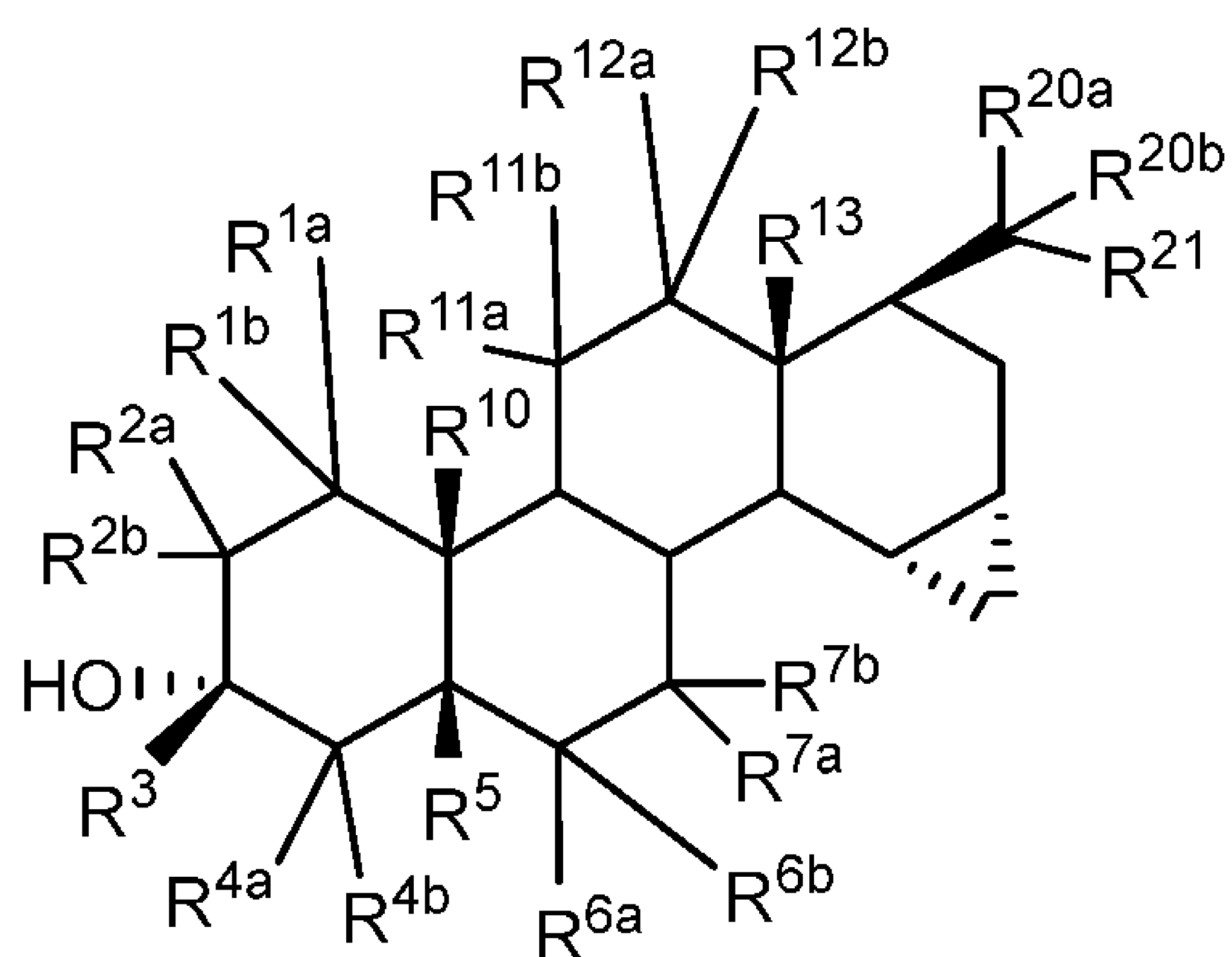
R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

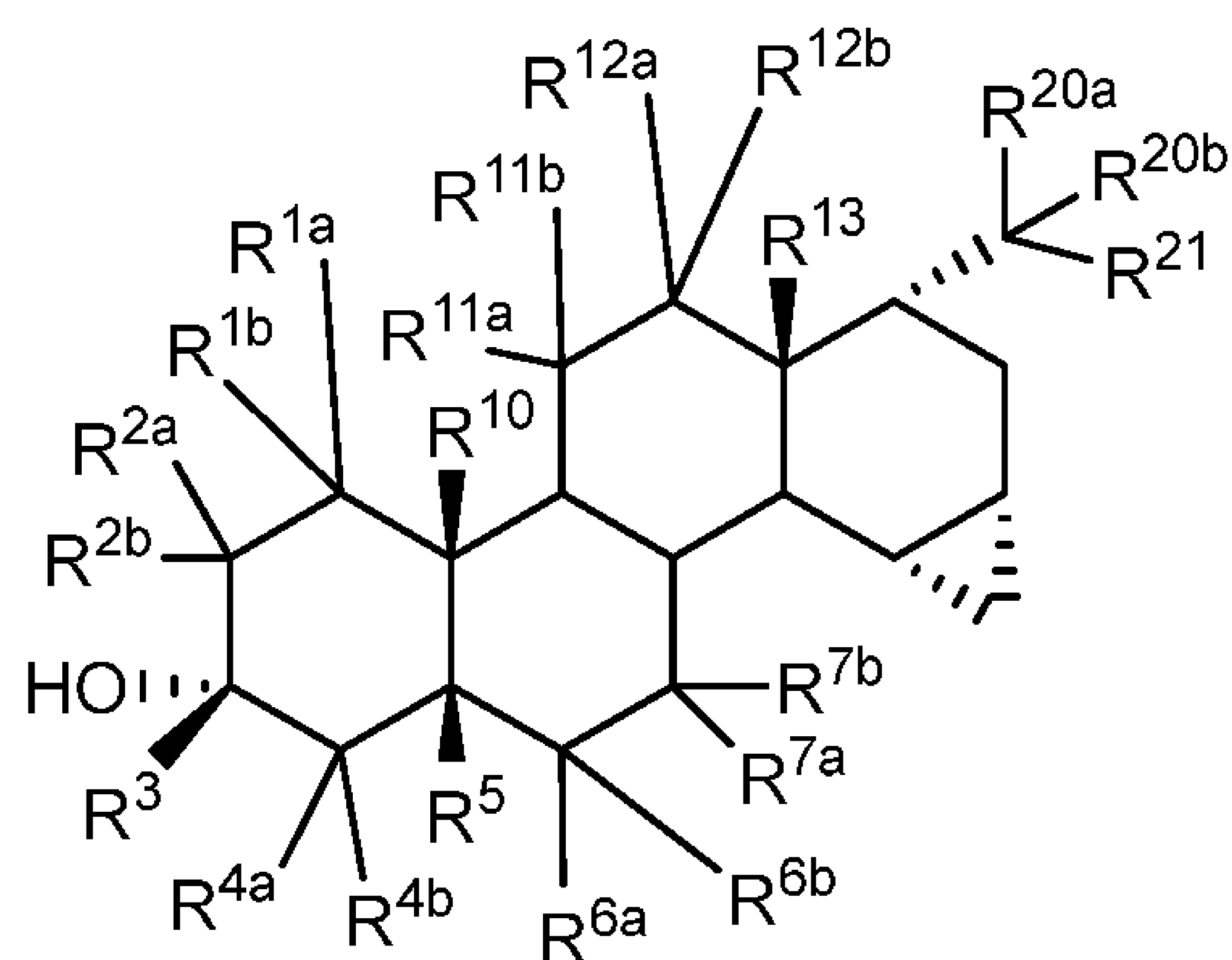
R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and

Each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or $-CH_3$.

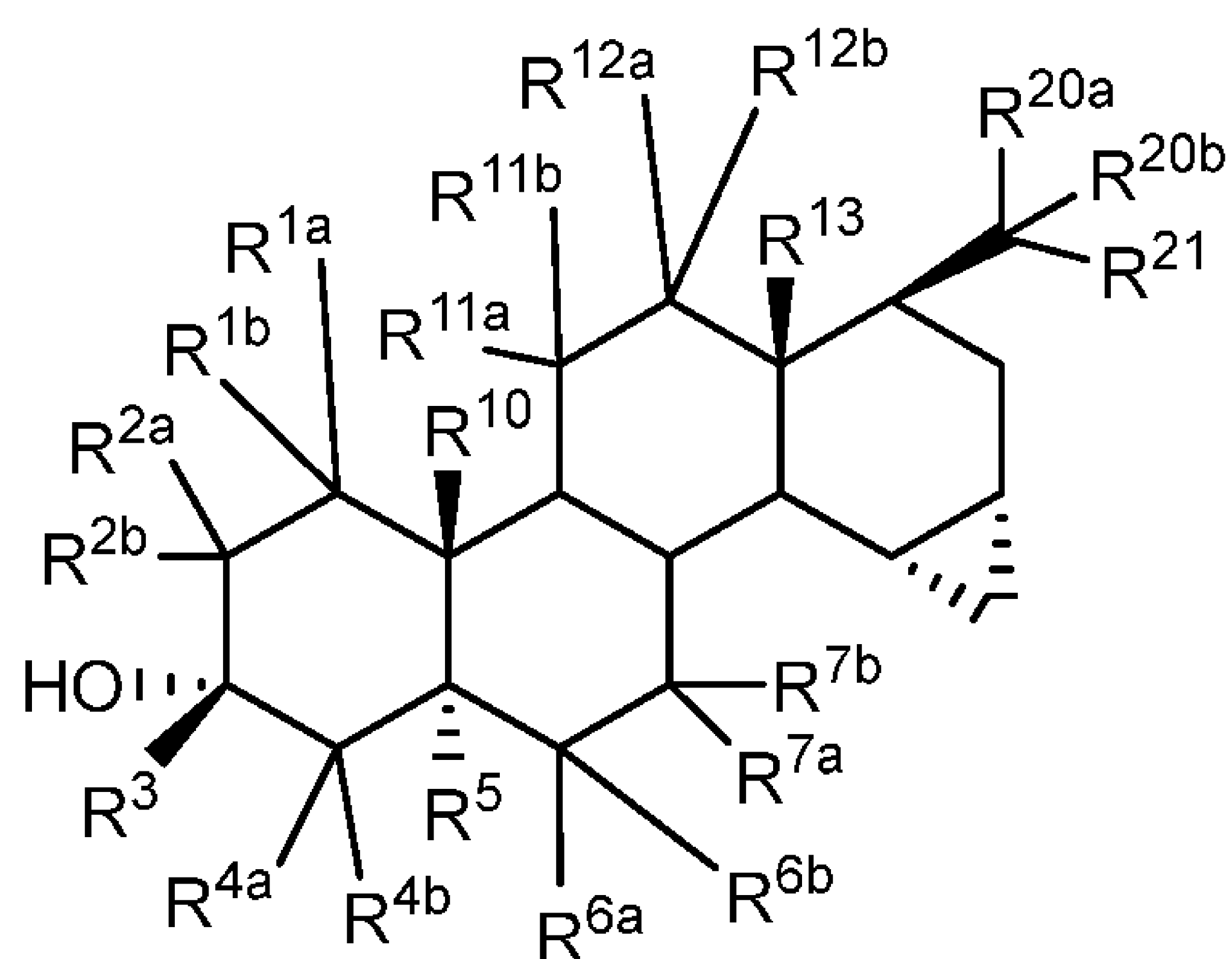
27. The compound or pharmaceutically acceptable salt of claim 22, wherein the compound of Formula (II-B2) is a compound of Formula (II-B2a), (II-B2b), (II-B2c) or (II-B2d)



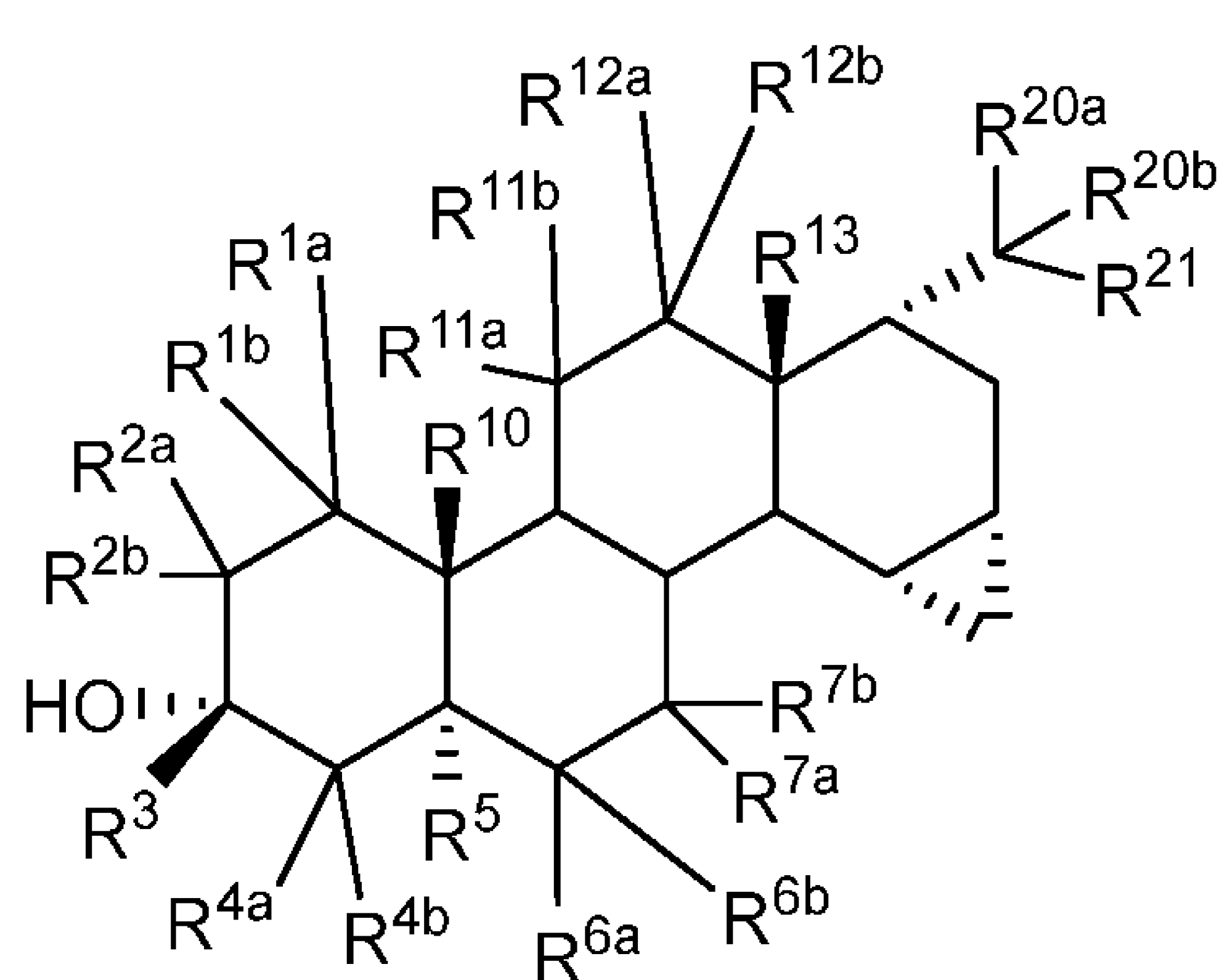
(II-B2a),



(II-B2b),



(II-B2c),



(II-B2d),

or

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl,

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

R^{21} is $-L^A-R^{30}$;

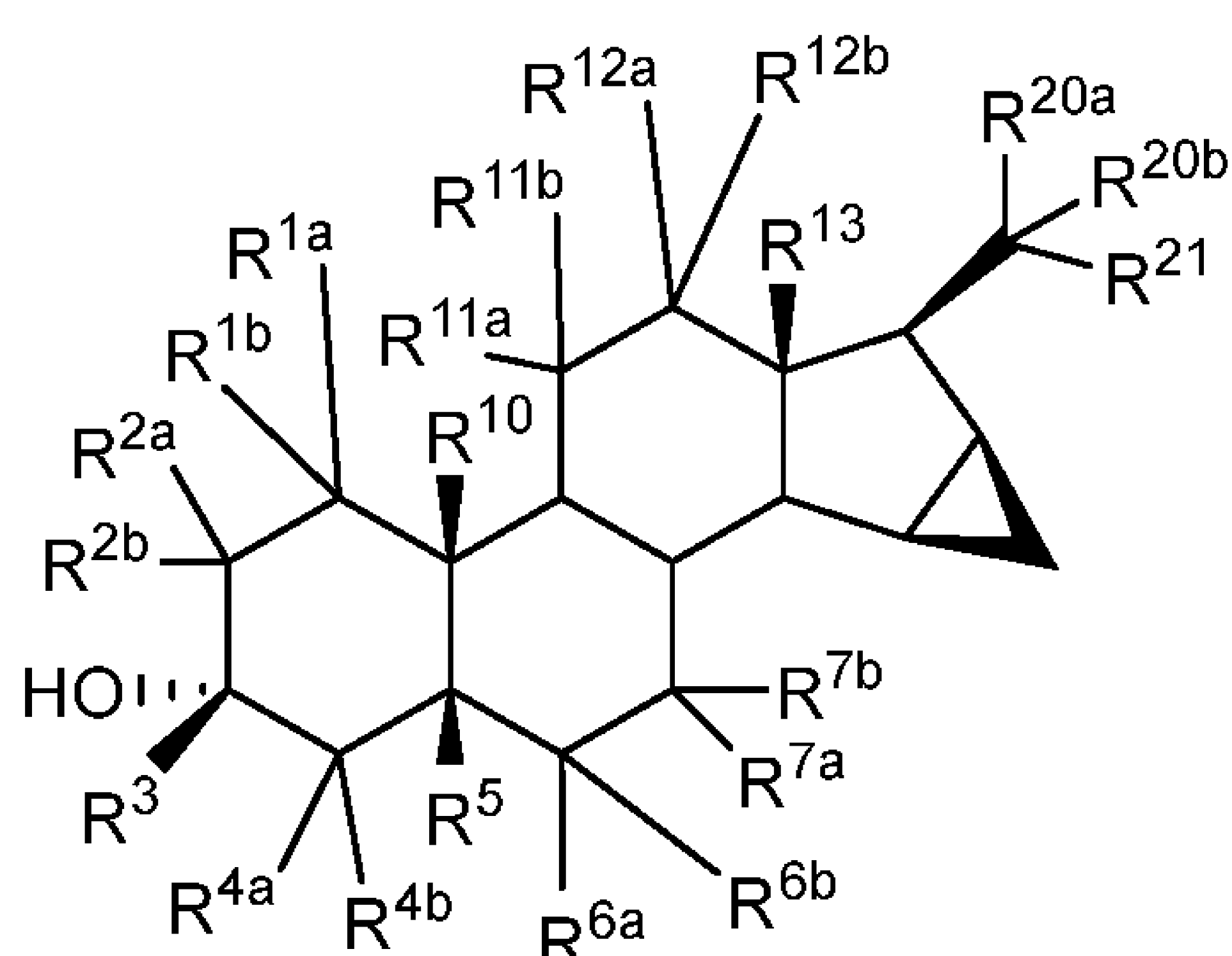
L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -,

–NR'C(O)O–, –S(O)₂NR'–, –NR'S(O)₂–, –C(O)NR'NR'–, –NR'C(O)NR'–, –OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, –S(O)–, or –S(O)₂–;

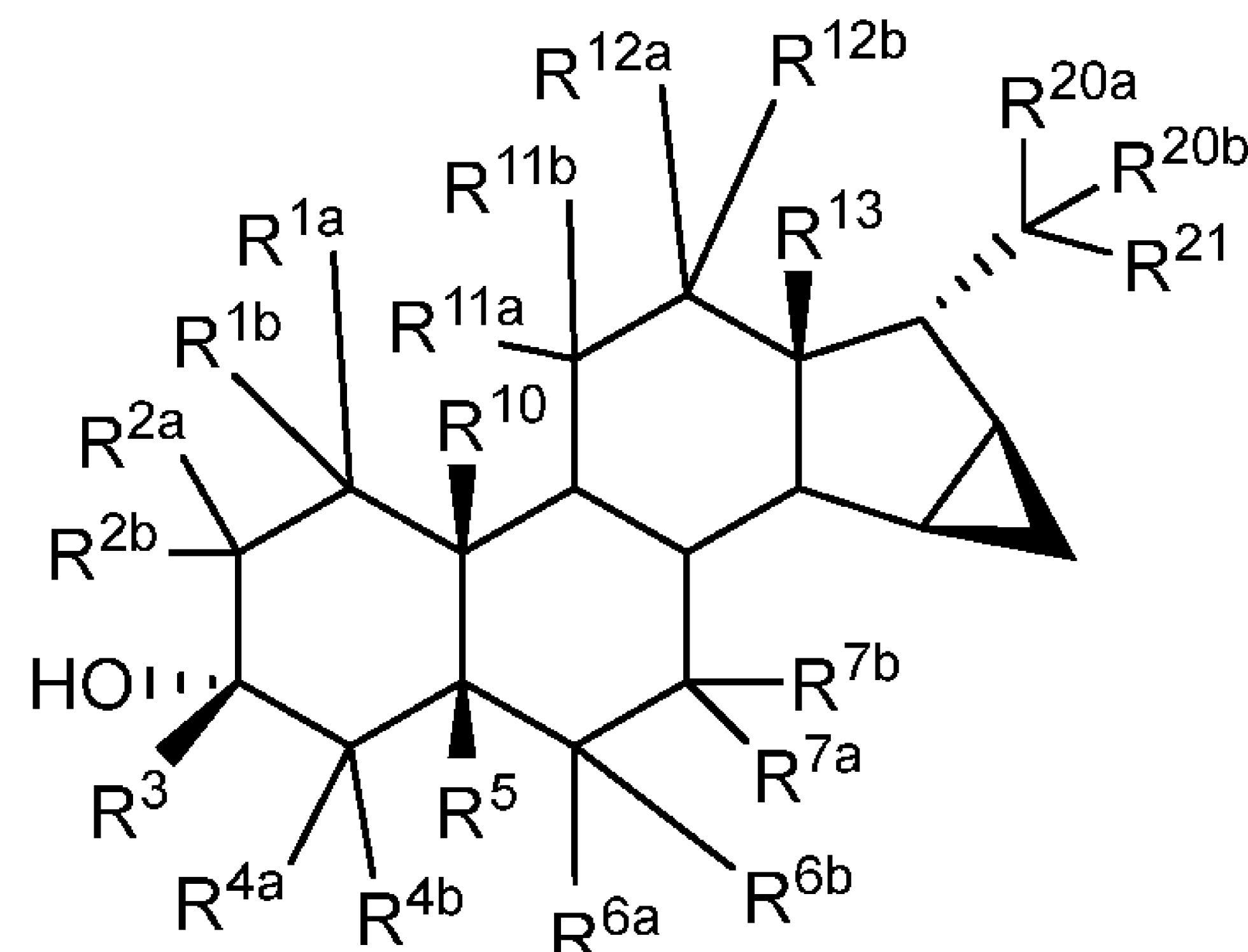
R³⁰ is selected from R', halo, –CN, –NO₂, and –CF₃; and

Each R' is independently selected from –H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, and –CH₃.

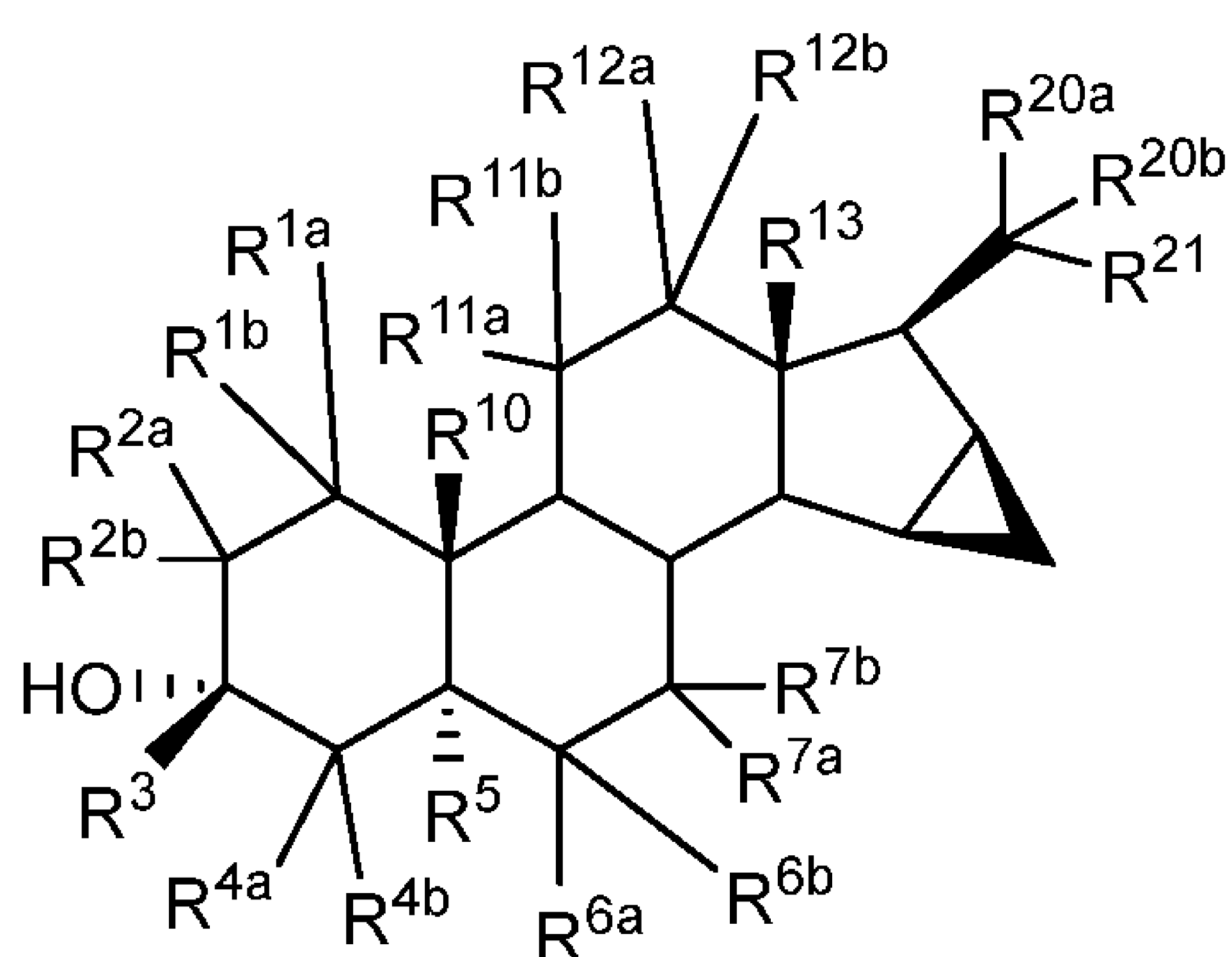
28. The compound or pharmaceutically acceptable salt of claim 23, wherein the compound of Formula (II-C1) is a compound of Formula (II-C1a), (II-C1b), (II-C1c) or (II-C1d)



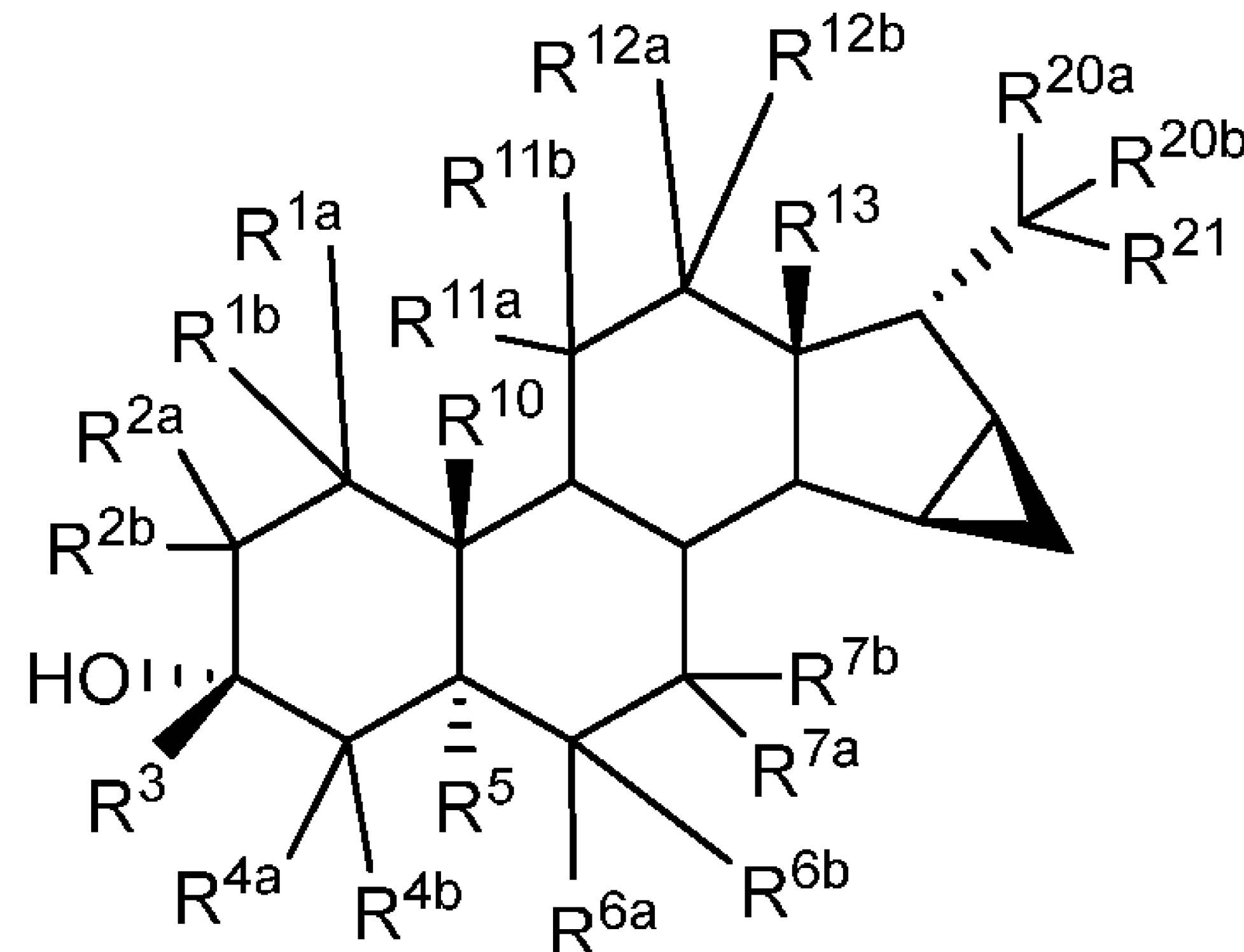
(II-C1a),



(II-C1b),



(II-C1c),



(II-C1d),

or

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, and R^{12b} is independently selected from –H and C₁₋₆ alkyl,

R³ is –H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl;

R⁵ is –H or C₁₋₆ alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

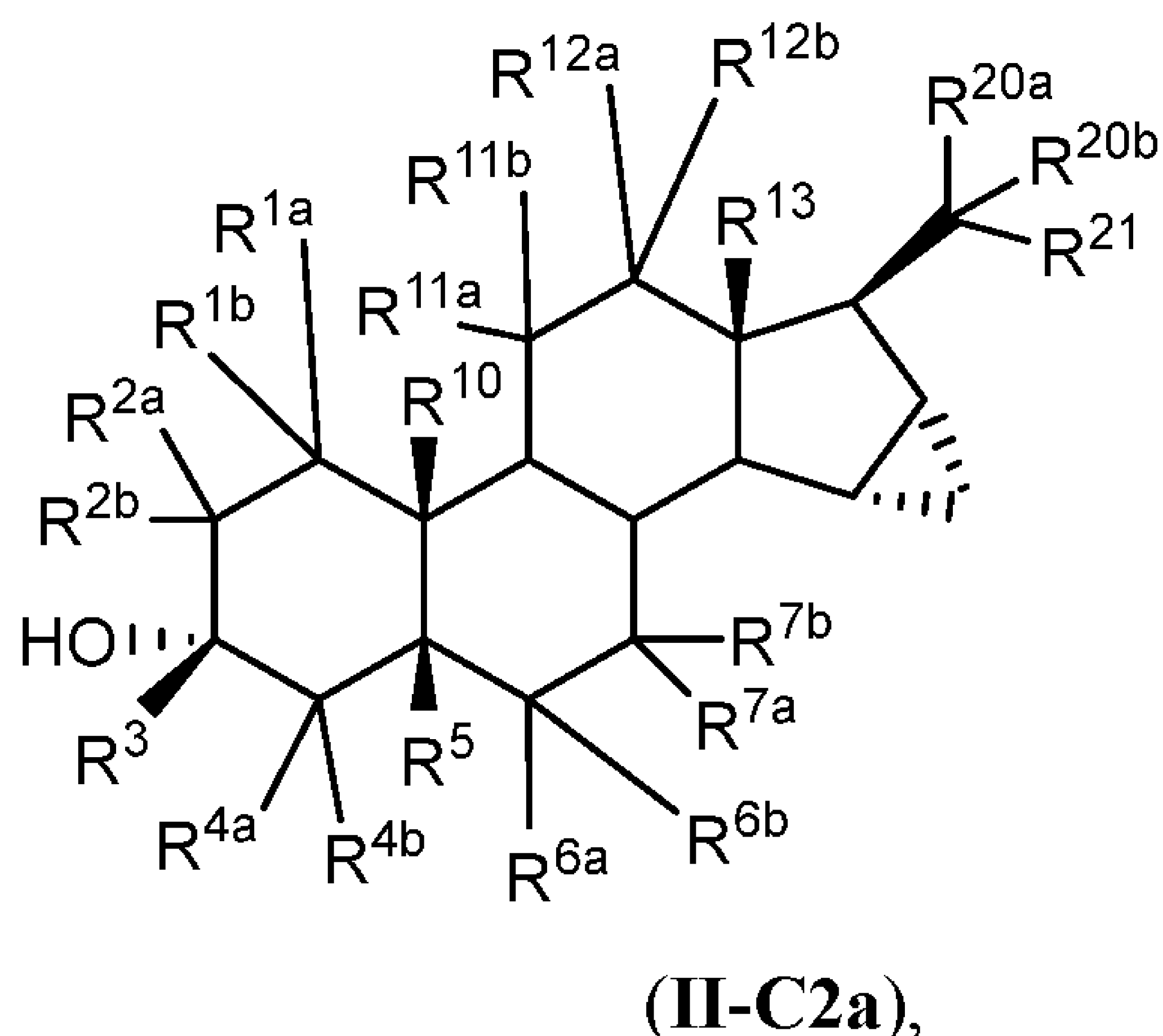
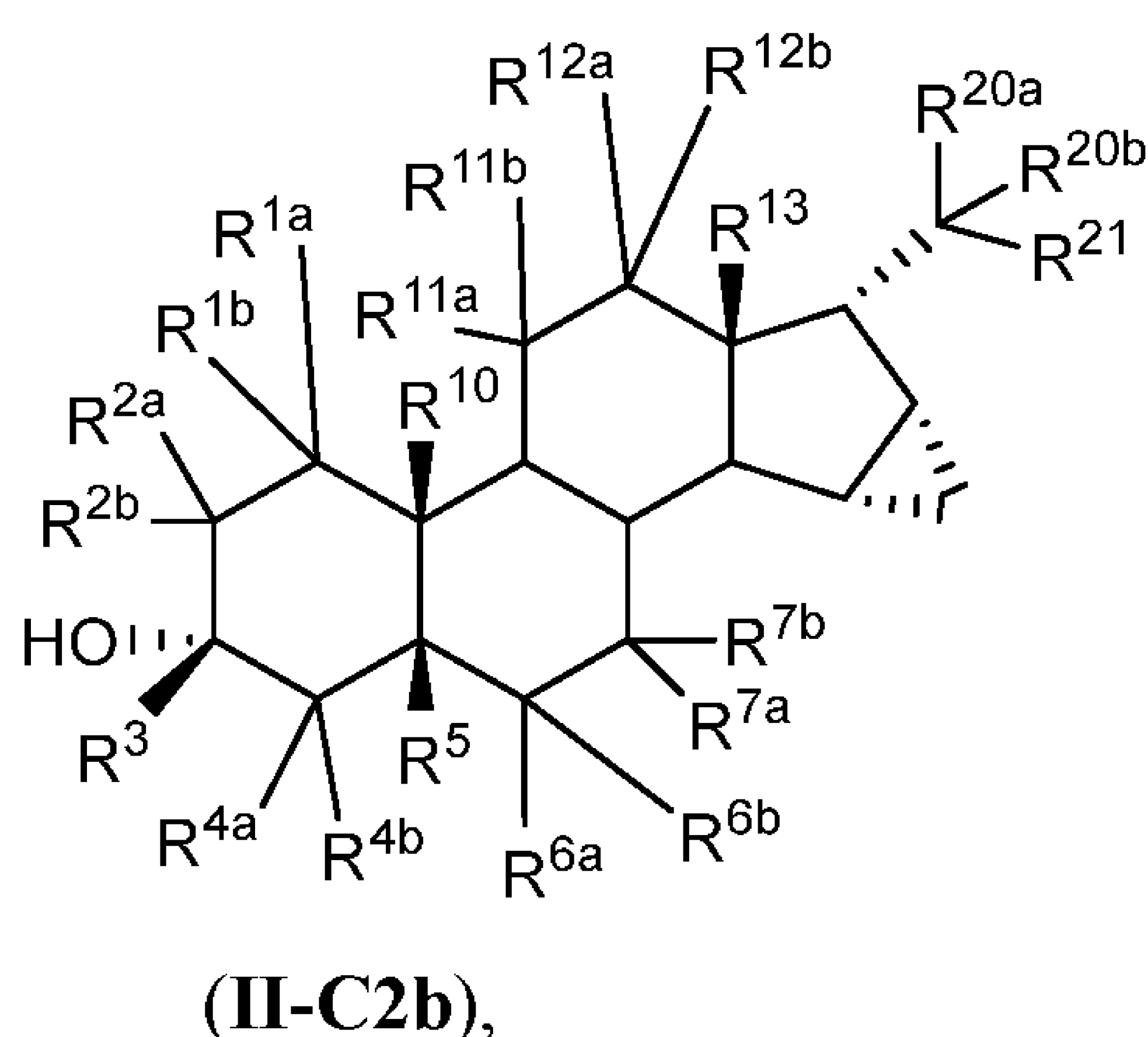
R^{21} is $-L^A-R^{30}$;

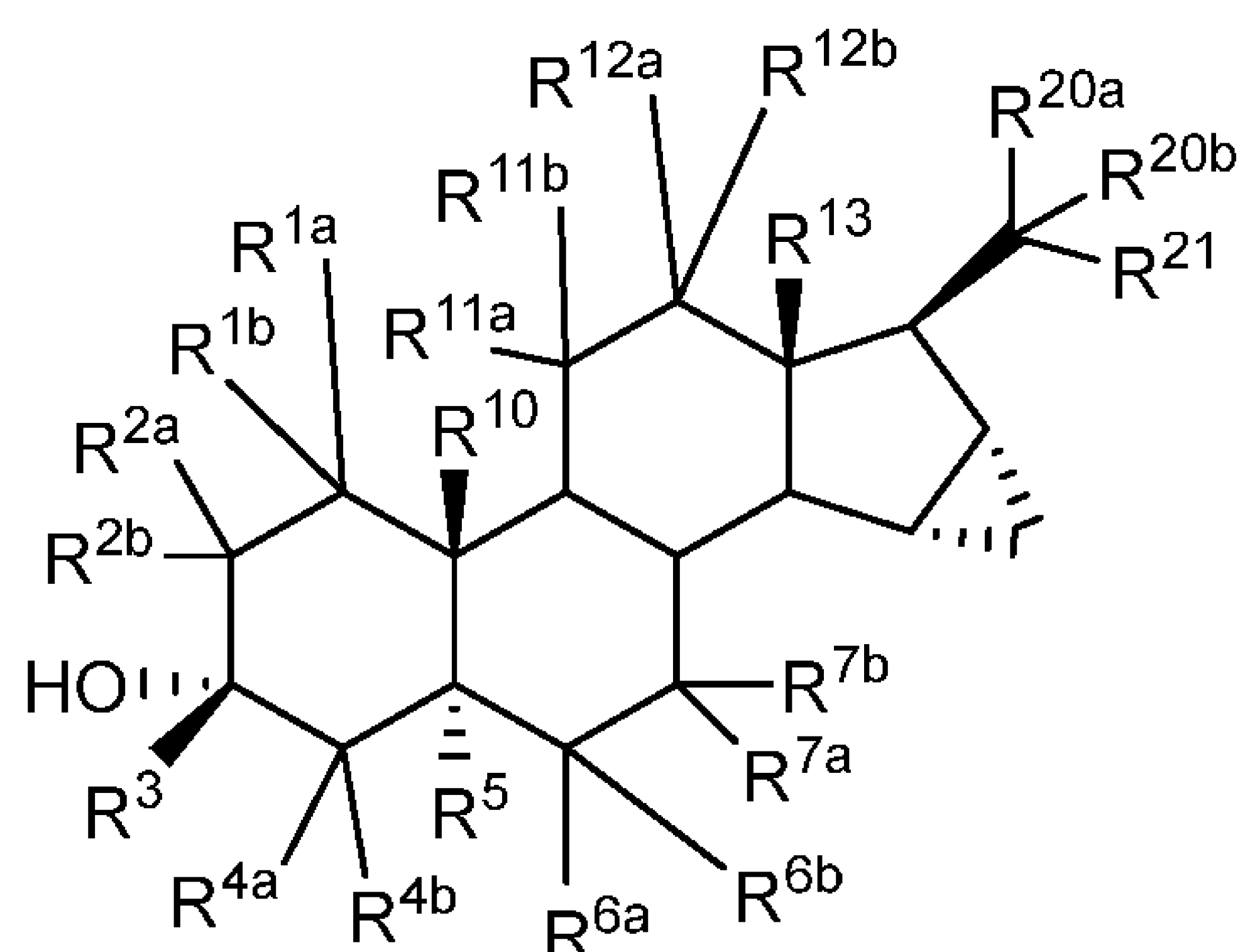
L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and

Each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

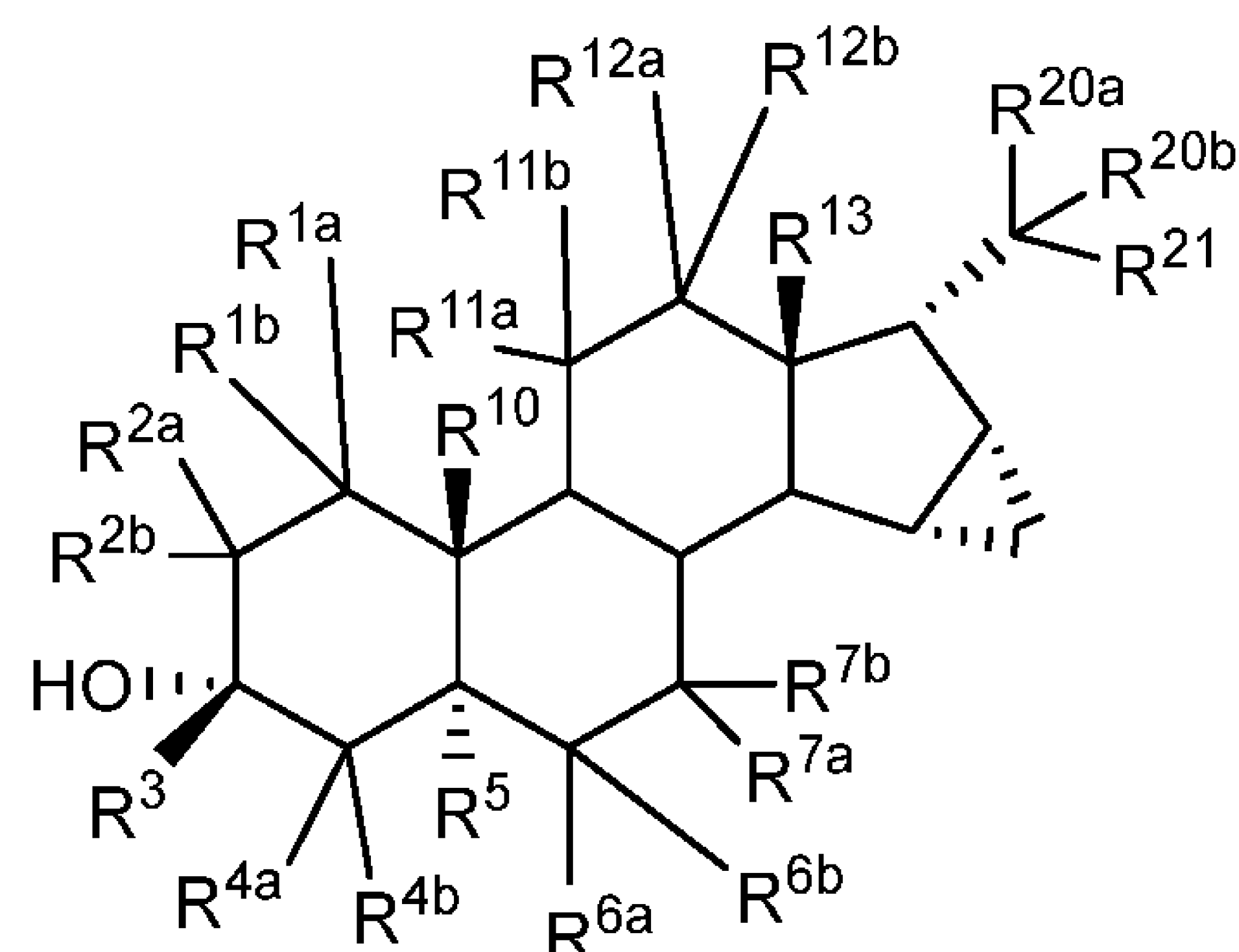
29. The compound or pharmaceutically acceptable salt of claim 23, wherein the compound of Formula (II-C2) is a compound of Formula (II-C2a), (II-C2b), (II-C2c) or (II-C2d)





(II-C2c),

or



(II-C2d),

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ or C_{1-6} alkyl,

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$ or optionally substituted C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently $-H$, $-OH$, $-C_{1-5}$ alkyl- OH , C_{1-6} alkyl, or $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

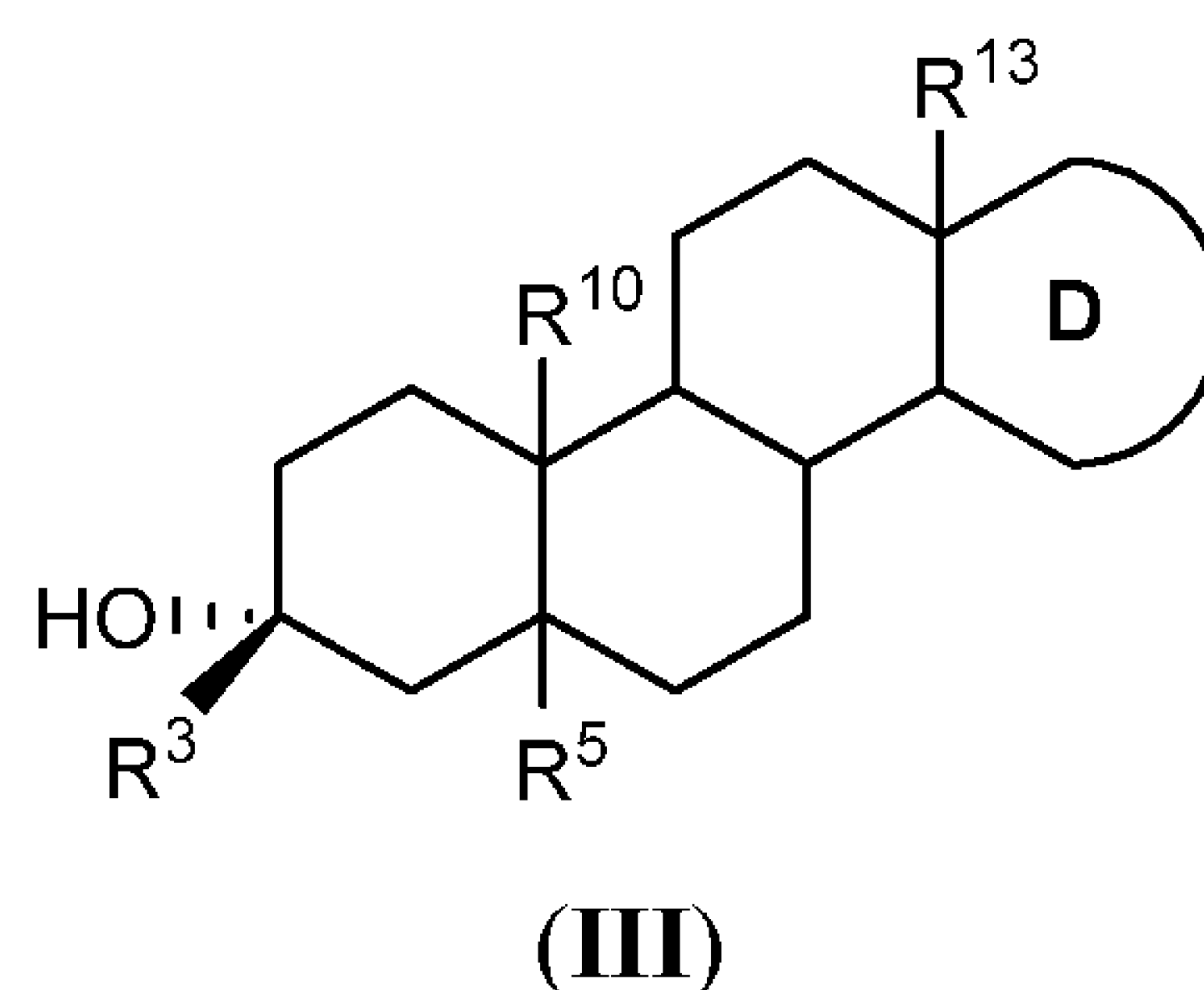
R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

R^{30} is selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$; and

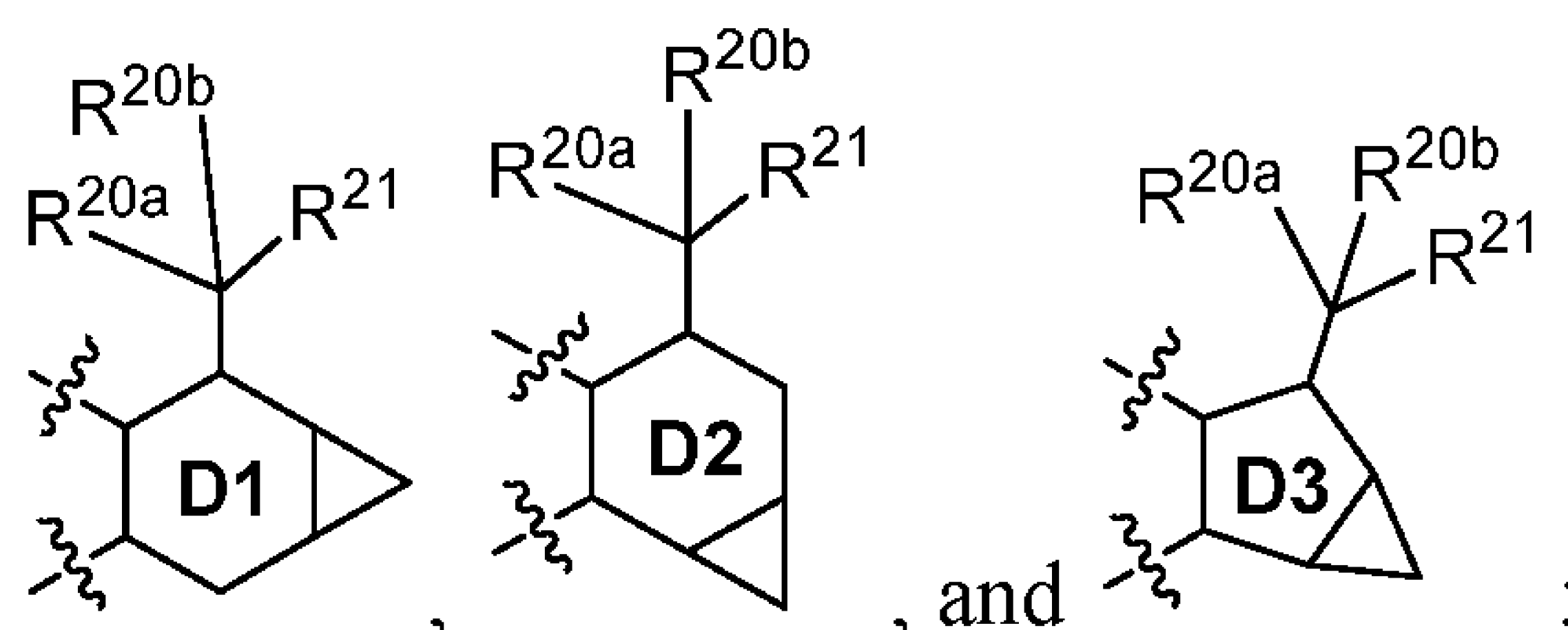
Each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

30. The compound or pharmaceutically acceptable salt of claim 2, wherein the compound of Formula (II) is a compound of Formula (III)



or a pharmaceutically acceptable salt thereof, wherein

Ring D is a fused bicyclic ring selected from



R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^{13} is $-H$ or C_{1-6} alkyl;

Each of R^{20a} and R^{20b} is independently $-H$, $-OH$, C_{1-6} alkyl, or

R^{20a} and R^{20b} taken together form oxo;

R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

31. The compound or pharmaceutically acceptable salt of claim 30, wherein R^{13} is C_{1-6} alkyl.

32. The compound or pharmaceutically acceptable salt of claim 30 or claim 31, wherein R^{13} is methyl, ethyl, or propyl.

33. The compound or pharmaceutically acceptable salt of any one of claims 30-32, wherein R^{13} is methyl.

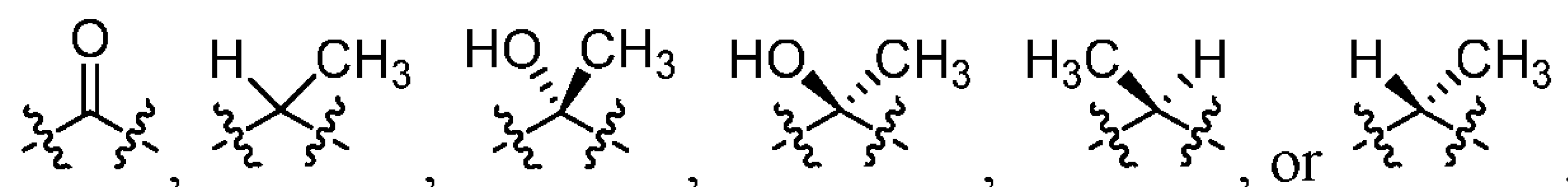
34. The compound or pharmaceutically acceptable salt of any one of claims 30-33, wherein R^{20a} and R^{20b} taken together form oxo.

35. The compound or pharmaceutically acceptable salt of any one of claims 30-33, wherein one of R^{20a} and R^{20b} is $-H$, and the other of R^{20a} and R^{20b} is C_{1-6} alkyl.

36. The compound or pharmaceutically acceptable salt of any one of claims 30-33, wherein one of R^{20a} and R^{20b} is C_{1-6} alkyl, and the other of R^{20a} and R^{20b} is $-OH$.

37. The compound or pharmaceutically acceptable salt of any one of claims 30-33 or 36 wherein one of R^{20a} and R^{20b} is methyl, ethyl, or propyl, and the other of R^{20a} and R^{20b} is $-OH$.

38. The compound or pharmaceutically acceptable salt of any one of claims 30-33, wherein R^{20a} , R^{20b} , and the carbon to which they are attached form



39. The compound or pharmaceutically acceptable salt of any one of claims 30-38, wherein R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-3} alkylene chain, or $-N(H)-$; and

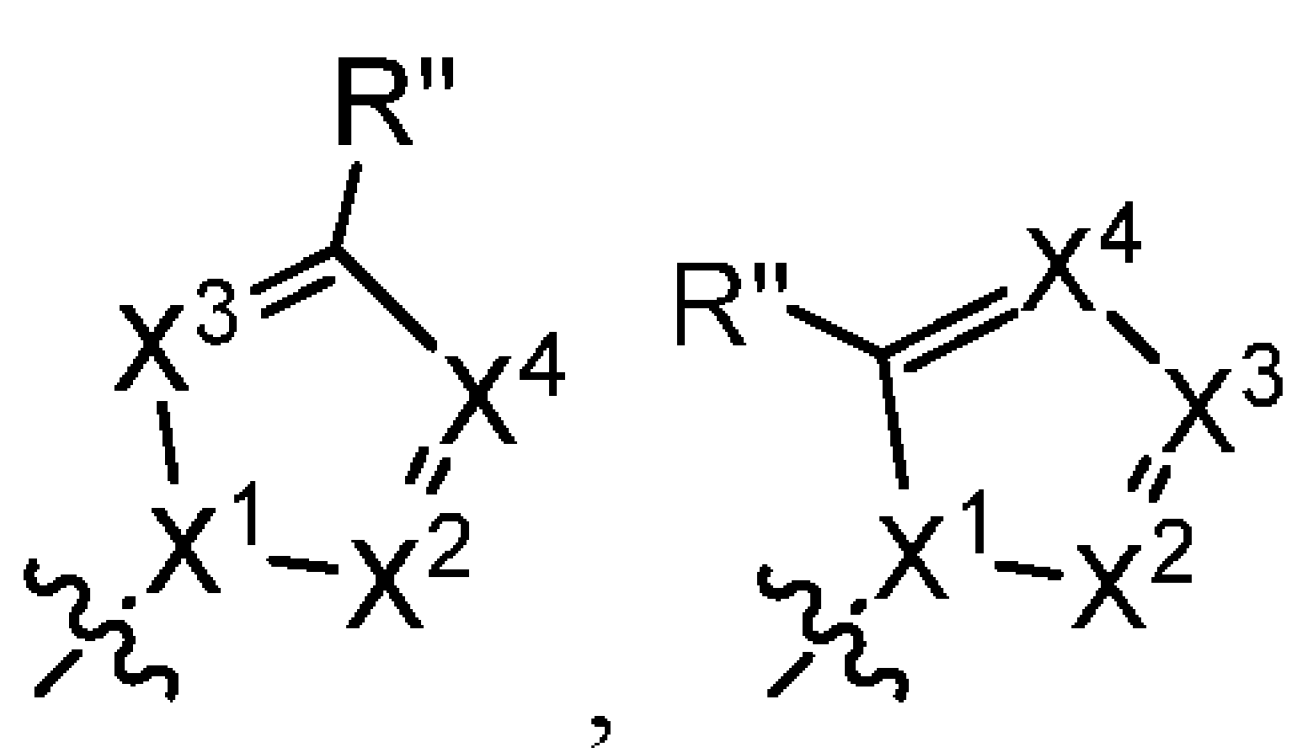
R^{30} is $-H$, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

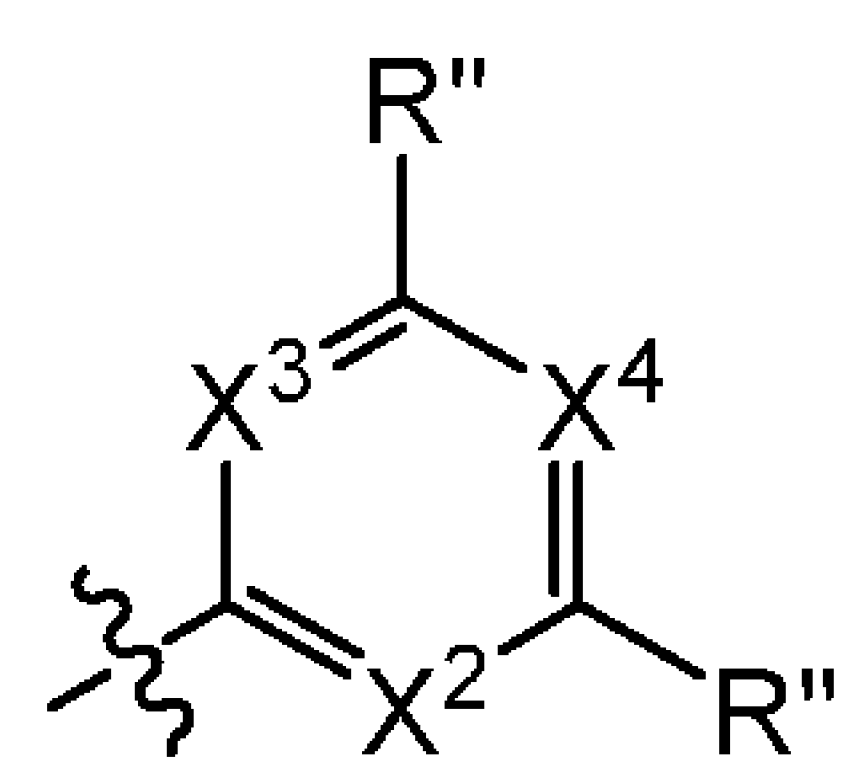
40. The compound or pharmaceutically acceptable salt of any one of claims 30-39, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, or $-N(H)-$; and R^{30} is $-H$ or a 5-6-membered

partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$.

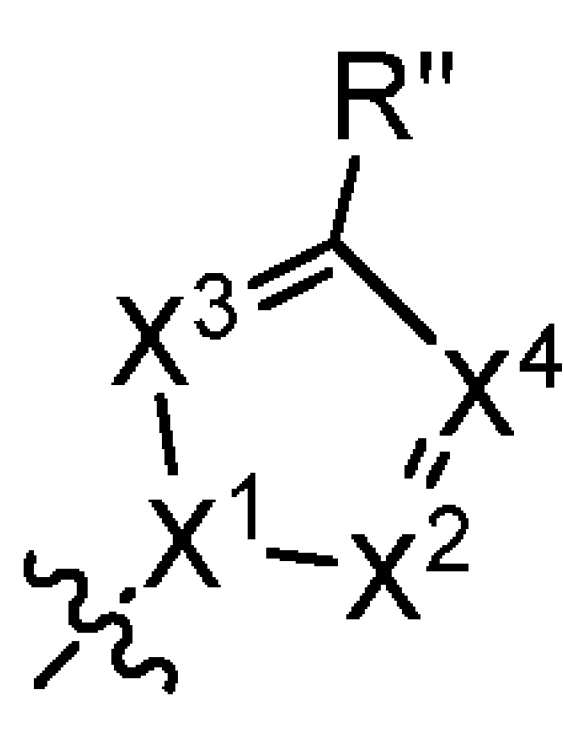
41. The compound or pharmaceutically acceptable salt of any one of claims 30-40, wherein R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, or $-\text{N}(\text{H})-$; and R^{30} is a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$.

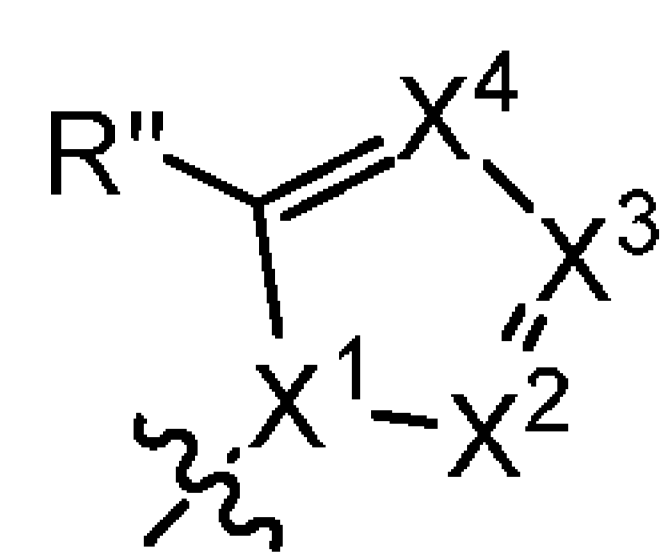
42. The compound or pharmaceutically acceptable salt of any one of claims 30-41, wherein

R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, $-\text{CH}_2-$, or $-\text{N}(\text{H})-$; and R^{30} is , or

, wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that

- (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and
- (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$.

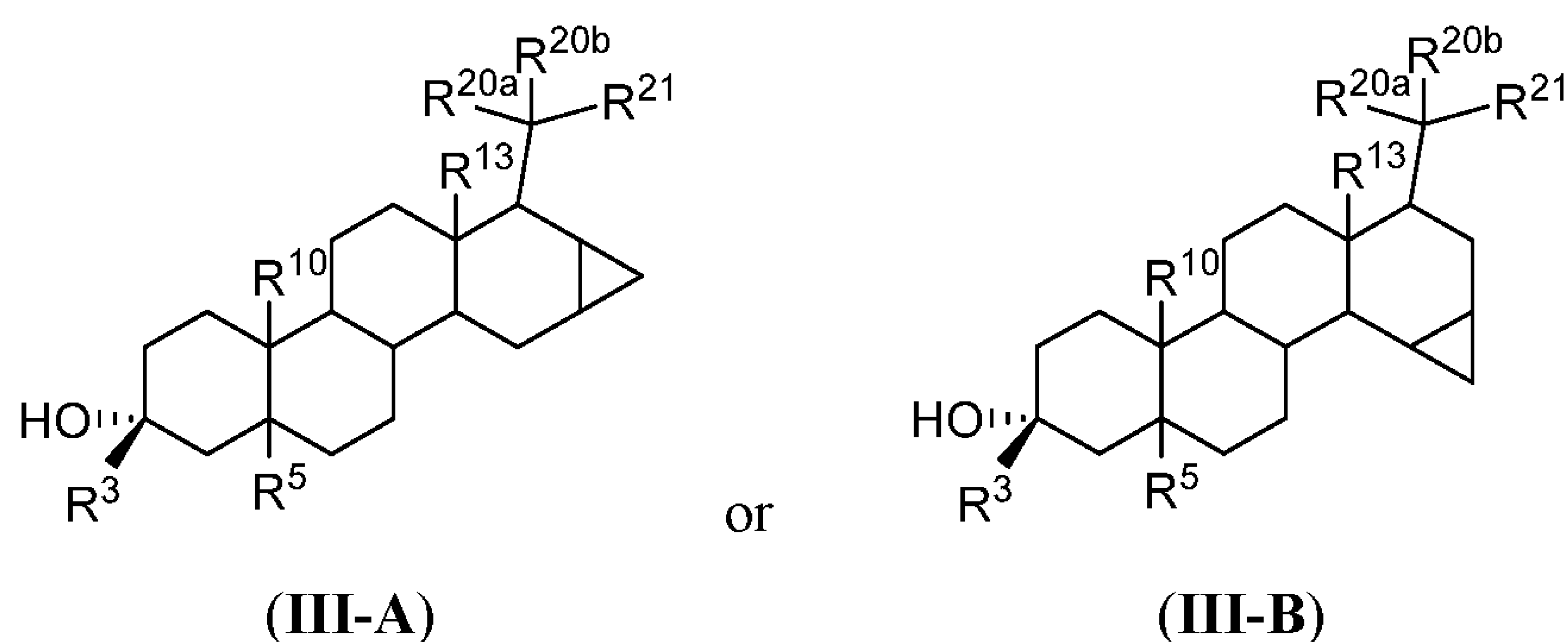
43. The compound or pharmaceutically acceptable salt of claim 41, wherein R^{30} is 

or , X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N or CR'' ,

wherein each R" is independently selected from -H, -OH, -CN, -NO₂, -CF₃, -CH₃, and -CH₂OH, provided that

(i) no greater than 2 instances of R" are independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, and -CH₂OH.

44. The compound or pharmaceutically acceptable salt of claim 30, wherein the compound of Formula (III) is a compound of Formula (III-A) or (III-B)



or a pharmaceutically acceptable salt thereof.

45. The compound or pharmaceutically acceptable salt of claim 44, wherein

R³ is methyl;

R⁵ is -H;

R¹⁰ is -H;

R¹³ is -H or methyl;

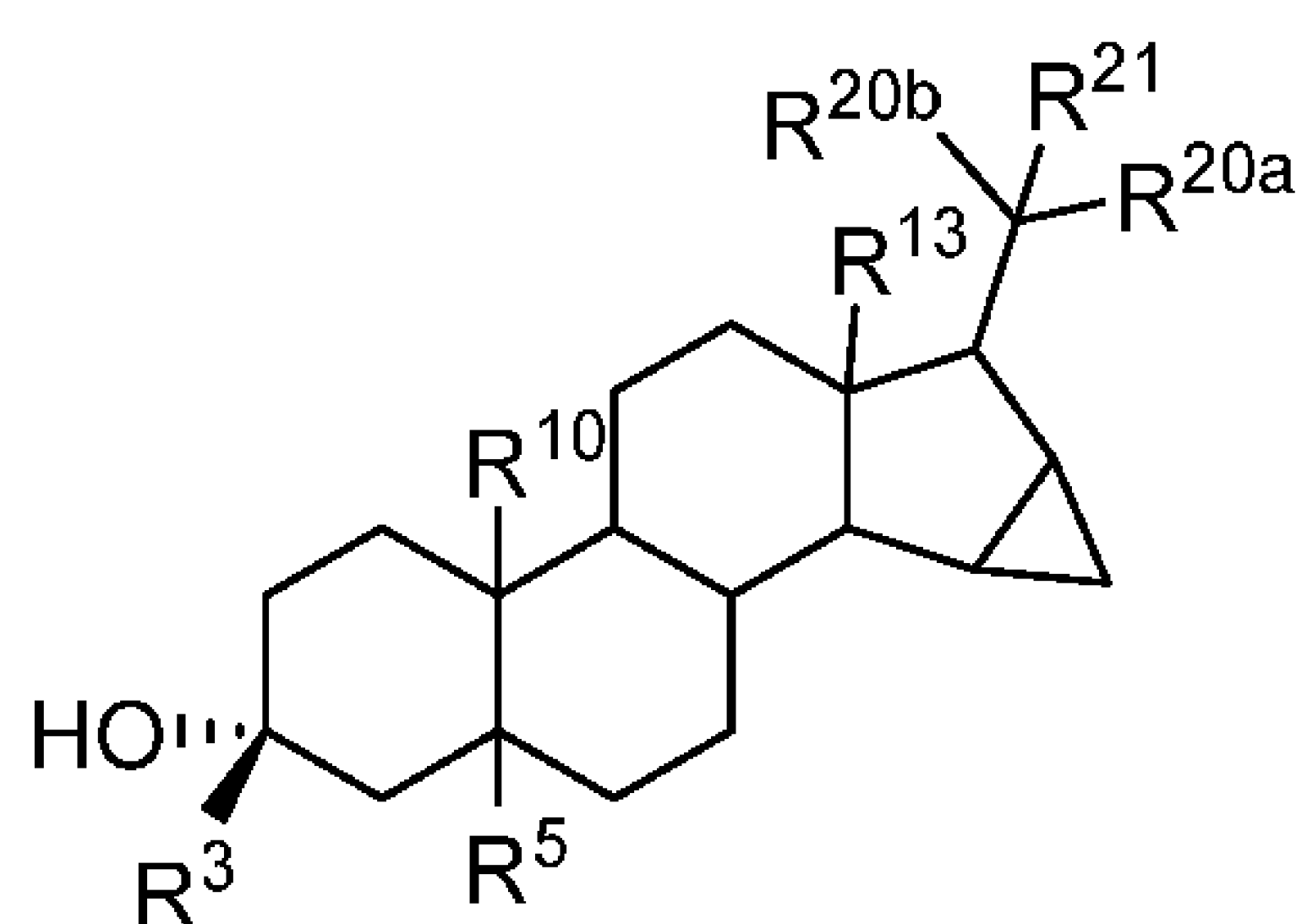
Each of R^{20a} and R^{20b} is independently selected from -H, -OH, and methyl, or R^{20a} and R^{20b} taken together form oxo;

R²¹ is -L^A-R³⁰;

L^A is a bond, -NH-, or -CH₂-;

R³⁰ is independently selected from pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C₁₋₆ alkyl, or cyano.

46. The compound or pharmaceutically acceptable salt of claim 30, wherein the compound of Formula (III) is a compound of Formula (III-C)



(III-C)

or a pharmaceutically acceptable salt thereof.

47. The compound or pharmaceutically acceptable salt of claim 46, wherein

R³ is methyl, ethyl, propyl, or methoxymethyl;

R⁵ is -H;

R¹⁰ is -H;

R¹³ is -H or methyl;

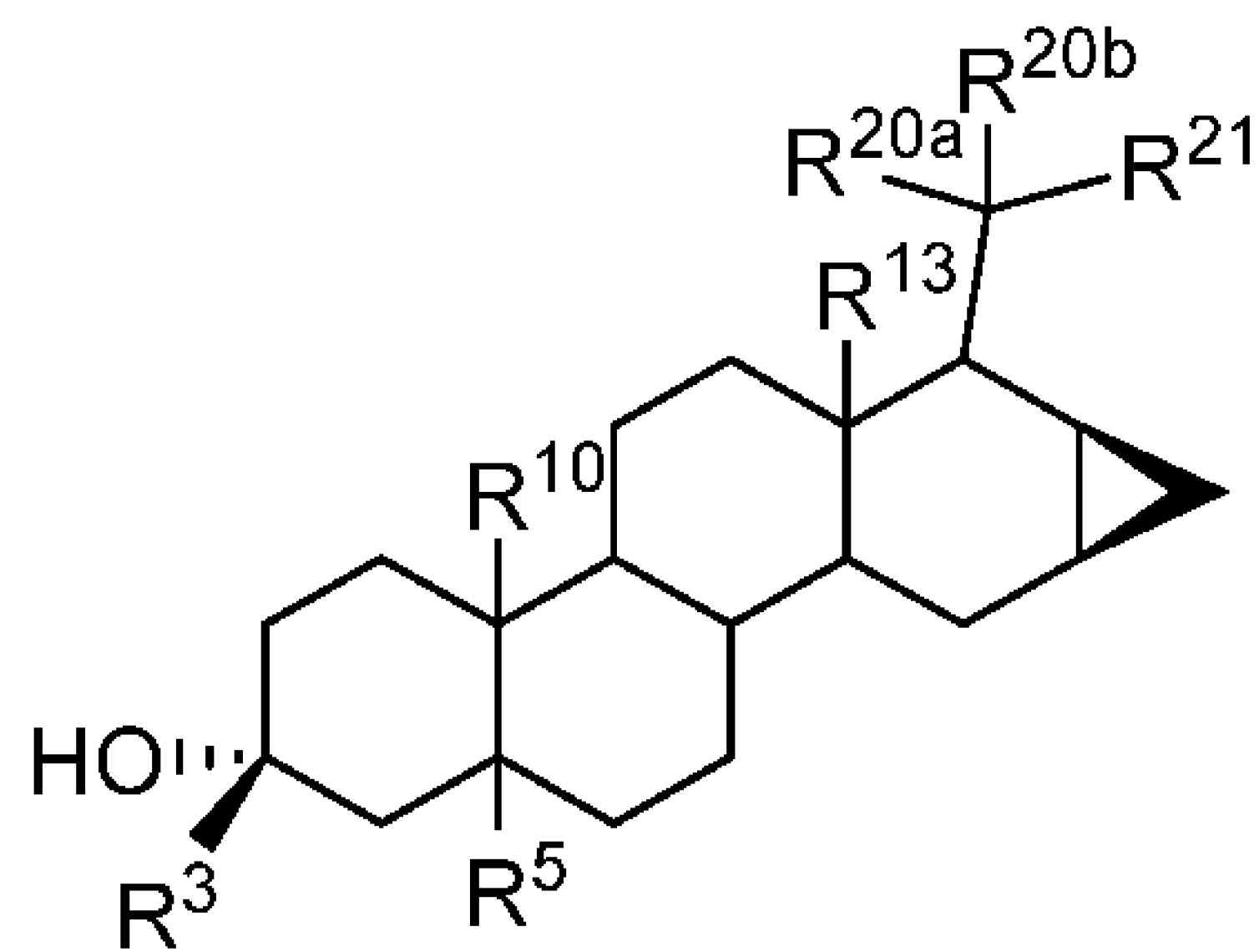
Each of R^{20a} and R^{20b} is independently selected from -H, -OH, and methyl, or R^{20a} and R^{20b} taken together form oxo;

R²¹ is -L^A-R³⁰,

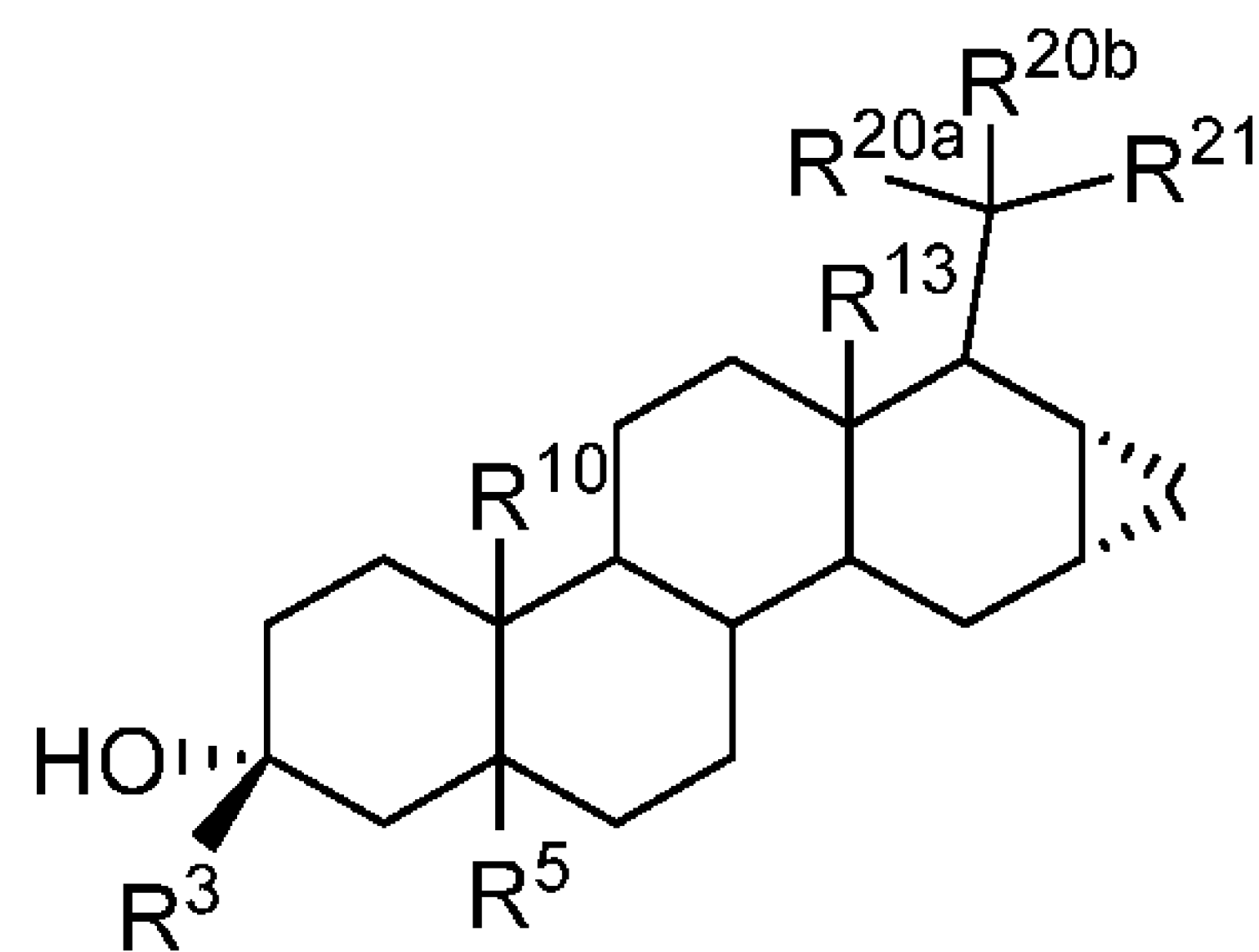
L^A is a bond, -NH-, or -CH₂-;

R³⁰ is independently selected from methyl, pyrazolyl, tetrazolyl, and pyridyl, each of which is optionally substituted with halo, C₁₋₆ alkyl, or cyano.

48. The compound or pharmaceutically acceptable salt of claim 44 or claim 45, wherein the compound of Formula (III-A) is a compound of Formula (III-A1) or (III-A2)



(III-A1)

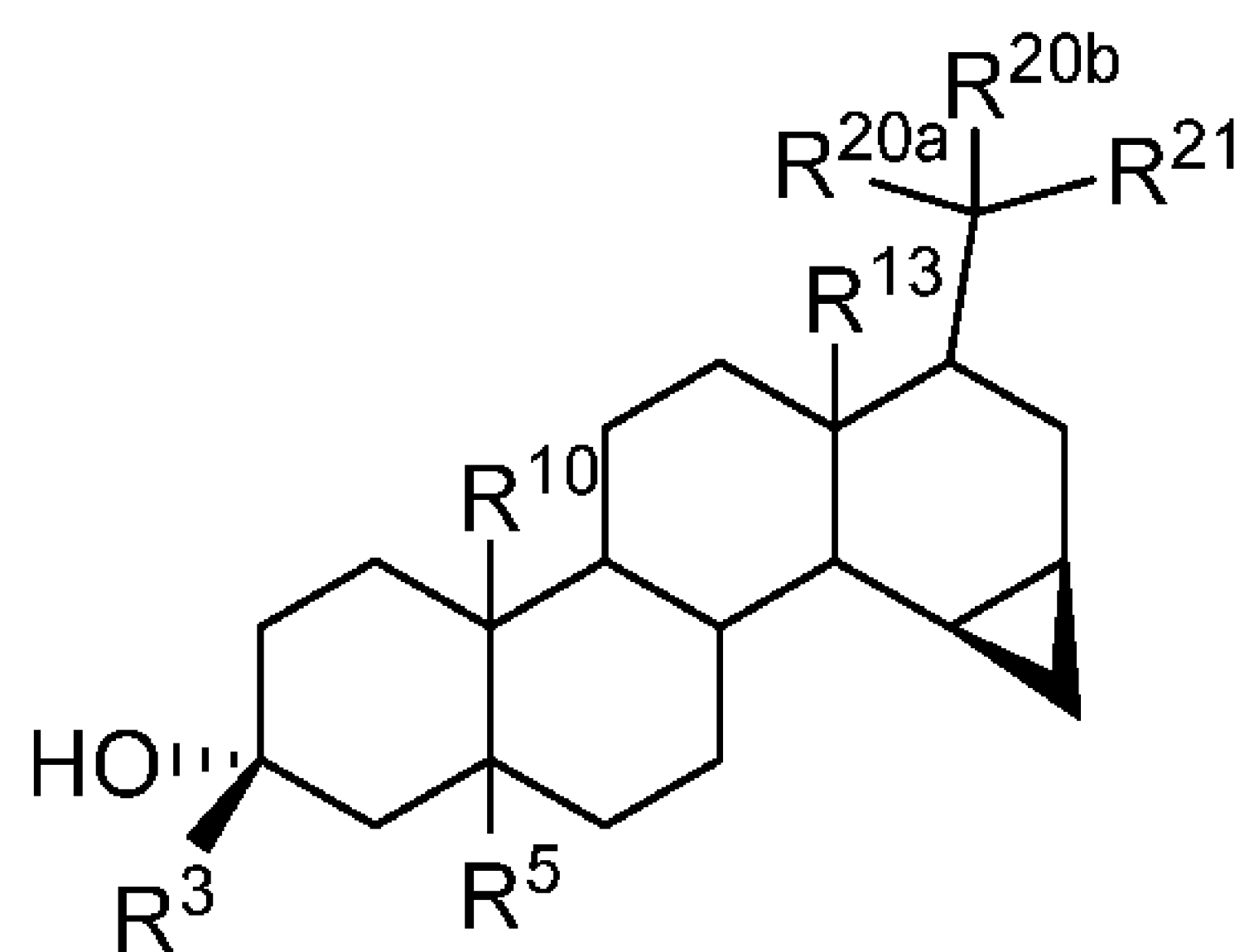


(III-A2)

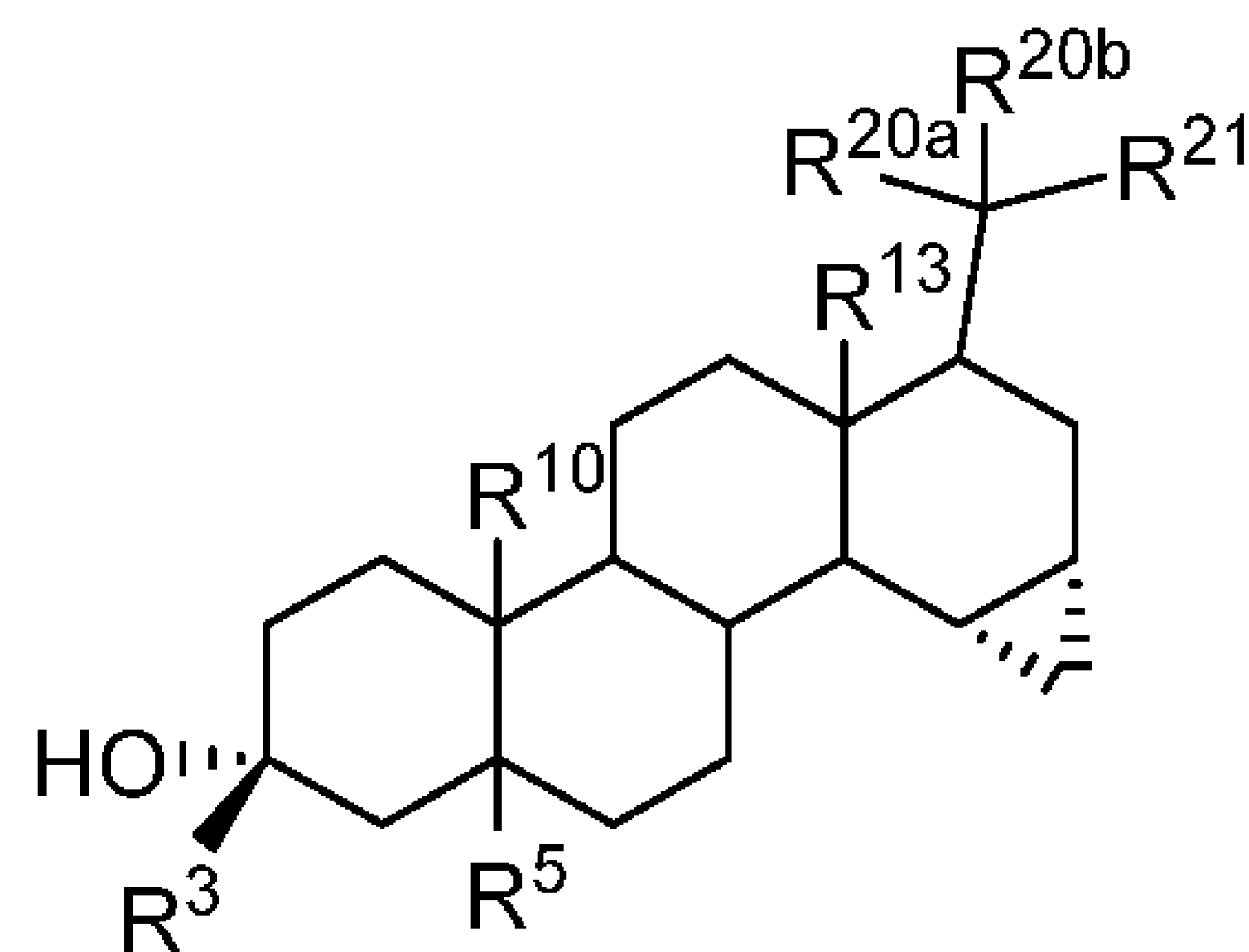
or

or a pharmaceutically acceptable salt thereof.

49. The compound or pharmaceutically acceptable salt of claim 44 or claim 45, wherein the compound of Formula **(III-B)** is a compound of Formula **(III-B1)** or **(III-B2)**

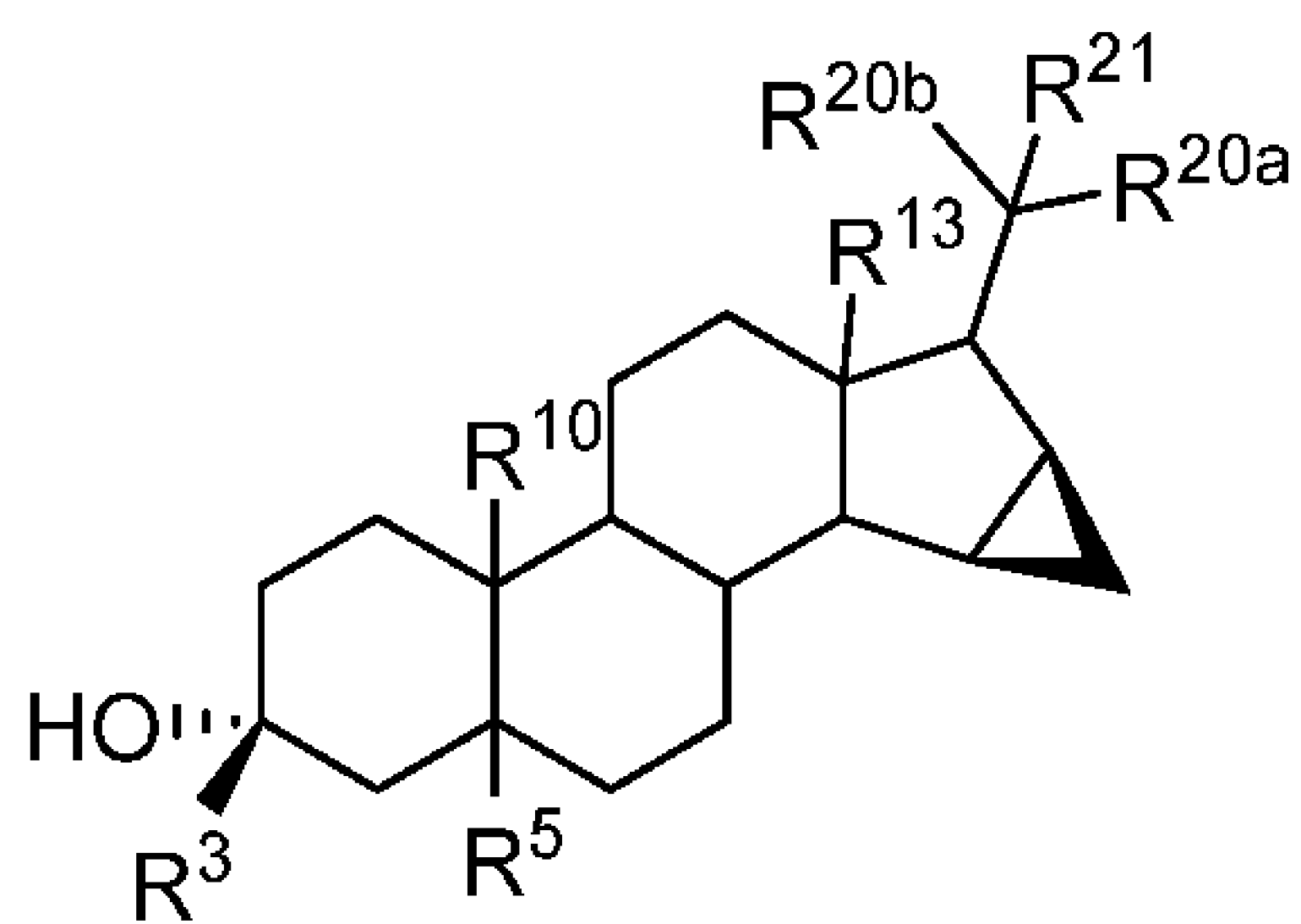
**(III-B1)**

or

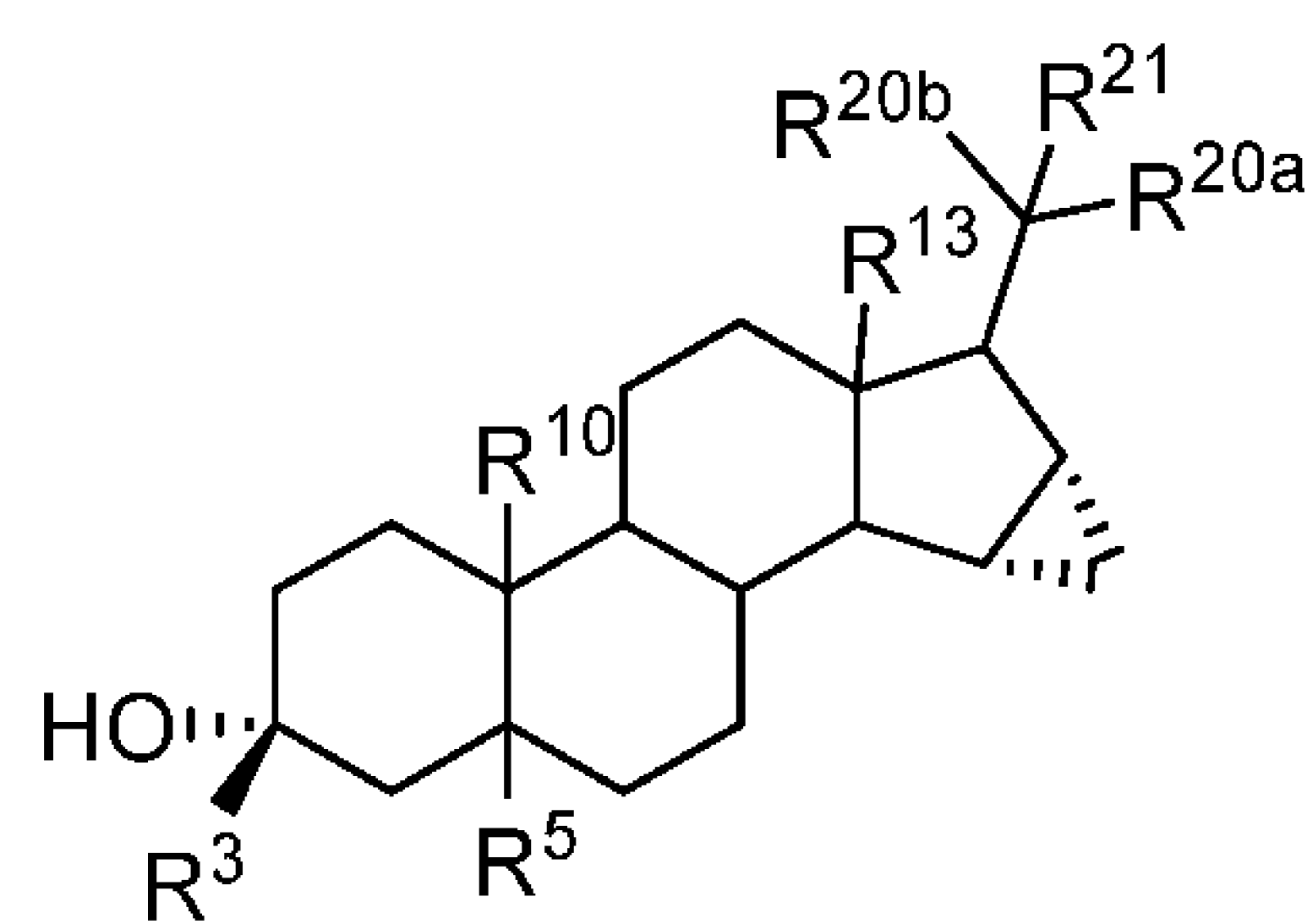
**(III-B2)**

or a pharmaceutically acceptable salt thereof.

50. The compound or pharmaceutically acceptable salt of claim 46 or claim 47, wherein the compound of Formula **(III-C)** is a compound of Formula **(III-C1)** or **(III-C2)**

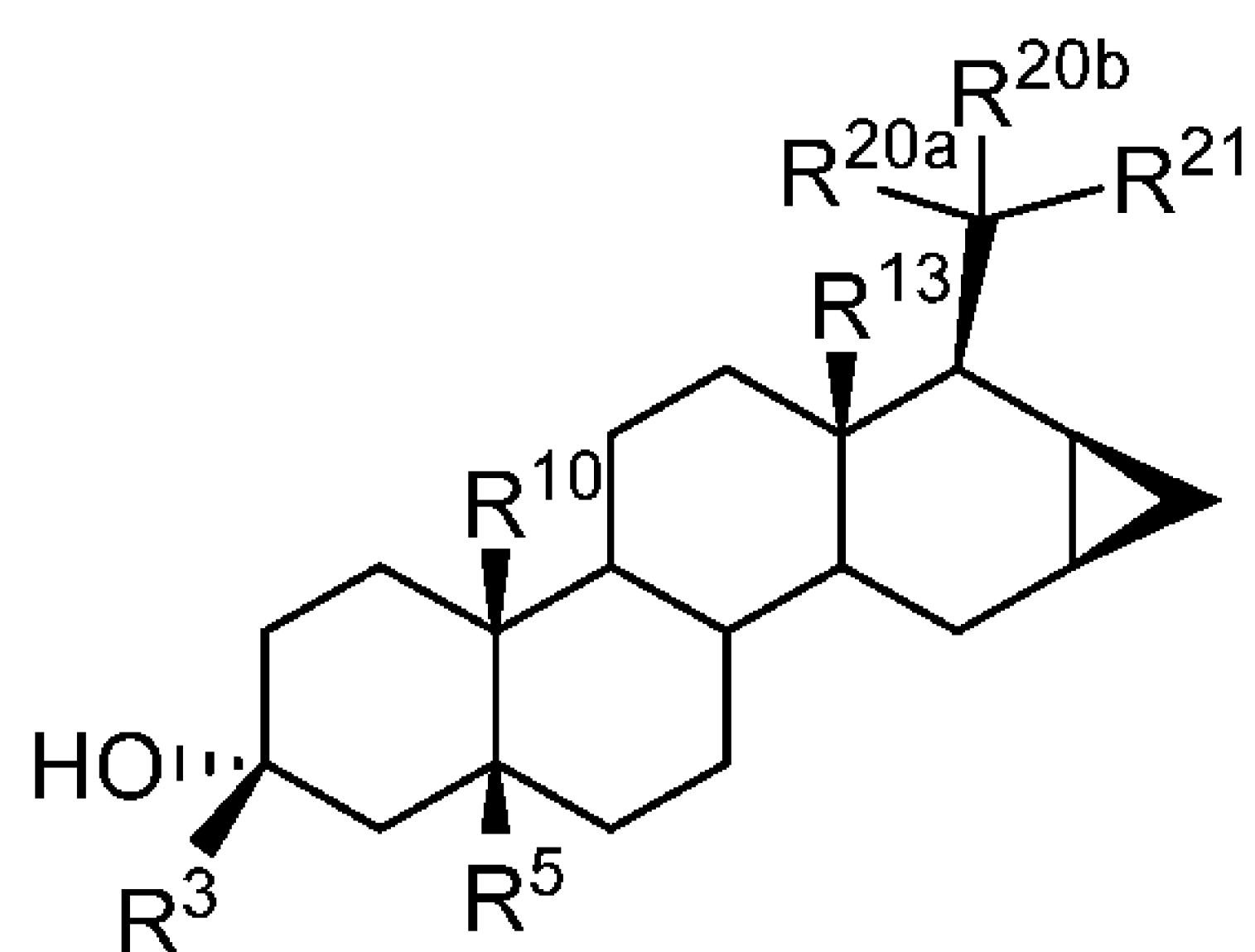
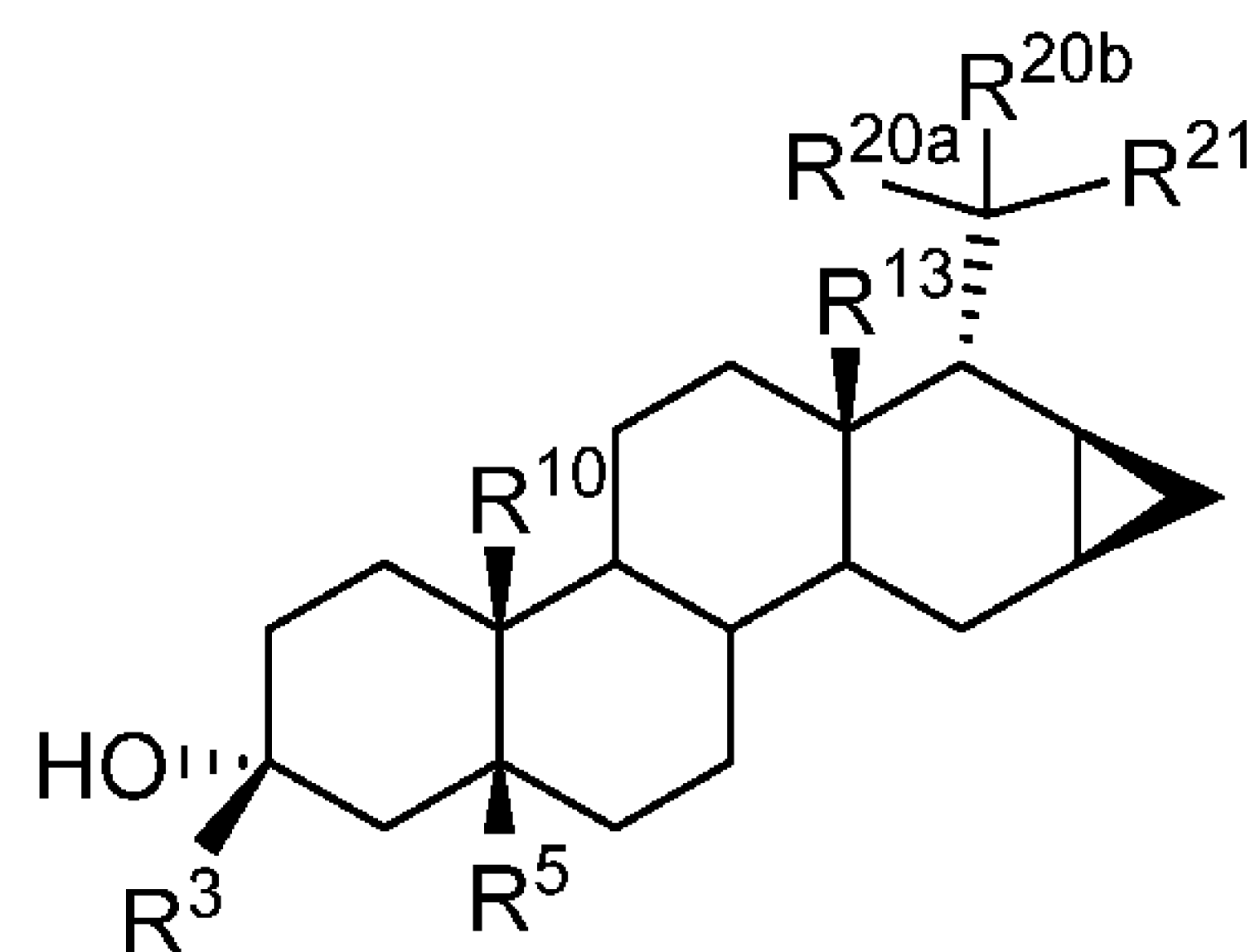
**(III-C1)**

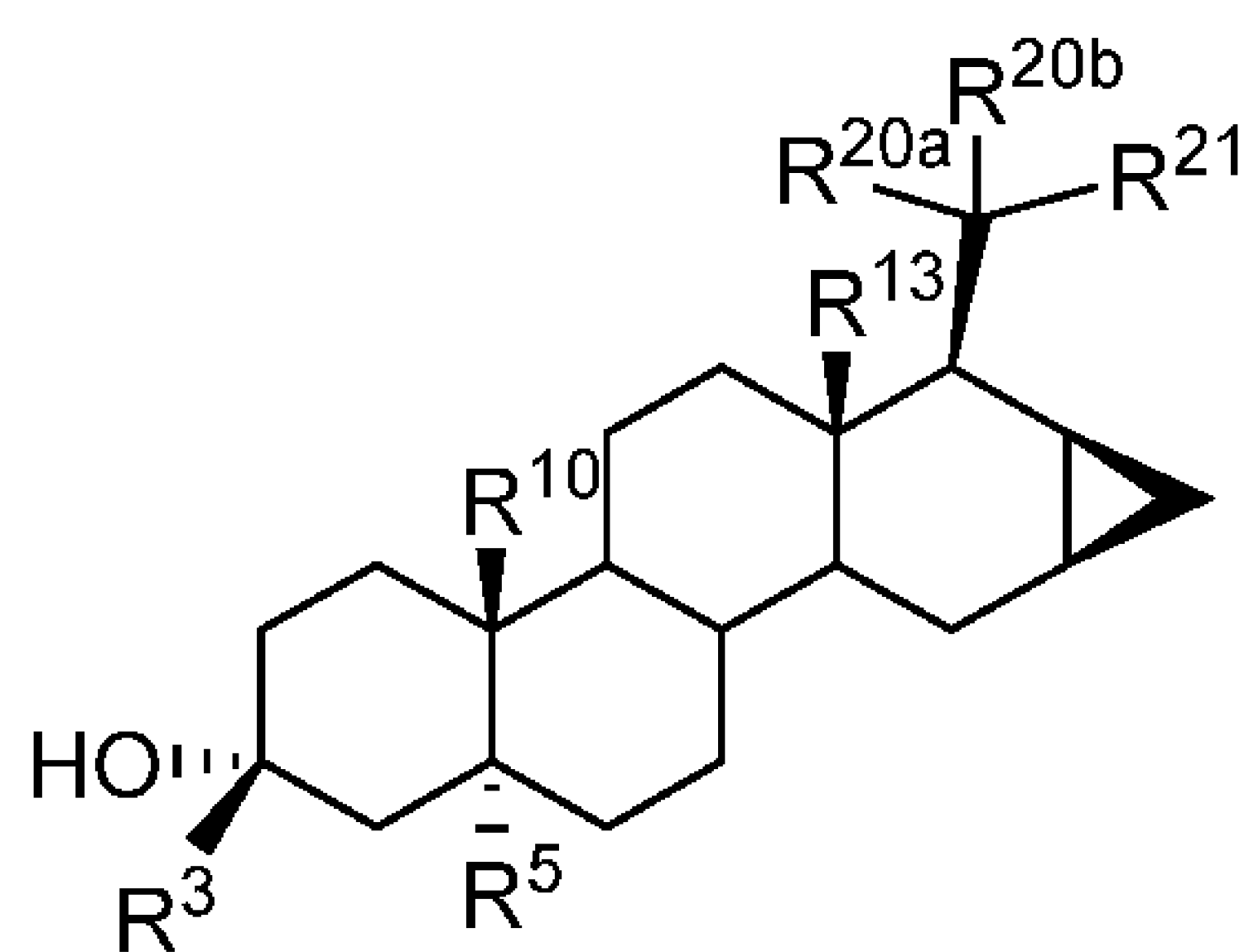
or

**(III-C2)**

or a pharmaceutically acceptable salt thereof.

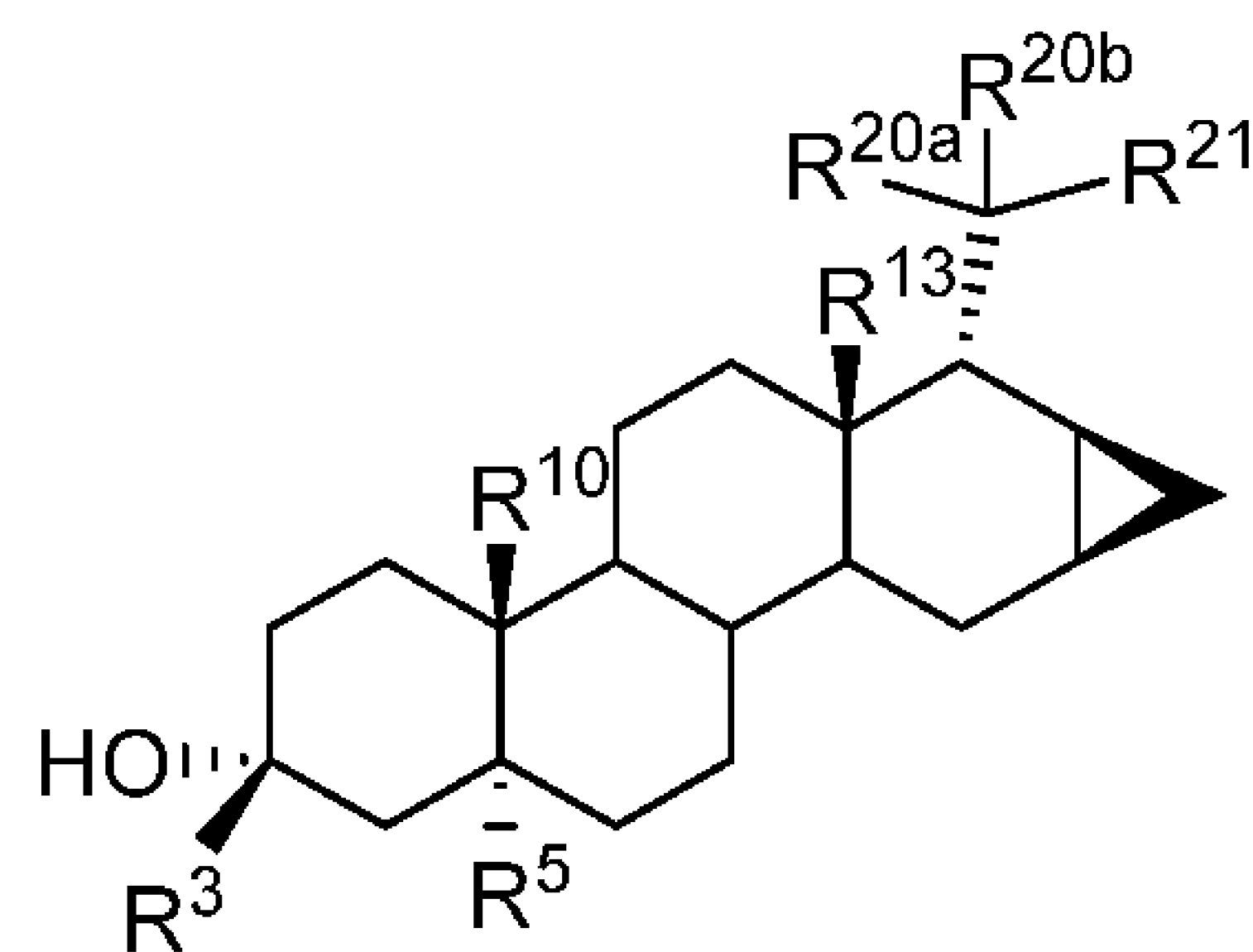
51. The compound or pharmaceutically acceptable salt of claim 48, wherein the compound of Formula **(III-A1)** is a compound of Formula **(III-A1a)**, **(III-A1b)**, **(III-A1c)**, or **(III-A1d)**

**(III-A1a),****(III-A1b),**



(III-A1c),

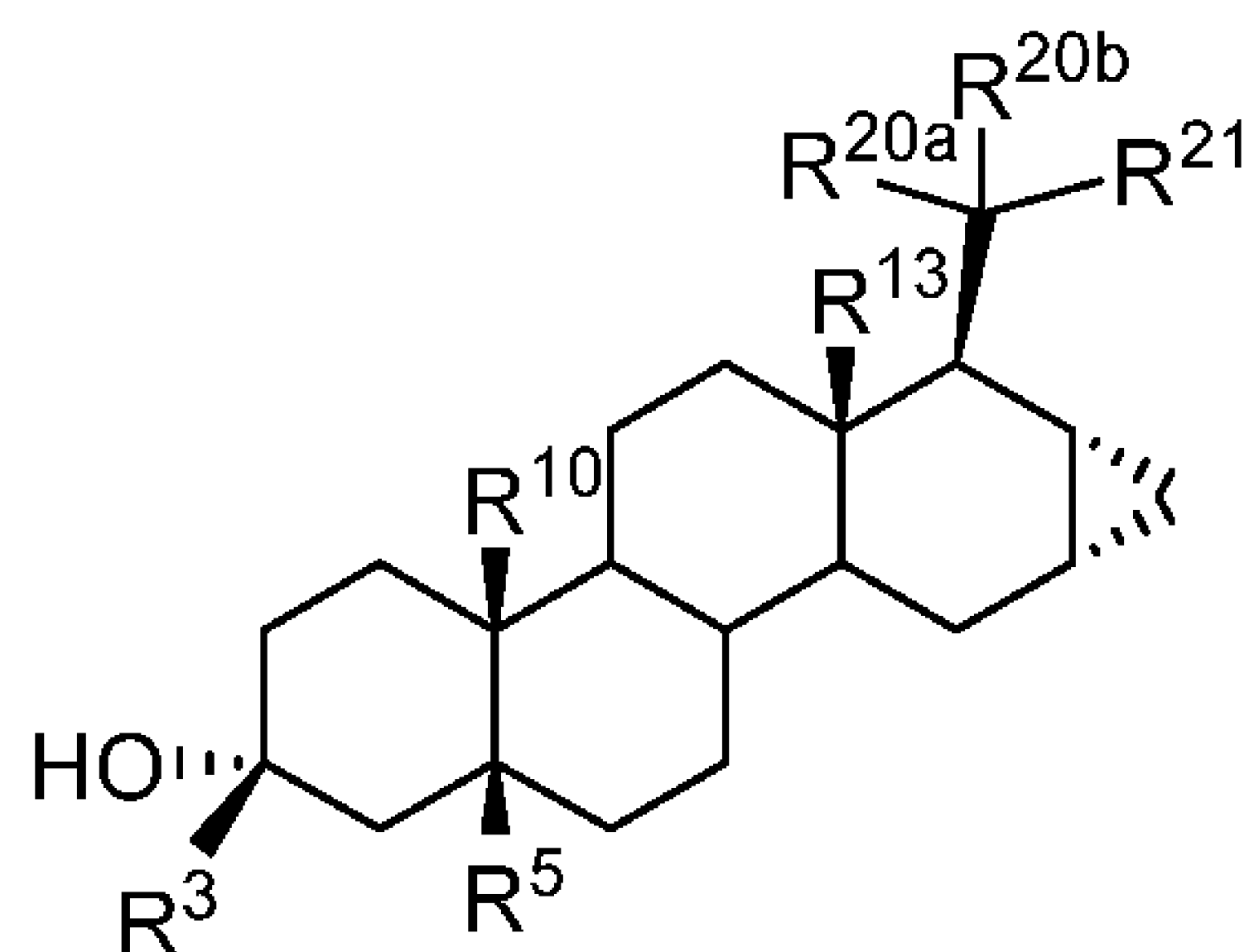
or



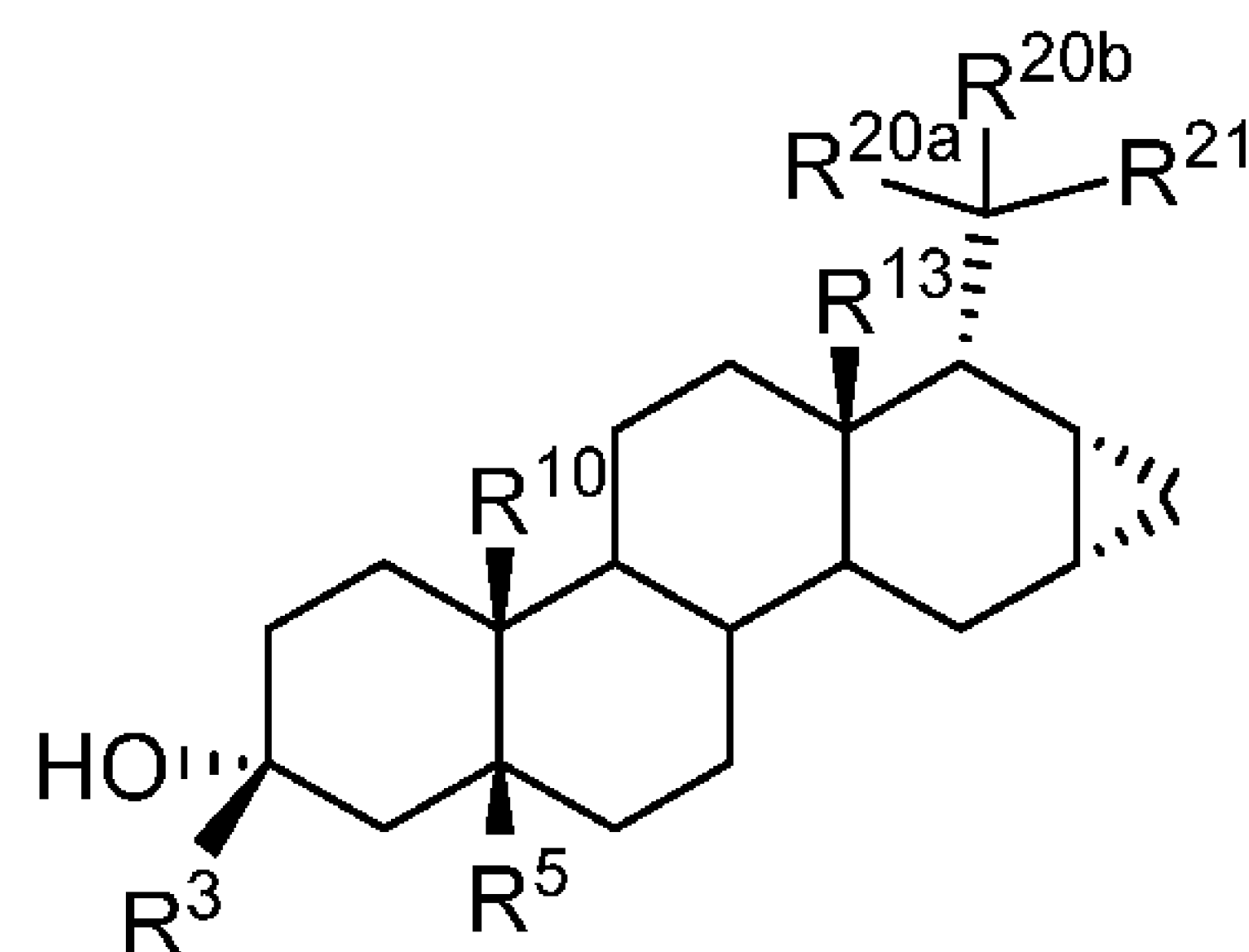
(III-A1d)

or a pharmaceutically acceptable salt thereof.

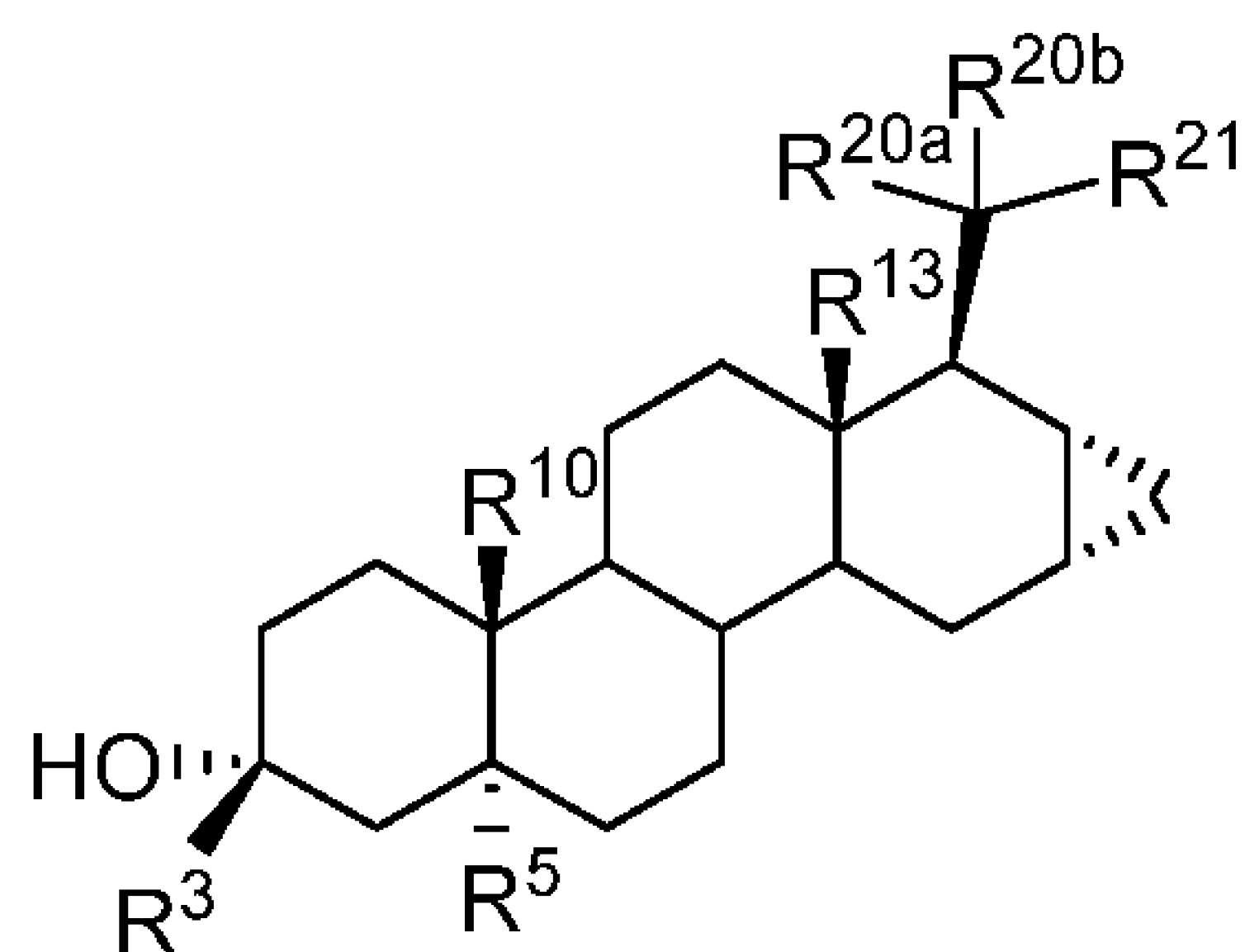
52. The compound or pharmaceutically acceptable salt of claim 48, wherein the compound of Formula (III-A2) is a compound of Formula (III-A2a), (III-A2b), (III-A2c) or (III-A2d)



(III-A2a),

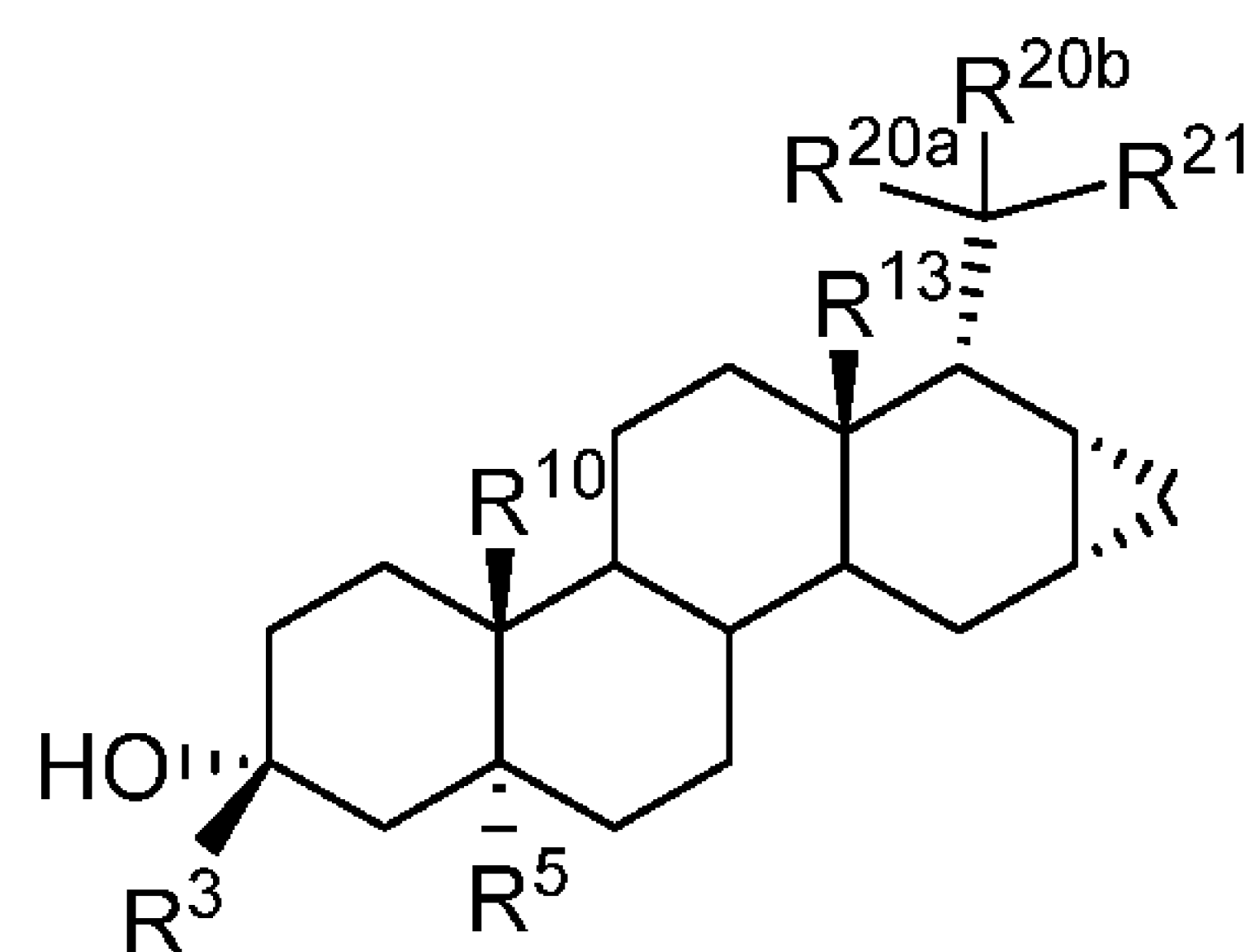


(III-A2b),



(III-A2c),

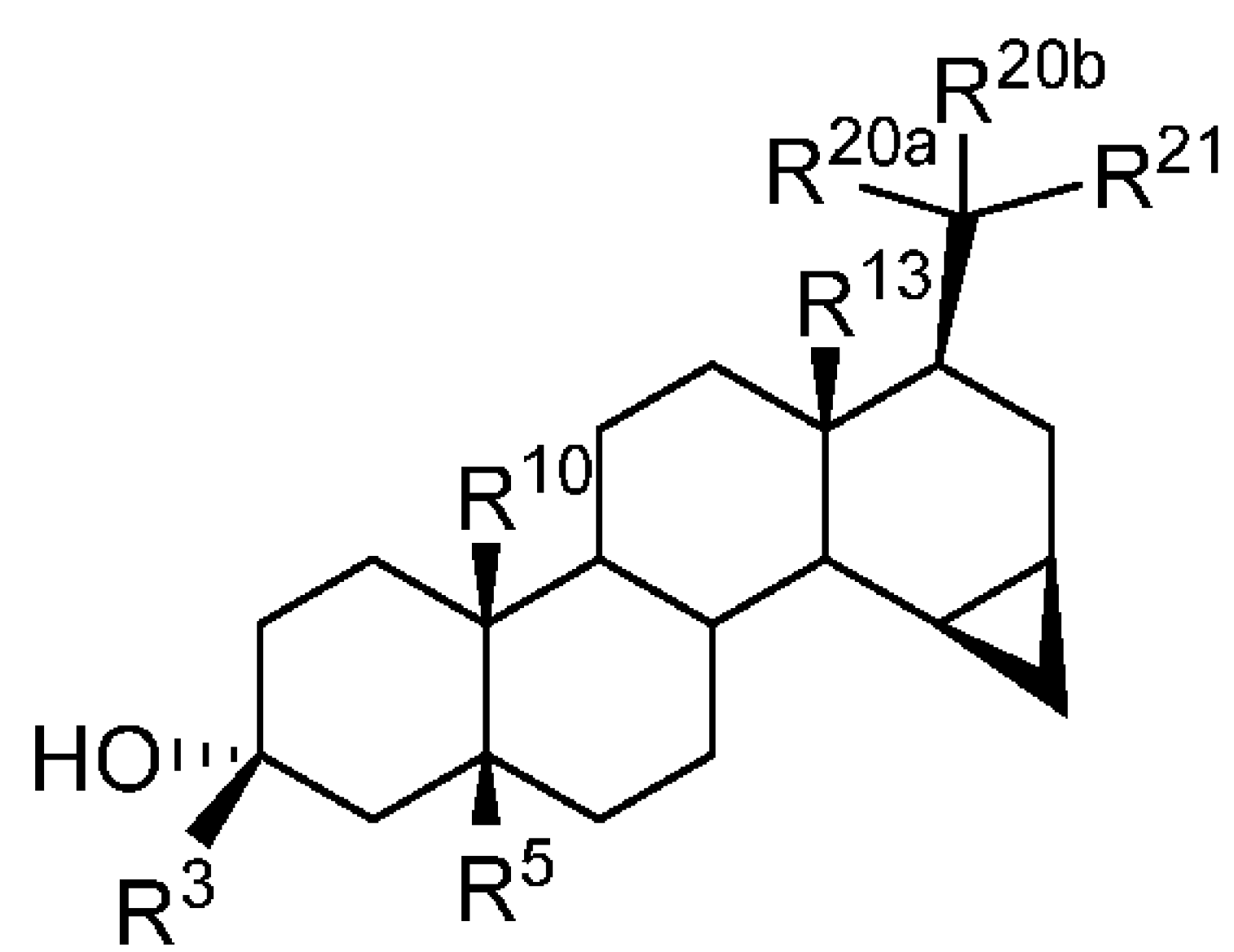
or



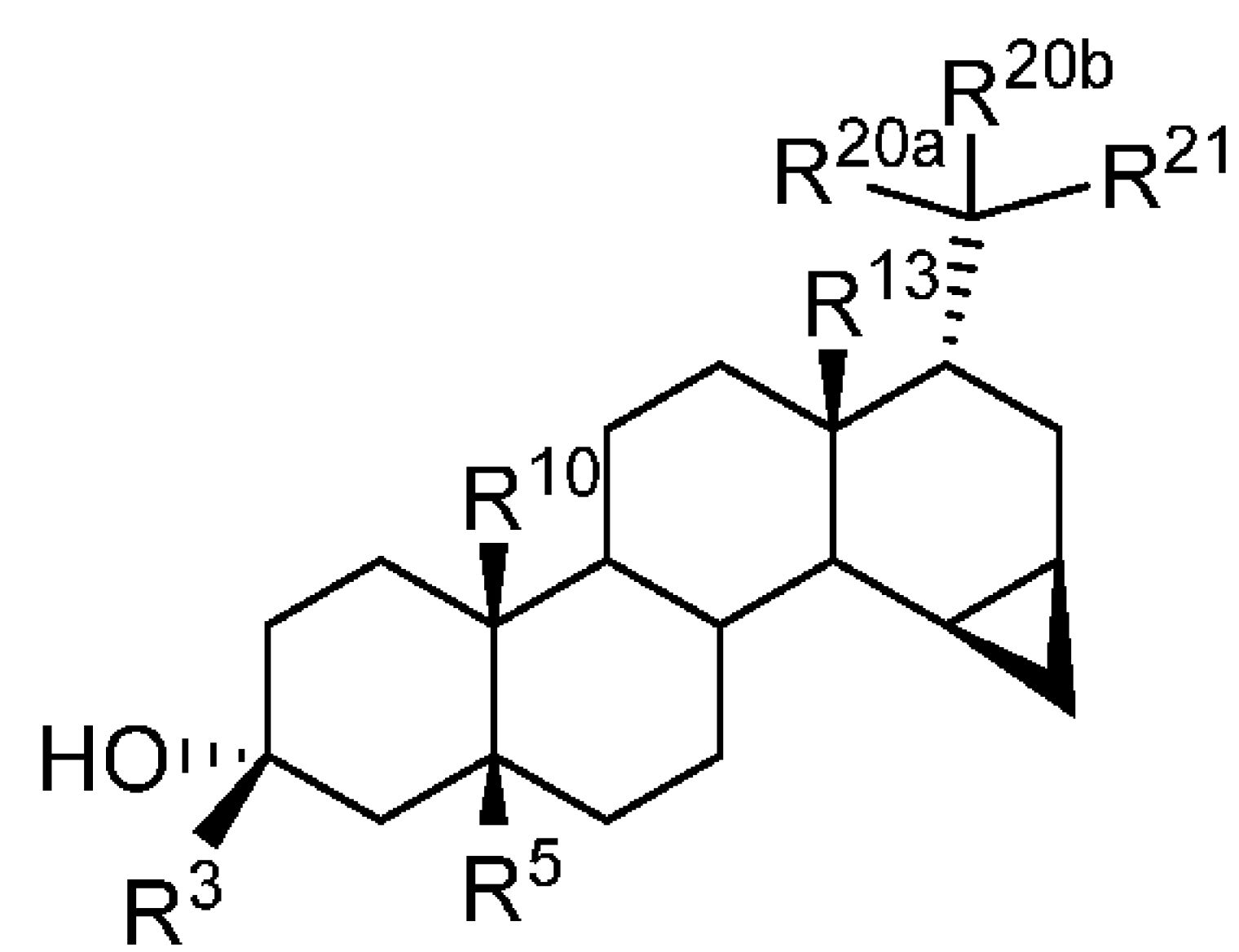
(III-A2d)

or a pharmaceutically acceptable salt thereof.

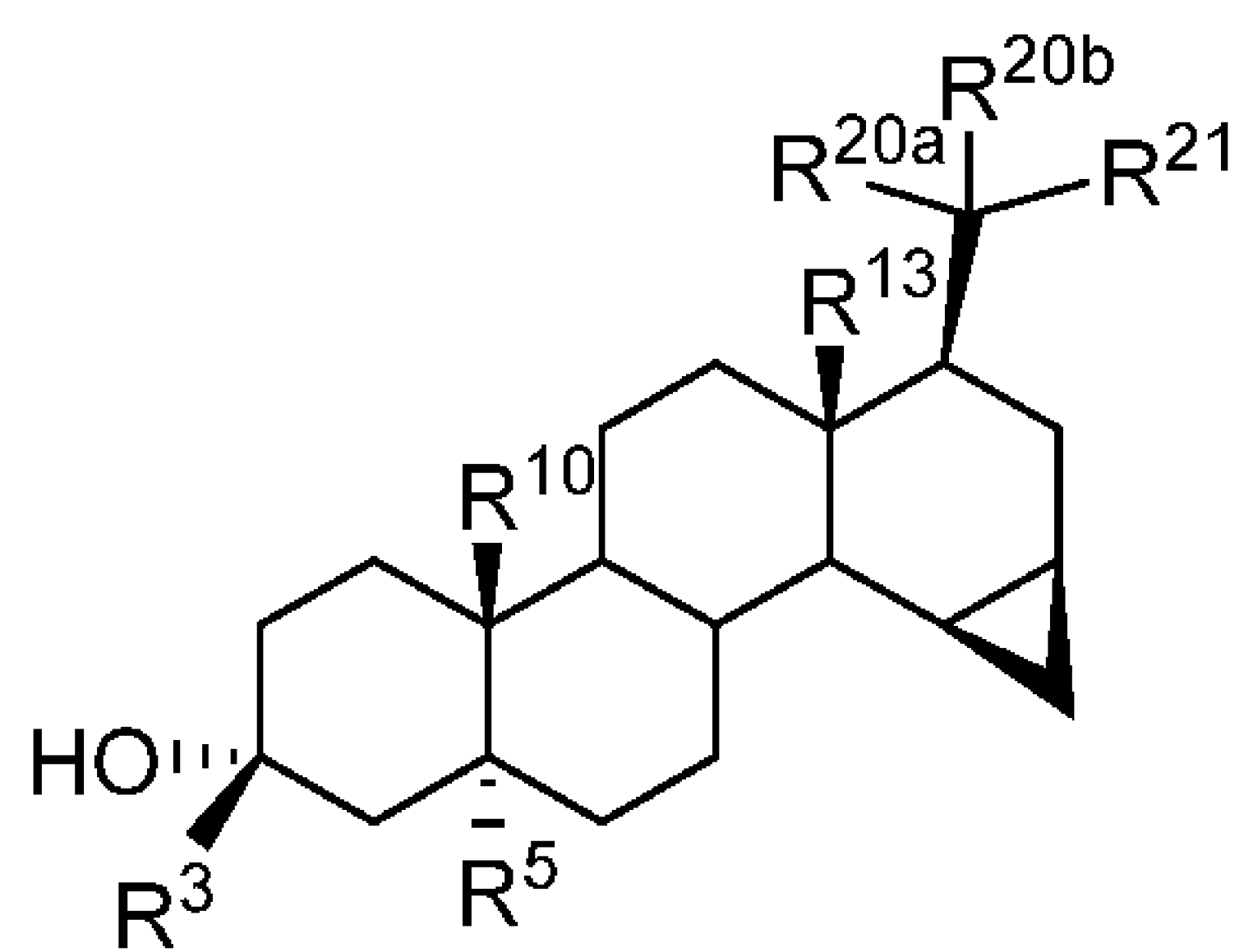
53. The compound or pharmaceutically acceptable salt of claim 49, wherein the compound of Formula (III-B1) is a compound of Formula (III-B1a), (III-B1b), (III-B1c), or (III-B1d)



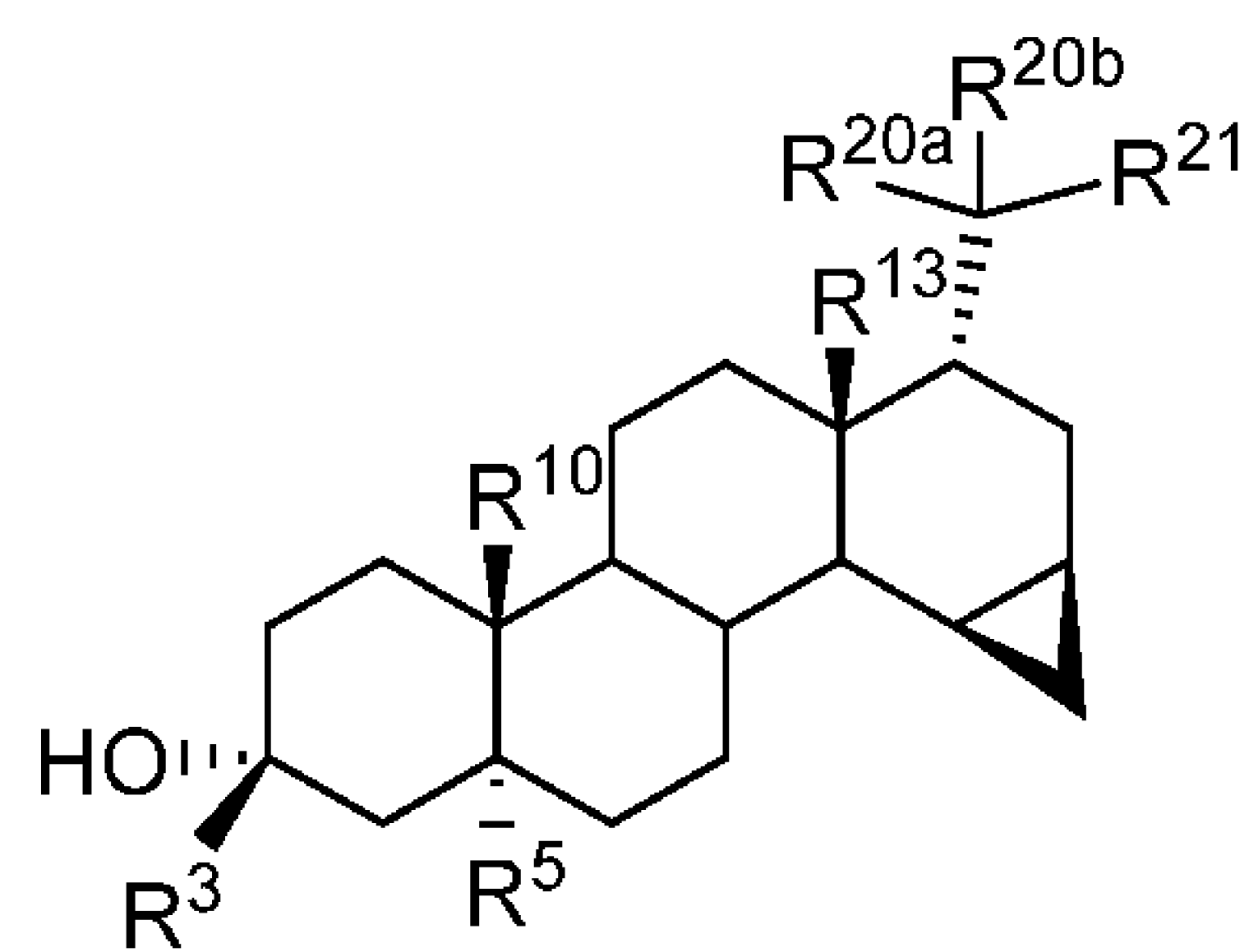
(III-B1a),



(III-B1b),



(III-B1c)

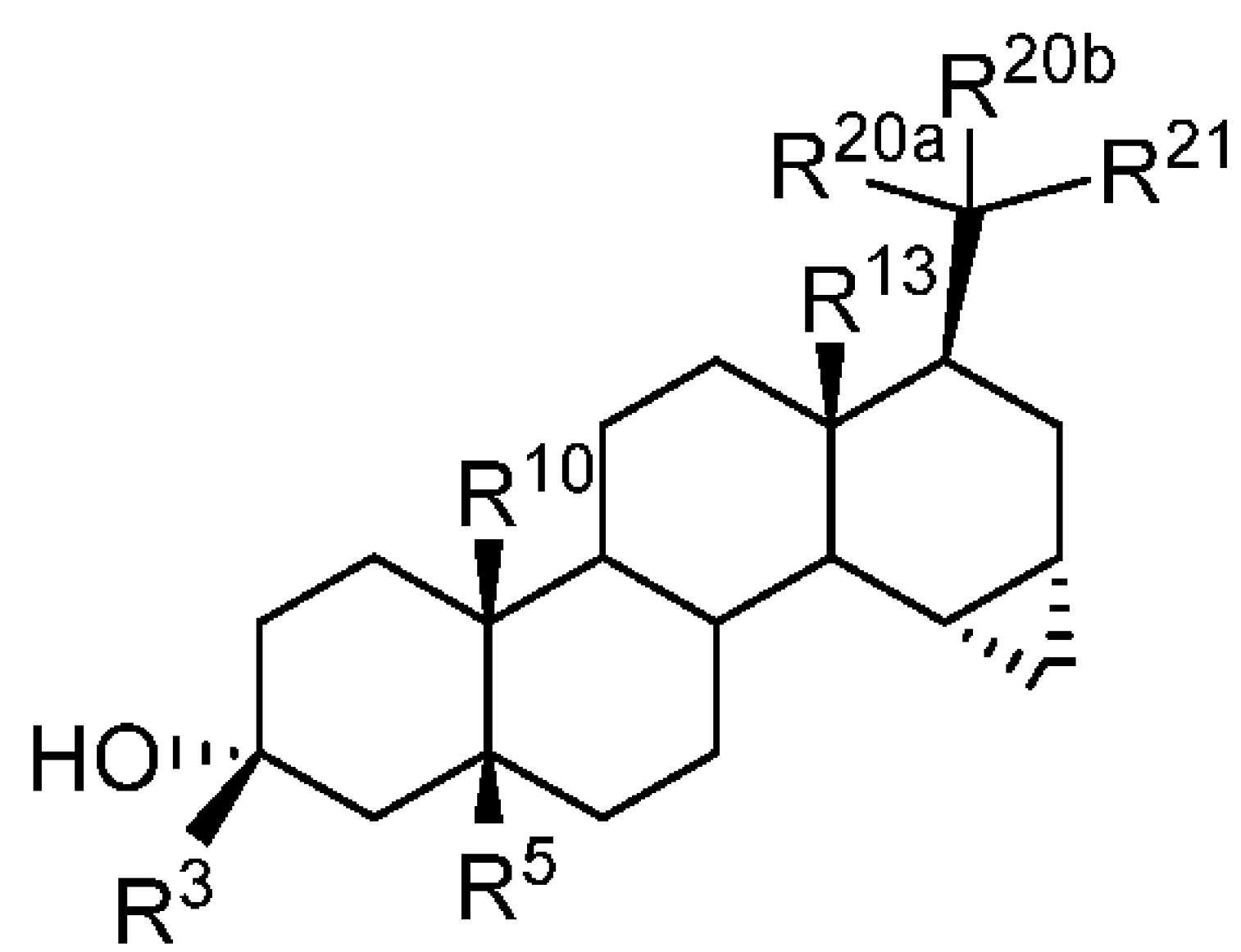


(III-B1d)

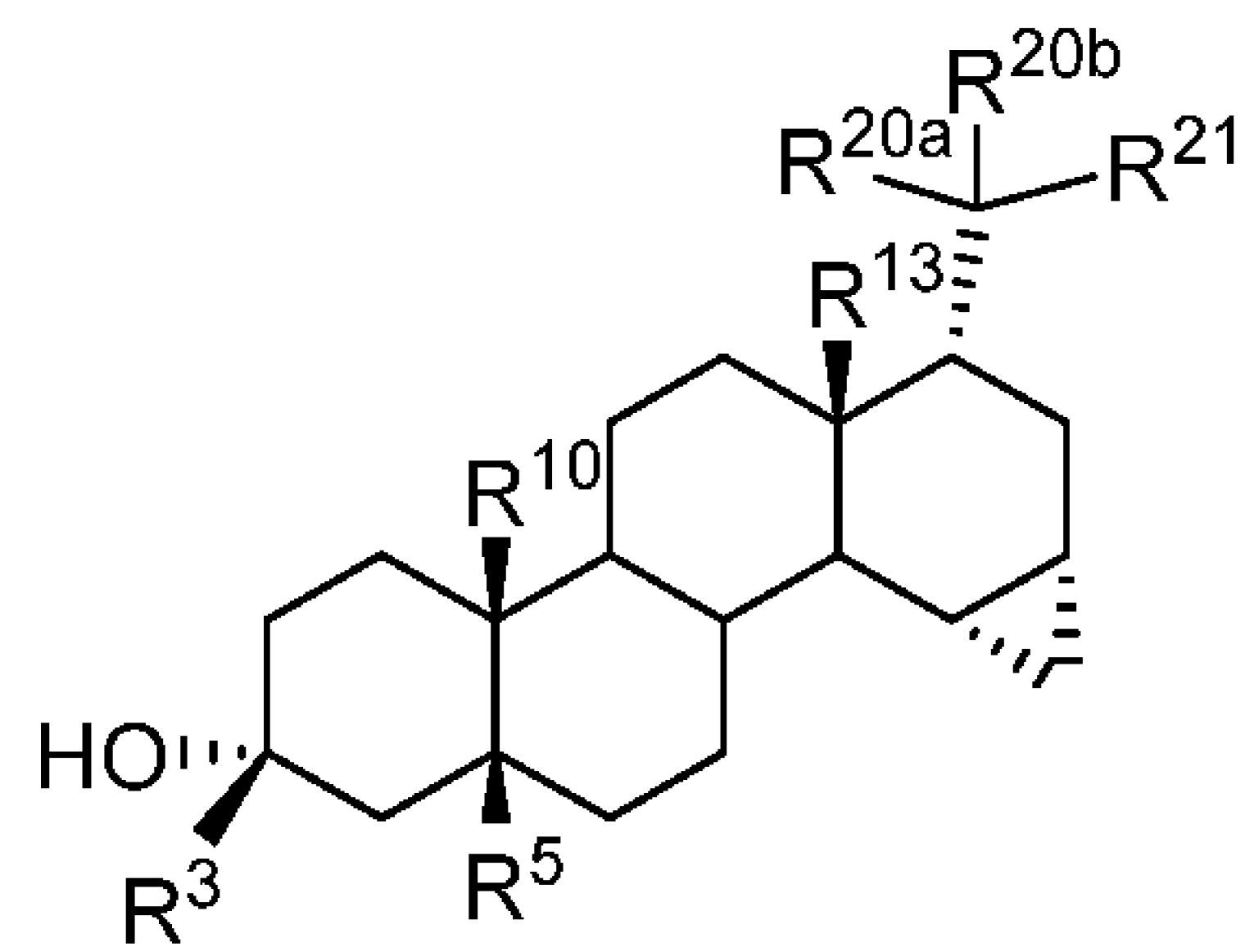
or

or a pharmaceutically acceptable salt thereof.

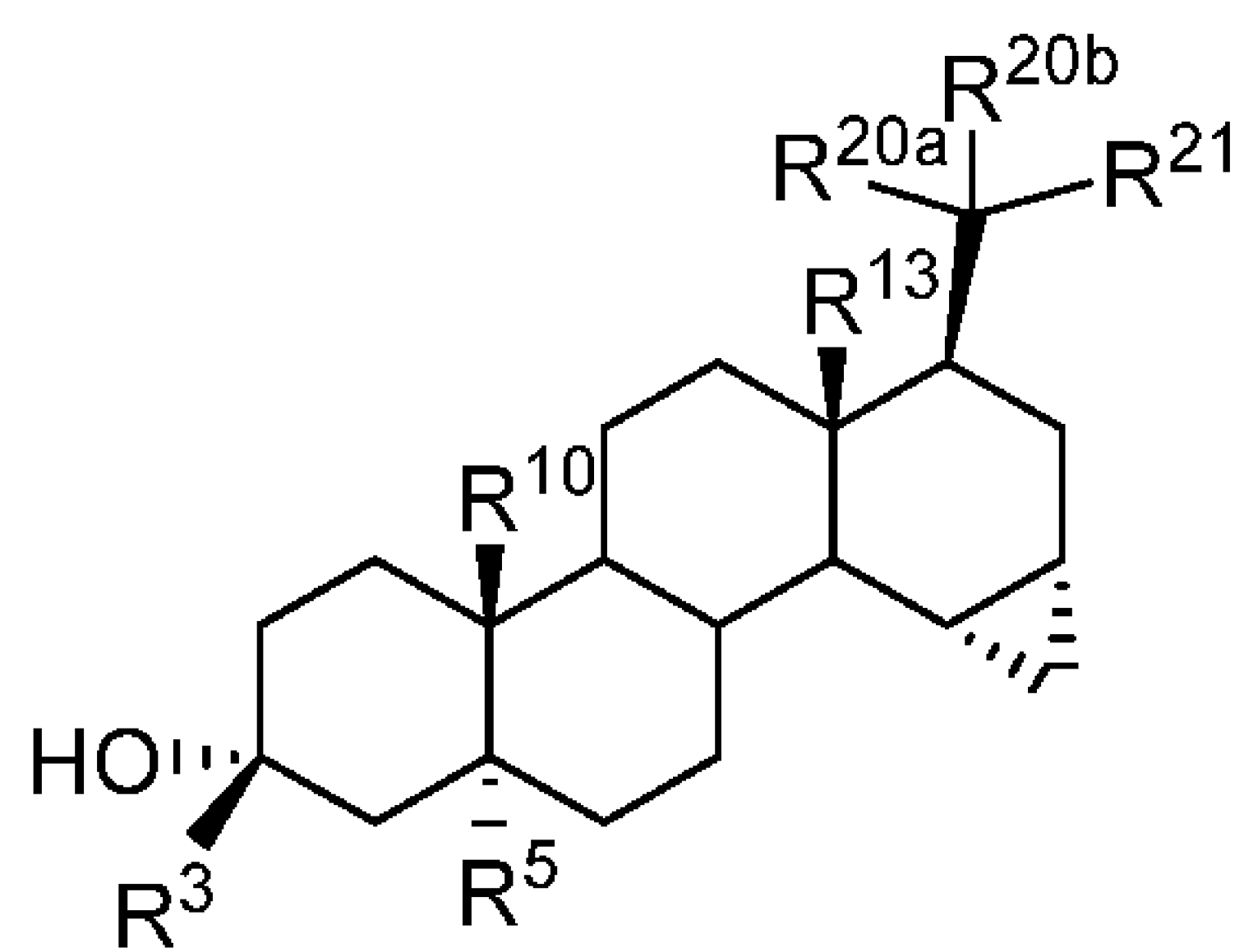
54. The compound or pharmaceutically acceptable salt of claim 49, wherein the compound of Formula (III-B2) is a compound of Formula (III-B2a), (III-B2b), (III-B2c) or (III-B2d)



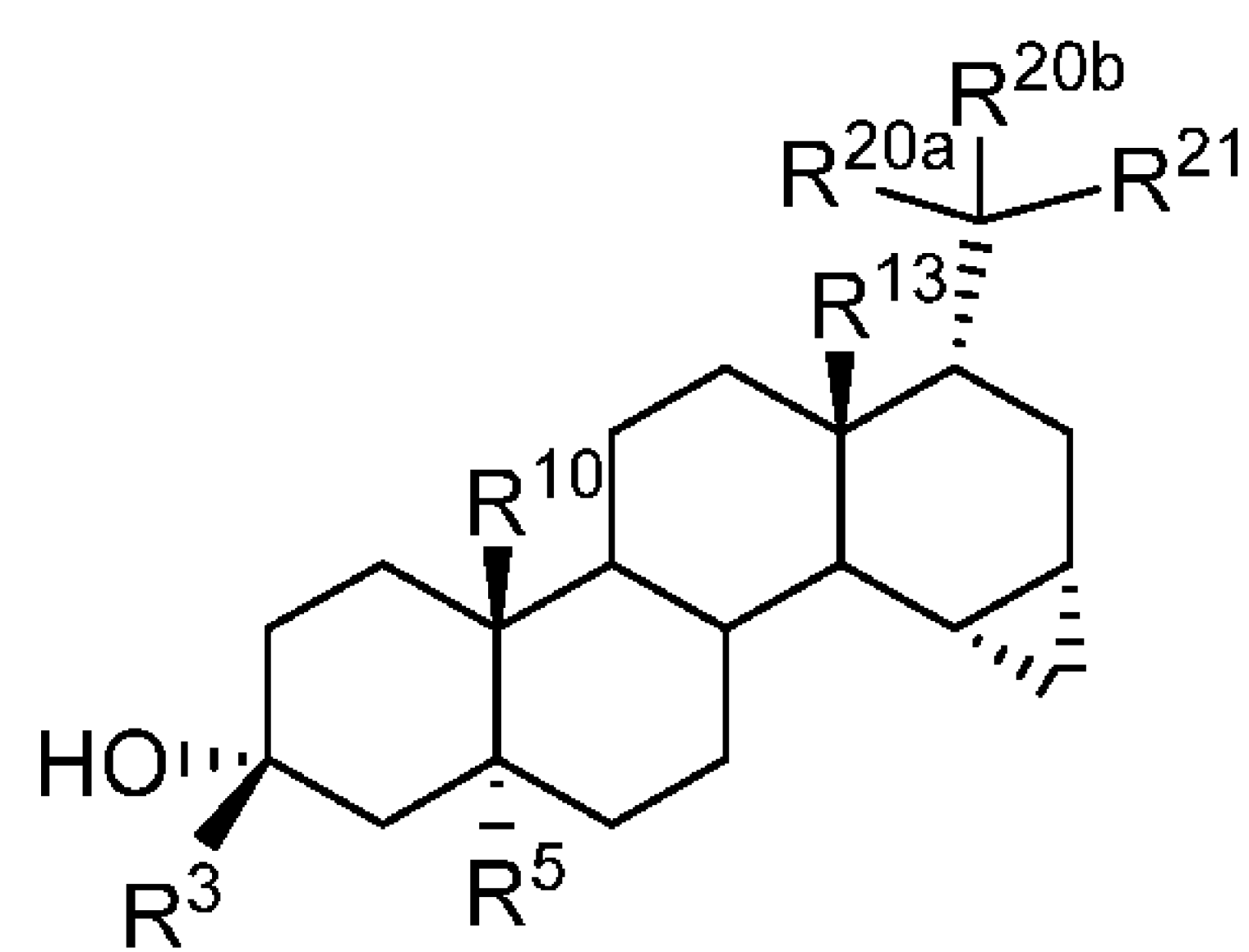
(III-B2a),



(III-B2b),



(III-B2c)

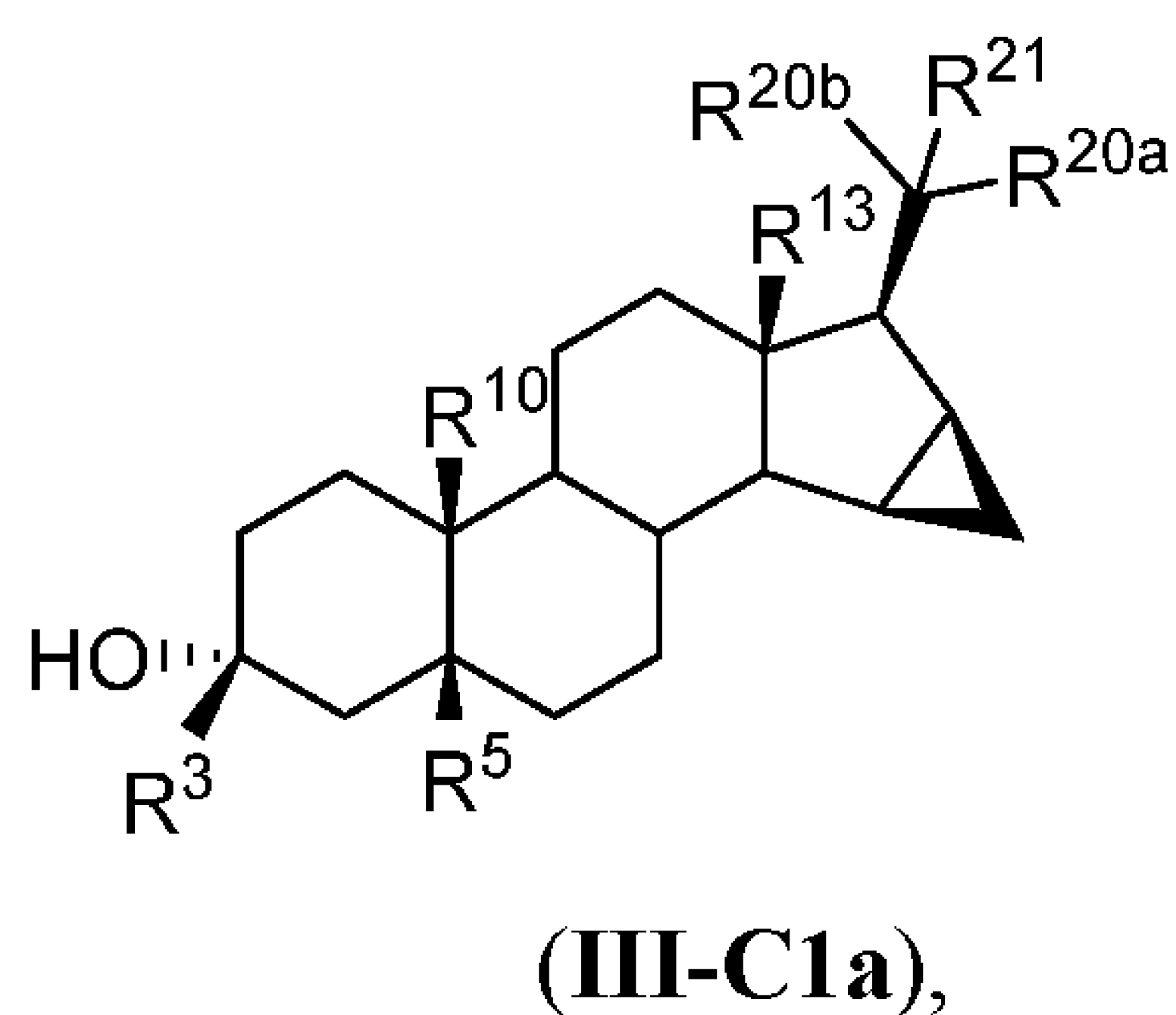
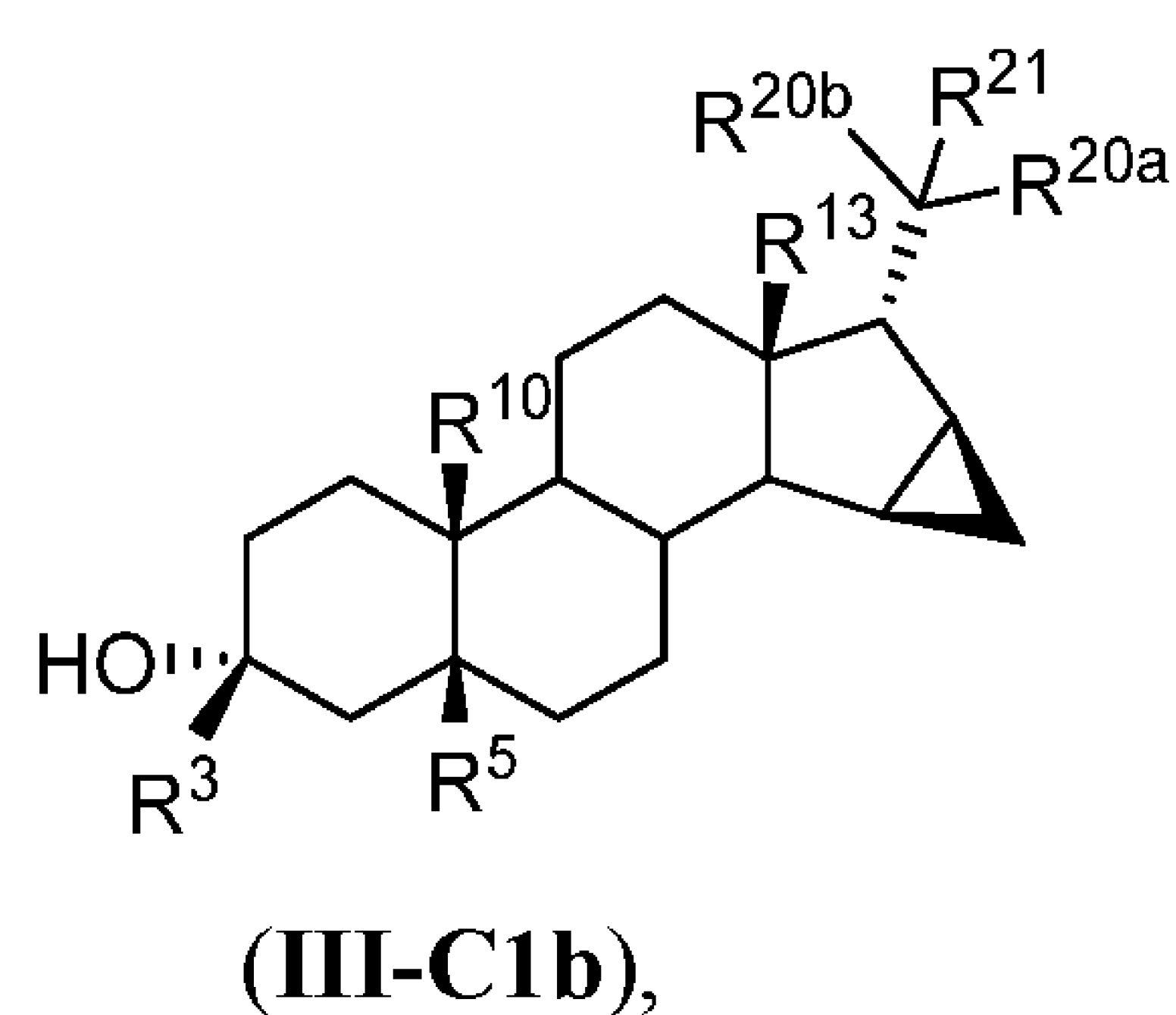
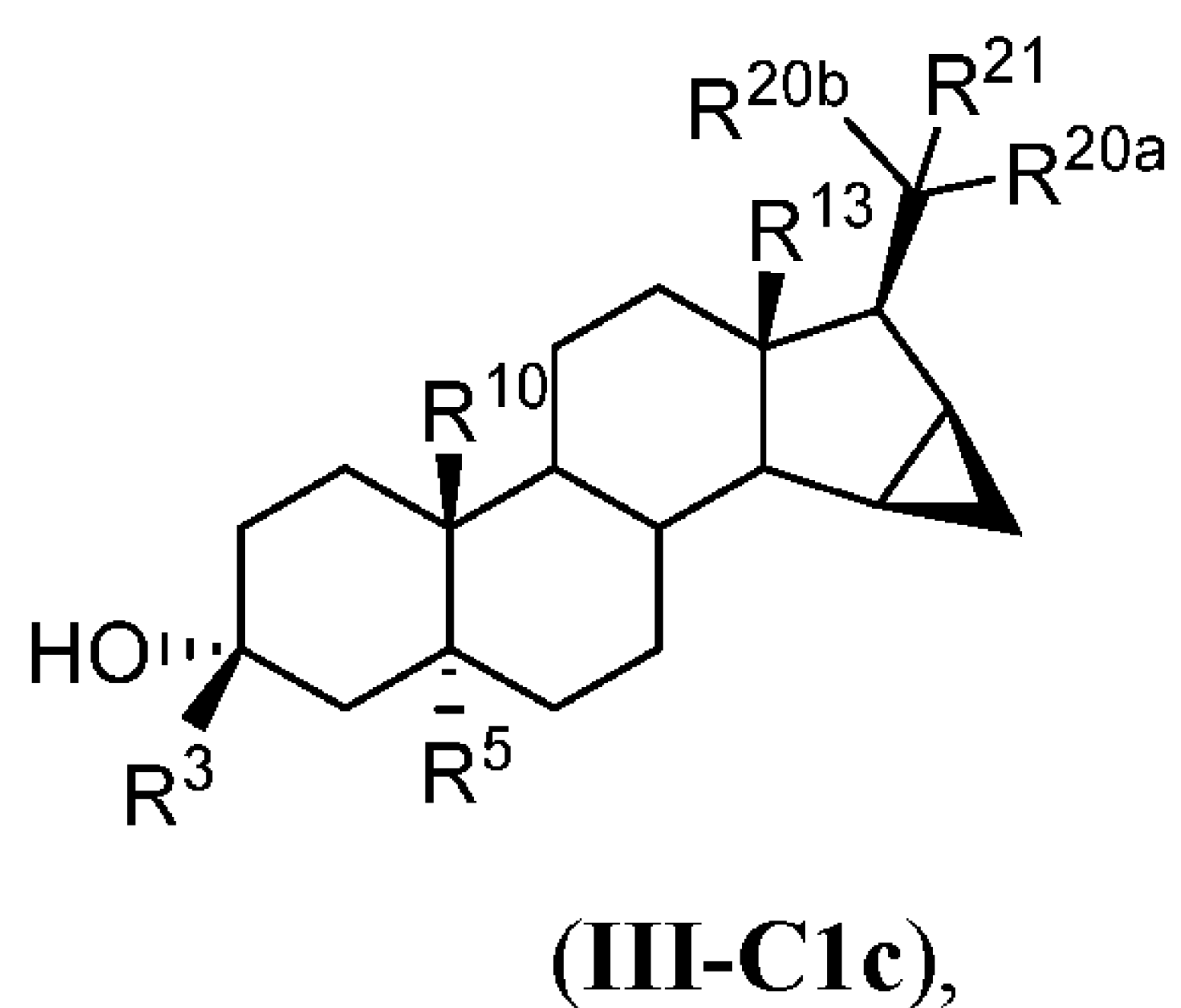


(III-B2d)

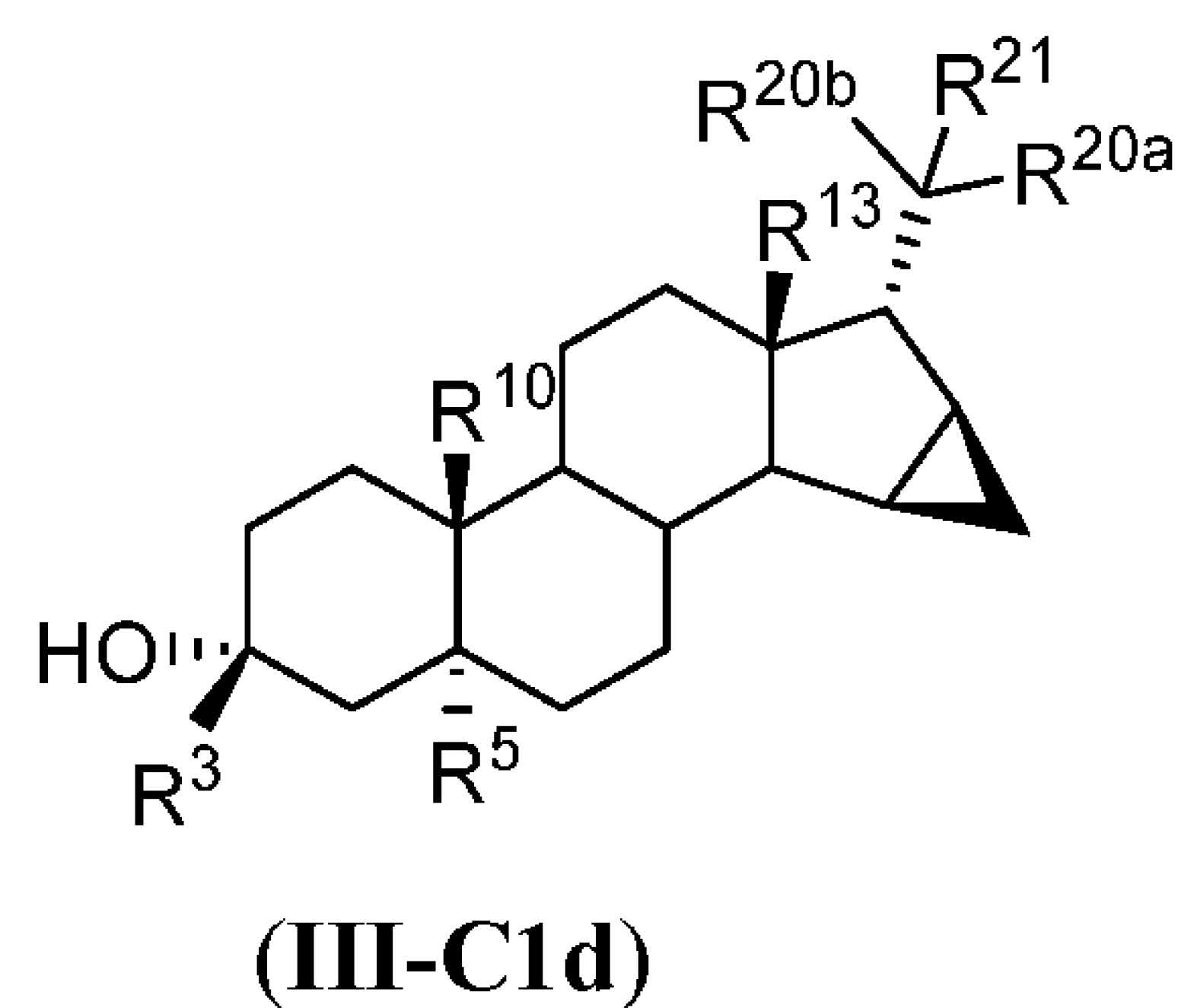
or

or a pharmaceutically acceptable salt thereof.

55. The compound or pharmaceutically acceptable salt of claim 50, wherein the compound of Formula (III-C1) is a compound of Formula (III-C1a), (III-C1b), (III-C1c) or (III-C1d)

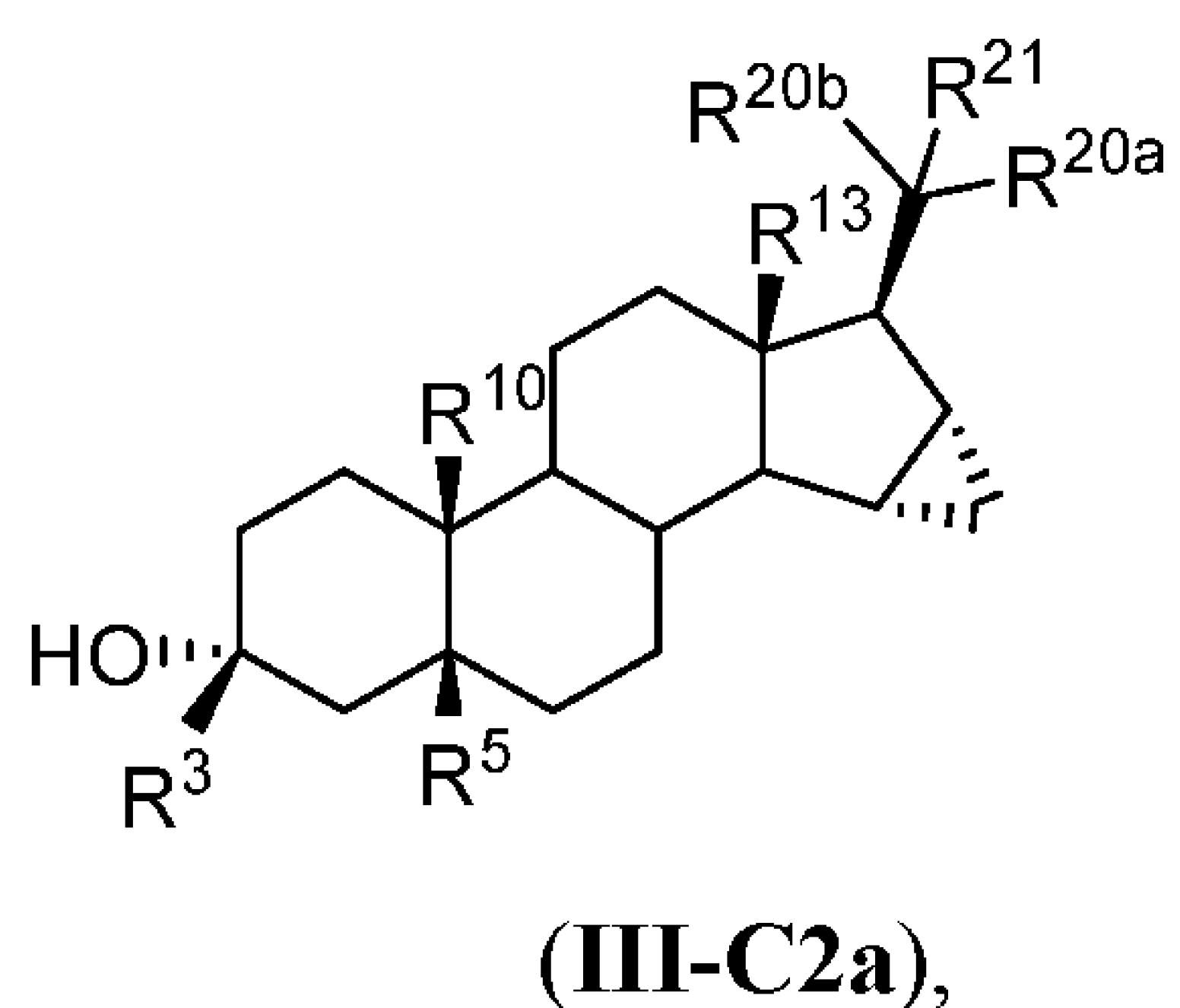
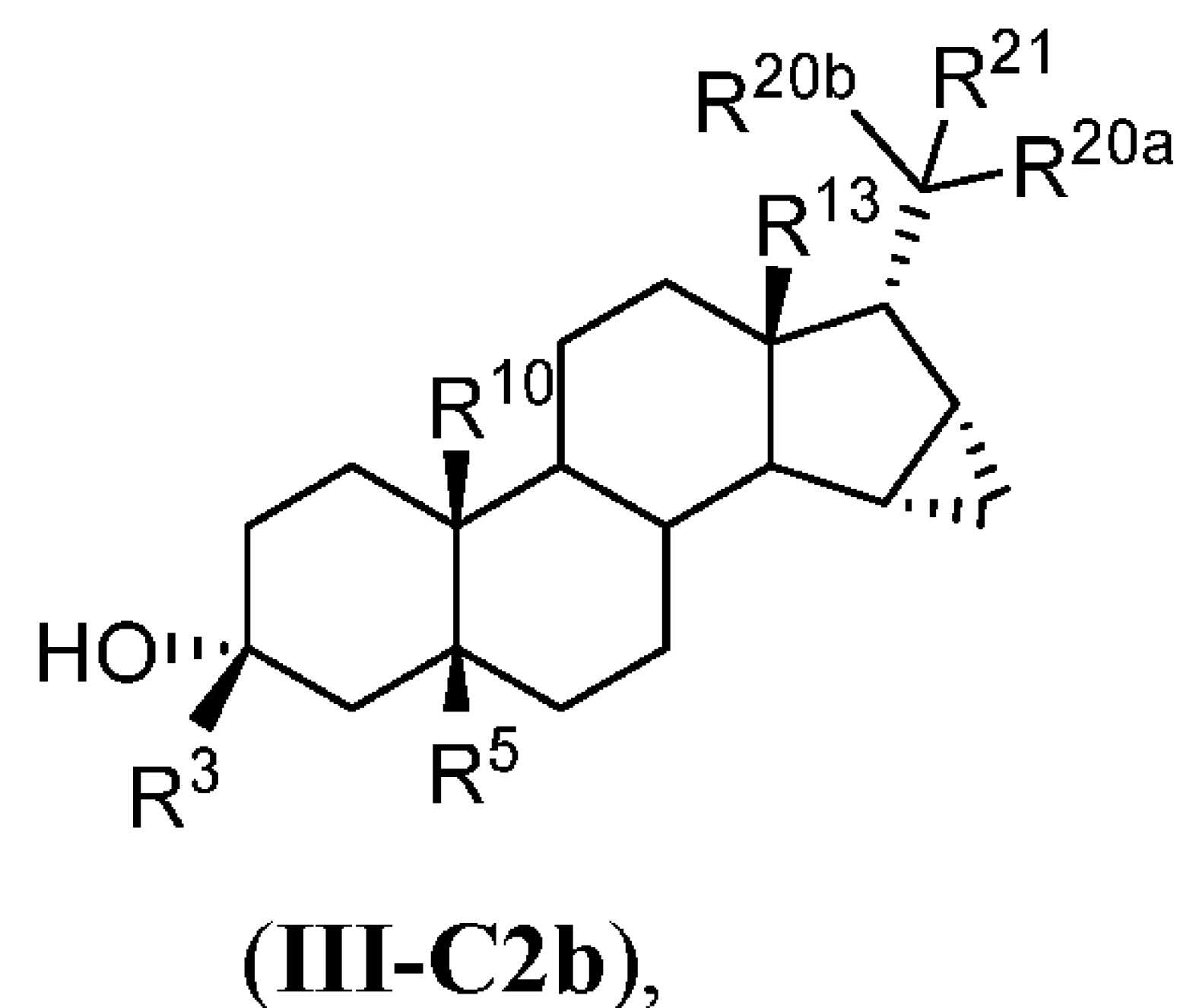
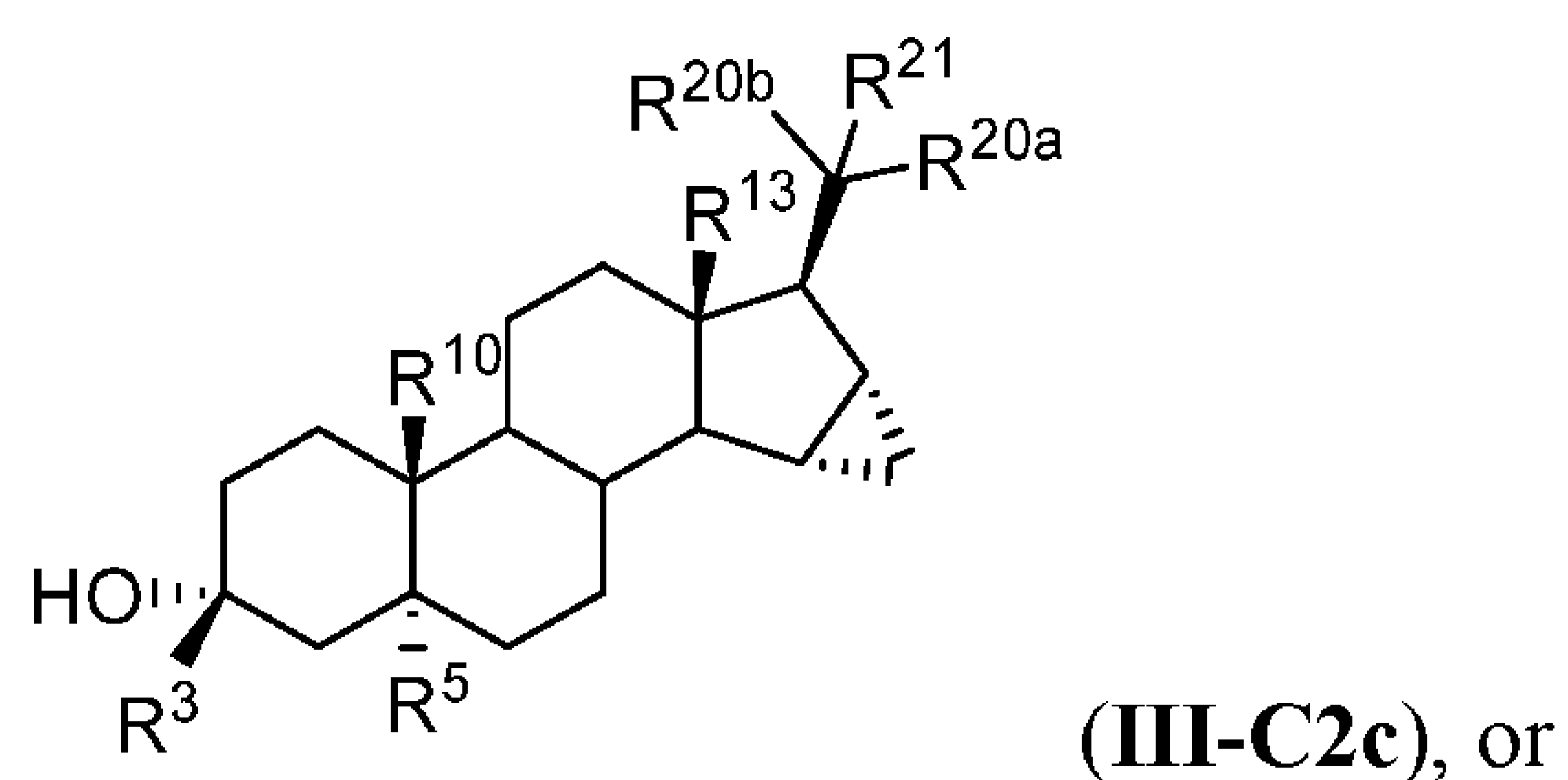
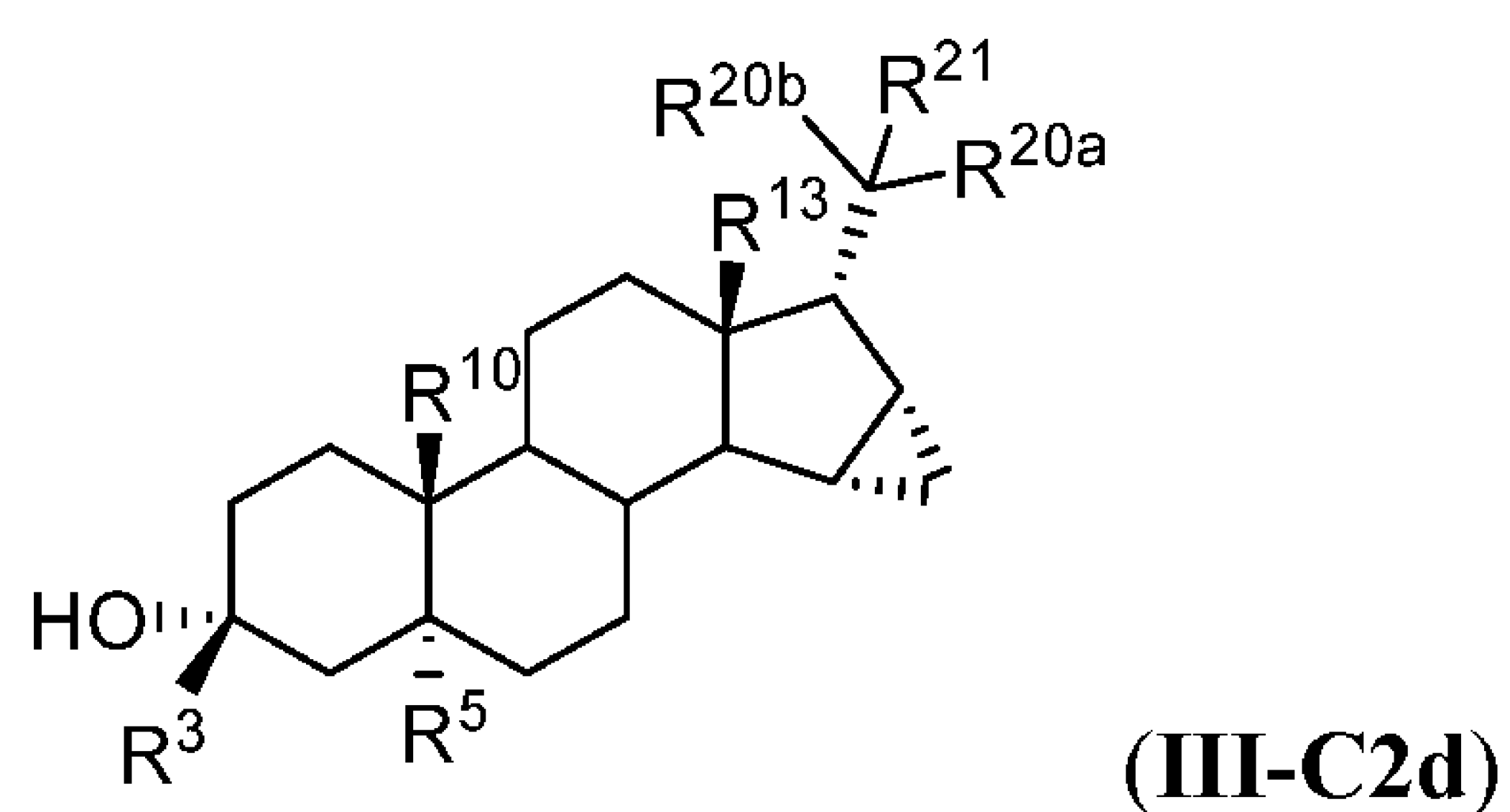


or



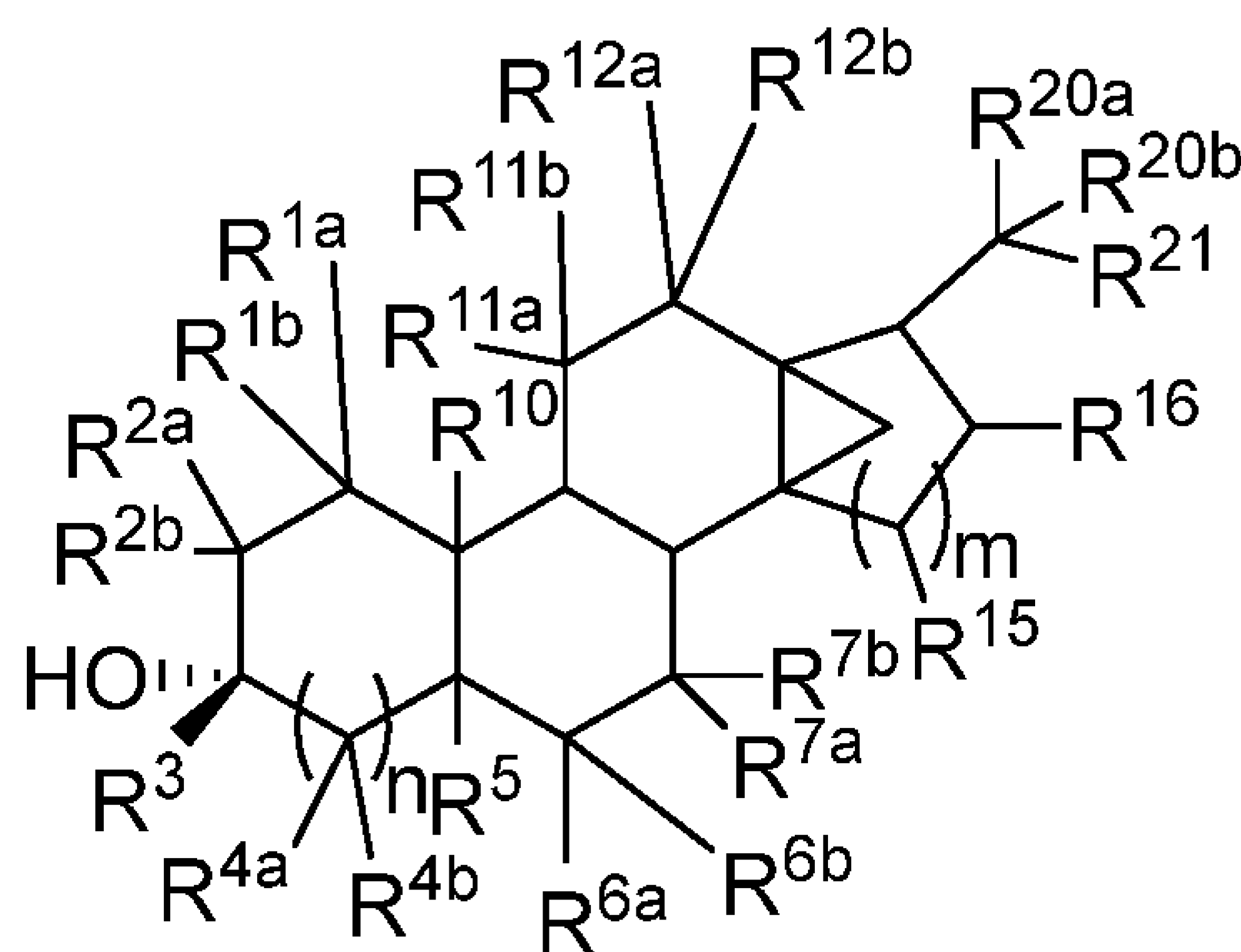
or a pharmaceutically acceptable salt thereof.

56. The compound or pharmaceutically acceptable salt of claim 50, wherein the compound of Formula (III-C2) is a compound of Formula (III-C2a), (III-C2b), (III-C2c) or (III-C2d)



or a pharmaceutically acceptable salt thereof.

57. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound of Formula (I) is a compound of Formula (IV)



(IV)

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{15} , R^{16} , R^{20a} , R^{20b} , and R^{21} is $-L^A-R^{30}$.

Each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -;

Each R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$;

Each R' is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, or $-C(CH_3)_3$, or

R^{1a} and R^{1b} taken together form oxo, or

R^{2a} and R^{2b} taken together form oxo, or

R^{4a} and R^{4b} taken together form oxo, or

R^{6a} and R^{6b} taken together form oxo, or

R^{7a} and R^{7b} taken together form oxo, or

R^{11a} and R^{11b} taken together form oxo, or

R^{12a} and R^{12b} taken together form oxo, or

R^{20a} and R^{20b} taken together form oxo;

R^5 is $-H$ or C_{1-3} alkyl;

R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

m is 1 or 2; and

n is 0, 1, or 2.

58. The compound or pharmaceutically acceptable salt of claim 57, wherein R^3 is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.

59. The compound or pharmaceutically acceptable salt of claim 57 or claim 58, wherein R^3 is $-H$ or C_{1-6} alkyl optionally substituted with R' .

60. The compound or pharmaceutically acceptable salt of any one of claims 57-59, wherein R^3 is $-H$, $-CH_3$, $-CH_2-CH_2-CH_3$, or $-CH_2-O-CH_3$.

61. The compound or pharmaceutically acceptable salt of any one of claims 57-60, wherein m is 1 and R^{15} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.

62. The compound or pharmaceutically acceptable salt of any one of claims 57-61, wherein m is 1 and R^{15} is $-H$ or C_{1-6} alkyl optionally substituted with R' .

63. The compound or pharmaceutically acceptable salt of any one of claims 57-62, wherein m is 1 and R^{15} is $-H$ or C_{1-3} alkyl.

64. The compound or pharmaceutically acceptable salt of any one of claims 57-63, wherein R^{16} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.

65. The compound or pharmaceutically acceptable salt of any one of claims 57-64, wherein R^{16} is $-H$ or C_{1-6} alkyl optionally substituted with R' .

66. The compound or pharmaceutically acceptable salt of any one of claims 57-65, wherein R^{16} is $-H$ or C_{1-3} alkyl.

67. The compound or pharmaceutically acceptable salt of any one of claims 57-66, wherein each of R^{20a} and R^{20b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo.

68. The compound or pharmaceutically acceptable salt of any one of claims 57-67, wherein each of R^{20a} and R^{20b} are independently selected from $-H$, C_{1-6} alkyl, $-N(R')_2$, and $-O-R'$, or R^{20a} and R^{20b} taken together form oxo.

69. The compound or pharmaceutically acceptable salt of any one of claims 57-68, wherein R^{20a} and R^{20b} taken together form oxo.

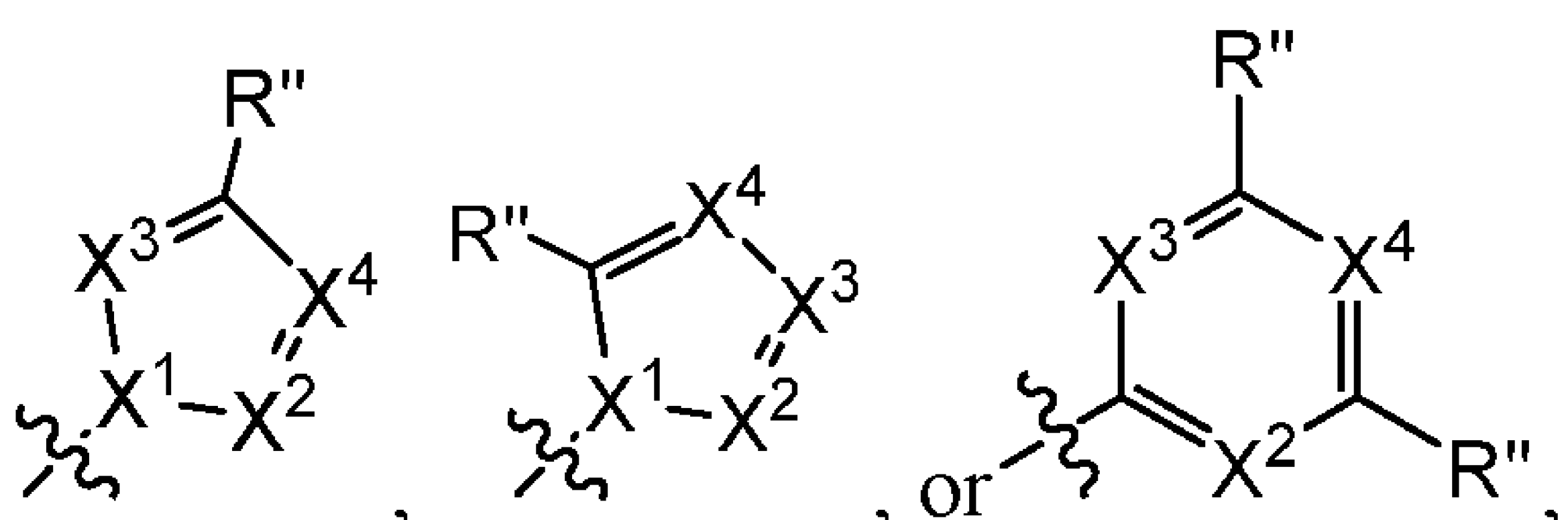
70. The compound or pharmaceutically acceptable salt of any one of claims 57-69, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, or $-NH-$; and R^{30} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

71. The compound or pharmaceutically acceptable salt of any one of claims 57-70, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, or $-NH-$; and R^{30} is a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

72. The compound or pharmaceutically acceptable salt of any one of claims 57-71, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond or $-CH_2-$; and R^{30} is a 5-6-membered partially unsaturated or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is

optionally substituted with 1-2 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$.

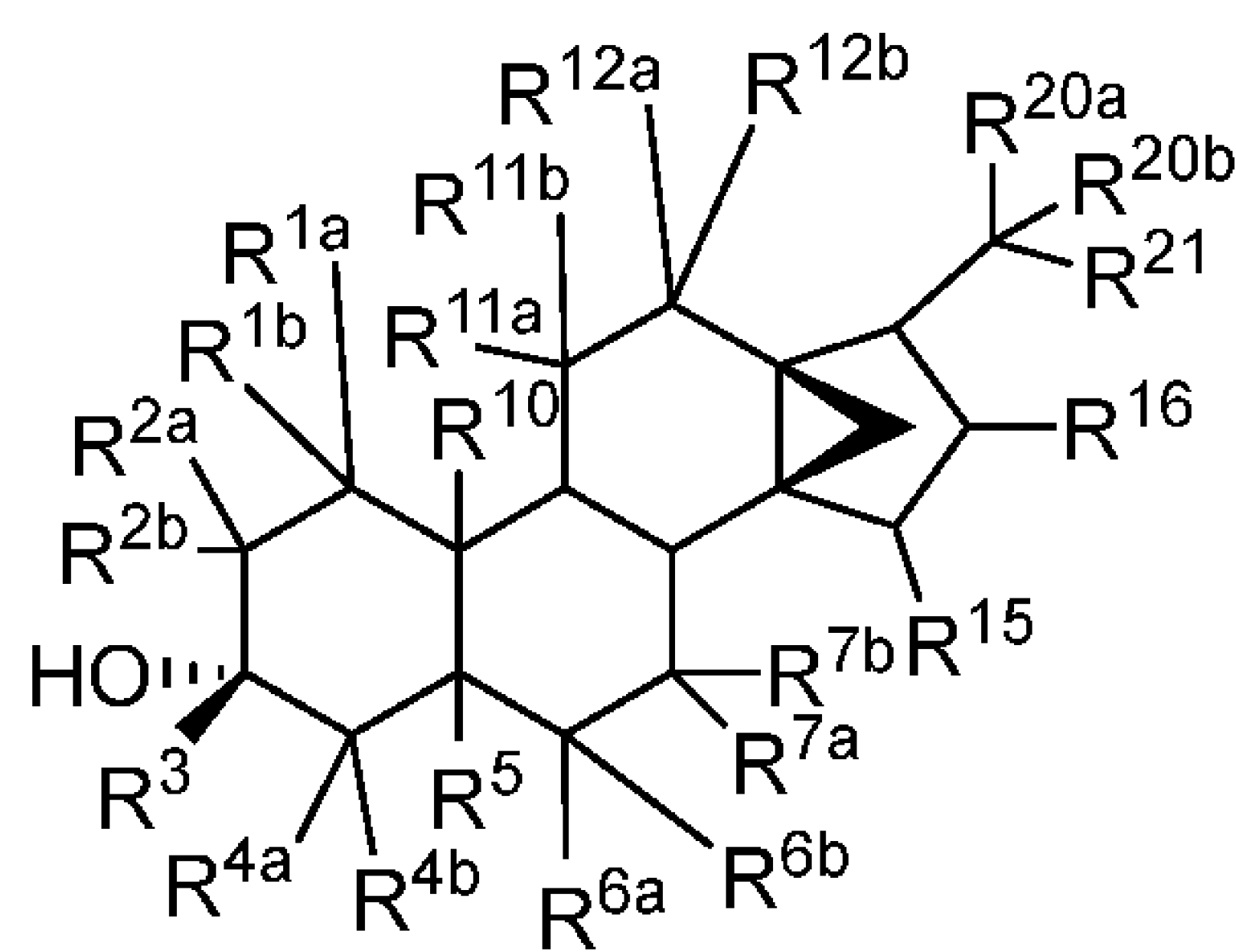
73. The compound or pharmaceutically acceptable salt of any one of claims 57-72, wherein

R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond or $-\text{CH}_2-$; and R^{30} is , wherein

each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that

- (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and
- (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$.

74. The compound or pharmaceutically acceptable salt of claim 57, wherein the compound of Formula (IV) is a compound of Formula (IV-A)



(IV-A)

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{15} , R^{16} , R^{20a} , R^{20b} , and R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$.

Each L^{A} is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^{A} are optionally and independently replaced by $-\text{NR}'-$, $-\text{S}-$, $-\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{C}(\text{O})-$,

–C(O)NR'–, –NR'C(O)–, –NR'C(O)O–, –S(O)₂NR'–, –NR'S(O)₂–, –C(O)NR'NR'–,
–NR'C(O)NR'–, –OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, –S(O)–, or –S(O)₂–;

Each R³⁰ is independently selected from R', halo, –CN, –NO₂, and –CF₃;

Each R' is independently selected from –H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, –CH₃, –CH₂OH, and –C(CH₃)₃, or

R^{20a} and R^{20b} taken together form oxo;

R⁵ is –H or C₁₋₃ alkyl; and

R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl.

75. The compound or pharmaceutically acceptable salt of claim 74, wherein each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹⁵, and R¹⁶ is independently selected from –H or C₁₋₆ alkyl;

R³ is –H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₅ alkyl-O-C₁₋₆ alkyl;

R⁵ is –H or C₁₋₃ alkyl;

R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl;

Each of R¹⁵ and R¹⁶ is independently –H or C₁₋₆ alkyl;

Each of R^{20a} and R^{20b} is independently selected from –H, –OH, –C₁₋₅ alkyl-OH, C₁₋₆ alkyl, and –NH₂, or R^{20a} and R^{20b} taken together form oxo;

R²¹ is –L^A-R³⁰;

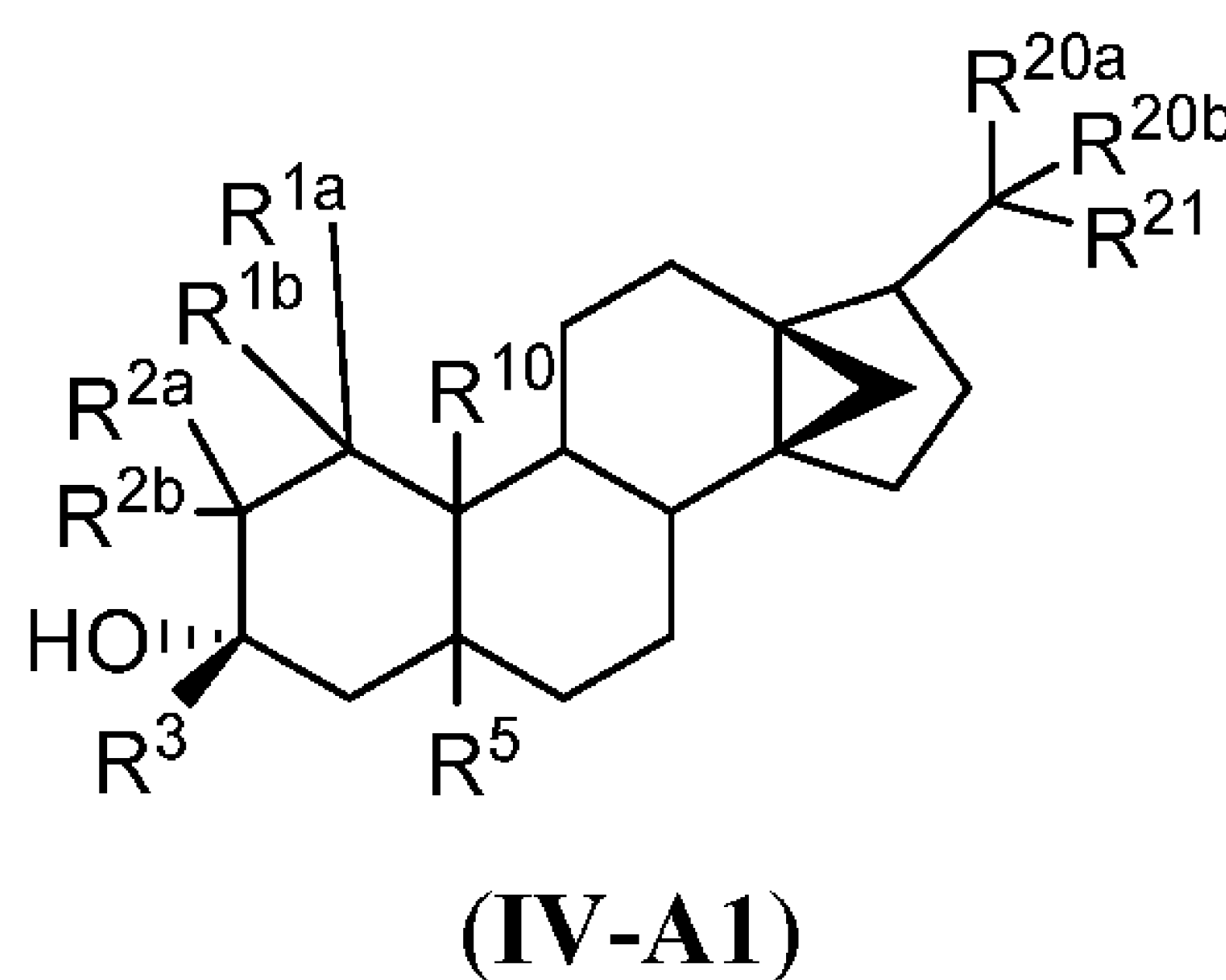
L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by –NR'–, –S–, –O–, –OC(O)–, –C(O)O–, –C(O)–, –C(O)C(O)–, –C(O)NR'–, –NR'C(O)–, –NR'C(O)O–, –S(O)₂NR'–, –NR'S(O)₂–, –C(O)NR'NR'–, –NR'C(O)NR'–, –OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, –S(O)–, or –S(O)₂–;

R³⁰ is R', halo, –CN, –NO₂, and –CF₃; and

Each R' is independently selected from –H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms,

wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

76. The compound or pharmaceutically acceptable salt of claim 74 or claim 75, wherein the compound of Formula (IV-A) is a compound of Formula (IV-A1)



or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently selected from -H and C₁₋₃ alkyl;

R³ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₆ alkyl;

R⁵ is -H or C₁₋₃ alkyl;

R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl;

Each of R^{20a} and R^{20b} is independently selected from -H, -OH, -CH₂OH, C₁₋₃ alkyl, and -NH₂, or R^{20a} and R^{20b} taken together form oxo;

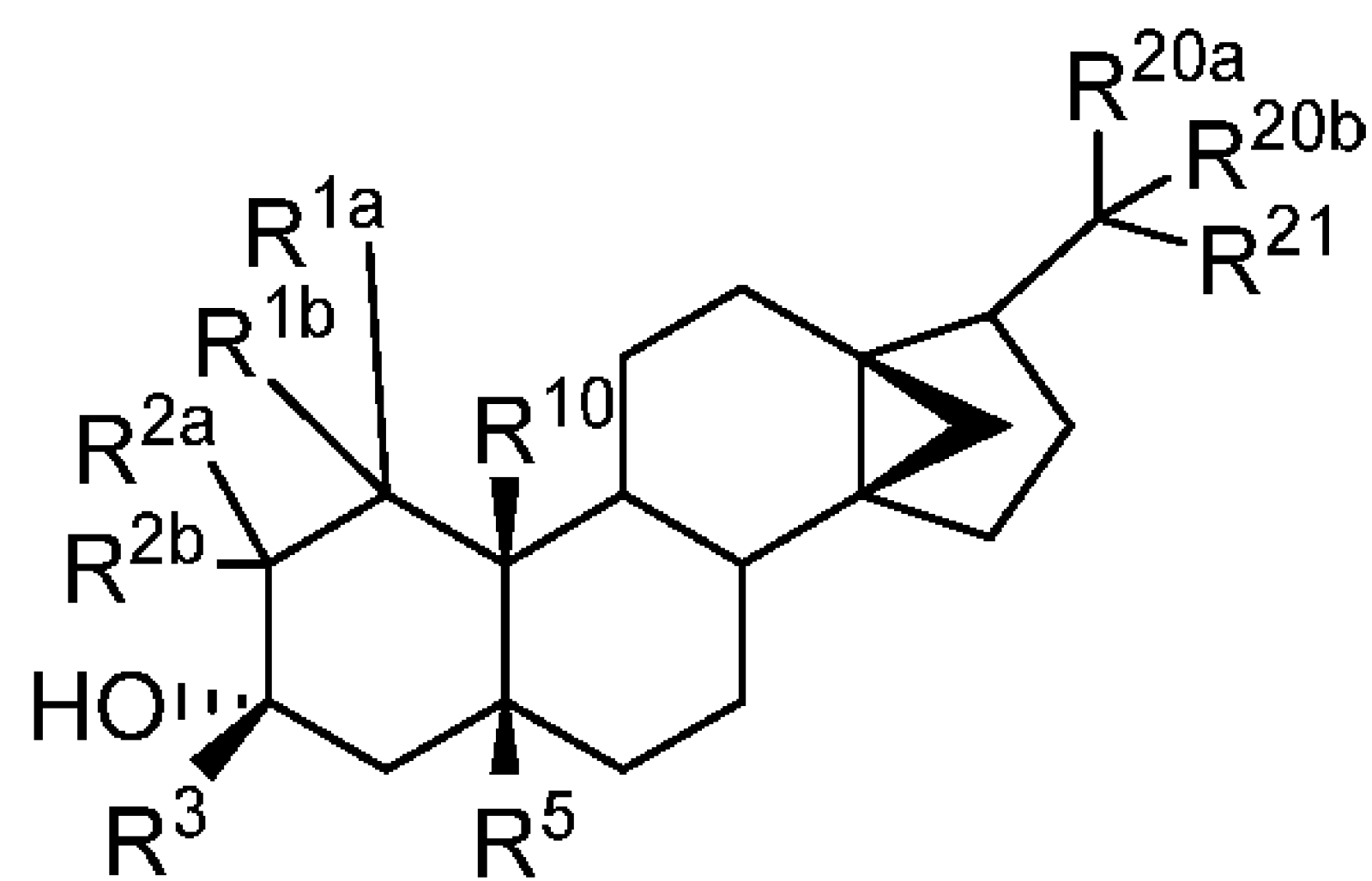
R²¹ is -L^A-R³⁰;

L^A is a bond or a straight or branched C₁₋₃ alkylene chain;

R³⁰ is R', halo, -CN, -NO₂, or -CF₃; and

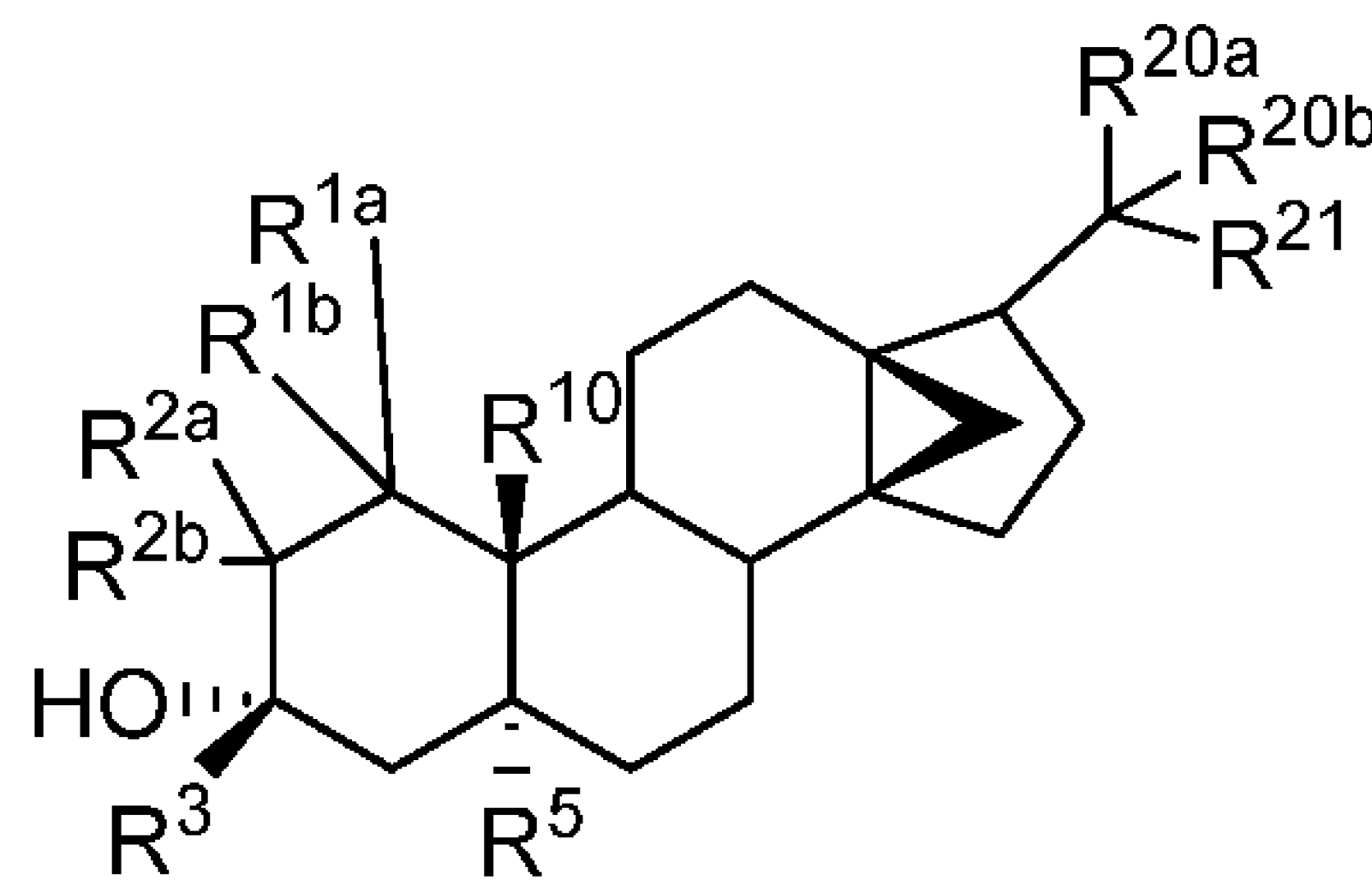
R' is -H, C₁₋₆ alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

77. The compound or pharmaceutically acceptable salt of claim 76, wherein the compound of Formula (IV-A1) is a compound of Formula (IV-A1a) or (IV-A1b)



(IV-A1a)

or



(IV-A1b),

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is selected from -H and C₁₋₃ alkyl;

R³ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl;

R⁵ is -H or C₁₋₃ alkyl;

R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl;

Each of R^{20a} and R^{20b} is independently selected from -H, -OH, -CH₂OH, C₁₋₃ alkyl, and -NH₂, or R^{20a} and R^{20b} taken together form oxo;

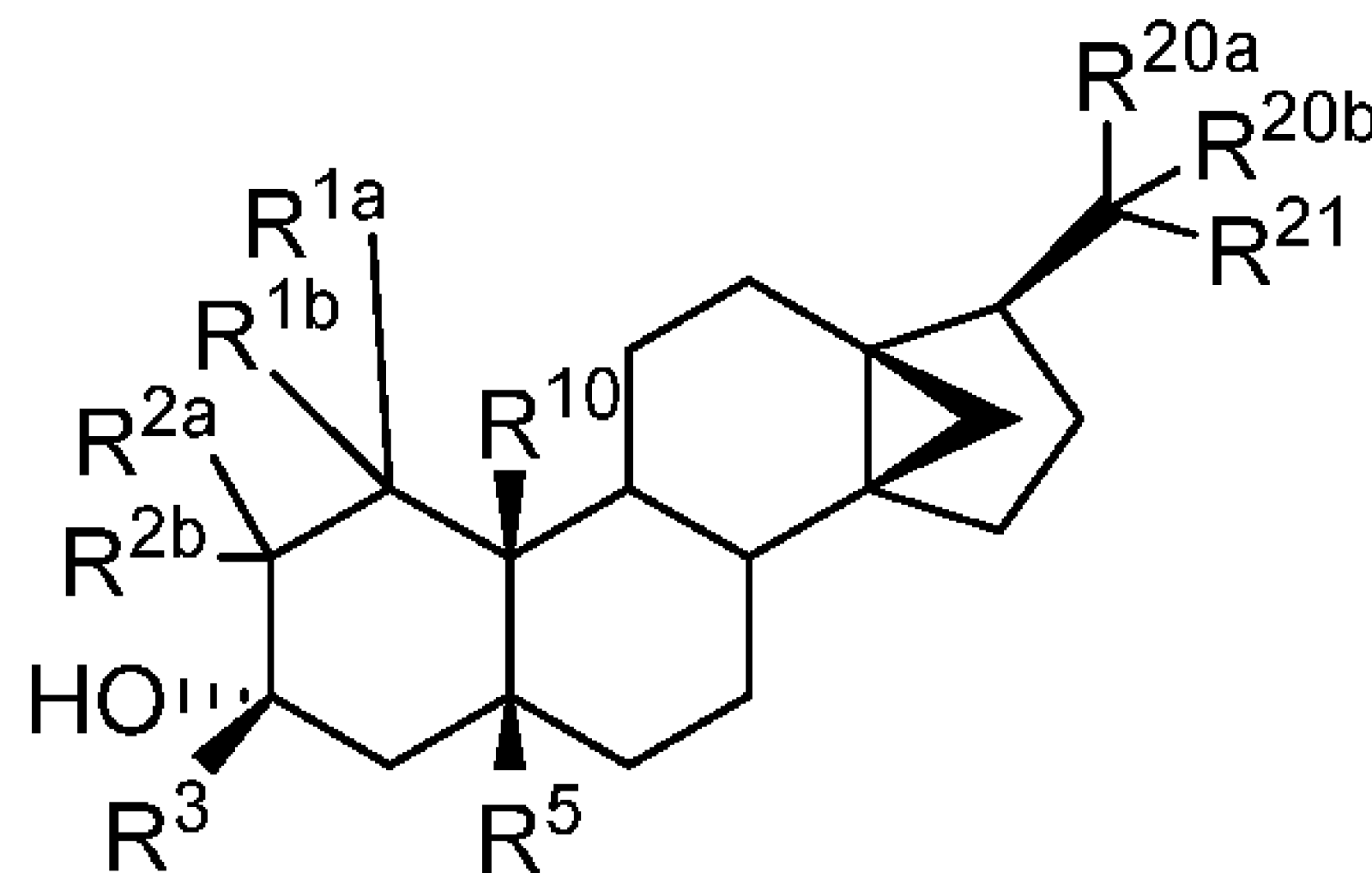
R²¹ is -L^A-R³⁰;

L^A is a bond or a straight or branched C₁₋₃ alkylene chain;

R³⁰ is R', halo, -CN, -NO₂, or -CF₃; and

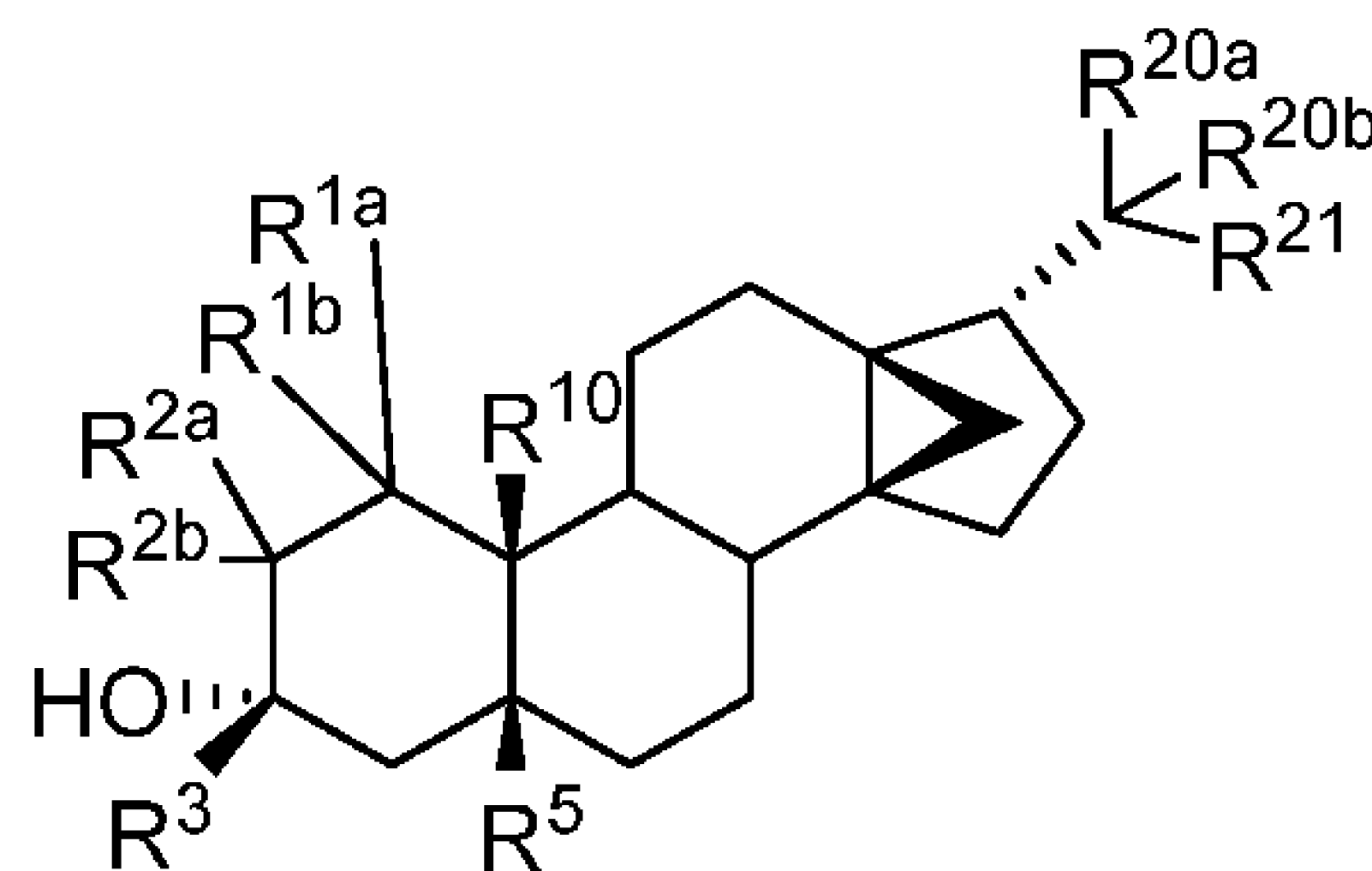
R' is -H, C₁₋₆ alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

78. The compound or pharmaceutically acceptable salt of claim 77, wherein the compound of Formula (IV-A1a) is a compound of Formula (IV-A1a1) or (IV-A1a2)



(IV-A1a1)

or



(IV-A1a2),

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently selected from -H and C₁₋₃ alkyl;

R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

R^5 is $-H$ or C_{1-3} alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-CH_2OH$, C_{1-3} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

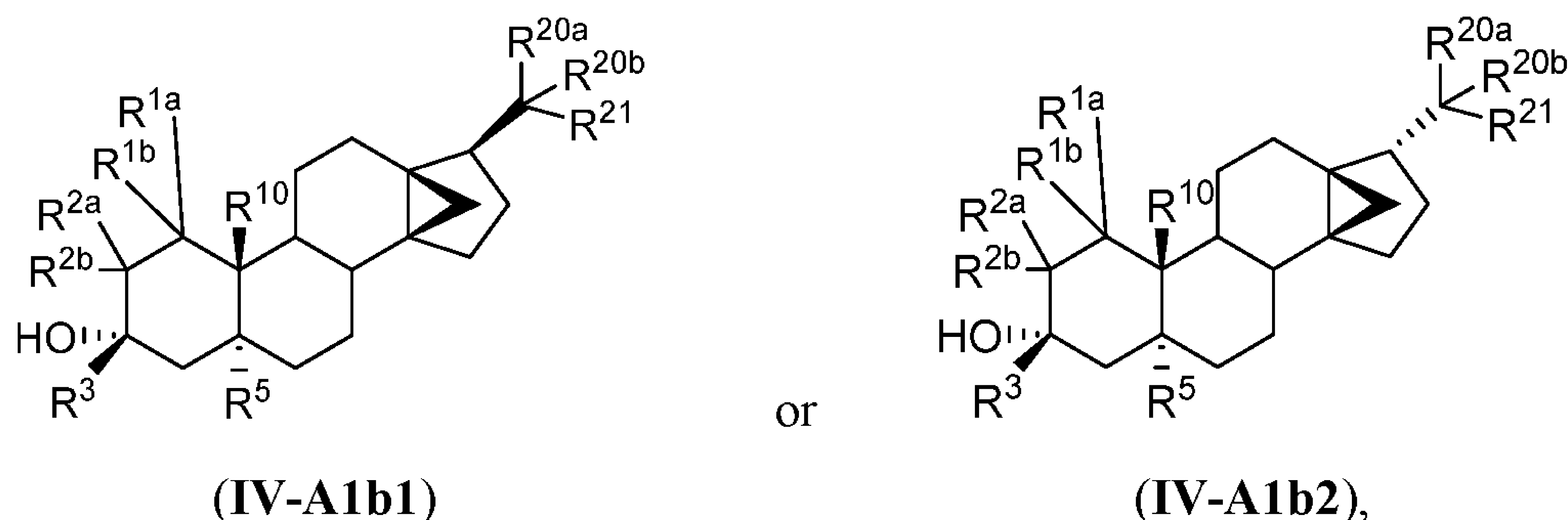
R^{21} is $-L^A-R^{30}$;

L^A is a bond or a straight C_{1-3} alkylene chain;

R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and

R' is $-H$, C_{1-6} alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

79. The compound or pharmaceutically acceptable salt of claim 77, wherein the compound of Formula (IV-A1b) is a compound of Formula (IV-A1b1) or (IV-A1b2)



or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , and R^{2b} is independently selected from $-H$ and C_{1-3} alkyl;

R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

R^5 is $-H$ or C_{1-3} alkyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, $-CH_2OH$, C_{1-3} alkyl, and $-NH_2$, or R^{20a} and R^{20b} taken together form oxo;

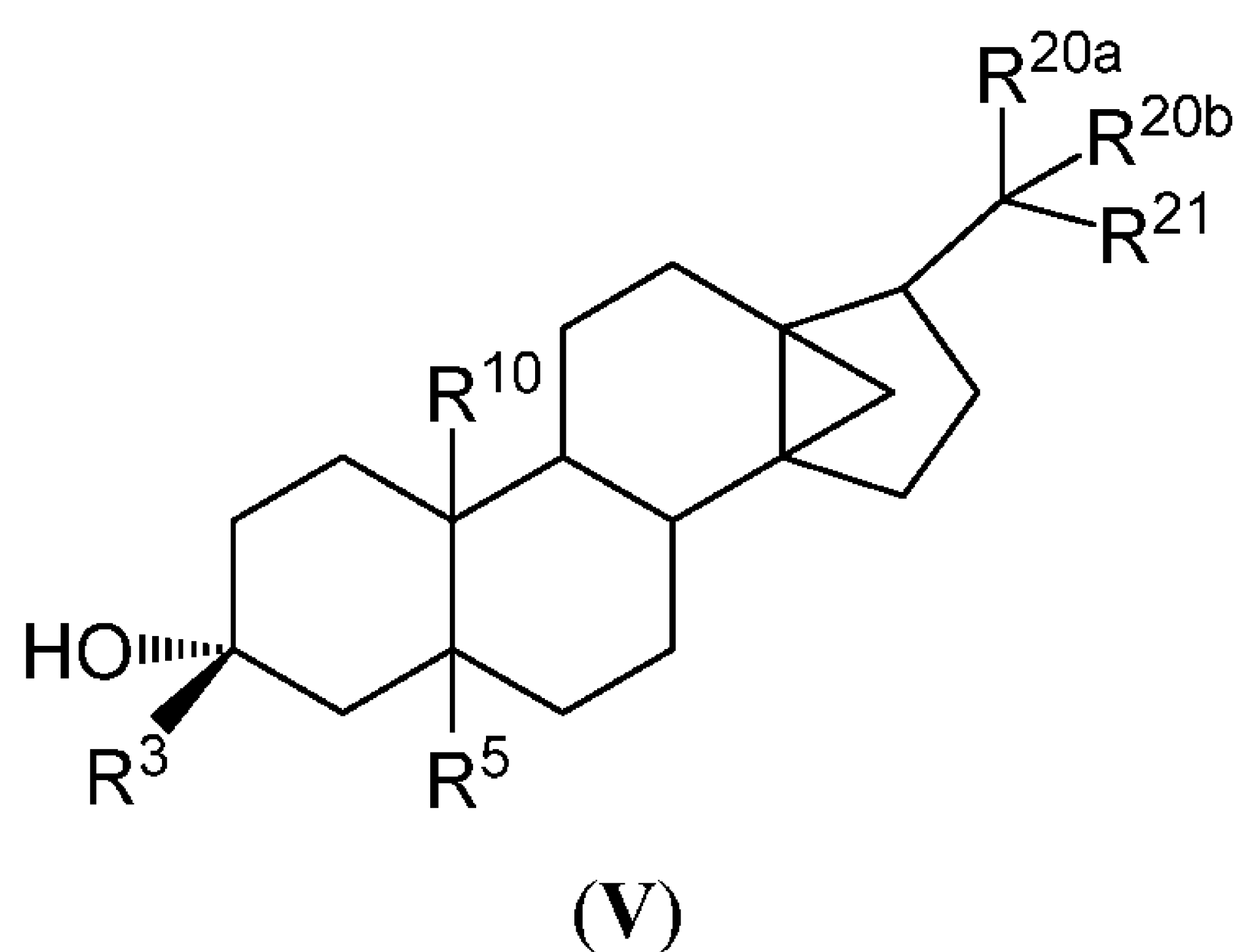
R^{21} is $-L^A-R^{30}$;

L^A is a bond or a straight C_{1-3} alkylene chain;

R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and

R' is -H, C₁₋₆ alkyl, or a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, and -CH₃.

80. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound of Formula (I) is a compound of Formula (V)



or a pharmaceutically acceptable salt thereof, wherein

R³ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl;

R⁵ is -H or C₁₋₆ alkyl;

R¹⁰ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl;

Each of R^{20a} and R^{20b} is independently selected from -H, -OH, and C₁₋₆ alkyl, or

R^{20a} and R^{20b} taken together form oxo;

R²¹ is -L^A-R³⁰;

L^A is a bond, a branched or straight C₁₋₆ alkylene chain, or -N(H)-; and

R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃.

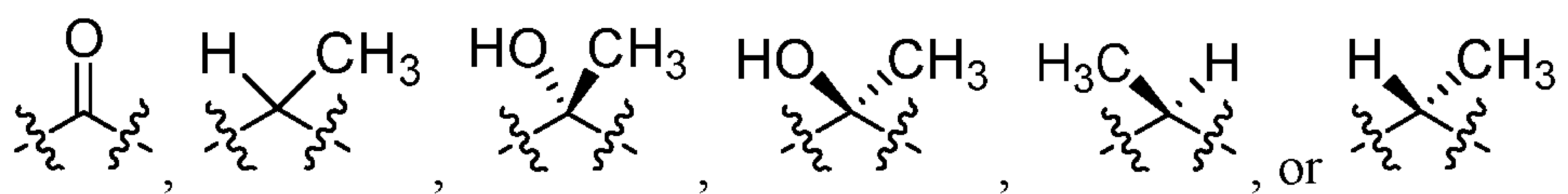
81. The compound or pharmaceutically acceptable salt of claim 80, wherein R^{20a} and R^{20b} taken together form oxo.

82. The compound or pharmaceutically acceptable salt of claim 80, wherein one of R^{20a} and R^{20b} is $-H$, and the other of R^{20a} and R^{20b} is C_{1-6} alkyl.

83. The compound or pharmaceutically acceptable salt of claim 80, wherein one of R^{20a} and R^{20b} is C_{1-6} alkyl, and the other of R^{20a} and R^{20b} is $-OH$.

84. The compound or pharmaceutically acceptable salt of claim 80 or claim 83, wherein one of R^{20a} and R^{20b} is methyl, ethyl, or propyl, and the other is $-OH$.

85. The compound or pharmaceutically acceptable salt of any one of claims 80, wherein R^{20a} , R^{20b} , and the carbon to which they are attached form



86. The compound or pharmaceutically acceptable salt of any one of claims 80-85, wherein R^{21} is $-L^A-R^{30}$,

L^A is a bond, a branched or straight C_{1-3} alkylene chain, or $-N(H)-$; and

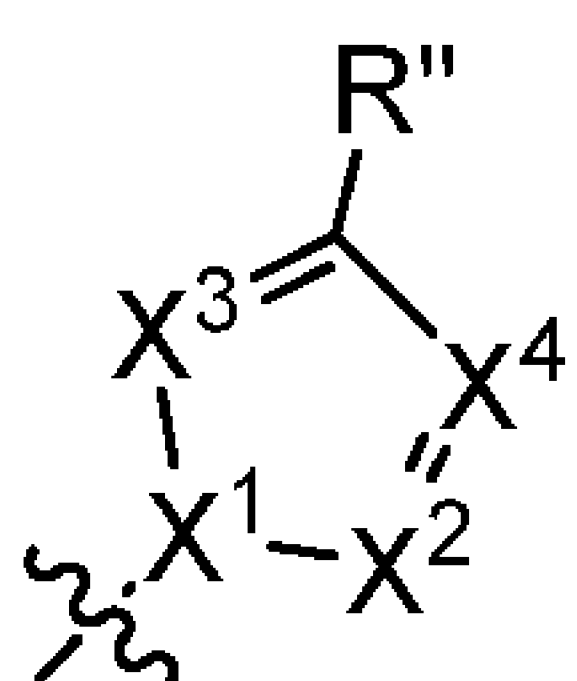
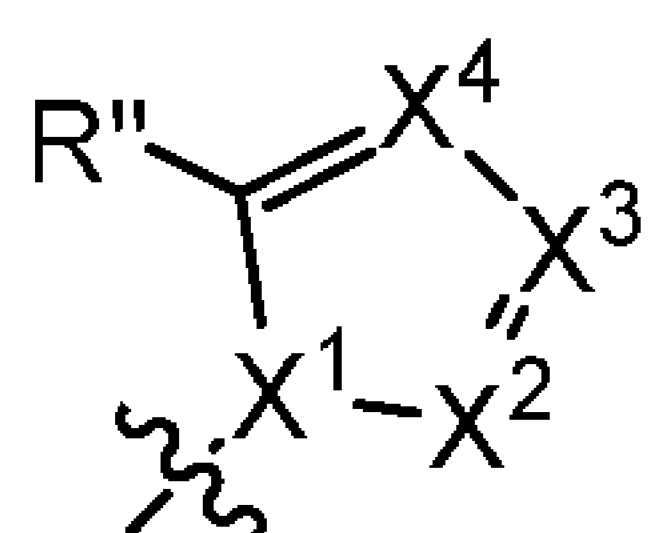
R^{30} is $-H$, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

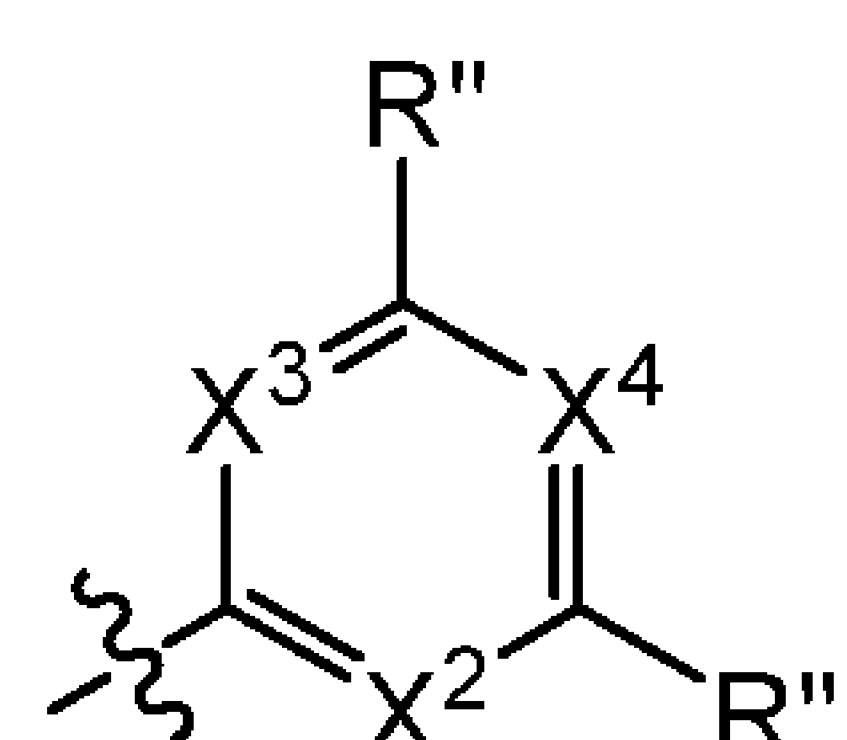
87. The compound or pharmaceutically acceptable salt of any one of claims 80-86, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, or $-N(H)-$; and R^{30} is $-H$ or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

88. The compound or pharmaceutically acceptable salt of any one of claims 80-87, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, or $-N(H)-$; and R^{30} is a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein

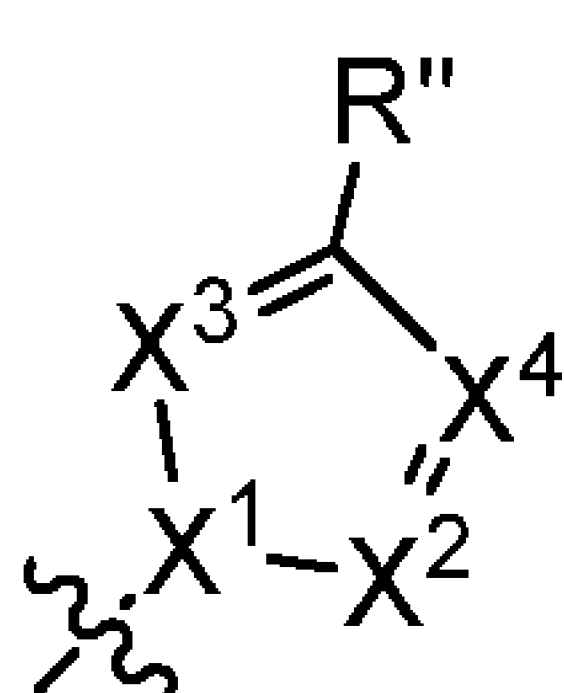
the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from –CN, –NO₂, –CF₃, –CH₃, –CH₂OH, and –C(CH₃)₃.

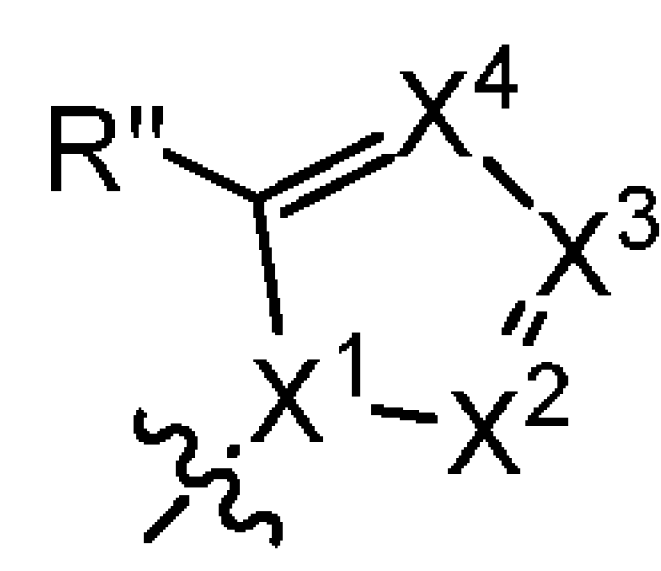
89. The compound or pharmaceutically acceptable salt of any one of claims 80-88, wherein

R²¹ is –L^A–R³⁰; L^A is a bond, –CH₂–, or –N(H)–; and R³⁰ is , , or

, wherein each of X¹, X², X³, and X⁴ is independently N or CR'', wherein each R'' is independently selected from –H, halo, –OH, –CN, –NO₂, –CF₃, –CH₃, –CH₂OH, and –C(CH₃)₃, provided that

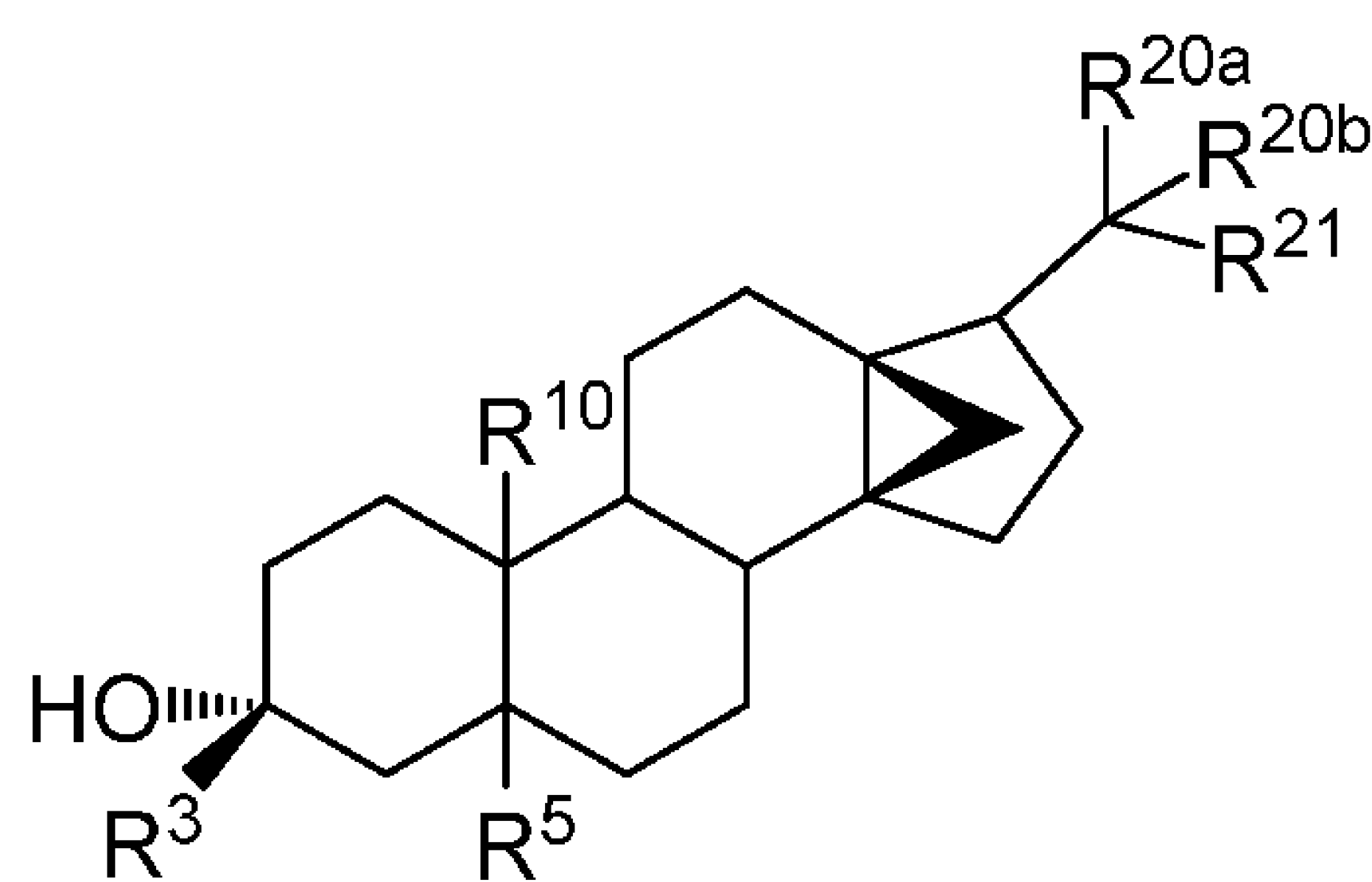
- (i) at least one of X¹, X², X³, and X⁴ is N, and
- (ii) no greater than 2 instances of R'' are independently selected from halo, –OH, –CN, –NO₂, –CF₃, –CH₃, and –CH₂OH.

90. The compound or pharmaceutically acceptable salt of claim 88, wherein R³⁰ is ,

or , X¹ is N; and each of X², X³, and X⁴ is independently selected from N or CR'', wherein each R'' is independently selected from –H, –OH, –CN, –NO₂, –CF₃, –CH₃, and –CH₂OH, provided that

- (i) no greater than 2 instances of R'' are independently selected from halo, –OH, –CN, –NO₂, –CF₃, –CH₃, and –CH₂OH.

91. The compound or pharmaceutically acceptable salt of claim 80, wherein the compound of Formula (V) is a compound of Formula (V-A)



(V-A)

or a pharmaceutically acceptable salt thereof, wherein

R³ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl;

R⁵ is -H or C₁₋₆ alkyl;

R¹⁰ is -H, C₁₋₆ alkyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl;

Each of R^{20a} and R^{20b} is independently selected from -H, -OH, and C₁₋₆ alkyl, or

R^{20a} and R^{20b} taken together form oxo;

R²¹ is -L^A-R³⁰,

L^A is a bond, a branched or straight C₁₋₆ alkylene chain, or -N(H)-; and

R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R³⁰ is optionally substituted with 1-3 groups independently selected from halo, -OH, -CN, -NO₂, -CF₃, -CH₃, -CH₂OH, and -C(CH₃)₃.

92. The compound or pharmaceutically acceptable salt of claim 91, wherein

R³ is -H, C₁₋₃ alkyl, C₁₋₃ alkyl-O-C₁₋₃ alkyl;

R⁵ is -H or methyl;

R¹⁰ is -H, C₁₋₃ alkyl, or C₁₋₃ alkyl-O-C₁₋₃ alkyl;

Each of R^{20a} and R^{20b} is independently selected from -H, -OH, and C₁₋₃ alkyl, or R^{20a} and R^{20b} taken together form oxo;

R²¹ is -L^A-R³⁰,

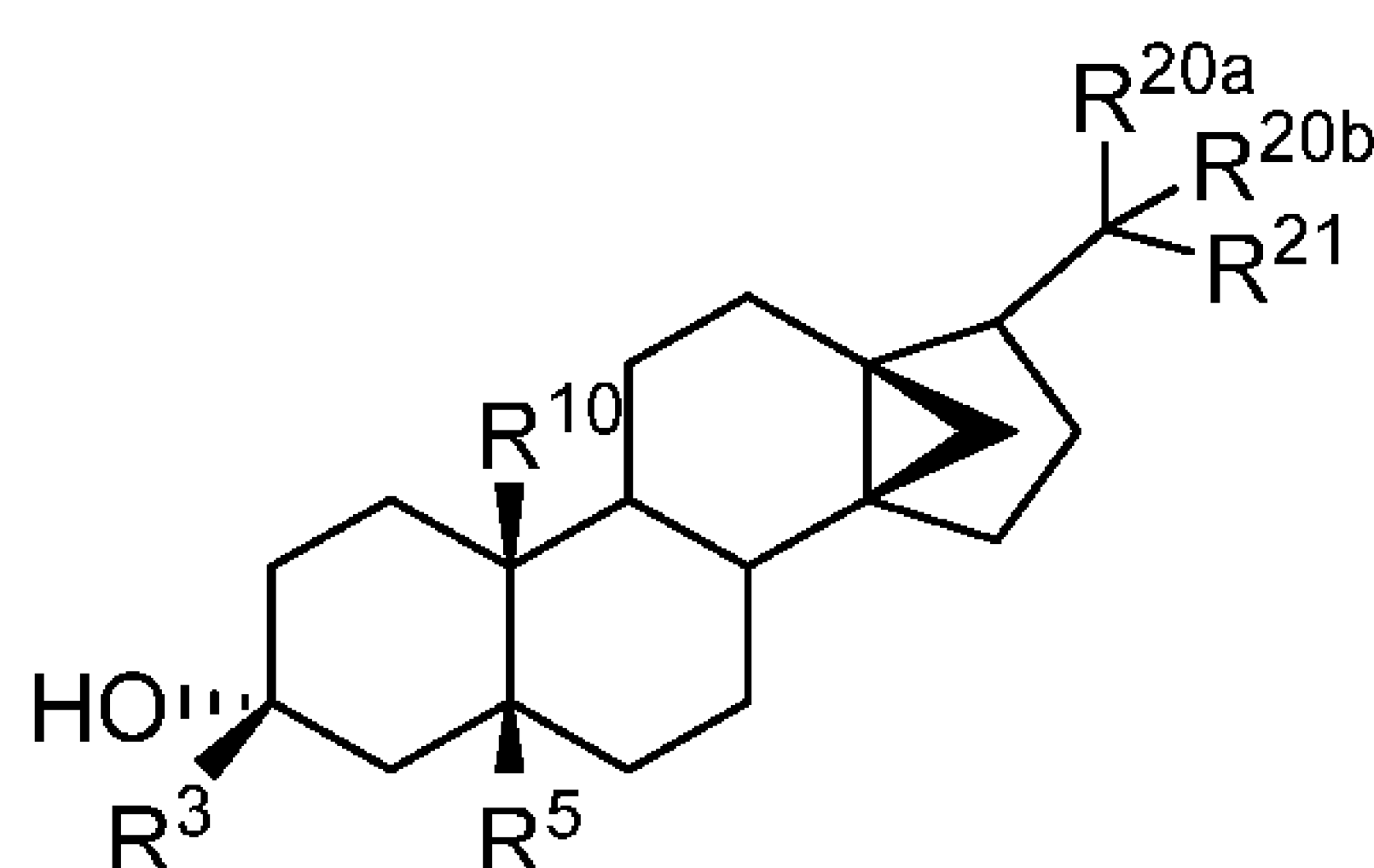
L^A is a bond or an optionally substituted branched or straight C₁₋₃ alkylene chain;

and

R³⁰ is -H, halo, -OH, -CN, -NO₂, -CF₃, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-

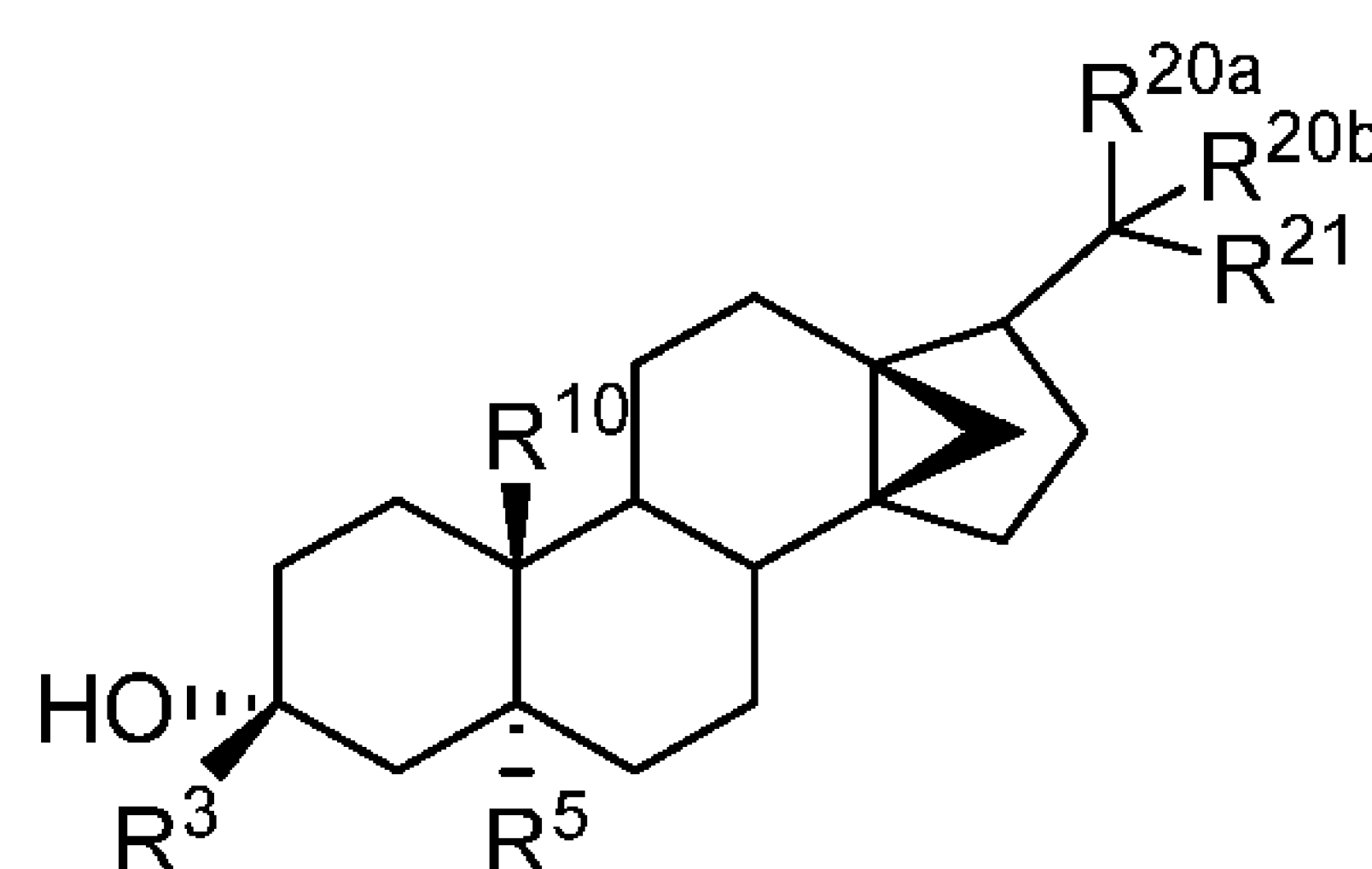
membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

93. The compound or pharmaceutically acceptable salt of claim 91, wherein the compound of Formula (V-A) is a compound of Formula (V-A1) or (V-A2)



(V-A1)

or



(V-A2),

or a pharmaceutically acceptable salt thereof, wherein

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or

R^{20a} and R^{20b} taken together form oxo;

R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

94. The compound or pharmaceutically acceptable salt of claim 93, wherein

R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl;

R^5 is $-H$ or methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

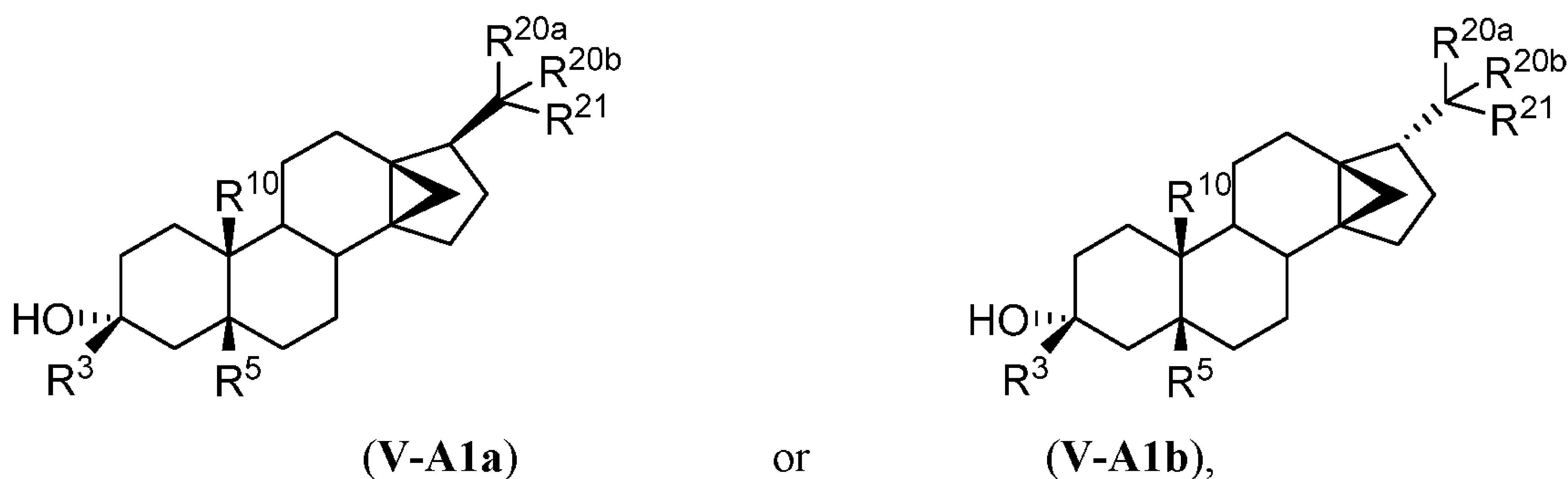
Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo;

R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain;
and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

95. The compound or pharmaceutically acceptable salt of claim 93, wherein the compound of Formula (V-A1) is a compound of Formula (V-A1a) or (V-A1b)



or a pharmaceutically acceptable salt thereof, wherein

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or

R^{20a} and R^{20b} taken together form oxo;

R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

96. The compound or pharmaceutically acceptable salt of claim 94, wherein

R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl- O - C_{1-3} alkyl;

R^5 is $-H$ or methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo;

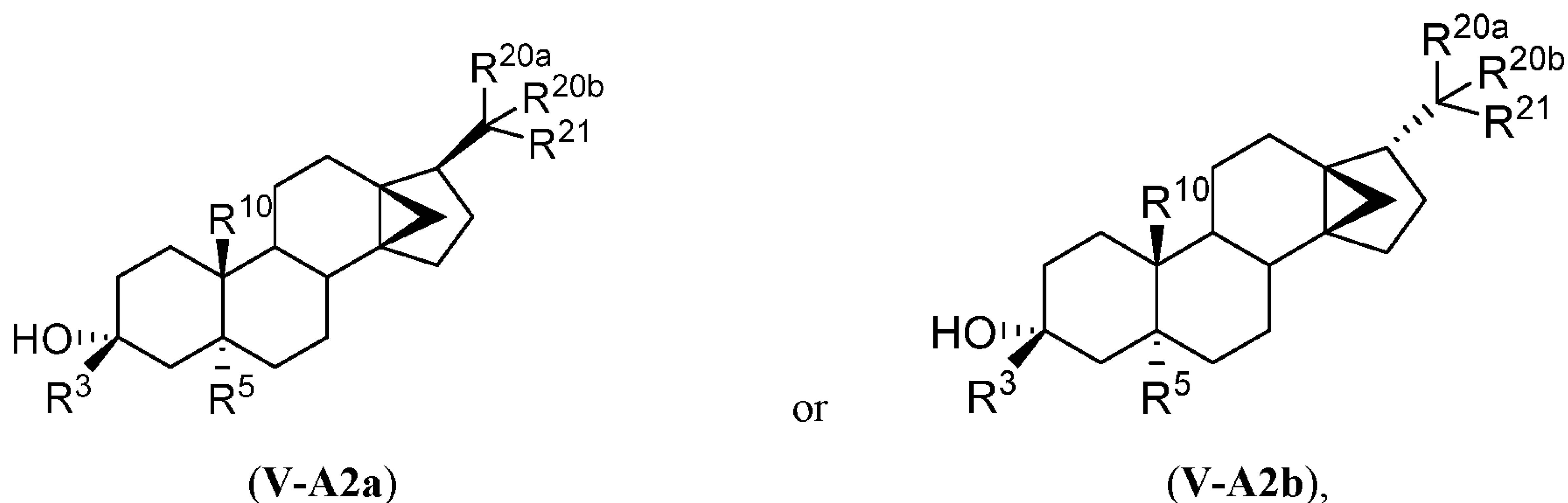
R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain;

and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

97. The compound or pharmaceutically acceptable salt of claim 93, wherein the compound of Formula (V-A2) is a compound of Formula (V-A2a) or (V-A2b)



or a pharmaceutically acceptable salt thereof, wherein

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-6} alkyl, or

R^{20a} and R^{20b} taken together form oxo;

R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

98. The compound or pharmaceutically acceptable salt of claim 97, wherein

R^3 is $-H$, C_{1-3} alkyl, C_{1-3} alkyl-O- C_{1-3} alkyl;

R^5 is $-H$ or methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl-O- C_{1-3} alkyl;

Each of R^{20a} and R^{20b} is independently selected from $-H$, $-OH$, and C_{1-3} alkyl, or R^{20a} and R^{20b} taken together form oxo;

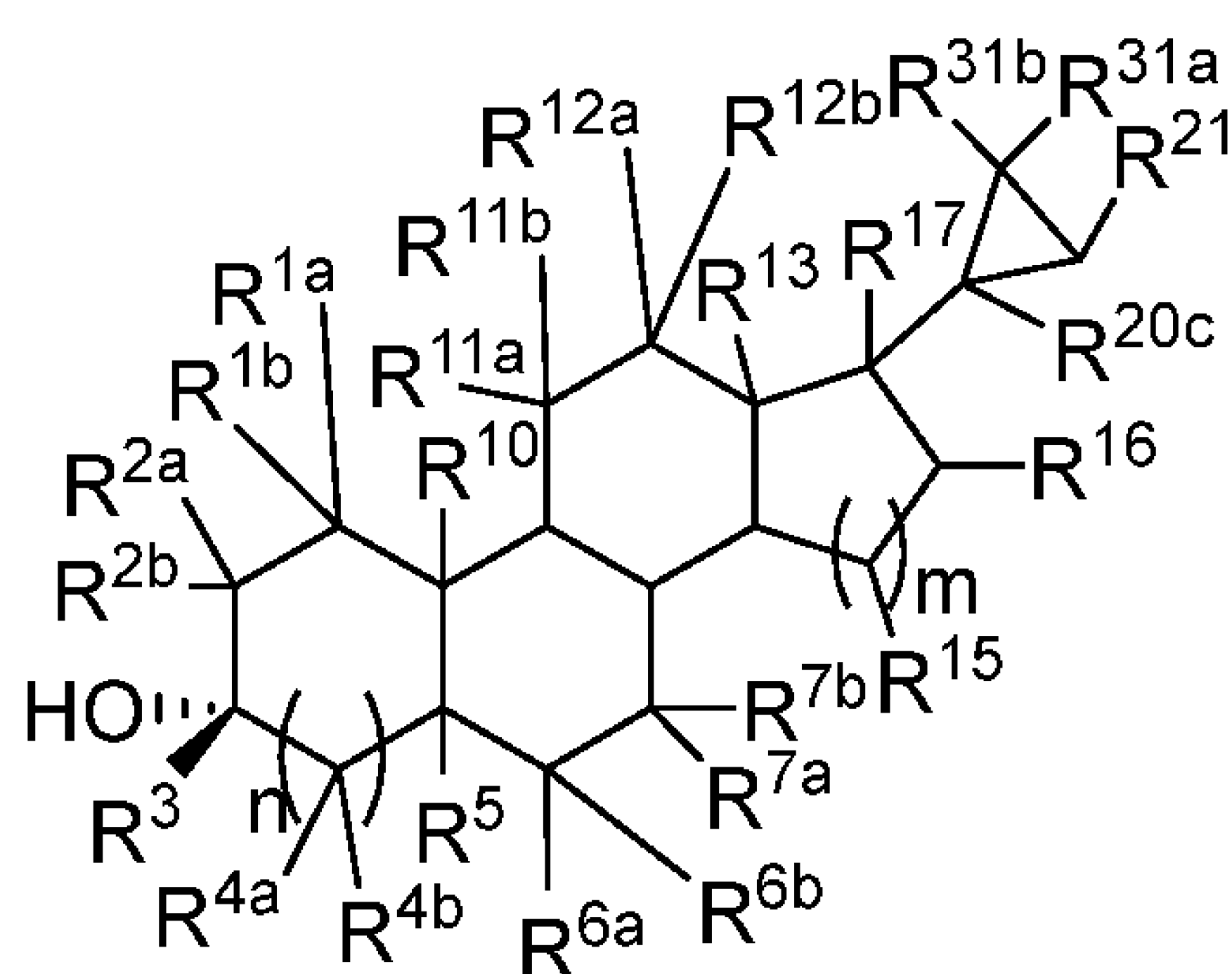
R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain;

and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

99. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound of Formula (I) is a compound of Formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , R^{17} , and R^{21} is $-L^A-R^{30}$.

Each L^A is independently selected from a bond and an optionally substituted branched or straight C_{1-6} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

Each R^{30} is independently selected from R' , halo, $-CN$, $-NO_2$, and $-CF_3$;

Each R' is independently selected from $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein each alkyl, alkenyl, alkynyl, or 3-8 membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$, or

R^{1a} and R^{1b} taken together form oxo, or

R^{2a} and R^{2b} taken together form oxo, or

R^{4a} and R^{4b} taken together form oxo, or

R^{6a} and R^{6b} taken together form oxo, or

R^{7a} and R^{7b} taken together form oxo, or

R^{11a} and R^{11b} taken together form oxo, or

R^{12a} and R^{12b} taken together form oxo;

Each of R^5 and R^{20c} is independently selected from $-H$ and methyl;

R^{10} is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

Each of R^{31a} and R^{31b} is

- (i) independently selected from $-H$, halo, and C_{1-6} alkyl, or
- (ii) when one of R^{31a} and R^{31b} is $-H$, the other of R^{31a} and R^{31b} is $-H$, halo, C_{1-6} alkyl, or $-OR^{32}$, wherein R^{32} is $-H$, C_{1-6} alkyl, or a 3-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S;

n is 0, 1, or 2; and

m is 1 or 2.

100. The compound or pharmaceutically acceptable salt of claim 99, wherein R^3 is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.
101. The compound or pharmaceutically acceptable salt of claim 99 or claim 100, wherein R^3 is $-H$ or C_{1-6} alkyl optionally substituted with R' .
102. The compound or pharmaceutically acceptable salt of any one of claims 99-101, wherein R^3 is $-H$ or methyl.
103. The compound or pharmaceutically acceptable salt of any one of claims 99-102, wherein R^{13} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.
104. The compound or pharmaceutically acceptable salt of any one of claims 99-103, wherein R^{13} is $-H$ or C_{1-6} alkyl optionally substituted with R' .
105. The compound or pharmaceutically acceptable salt of any one of claims 99-104, wherein R^{13} is $-H$ or C_{1-3} alkyl.
106. The compound or pharmaceutically acceptable salt of any one of claims 99-105, wherein R^{13} is methyl.
107. The compound or pharmaceutically acceptable salt of any one of claims 99-106, wherein m is 1 and R^{15} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.
108. The compound or pharmaceutically acceptable salt of any one of claims 99-107, wherein m is 1 and R^{15} is $-H$ or C_{1-6} alkyl optionally substituted with R' .
109. The compound or pharmaceutically acceptable salt of any one of claims 99-108, wherein m is 1 and R^{15} is $-H$ or C_{1-3} alkyl.

110. The compound or pharmaceutically acceptable salt of any one of claims 99-109, wherein R^{16} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.

111. The compound or pharmaceutically acceptable salt of any one of claims 99-110, wherein R^{16} is $-H$ or C_{1-6} alkyl optionally substituted with R' .

112. The compound or pharmaceutically acceptable salt of any one of claims 99-111, wherein R^{16} is $-H$ or C_{1-3} alkyl.

113. The compound or pharmaceutically acceptable salt of any one of claims 99-112, wherein R^{17} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.

114. The compound or pharmaceutically acceptable salt of any one of claims 99-113, wherein R^{17} is $-H$ or C_{1-6} alkyl optionally substituted with R' .

115. The compound or pharmaceutically acceptable salt of any one of claims 99-114, wherein R^{17} is $-H$ or C_{1-3} alkyl.

116. The compound or pharmaceutically acceptable salt of any one of claims 99-115, wherein R^{20c} is $-H$.

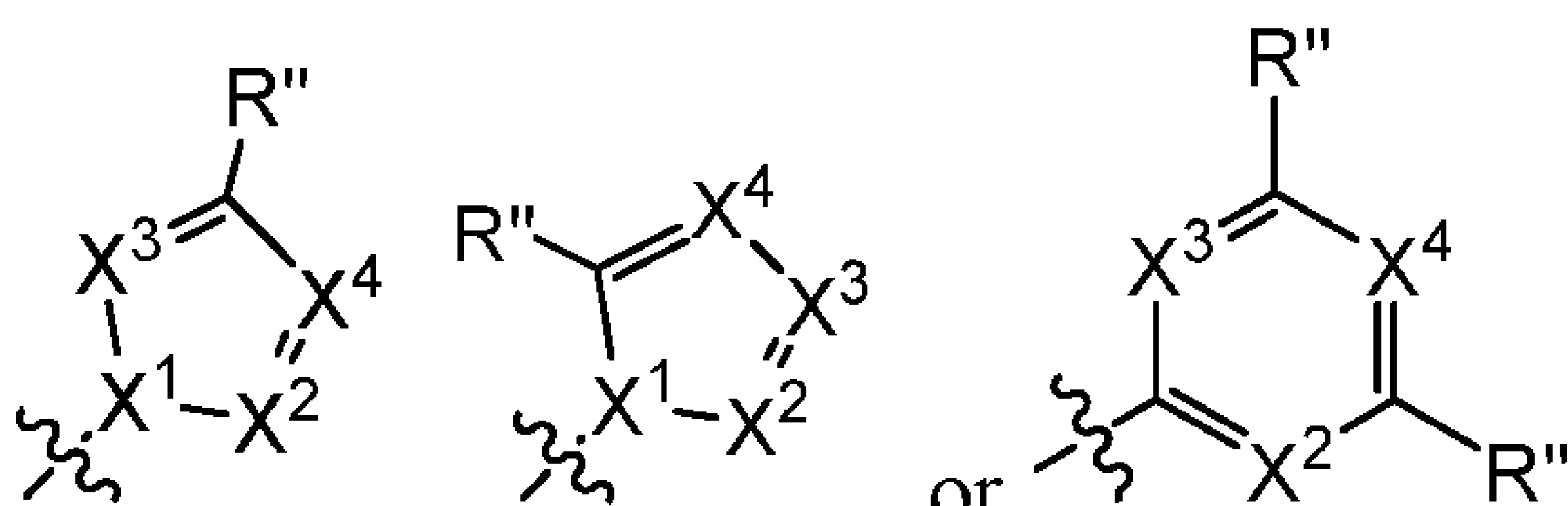
117. The compound or pharmaceutically acceptable salt of any one of claims 99-116, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-CH_2-$, or $-CH_2-CH_2-$; and R^{30} is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

118. The compound or pharmaceutically acceptable salt of any one of claims 99-117, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond or $-CH_2-$; and R^{30} is a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected

from N, O, and S, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$.

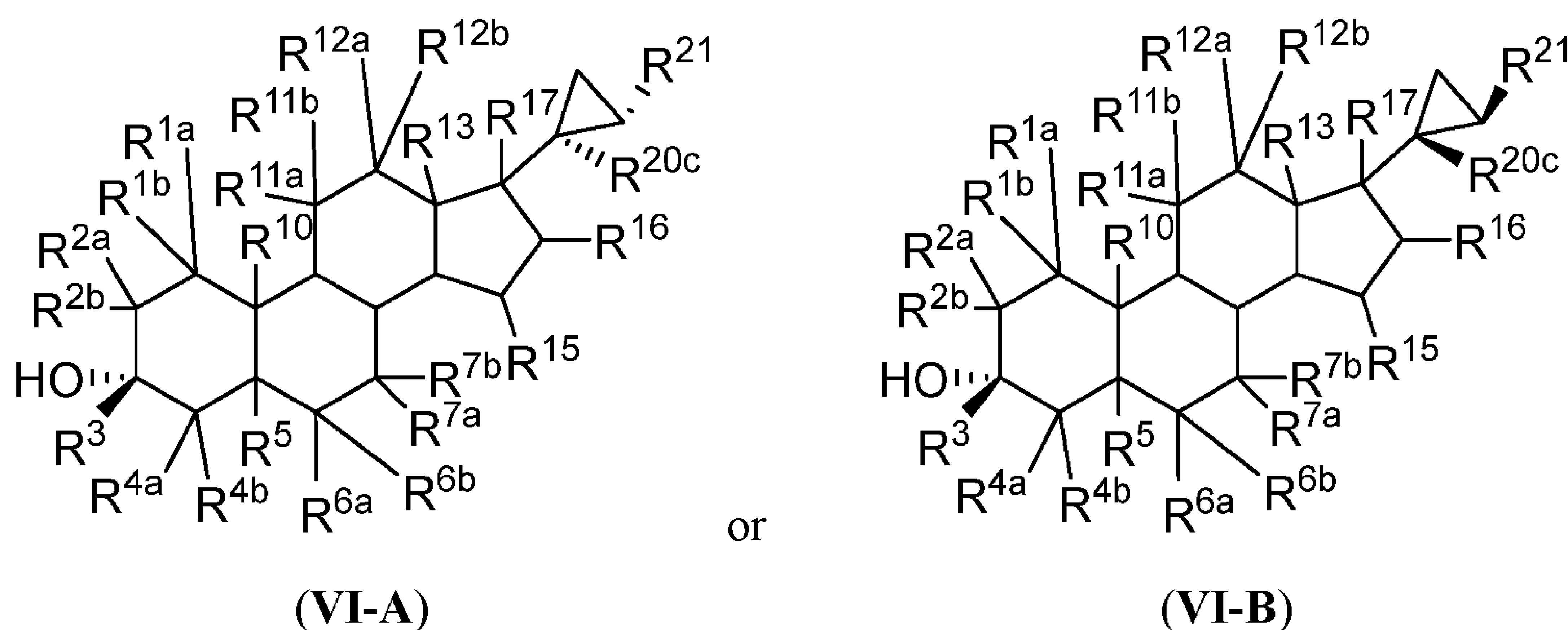
119. The compound or pharmaceutically acceptable salt of any one of claims 99-118, wherein R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond or $-\text{CH}_2-$; and R^{30} is a 5-6-membered partially unsaturated or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-2 groups independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$.

120. The compound or pharmaceutically acceptable salt of any one of claims 99-119, wherein

R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond or $-\text{CH}_2-$; and R^{30} is , wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that

- (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and
- (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$.

121. The compound of pharmaceutically acceptable salt of claim 99, wherein the compound of Formula (VI) is a compound of Formula (VI-A) or (VI-B)



or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , and R^{17} is independently selected from $-H$ and C_{1-6} alkyl;

R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

Each of R^5 and R^{20c} is independently selected from $-H$ and methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

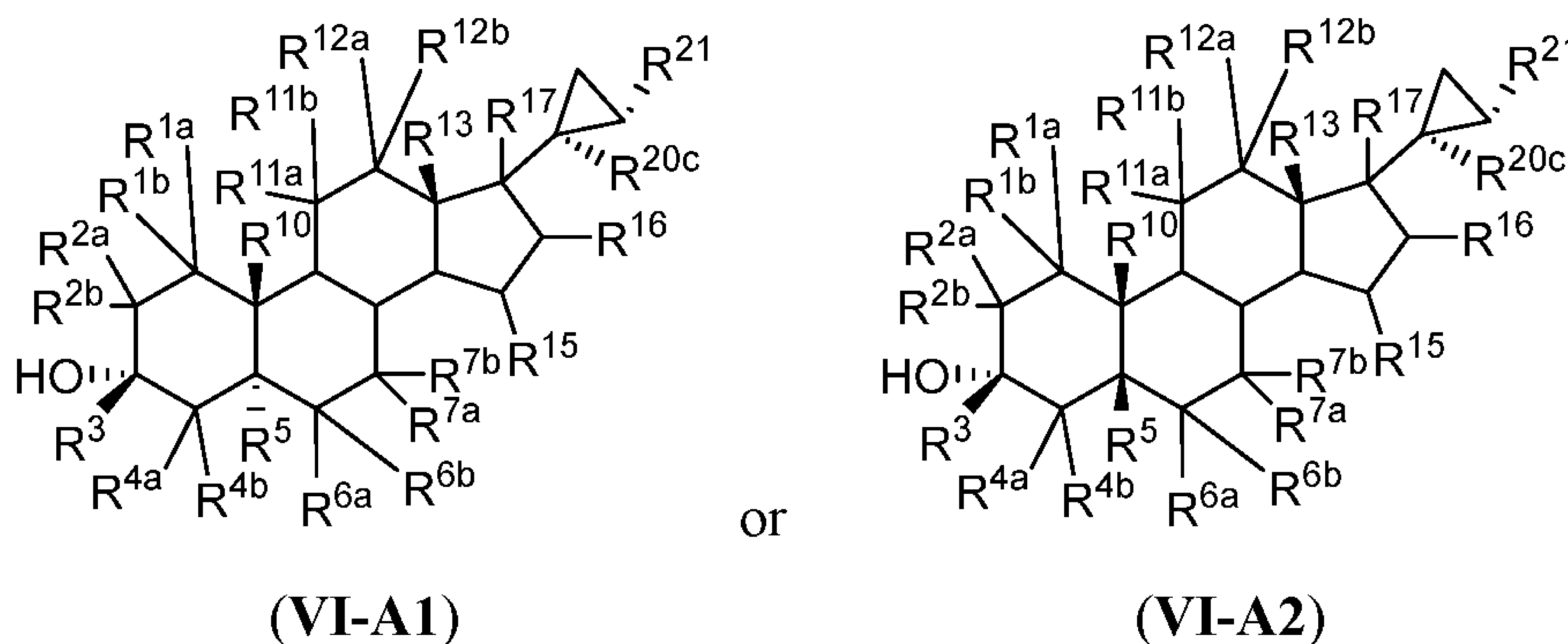
R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and

Each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

122. The compound or pharmaceutically acceptable salt of claim 121, wherein the compound of Formula (VI-A) is a compound of Formula (VI-A1) or (VI-A2)



or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , and R^{17} is independently selected from $-H$ or C_{1-6} alkyl;

R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

Each of R^5 and R^{20c} is independently selected from $-H$ and methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

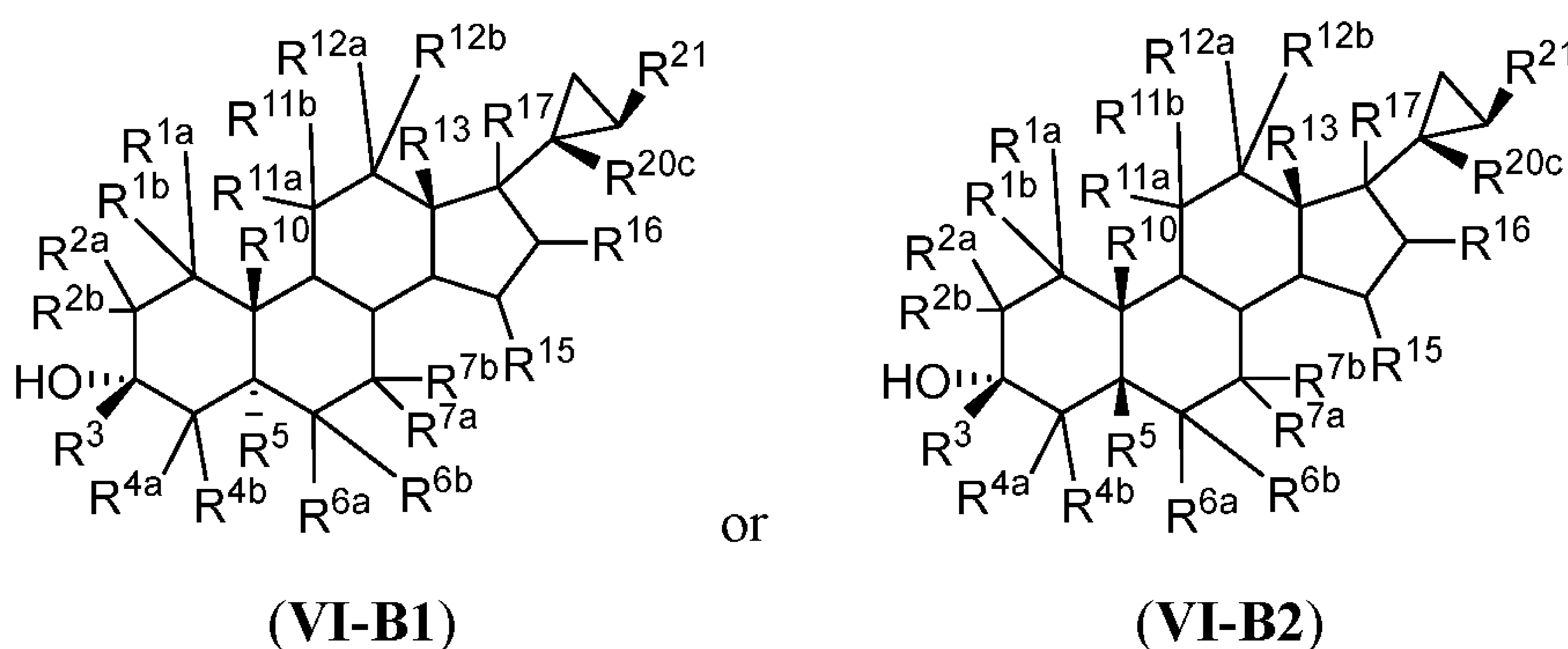
R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$ -;

R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and

Each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

123. The compound or pharmaceutically acceptable salt of claim 121, wherein the compound of Formula (VI-B) is a compound of Formula (VI-B1) or (VI-B2)



or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , and R^{17} is independently selected from $-H$ or C_{1-6} alkyl;

R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

Each of R^5 and R^{20c} is independently selected from $-H$ and methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

R^{21} is $-L^A-R^{30}$;

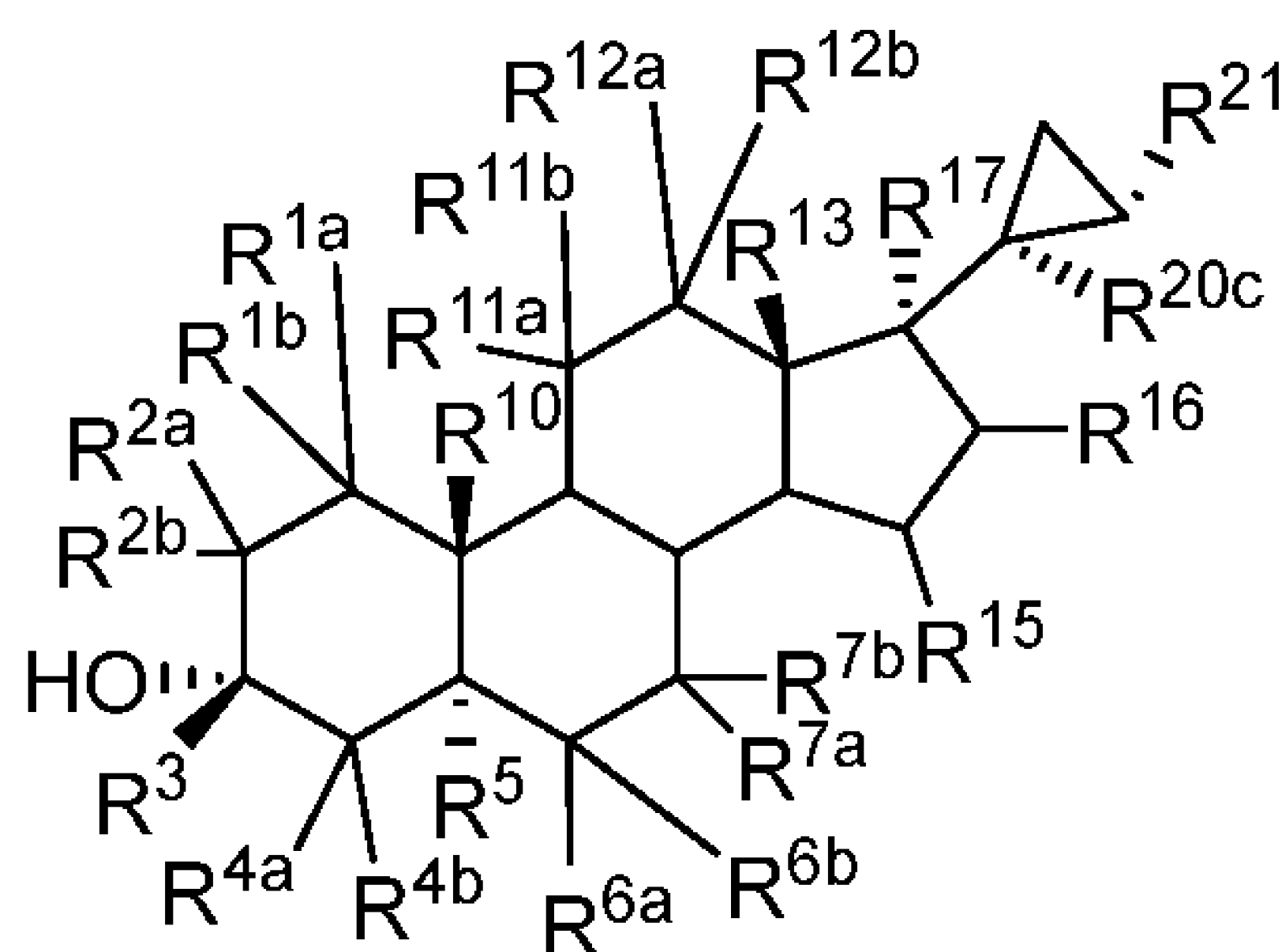
L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by

–NR'–, –S–, –O–, –OC(O)–, –C(O)O–, –C(O)–, –C(O)C(O)–, –C(O)NR'–, –NR'C(O)–, –NR'C(O)O–, –S(O)₂NR'–, –NR'S(O)₂–, –C(O)NR'NR'–, –NR'C(O)NR'–, –OC(O)NR'–, –NR'NR'–, –NR'S(O)₂NR'–, –S(O)–, or –S(O)₂–;

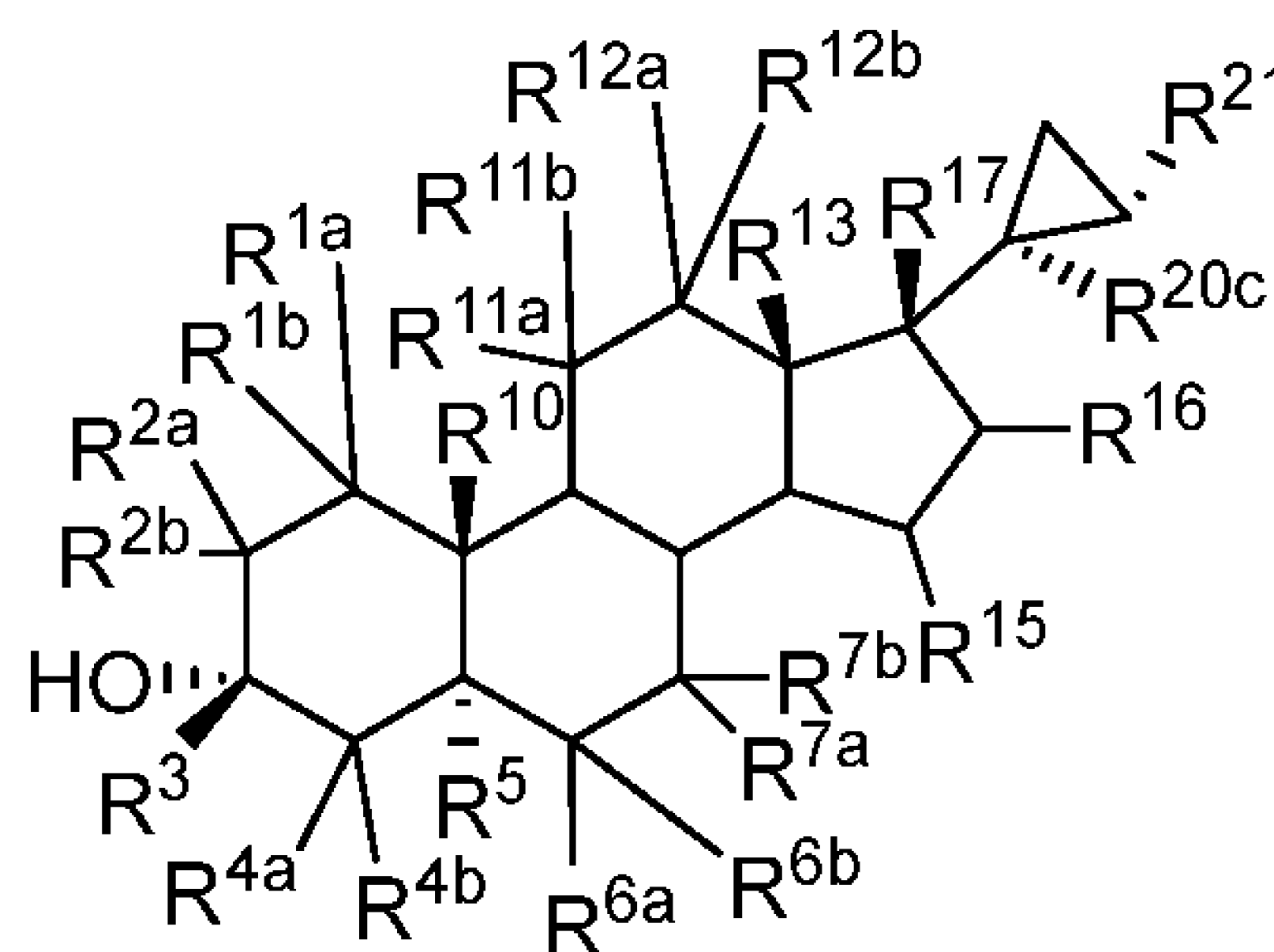
R³⁰ is R', halo, –CN, –NO₂, or –CF₃; and

Each R' is independently selected from –H, C₁₋₆ alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, –OH, –CN, –NO₂, –CF₃, and –CH₃.

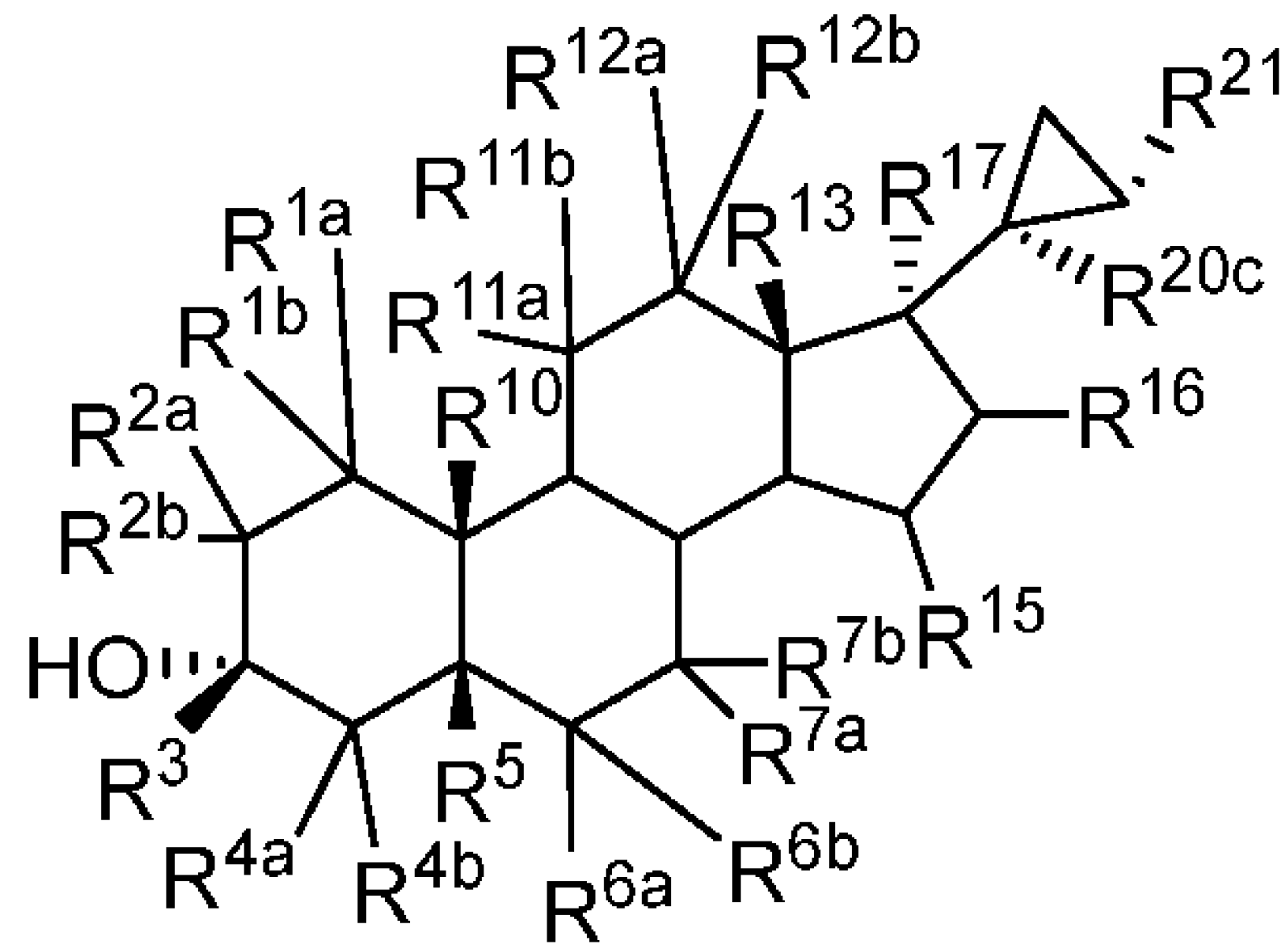
124. The compound or pharmaceutically acceptable salt of claim 121 wherein the compound of Formula (VI-A) is a compound of Formula (VI-A1a), (VI-A1b), (VI-A1c), or (VI-A1d)



(VI-A1a),

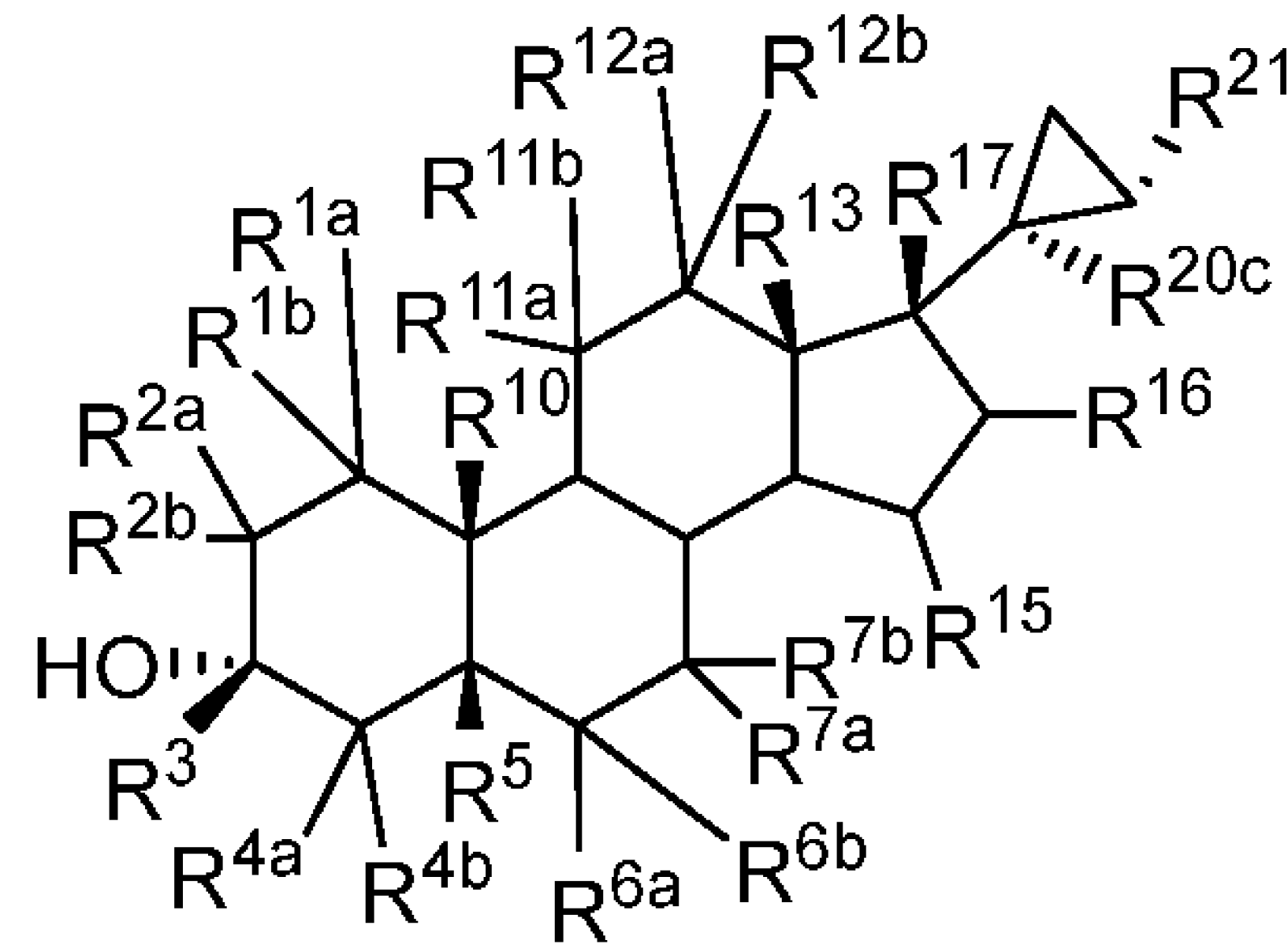


(VI-A1b),



(VI-A1c),

or



(VI-A1d),

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{4a}, R^{4b}, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R¹³, R¹⁵, R¹⁶, and R¹⁷ is independently selected from –H and C₁₋₆ alkyl;

R³ is –H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₁₋₆ alkyl-O-C₁₋₆ alkyl;

Each of R⁵ and R^{20c} is independently selected from –H and methyl;

R¹⁰ is –H, C₁₋₃ alkyl, or C₁₋₆ alkyl-O-C₁₋₃ alkyl;

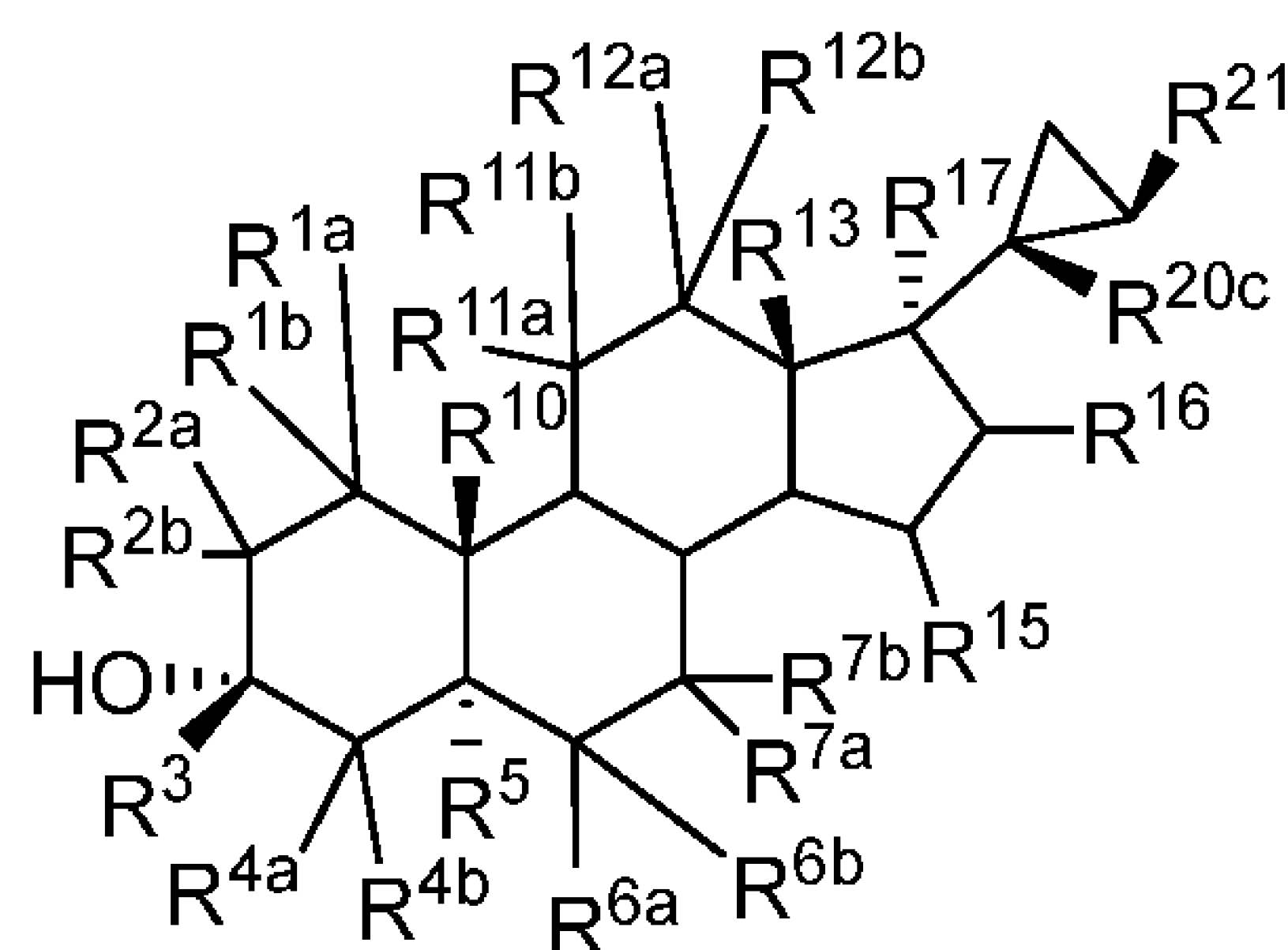
R²¹ is –L^A-R³⁰;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

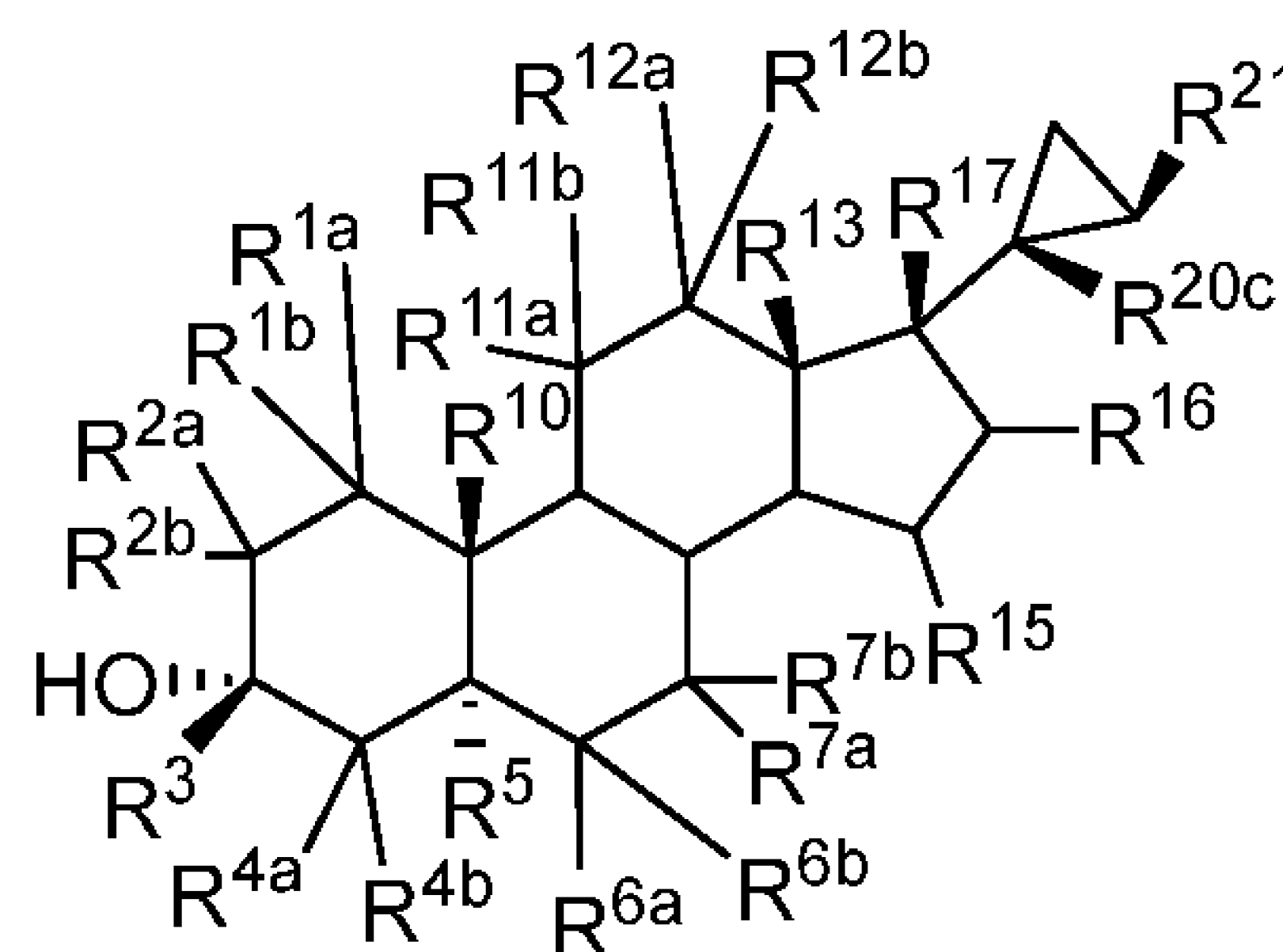
R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and

Each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

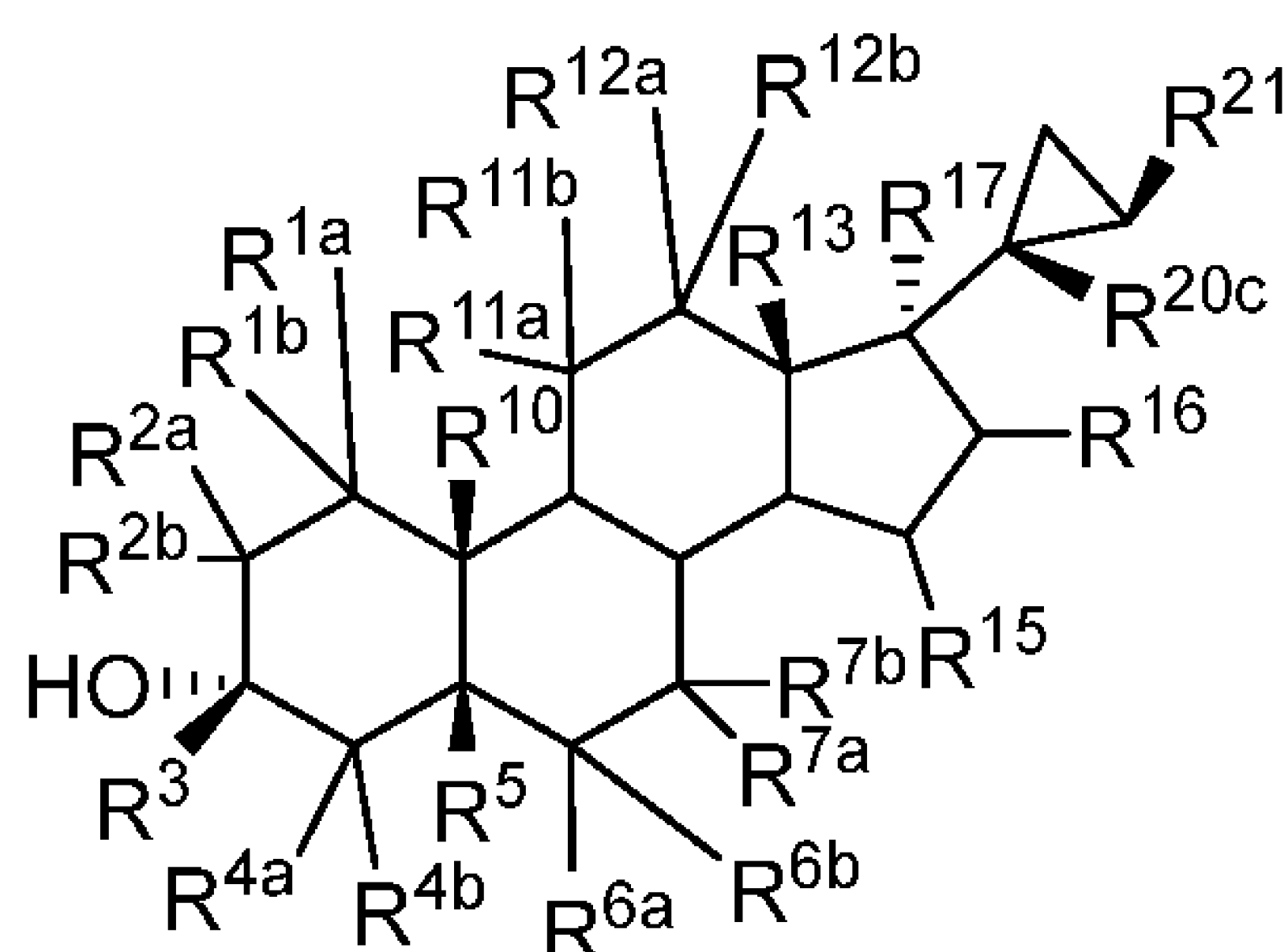
125. The compound or pharmaceutically acceptable salt of claim 121, wherein the compound of Formula (VI-B) is a compound of Formula (VI-B1a), (VI-B1b), (VI-B1c), or (VI-B1d)



(VI-B1a),

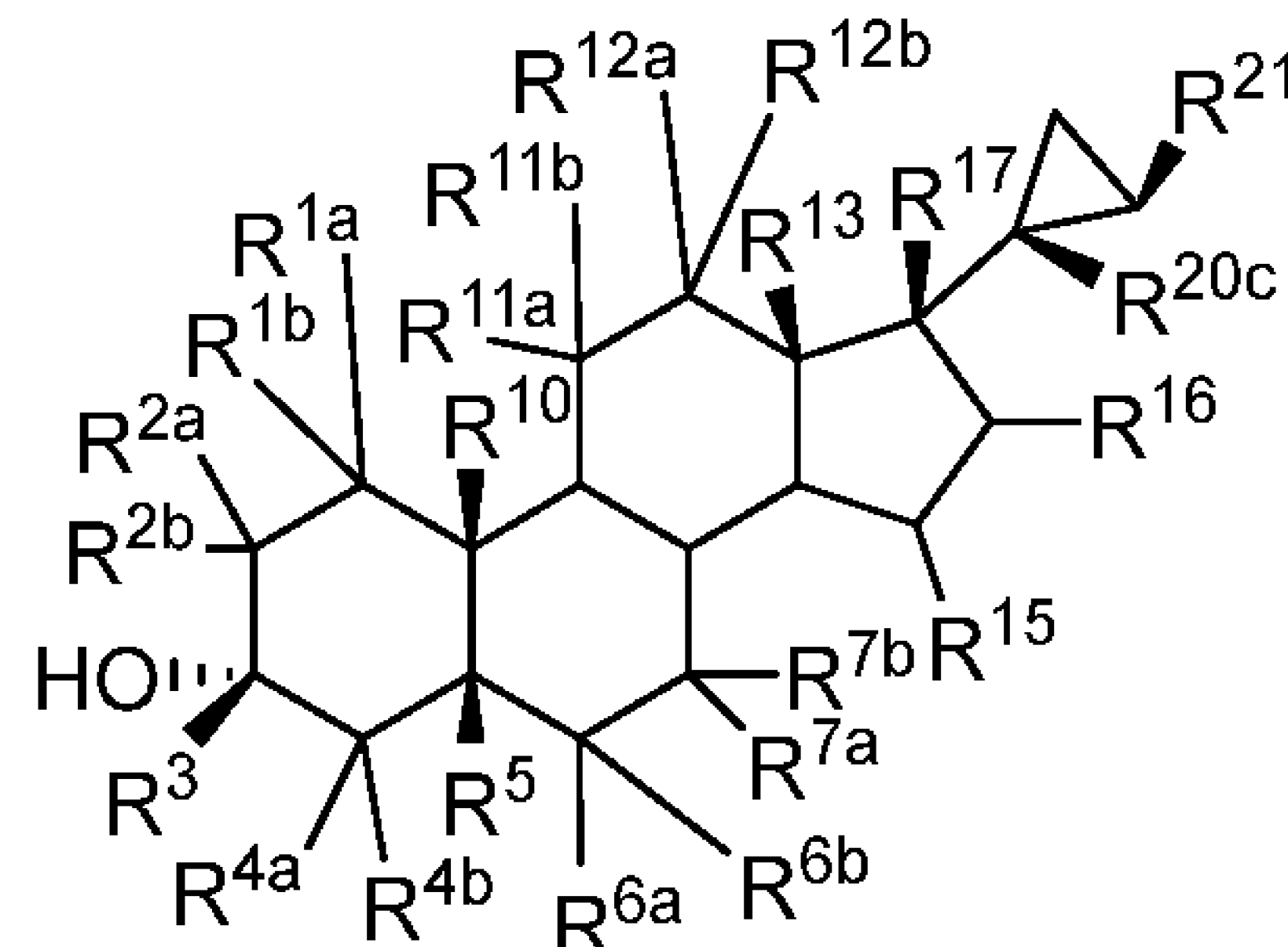


(VI-B1b),



(VI-B1c),

or



(VI-B1d),

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^{4a} , R^{4b} , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{11a} , R^{11b} , R^{12a} , R^{12b} , R^{13} , R^{15} , R^{16} , and R^{17} is independently selected from $-H$ and C_{1-6} alkyl;

R^3 is $-H$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

Each of R^5 and R^{20c} is independently selected from $-H$ and methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

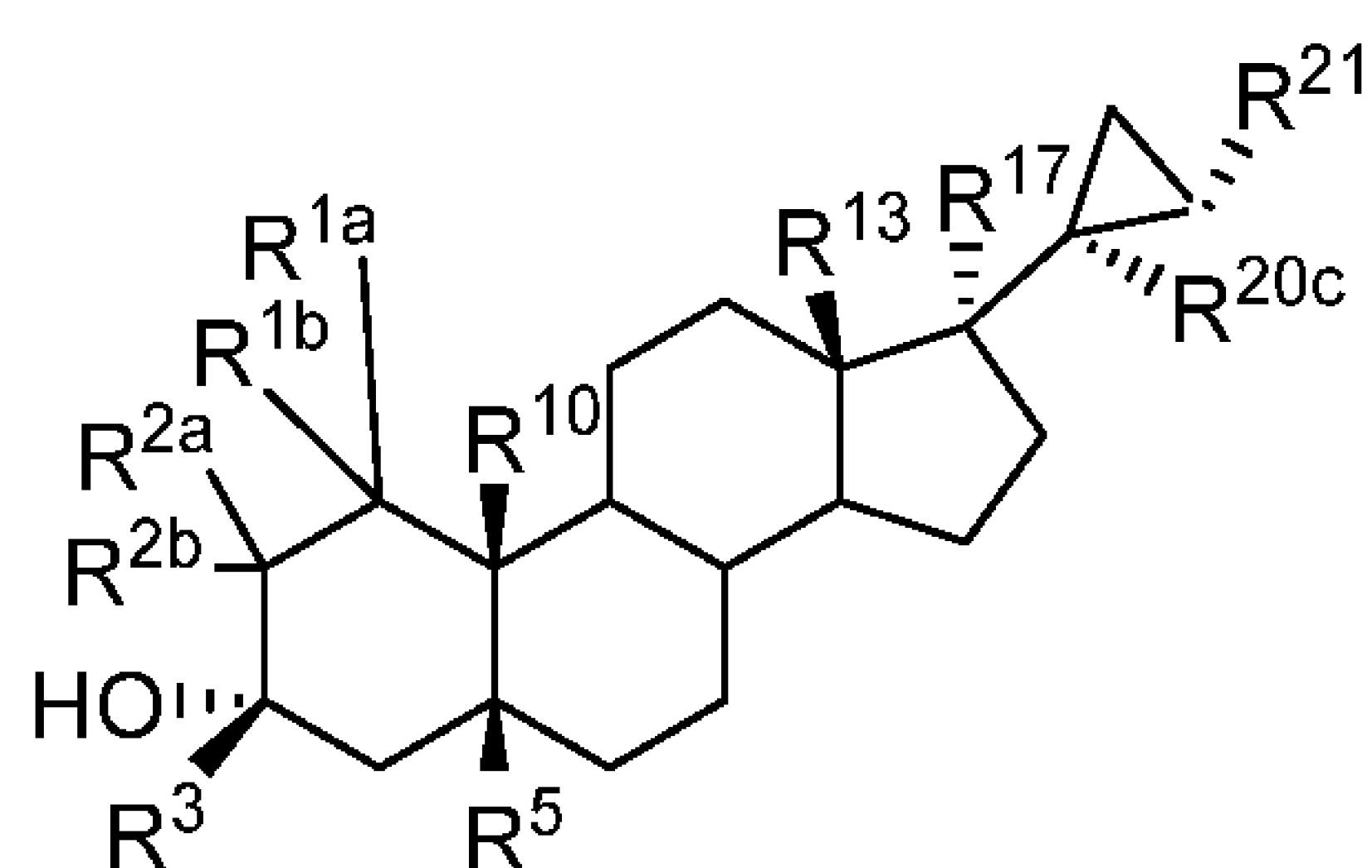
R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain, wherein up to two carbon atoms of L^A are optionally and independently replaced by $-NR'$ -, $-S$ -, $-O$ -, $-OC(O)$ -, $-C(O)O$ -, $-C(O)$ -, $-C(O)C(O)$ -, $-C(O)NR'$ -, $-NR'C(O)$ -, $-NR'C(O)O$ -, $-S(O)_2NR'$ -, $-NR'S(O)_2$ -, $-C(O)NR'NR'$ -, $-NR'C(O)NR'$ -, $-OC(O)NR'$ -, $-NR'NR'$ -, $-NR'S(O)_2NR'$ -, $-S(O)$ -, or $-S(O)_2$;

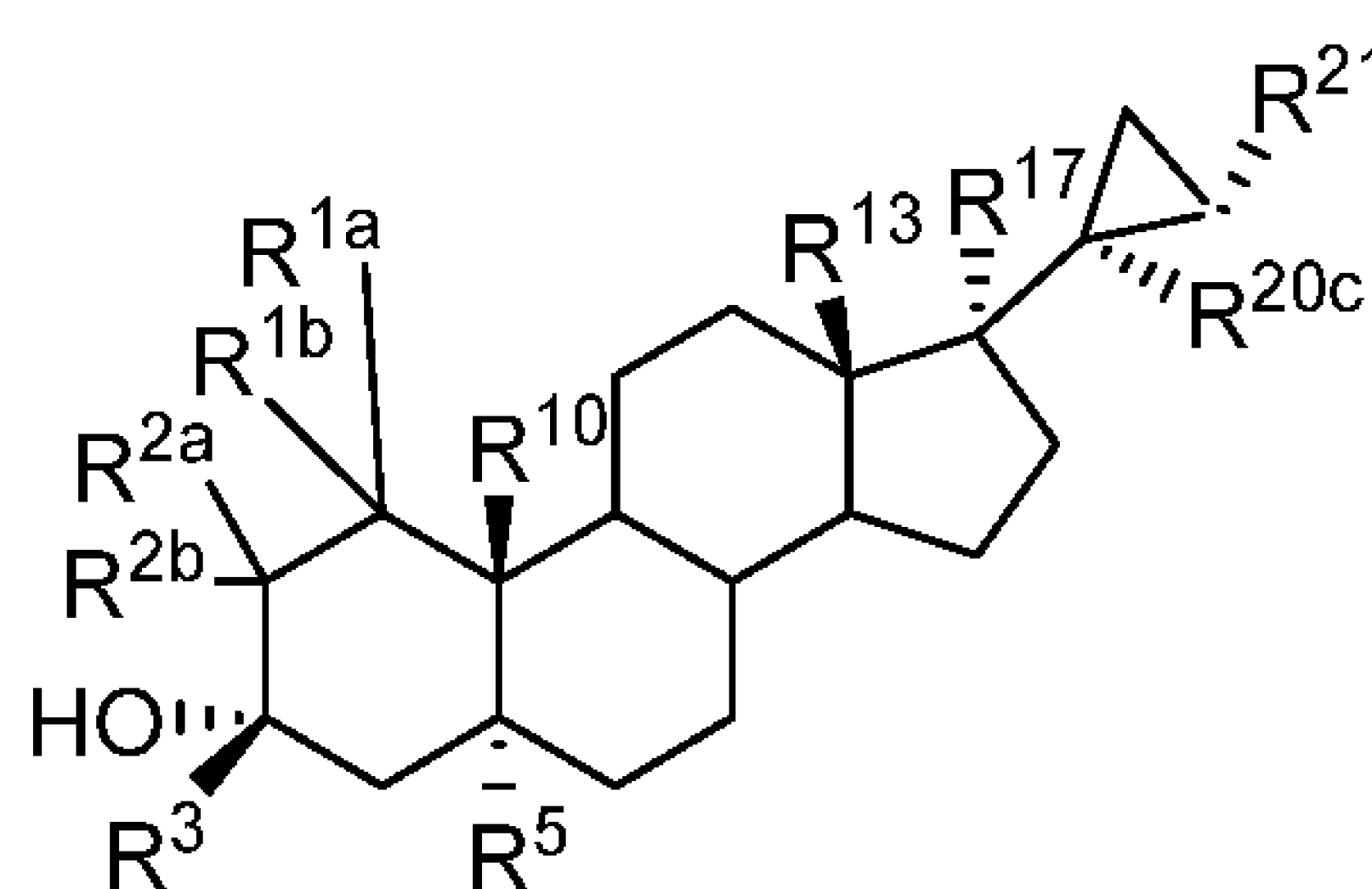
R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and

Each R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein each alkyl or 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

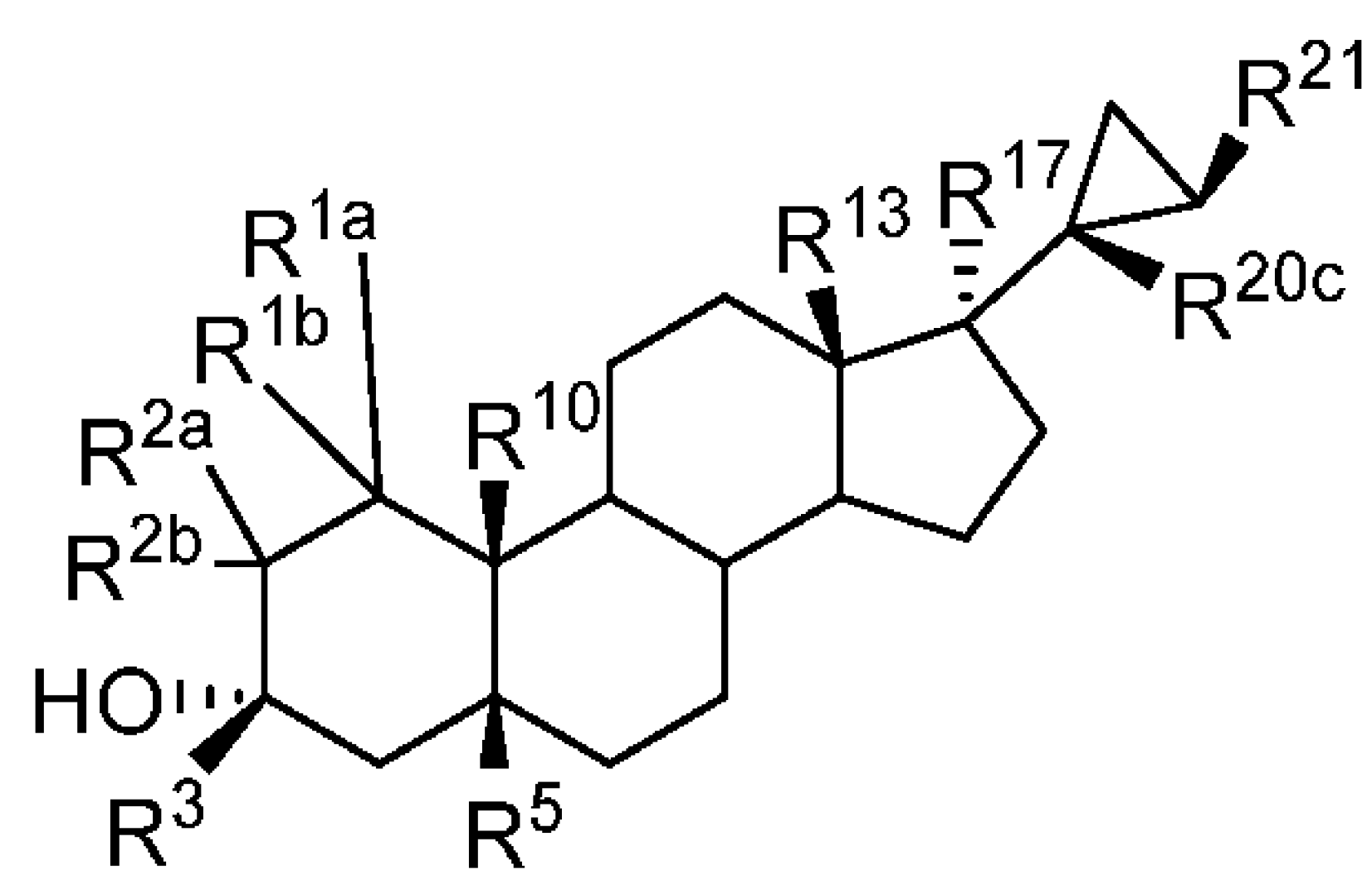
126. The compound or pharmaceutically acceptable salt of claim 99, wherein the compound of Formula (VI) is a compound of Formula (VI-A3a), (VI-A3b), (VI-B3a), or (VI-B3b)



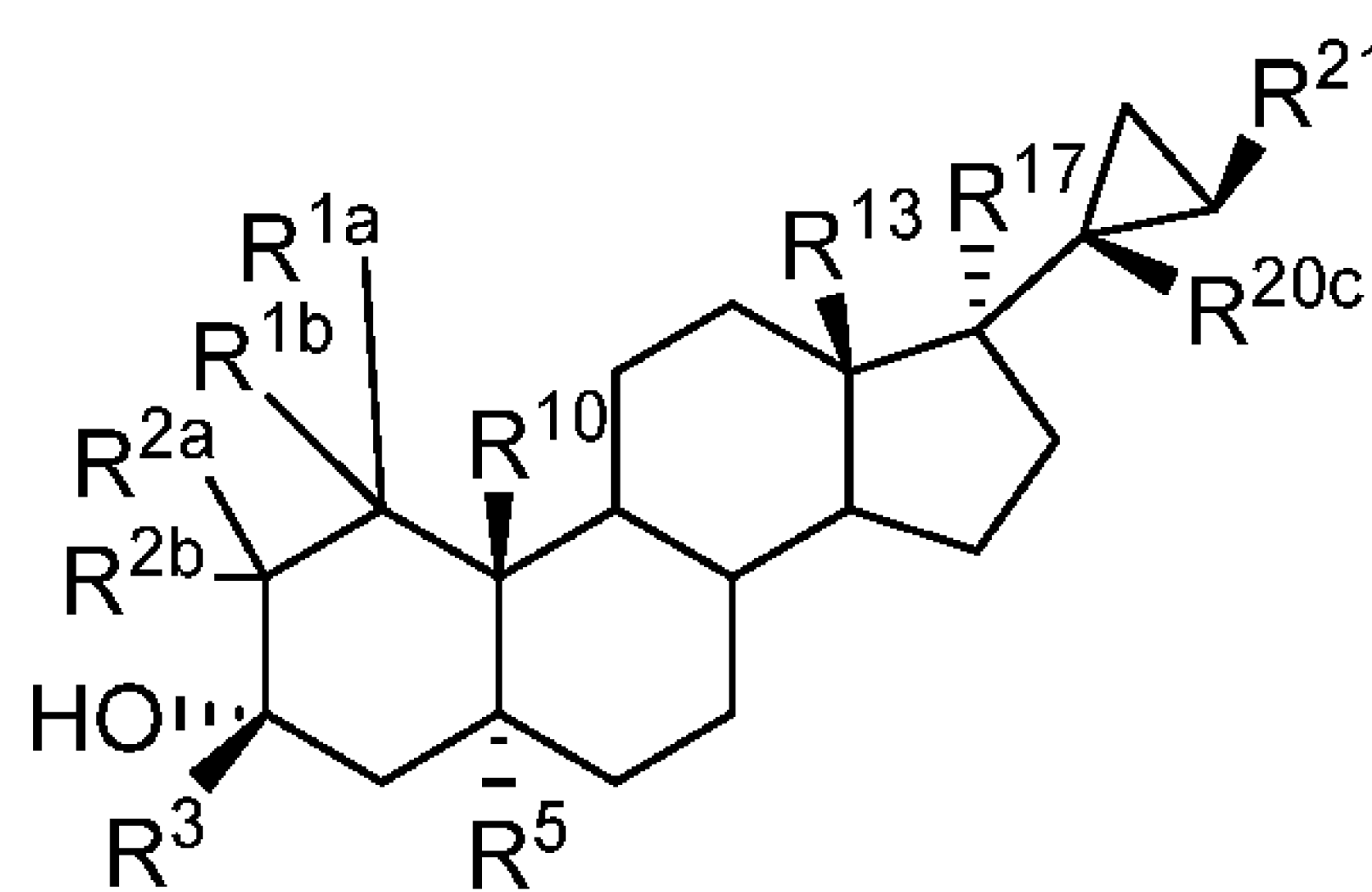
(VI-A3a),



(VI-A3b),



(VI-B3a),



(VI-B3b),

or

or a pharmaceutically acceptable salt thereof, wherein

Each of R^{1a} , R^{1b} , R^{2a} , and R^{2b} is independently selected from $-H$ and C_{1-3} alkyl;

R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

Each of R^5 , R^{13} , R^{17} , and R^{20c} is independently selected from $-H$ and methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-6} alkyl- O - C_{1-3} alkyl;

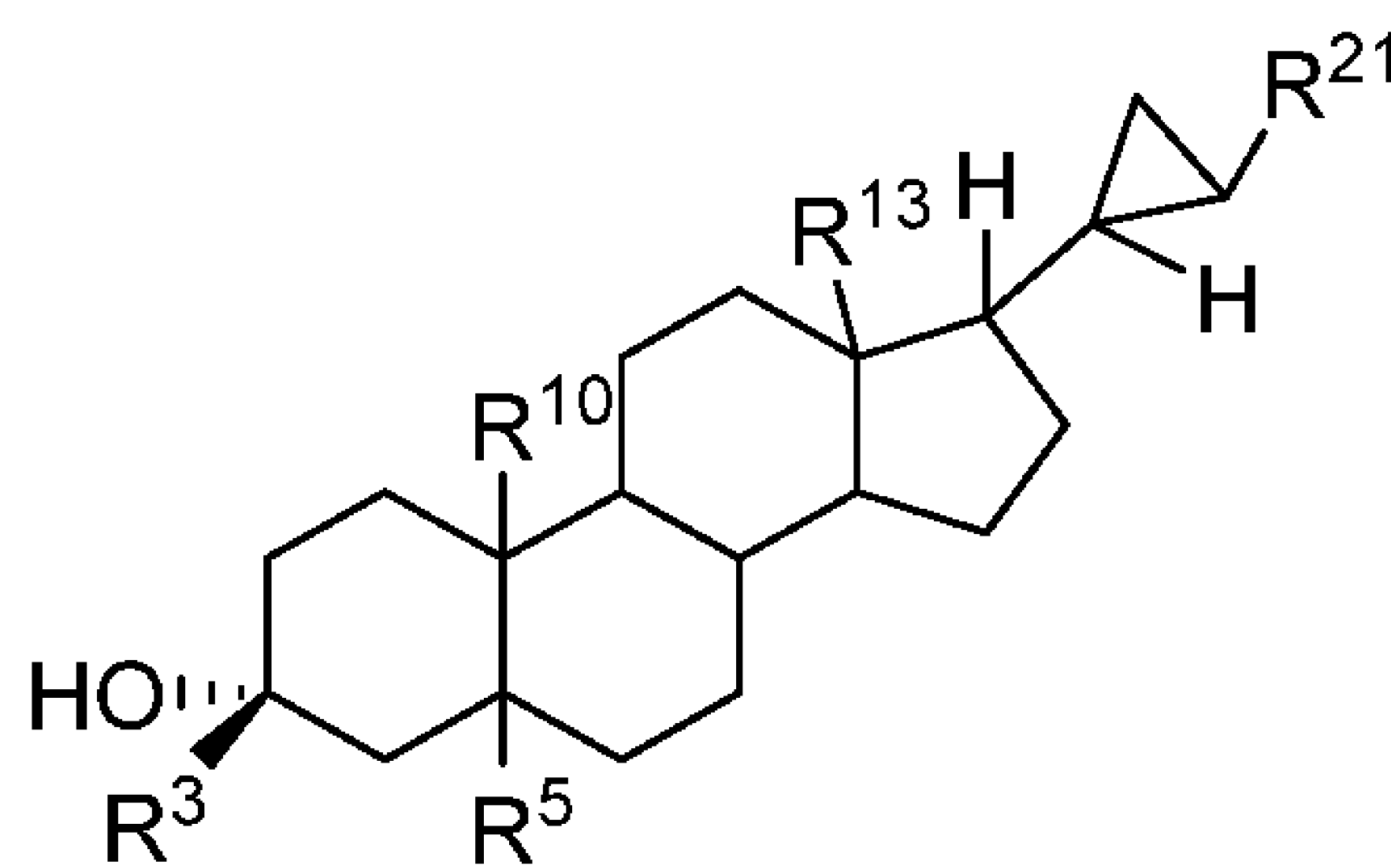
R^{21} is $-L^A-R^{30}$;

L^A is a bond or a straight C_{1-3} alkylene chain;

R^{30} is R' , halo, $-CN$, $-NO_2$, or $-CF_3$; and

R' is independently selected from $-H$, C_{1-6} alkyl, and a 3-8-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 nitrogen atoms, wherein the 3-8-membered ring of R' is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, and $-CH_3$.

127. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound of Formula (I) is a compound of Formula (VII)



(VII)

or a pharmaceutically acceptable salt thereof, wherein

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

Each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl;

R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

128. The compound or pharmaceutically acceptable salt of claim 127, wherein R^{13} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl.

129. The compound or pharmaceutically acceptable salt claim 127 or claim 128, wherein R^{13} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl.

130. The compound or pharmaceutically acceptable salt of any one of claims 127-129, wherein R^{13} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl.

131. The compound or pharmaceutically acceptable salt of any one of claims 127-130, wherein R^{13} is methyl.

132. The compound or pharmaceutically acceptable salt of any one of claims 127-131, wherein R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-3} alkylene chain, or $-N(H)-$; and

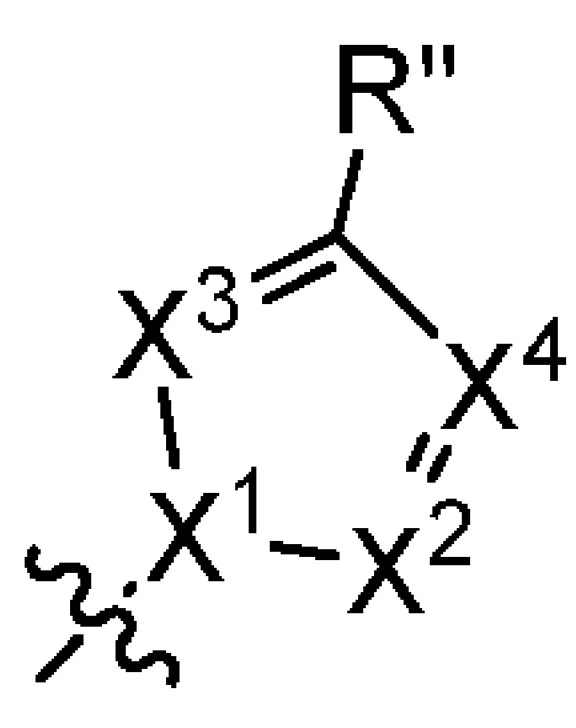
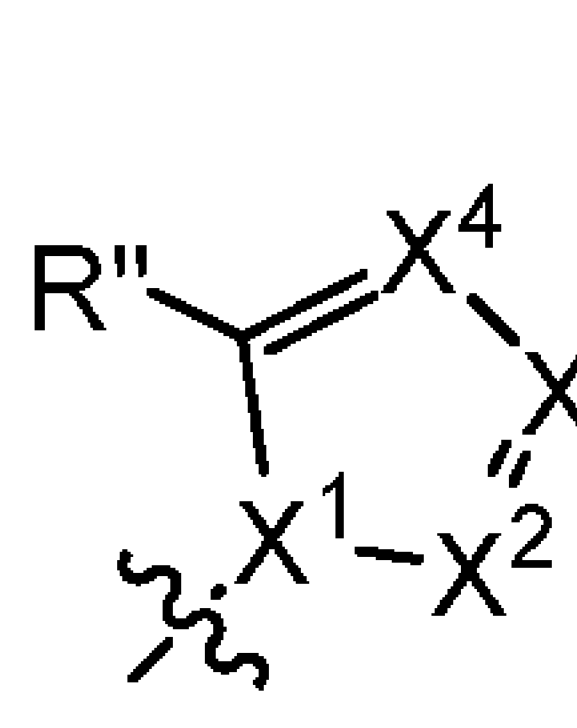
R^{30} is $-H$, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 5-6 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

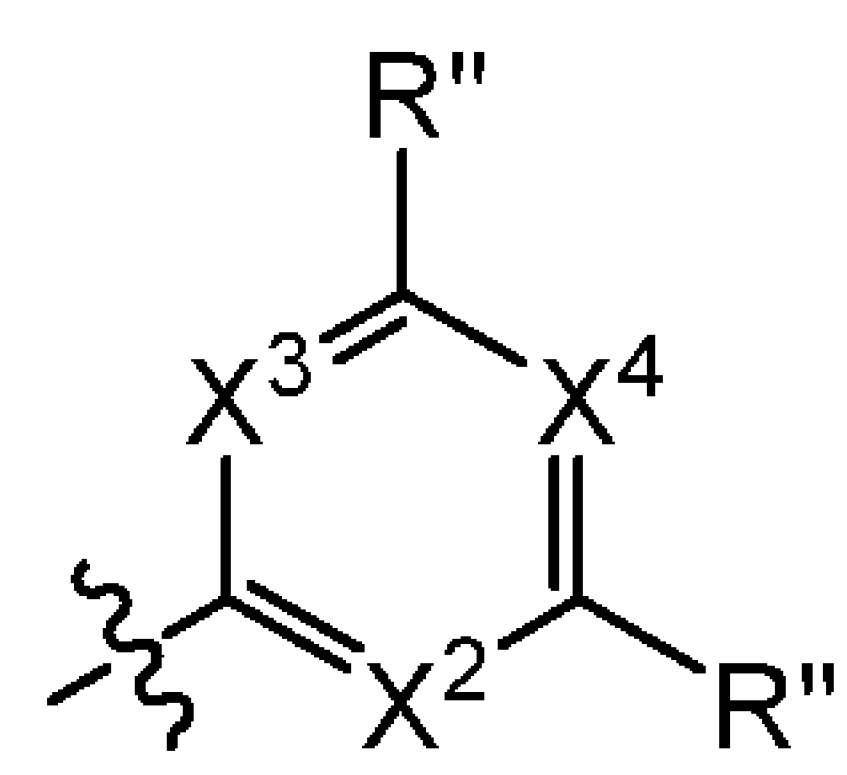
133. The compound or pharmaceutically acceptable salt of any one of claims 127-132, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, or $-N(H)-$; and R^{30} is $-H$ or a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

134. The compound or pharmaceutically acceptable salt of any one of claims 127-133, wherein R^{21} is $-L^A-R^{30}$; L^A is a bond, $-CH_2-$, $-CH_2-CH_2-$, or $-N(H)-$; and R^{30} is a 5-6-membered partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms,

wherein the 5-6-membered ring is optionally substituted with 1-3 groups independently selected from $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$.

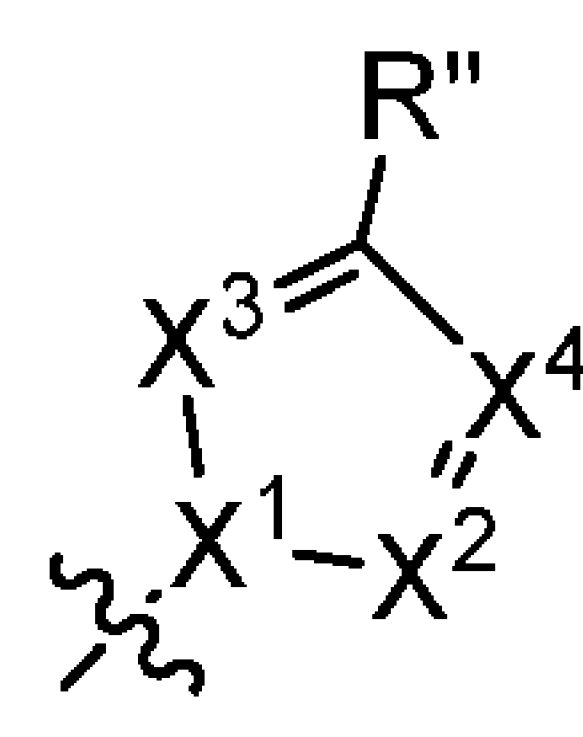
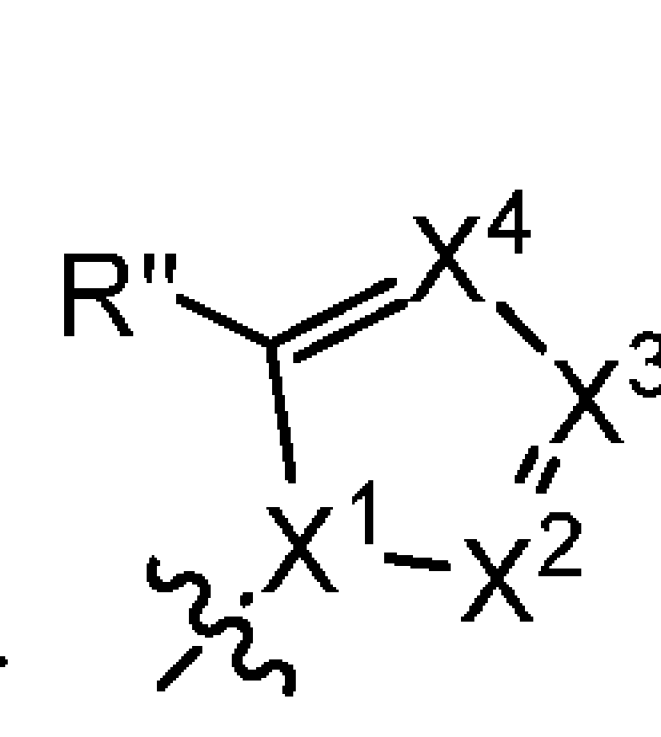
135. The compound or pharmaceutically acceptable salt of any one of claims 127-134,

wherein R^{21} is $-\text{L}^{\text{A}}-\text{R}^{30}$; L^{A} is a bond, $-\text{CH}_2-$, or $-\text{N}(\text{H})-$; and R^{30} is , , or

, wherein each of X^1 , X^2 , X^3 , and X^4 is independently N or CR'' , wherein each R'' is independently selected from $-\text{H}$, halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{C}(\text{CH}_3)_3$, provided that

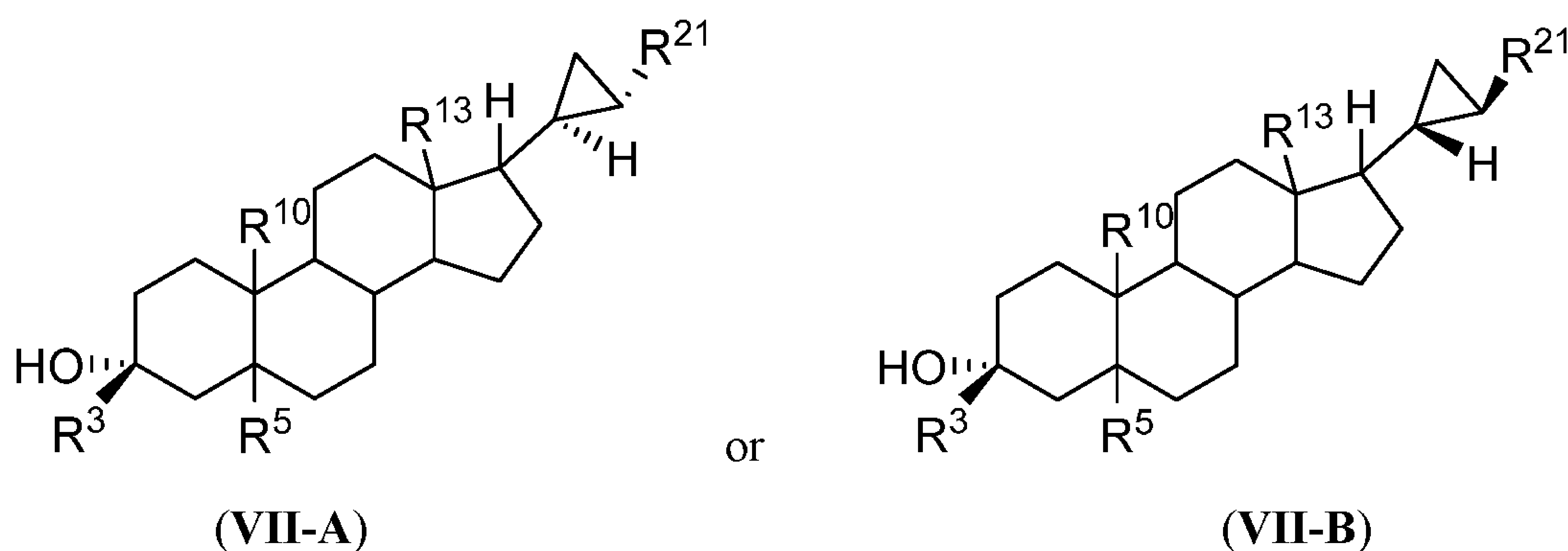
- (i) at least one of X^1 , X^2 , X^3 , and X^4 is N, and
- (ii) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$.

136. The compound or pharmaceutically acceptable salt of claim 134, wherein R^{30} is

 or , X^1 is N; and each of X^2 , X^3 , and X^4 is independently selected from N or CR'' , wherein each R'' is independently selected from $-\text{H}$, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$, provided that

- (i) no greater than 2 instances of R'' are independently selected from halo, $-\text{OH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CH}_3$, and $-\text{CH}_2\text{OH}$.

137. The compound or pharmaceutically acceptable salt of claim 127, wherein the compound of Formula (VII) is a compound of Formula (VII-A) or (VII-B)



or a pharmaceutically acceptable salt thereof, wherein

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

Each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl;

R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

138. The compound or pharmaceutically acceptable salt of claim 137, wherein

R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

R^5 is $-H$ or methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$, or C_{1-3} alkyl;

R^{21} is $-L^A-R^{30}$;

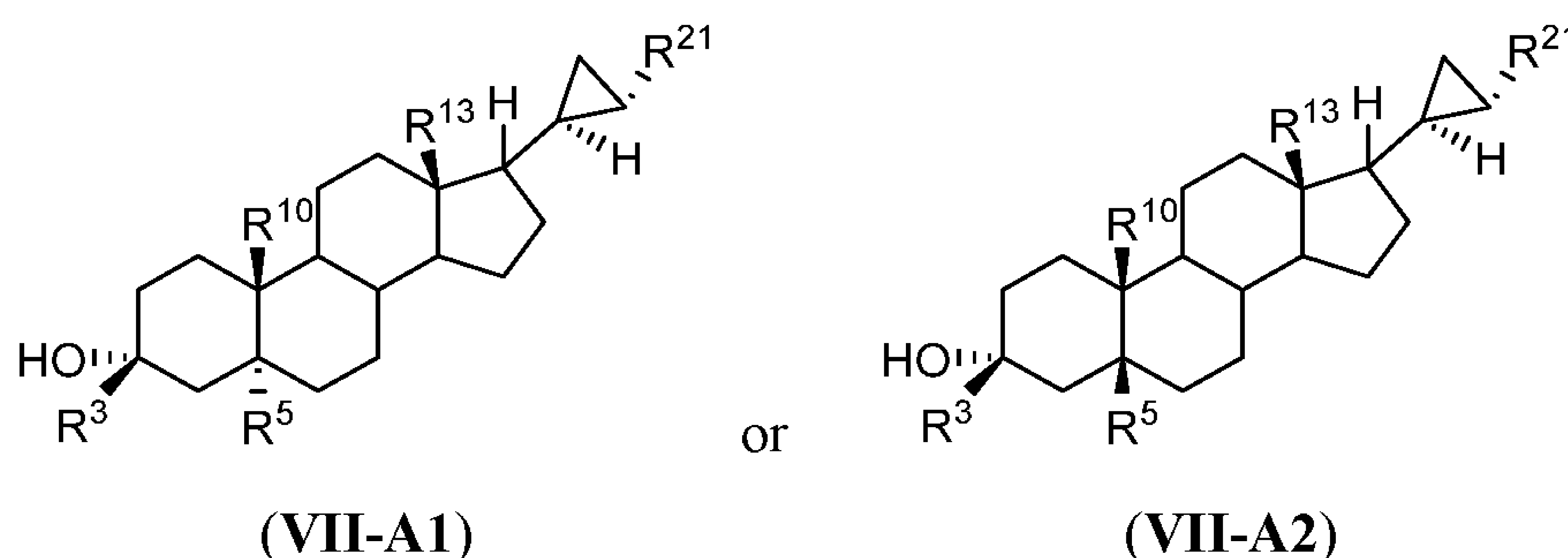
L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain;

and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-

membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

139. The compound or pharmaceutically acceptable salt of claim 137, wherein the compound of Formula (VII-A) is a compound of Formula (VII-A1) or (VII-A2)



or a pharmaceutically acceptable salt thereof, wherein

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

Each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl;

R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

140. The compound or pharmaceutically acceptable salt of claim 139, wherein

R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

R^5 is $-H$ or methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

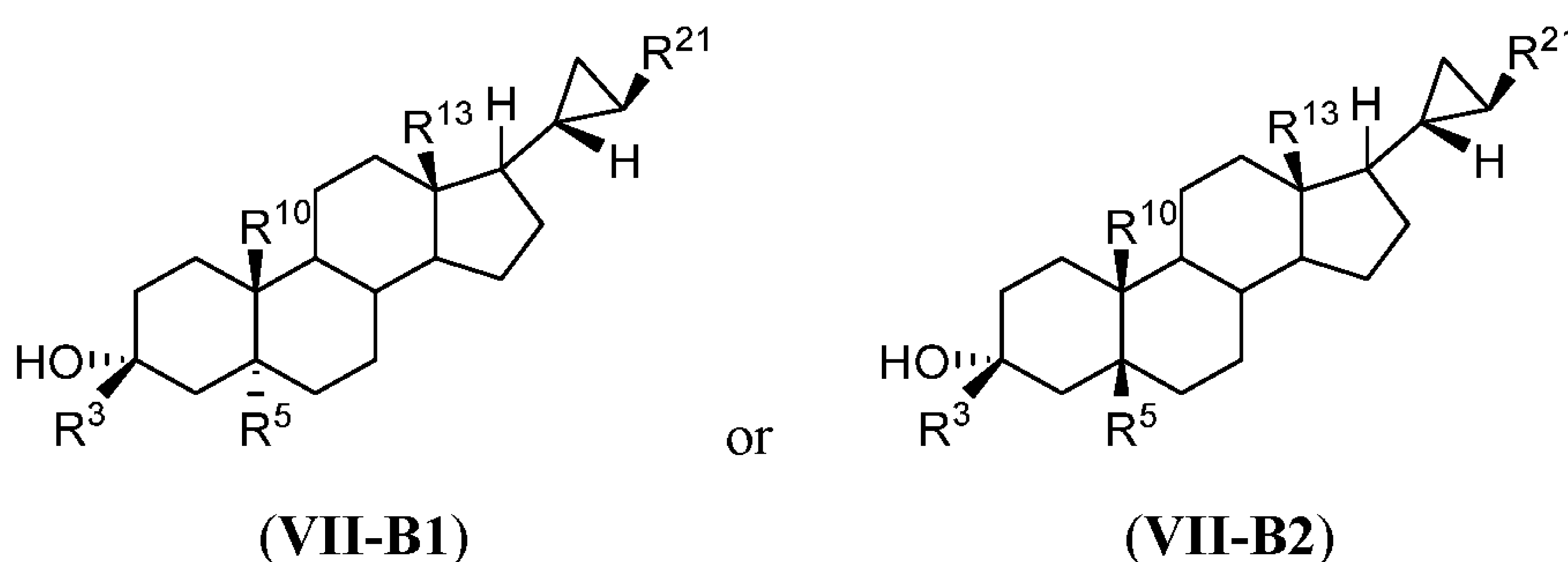
R^{13} is $-H$, or C_{1-3} alkyl;

R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain;
and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

141. The compound or pharmaceutically acceptable salt of claim 137, wherein the compound of Formula (VII-B) is a compound of Formula (VII-B1) or (VII-B2)



or a pharmaceutically acceptable salt thereof, wherein

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

Each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl;

R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

142. The compound or pharmaceutically acceptable salt of claim 141, wherein

R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

R^5 is $-H$ or methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$, or C_{1-3} alkyl;

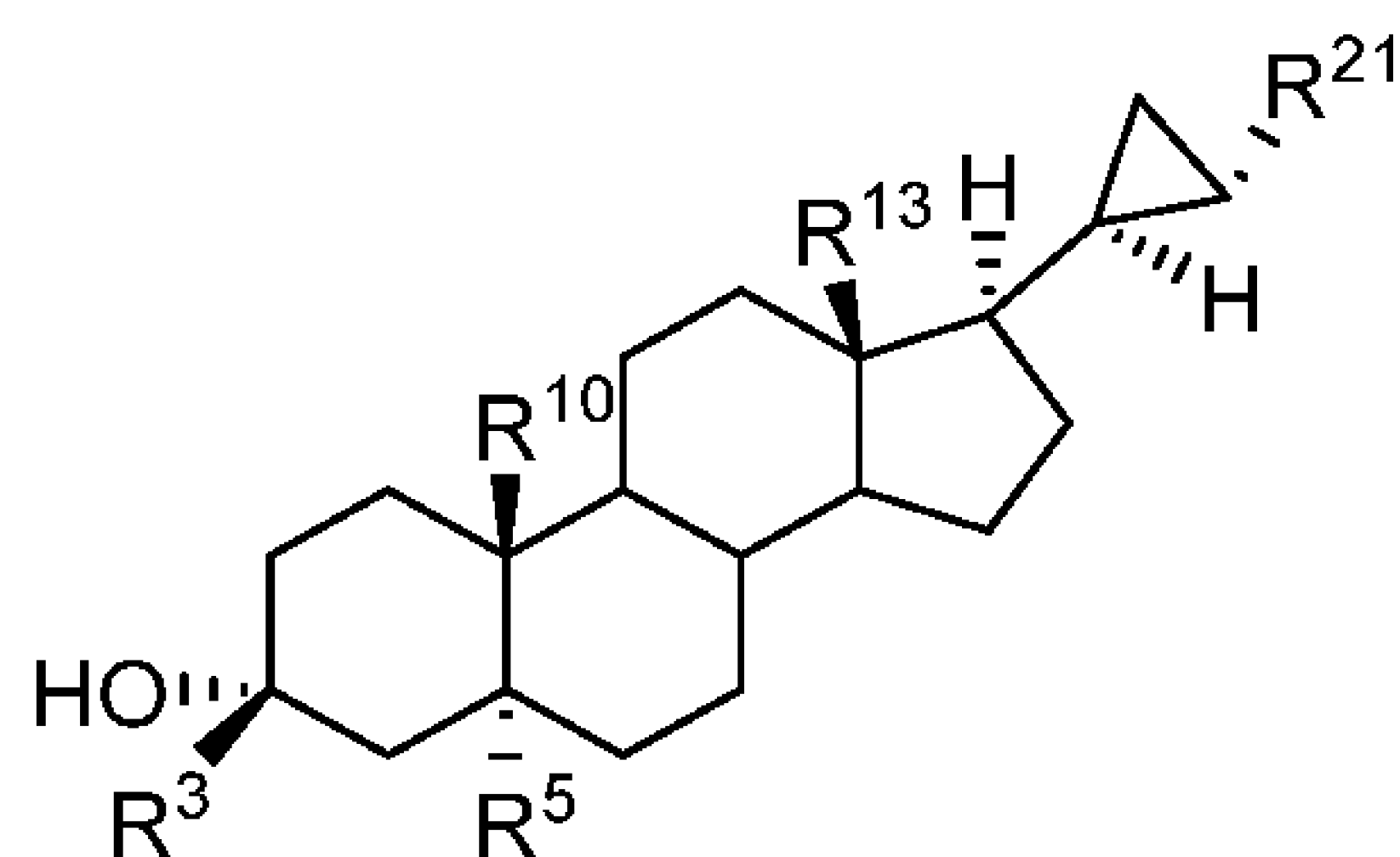
R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain;

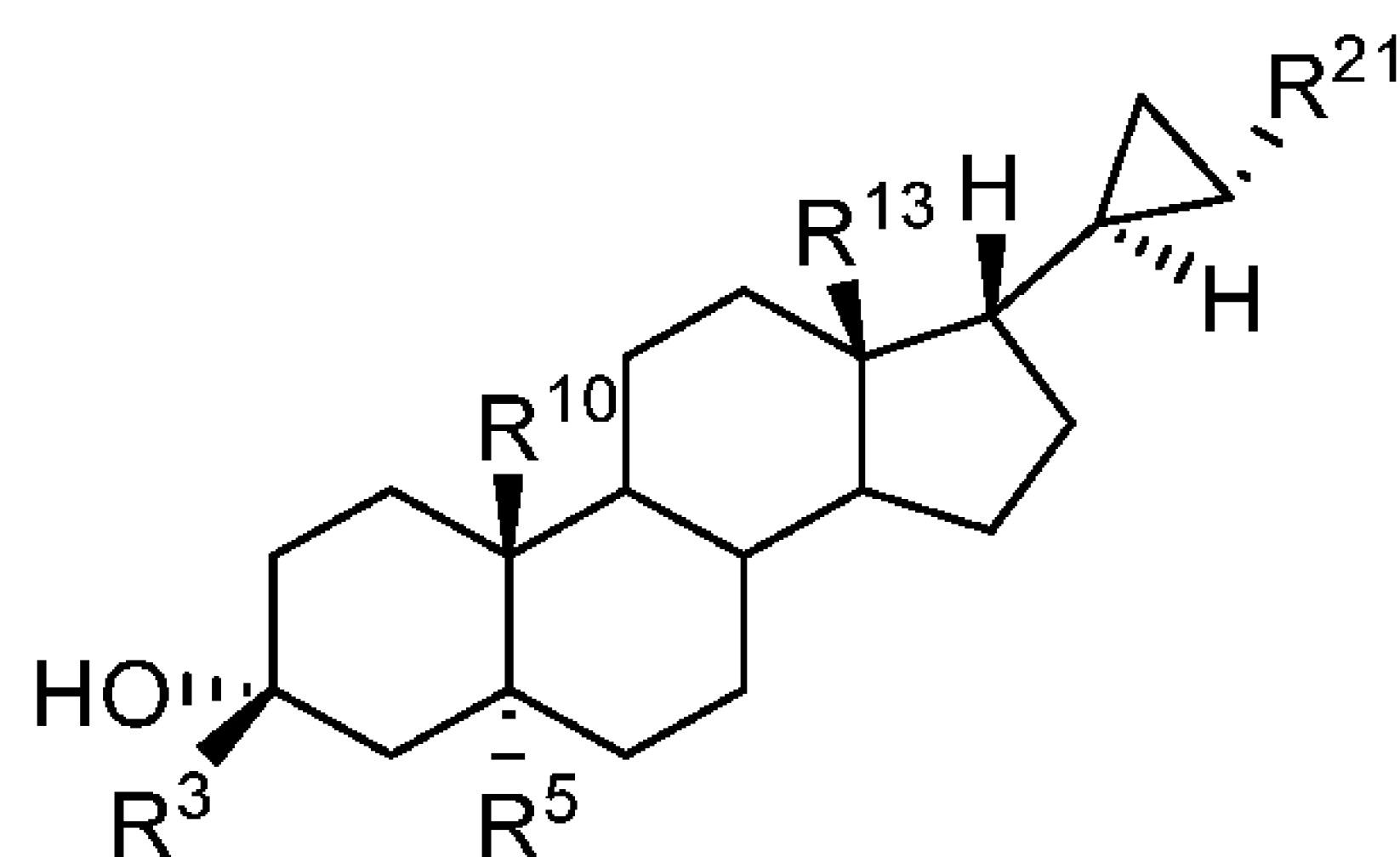
and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

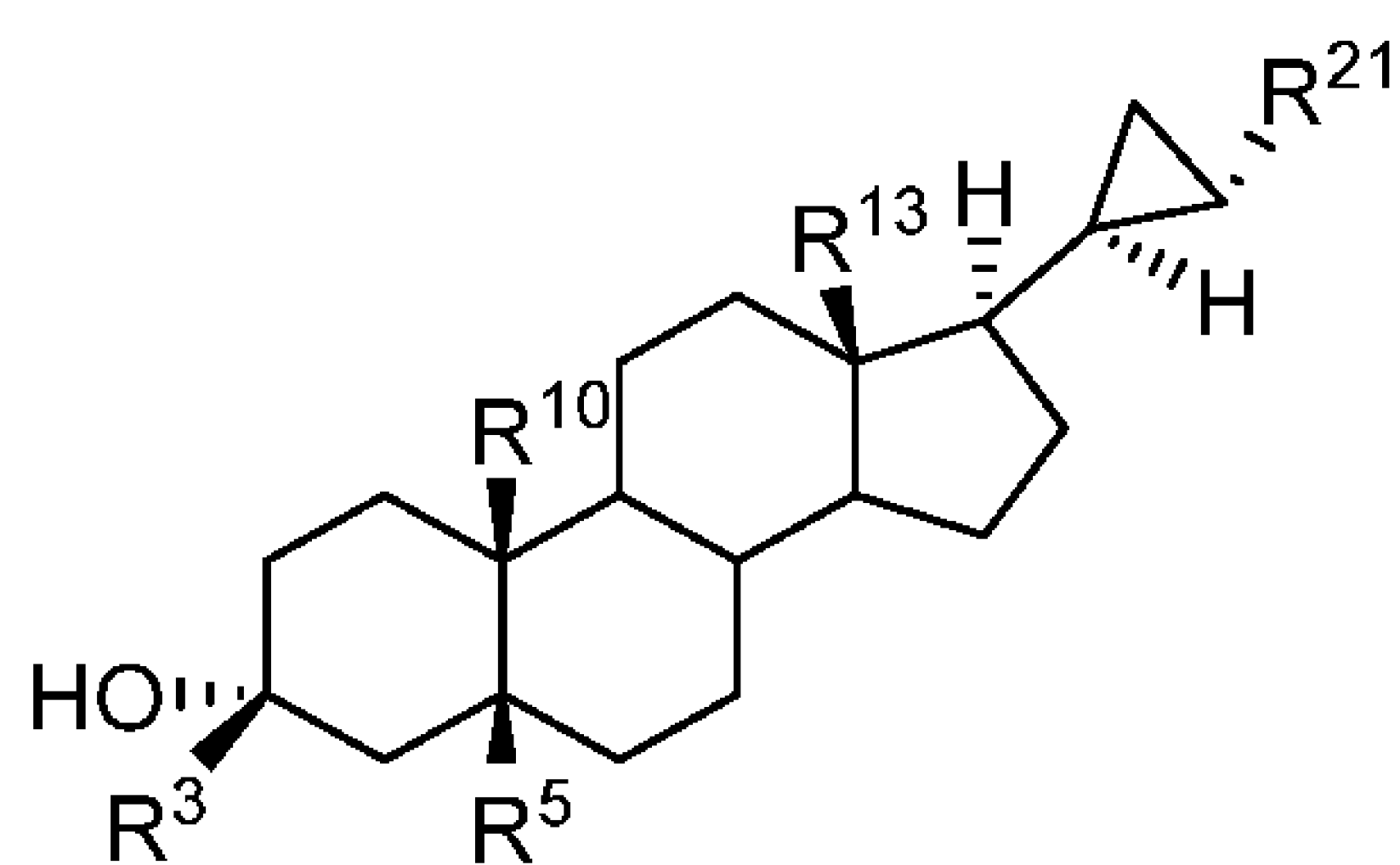
143. The compound or pharmaceutically acceptable salt of claim 137, wherein the compound of Formula (VII-A) is a compound of Formula (VII-A1a), (VII-A1b), (VII-A1c), or (VII-A1d)



(VII-A1a),

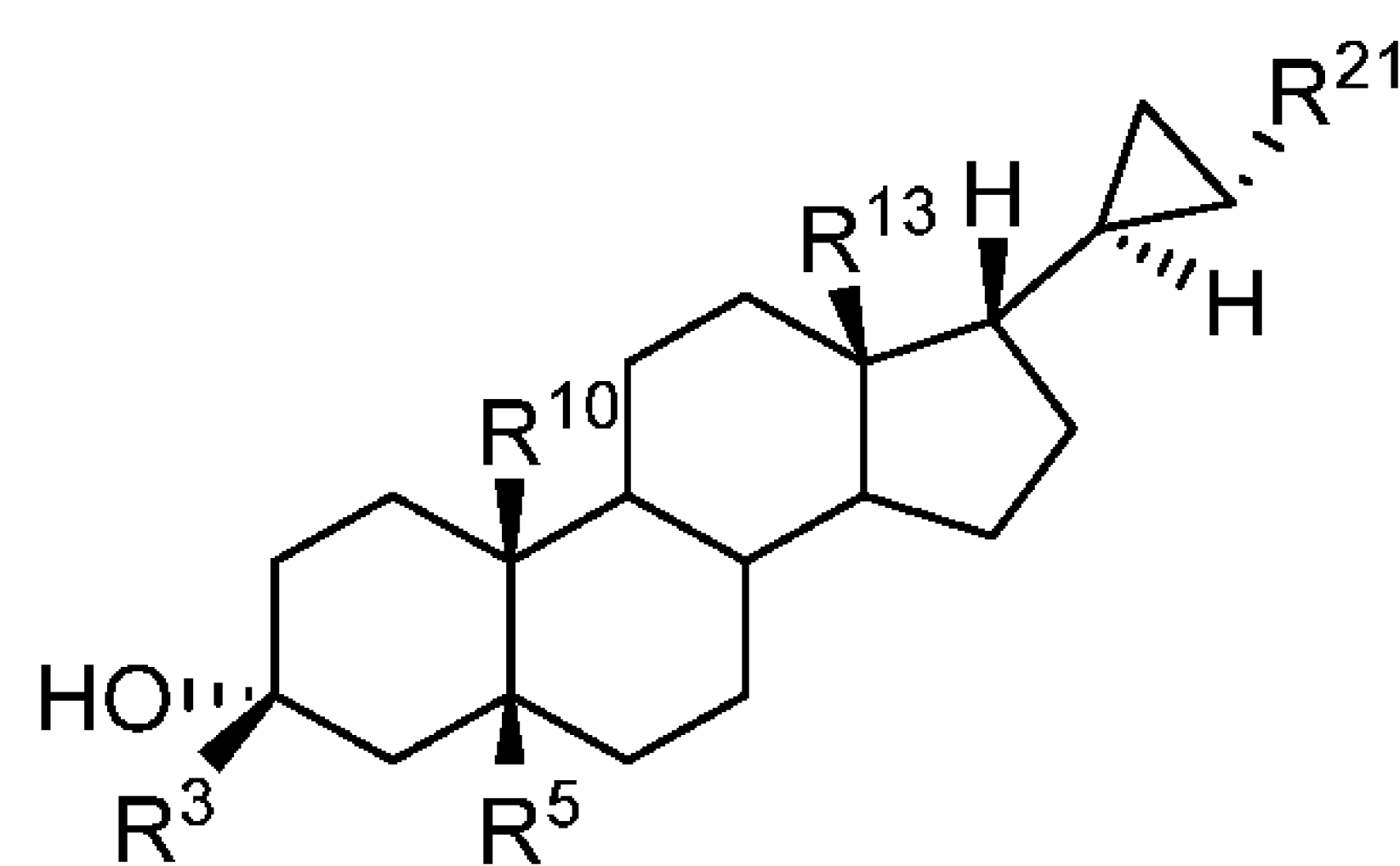


(VII-A1b),



(VII-A1c),

or



(VII-A1d),

or a pharmaceutically acceptable salt thereof, wherein

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

Each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl;

R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

144. The compound or pharmaceutically acceptable salt of claim 143, wherein

R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

R^5 is $-H$ or methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$, or C_{1-3} alkyl;

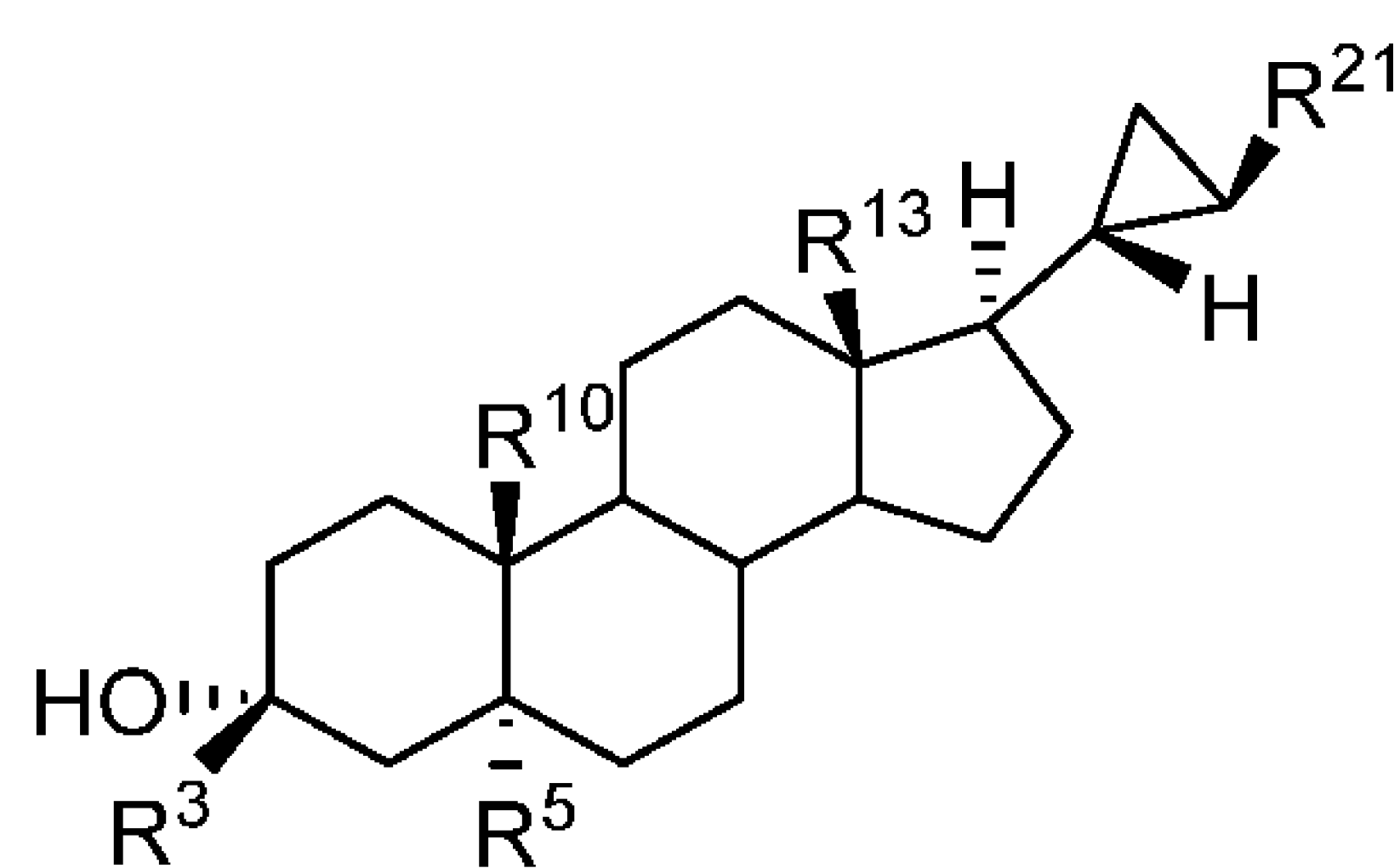
R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain;

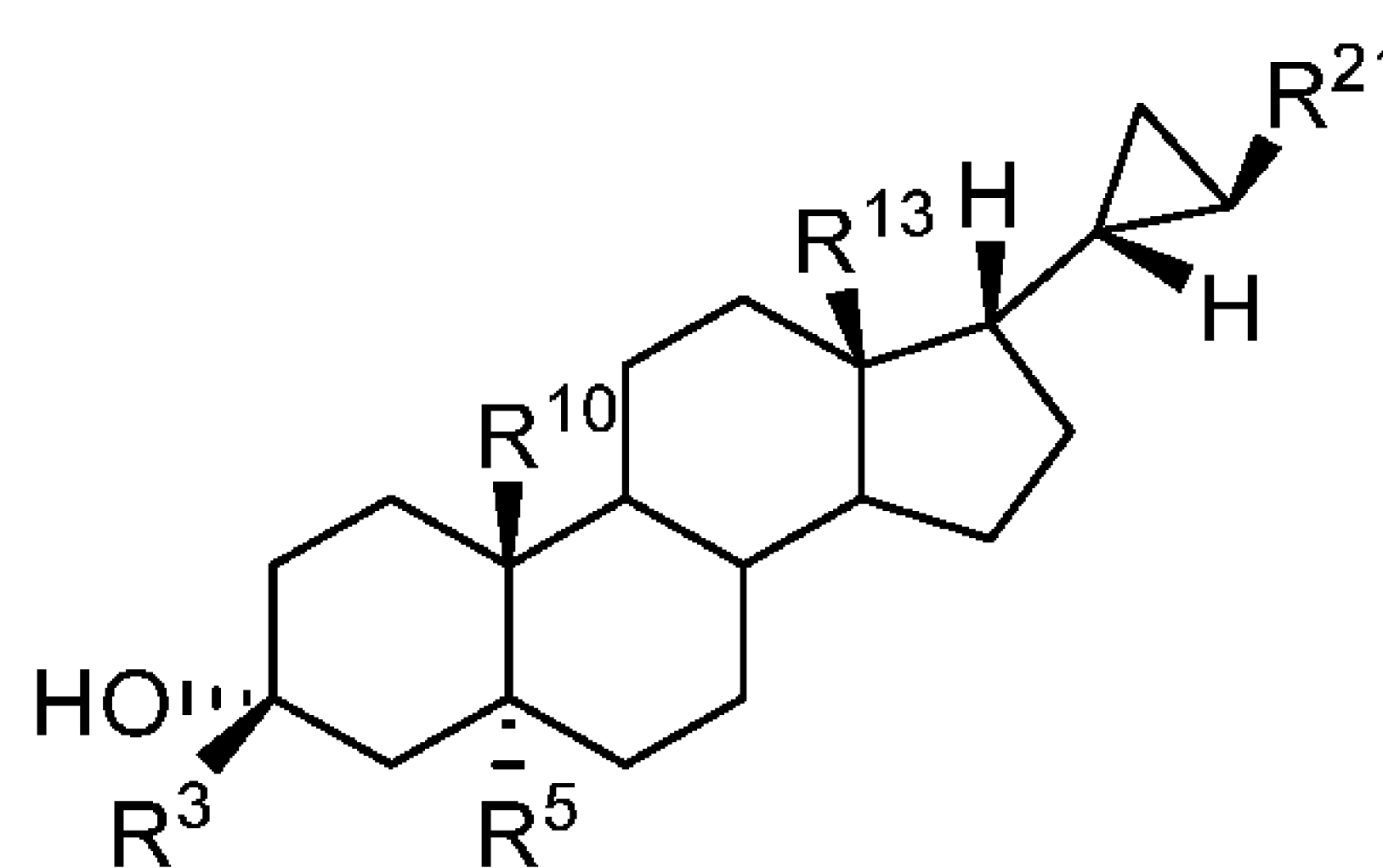
and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

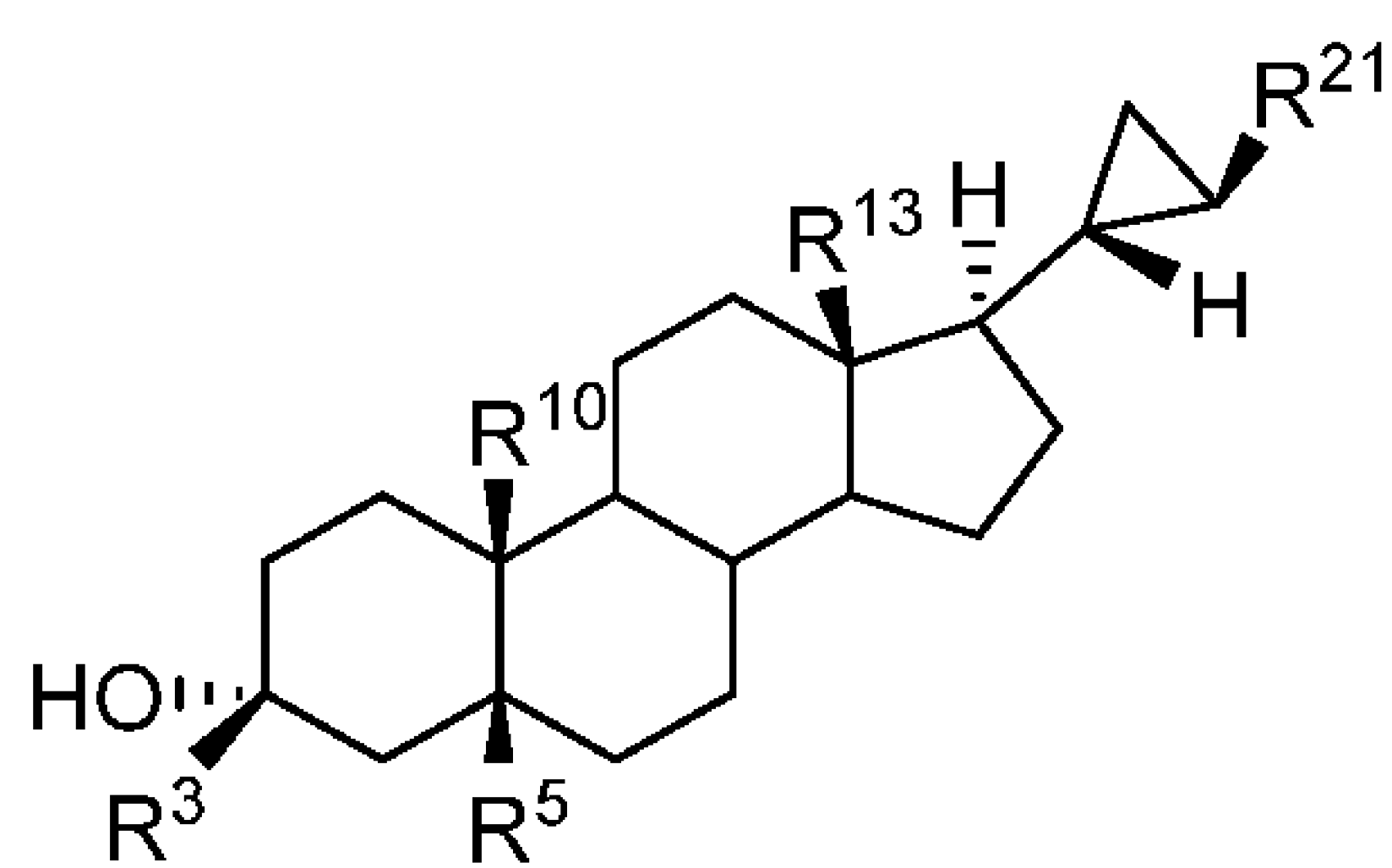
145. The compound or pharmaceutically acceptable salt of claim 137, wherein the compound of Formula (VII-B) is a compound of Formula (VII-B1a), (VII-B1b), (VII-B1c), or (VII-B1d)



(VII-B1a),

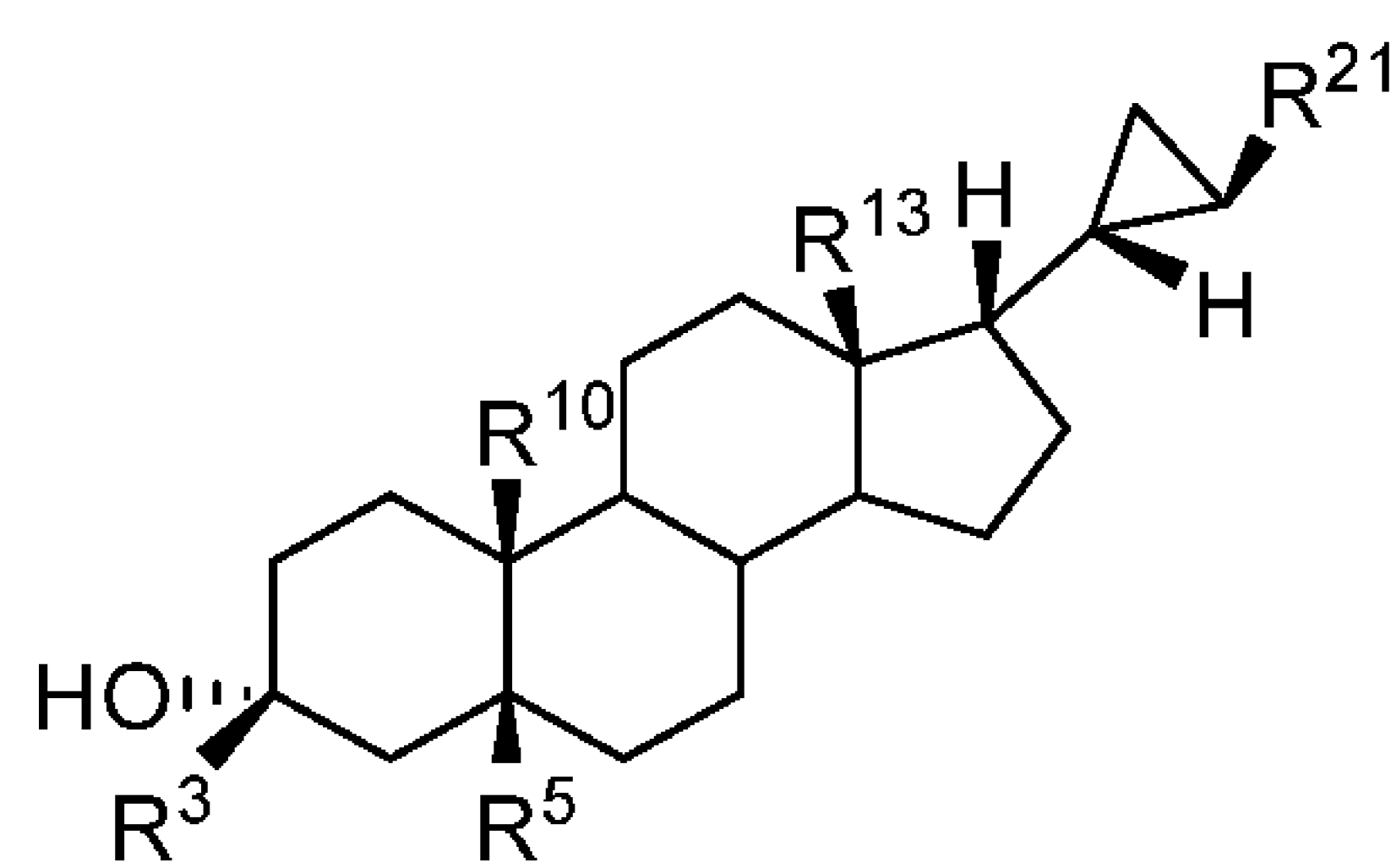


(VII-B1b),



(VII-B1c),

or



(VII-B1d),

or a pharmaceutically acceptable salt thereof, wherein

R^3 is $-H$, C_{1-6} alkyl, or C_{1-6} alkyl- O - C_{1-6} alkyl;

R^5 is $-H$ or C_{1-6} alkyl;

Each of R^{10} and R^{13} is independently selected from $-H$, C_{1-6} alkyl, and C_{1-6} alkyl- O - C_{1-6} alkyl;

R^{21} is $-L^A-R^{30}$;

L^A is a bond, a branched or straight C_{1-6} alkylene chain, or $-N(H)-$; and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-4 heteroatoms independently selected from N, O, and S, wherein the 3-8 membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

146. The compound or pharmaceutically acceptable salt of claim 145, wherein

R^3 is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

R^5 is $-H$ or methyl;

R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl;

R^{13} is $-H$, or C_{1-3} alkyl;

R^{21} is $-L^A-R^{30}$;

L^A is a bond or an optionally substituted branched or straight C_{1-3} alkylene chain;

and

R^{30} is $-H$, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, or a 5-6-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 1-4 nitrogen atoms, wherein the 5-6-membered ring of R^{30} is optionally substituted with 1-3 groups independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-CH_3$, $-CH_2OH$, and $-C(CH_3)_3$.

147. The compound of pharmaceutically acceptable salt of any one of claims 2-16, 57-73, or 99-120, wherein each of R^{1a} and R^{1b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{1a} and R^{1b} taken together form oxo.

148. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147, wherein each of R^{1a} and R^{1b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{1a} and R^{1b} taken together form oxo.

149. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147, wherein one of R^{1a} and R^{1b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.

150. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-149, wherein one of R^{1a} and R^{1b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' .

151. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-150, wherein each of R^{1a} and R^{1b} is $-H$.

152. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-151, wherein each of R^{2a} and R^{2b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{2a} and R^{2b} taken together form oxo.

153. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-152, wherein each of R^{2a} and R^{2b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' , or R^{2a} and R^{2b} taken together form oxo.

154. The compound or pharmaceutically acceptable salt of any one of 2-16, 57-73, 99-120, or 147-152, wherein one of R^{2a} and R^{2b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.

155. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, 147-152, or 154, wherein one of R^{2a} and R^{2b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' .
156. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-155, wherein each of R^{2a} and R^{2b} is $-H$.
157. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-156, wherein n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{4a} and R^{4b} taken together form oxo.
158. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-157, wherein n is 1 and each of R^{4a} and R^{4b} is independently selected from $-H$ or C_{1-6} alkyl optionally substituted with R' , or R^{4a} and R^{4b} taken together form oxo.
159. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-156, wherein n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.
160. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, 147-156, or 159, wherein n is 1, one of R^{4a} and R^{4b} is $-H$, and the other is $-H$ or C_{1-6} alkyl optionally substituted with R' .
161. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-160, wherein n is 1 and each of R^{4a} and R^{4b} is $-H$.
162. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-161, wherein R^5 is $-H$.

163. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-162, wherein each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{6a} and R^{6b} taken together form oxo, or R^{7a} and R^{7b} taken together form oxo.

164. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-163, wherein each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' .

165. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-163, wherein two of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other two of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$.

166. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, 147-163, or 165, wherein three of R^{6a} , R^{6b} , R^{7a} , and R^{7b} are $-H$, and the other of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.

167. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-166, wherein each of R^{6a} , R^{6b} , R^{7a} , and R^{7b} is $-H$.

168. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-167, wherein R^{10} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl.

169. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-168, wherein R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl.

170. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-169, wherein R^{10} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, methoxyethyl, or ethoxyethyl.

171. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-170, wherein each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$, or R^{11a} and R^{11b} taken together form oxo, or R^{12a} and R^{12b} taken together form oxo.

172. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-171, wherein each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is independently selected from $-H$ and C_{1-6} alkyl optionally substituted with R' .

173. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-171, wherein two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other two of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are independently selected from $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, and $-O-R'$.

174. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, 147-171, or 173, wherein three of R^{11a} , R^{11b} , R^{12a} , and R^{12b} are $-H$, and the other of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is $-H$, C_{1-6} alkyl optionally substituted with R' , $-N(R')_2$, or $-O-R'$.

175. The compound or pharmaceutically acceptable salt of any one of claims 2-16, 57-73, 99-120, or 147-174, wherein each of R^{11a} , R^{11b} , R^{12a} , and R^{12b} is $-H$.

176. The compound or pharmaceutically acceptable salt of any one of claims 30-43, 80-90, or 127-136, wherein R^3 is C_{1-6} alkyl or C_{1-6} alkyl- O - C_{1-6} alkyl.

177. The compound or pharmaceutically acceptable salt of any one of claims 30-43, 80-90, 127-136, or 176, wherein R^3 is methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, neopentyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl.

178. The compound or pharmaceutically acceptable salt of any one of claims 30-43, 80-90, 127-136, 176, or 177, wherein R^3 is $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, or $-CH_2-O-CH_3$.

179. The compound or pharmaceutically acceptable salt of any one of claims 30-43, 80-90, 127-136, or 176-178, wherein R^5 is $-H$ or C_{1-3} alkyl.

180. The compound or pharmaceutically acceptable salt of any one of claims 30-43, 80-90, 127-136, or 176-179, wherein R^5 is $-H$ or methyl.

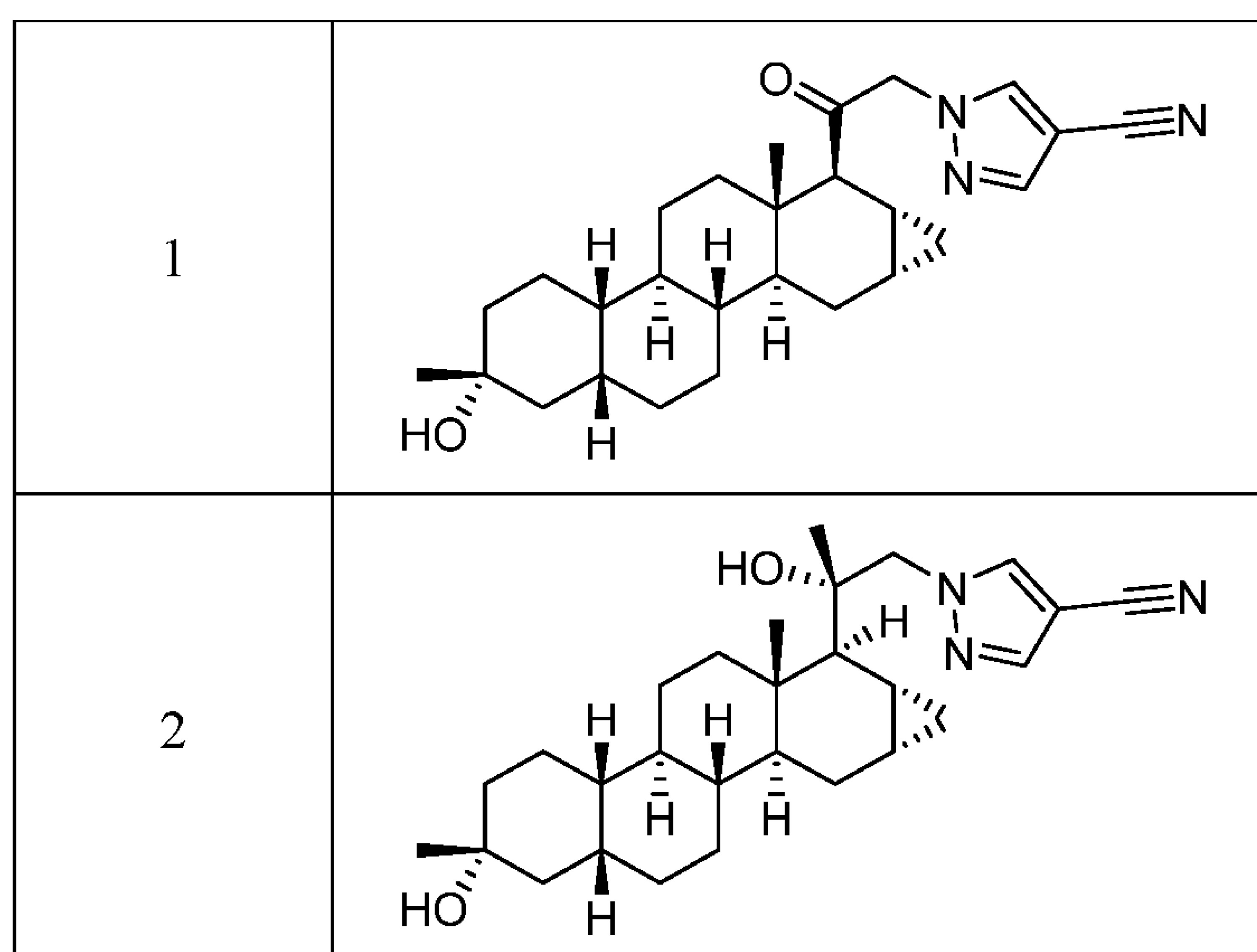
181. The compound or pharmaceutically acceptable salt of any one of claims 30-43, 80-90, 127-136, or 176-180, wherein R^{10} is $-H$, C_{1-6} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl.

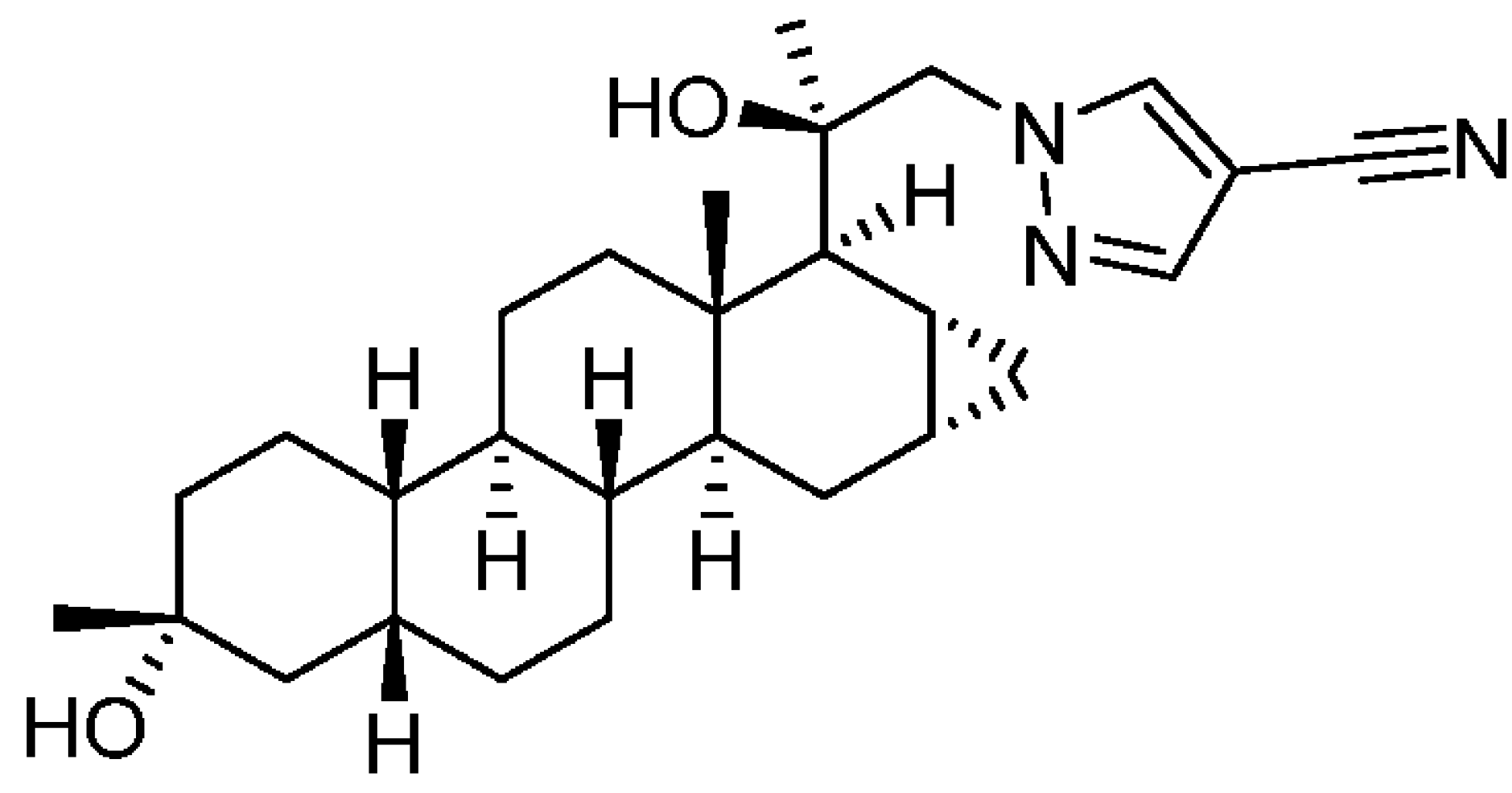
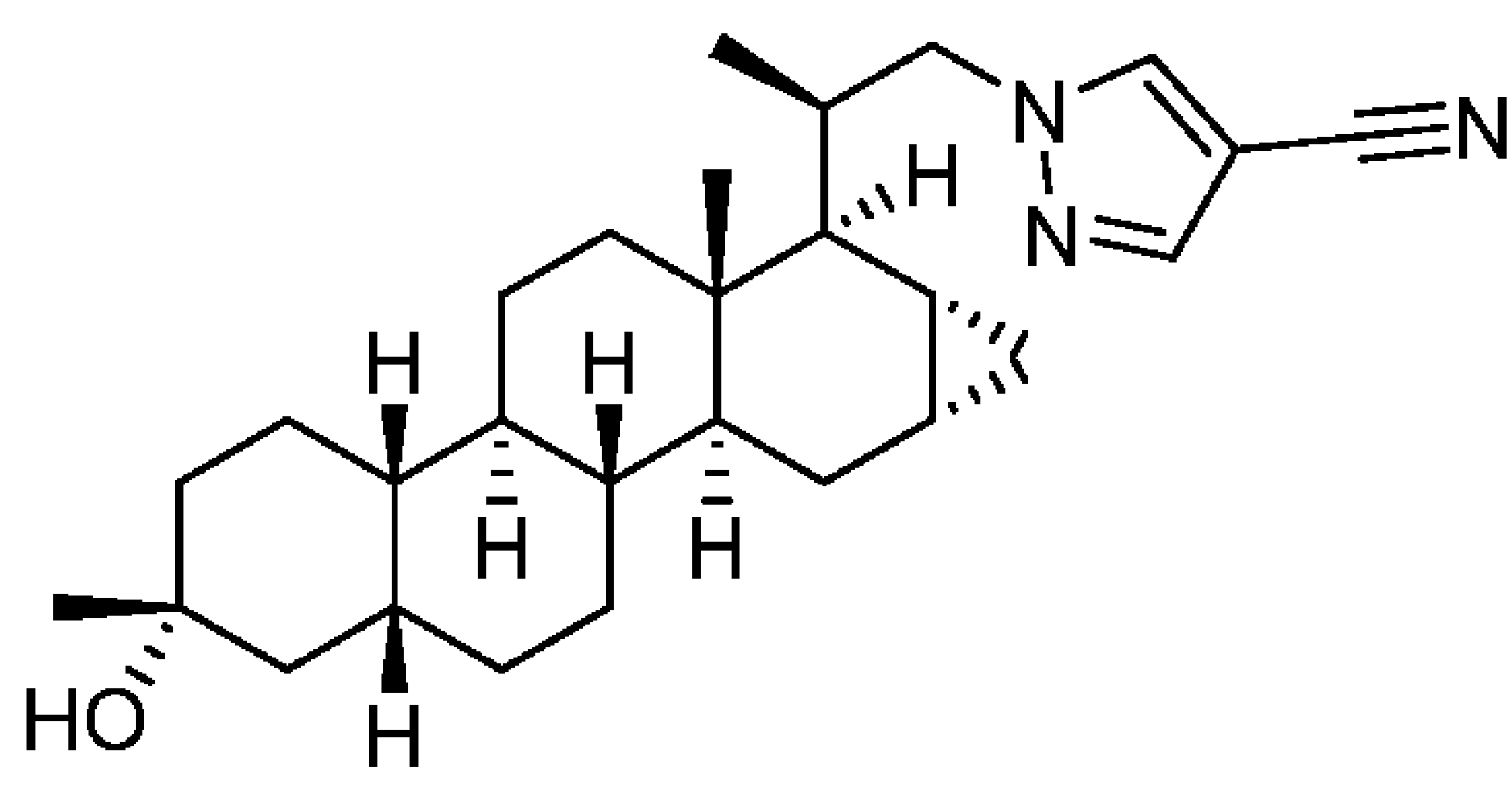
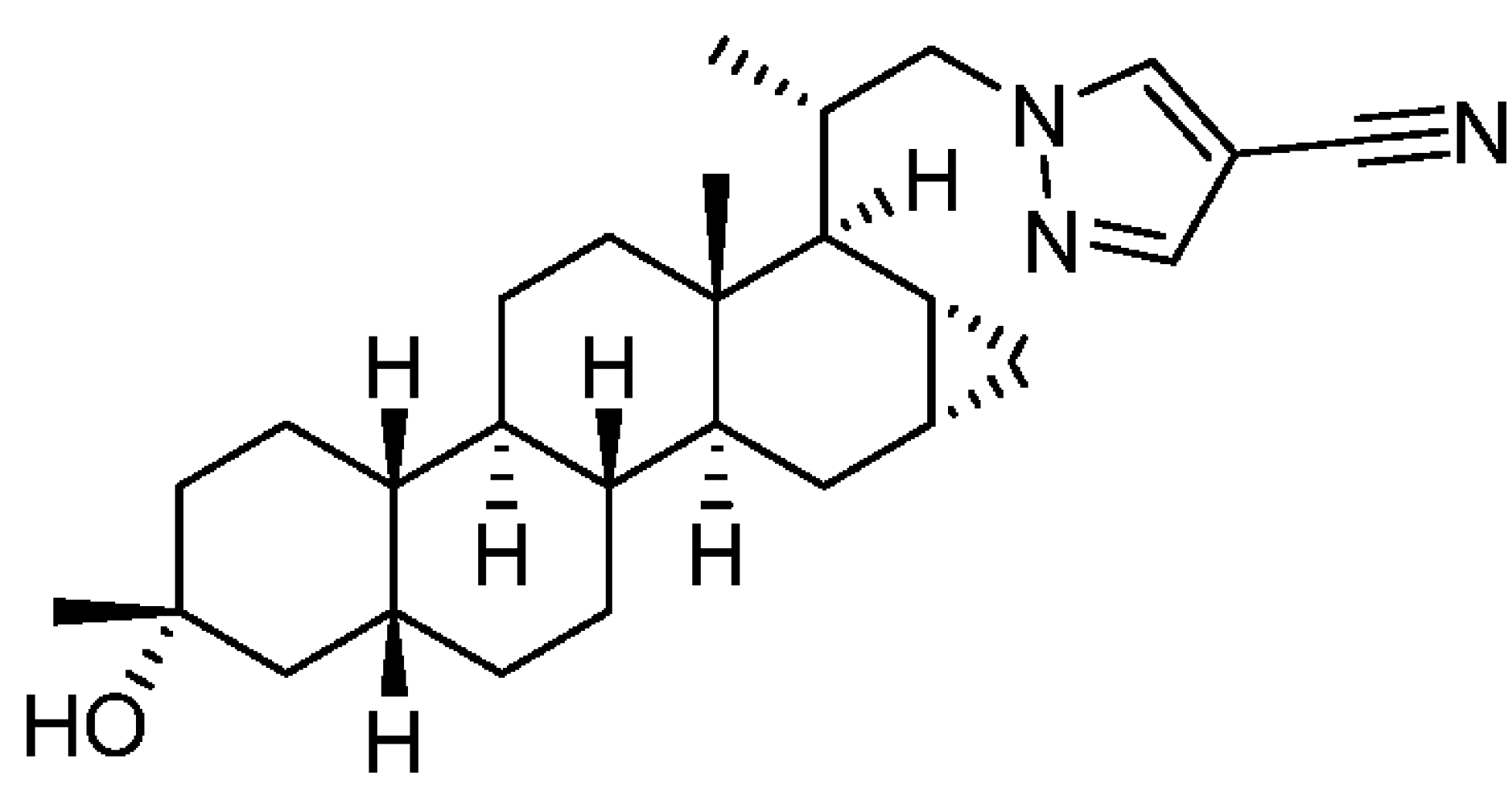
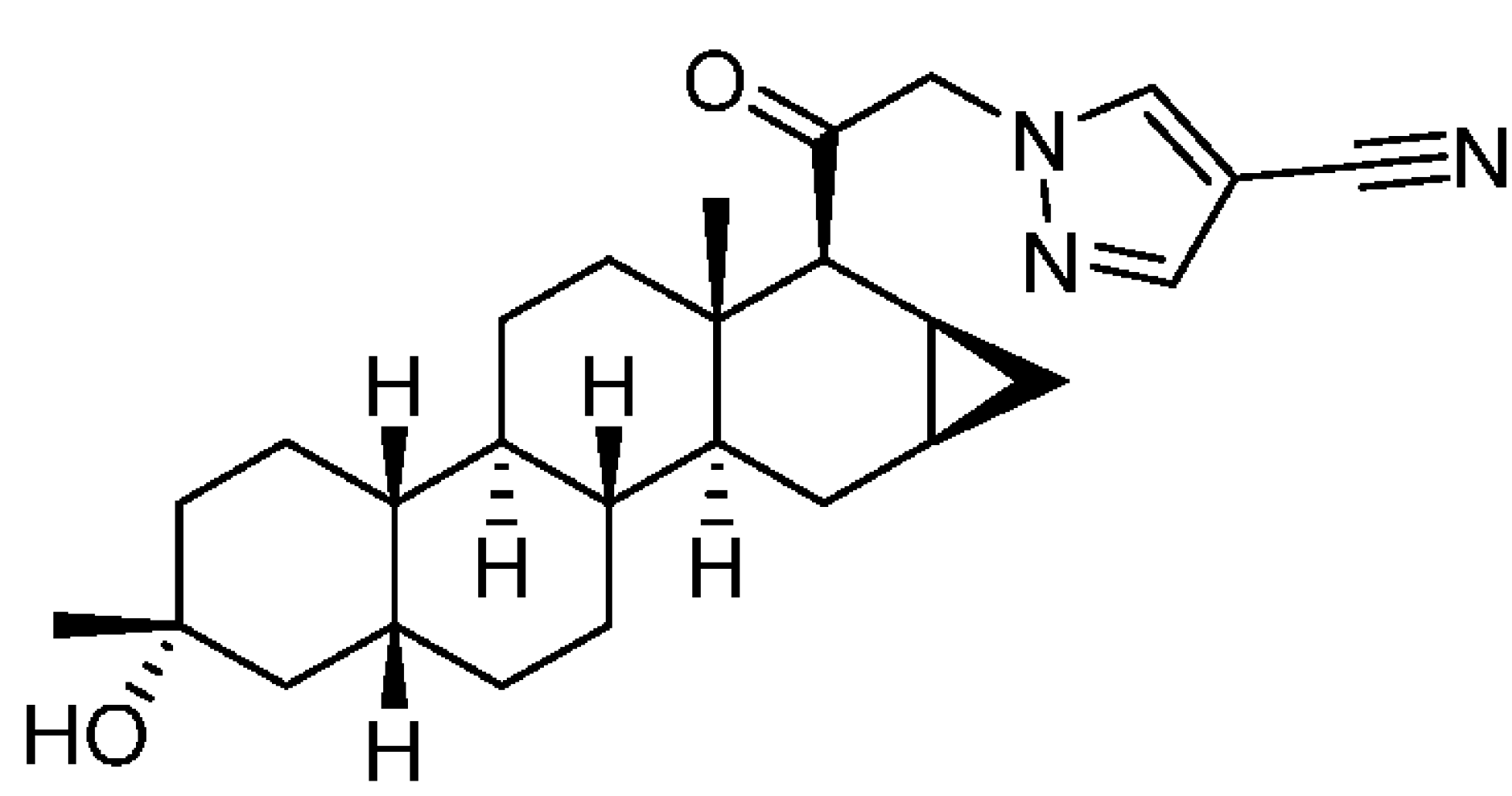
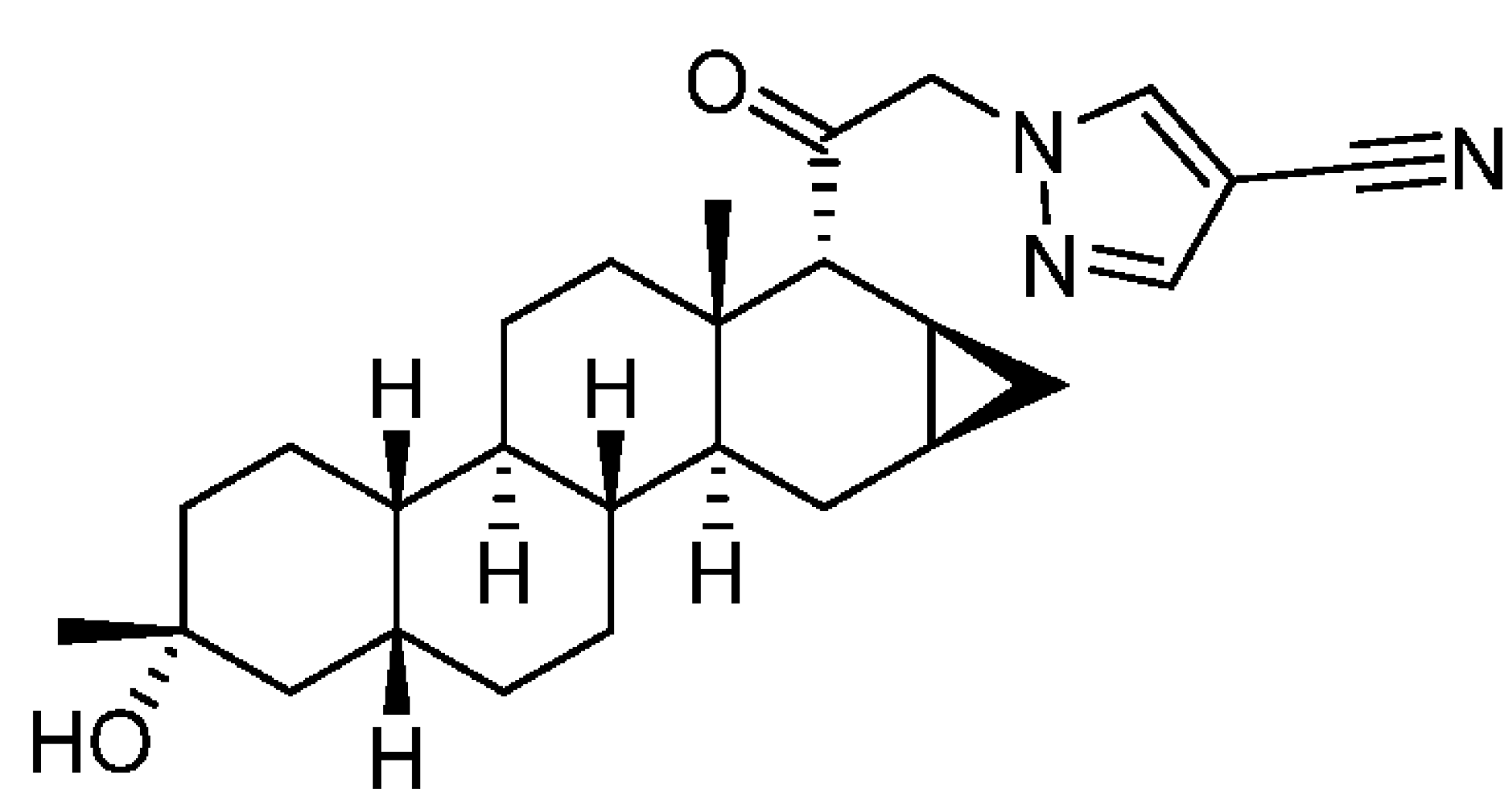
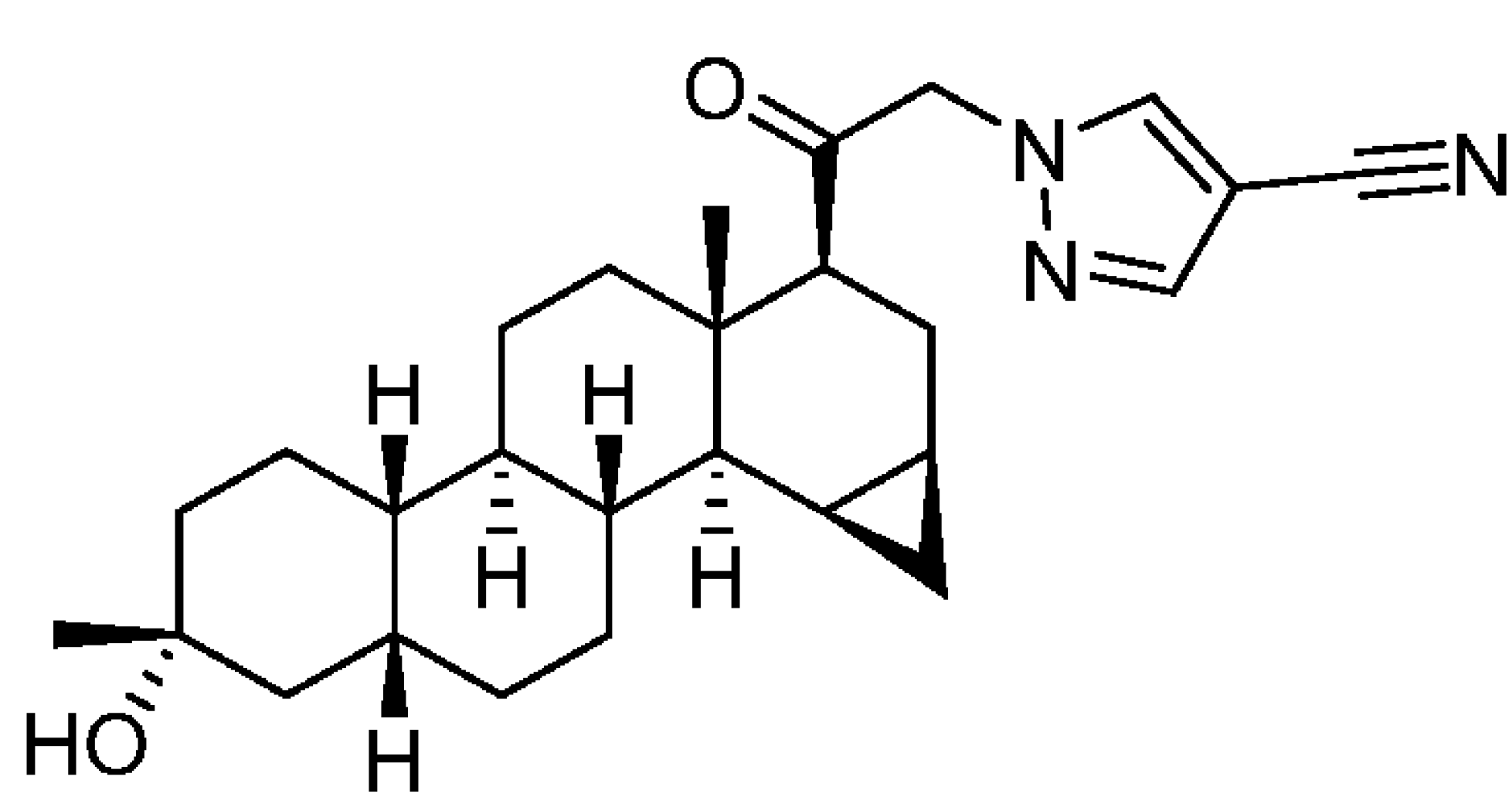
182. The compound or pharmaceutically acceptable salt of any one of claims 30-43, 80-90, 127-136, or 176-181, wherein R^{10} is $-H$, C_{1-3} alkyl, or C_{1-3} alkyl- O - C_{1-3} alkyl.

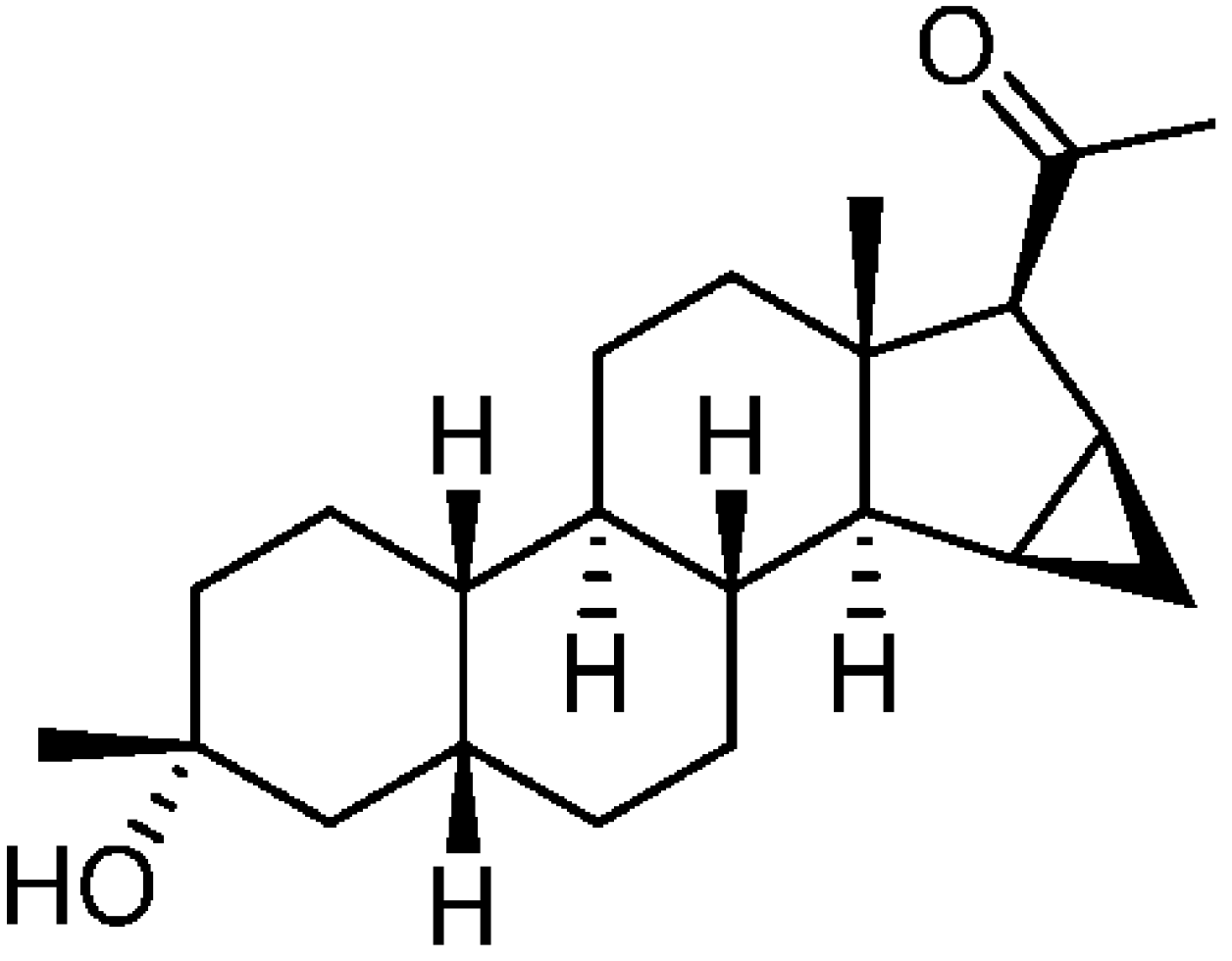
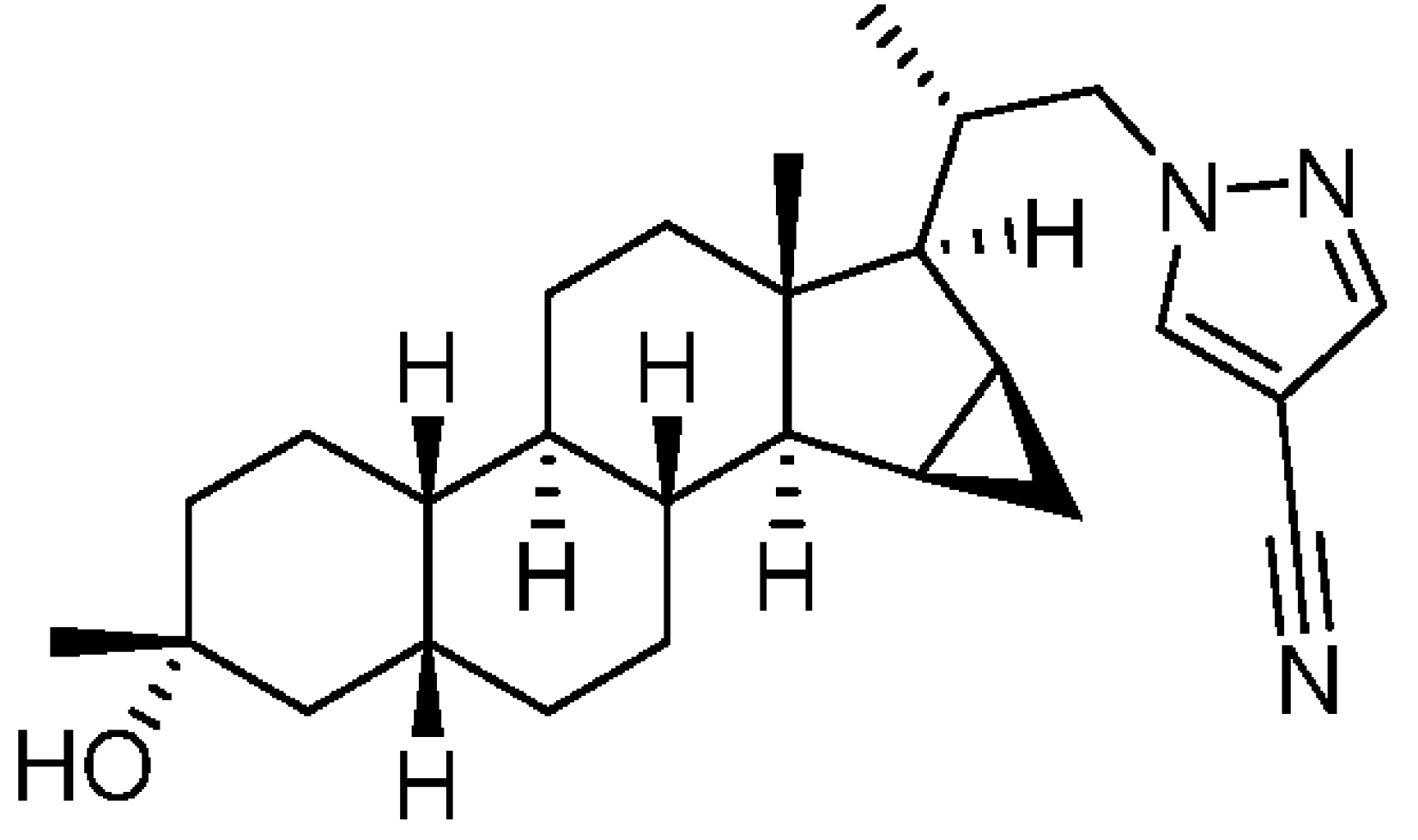
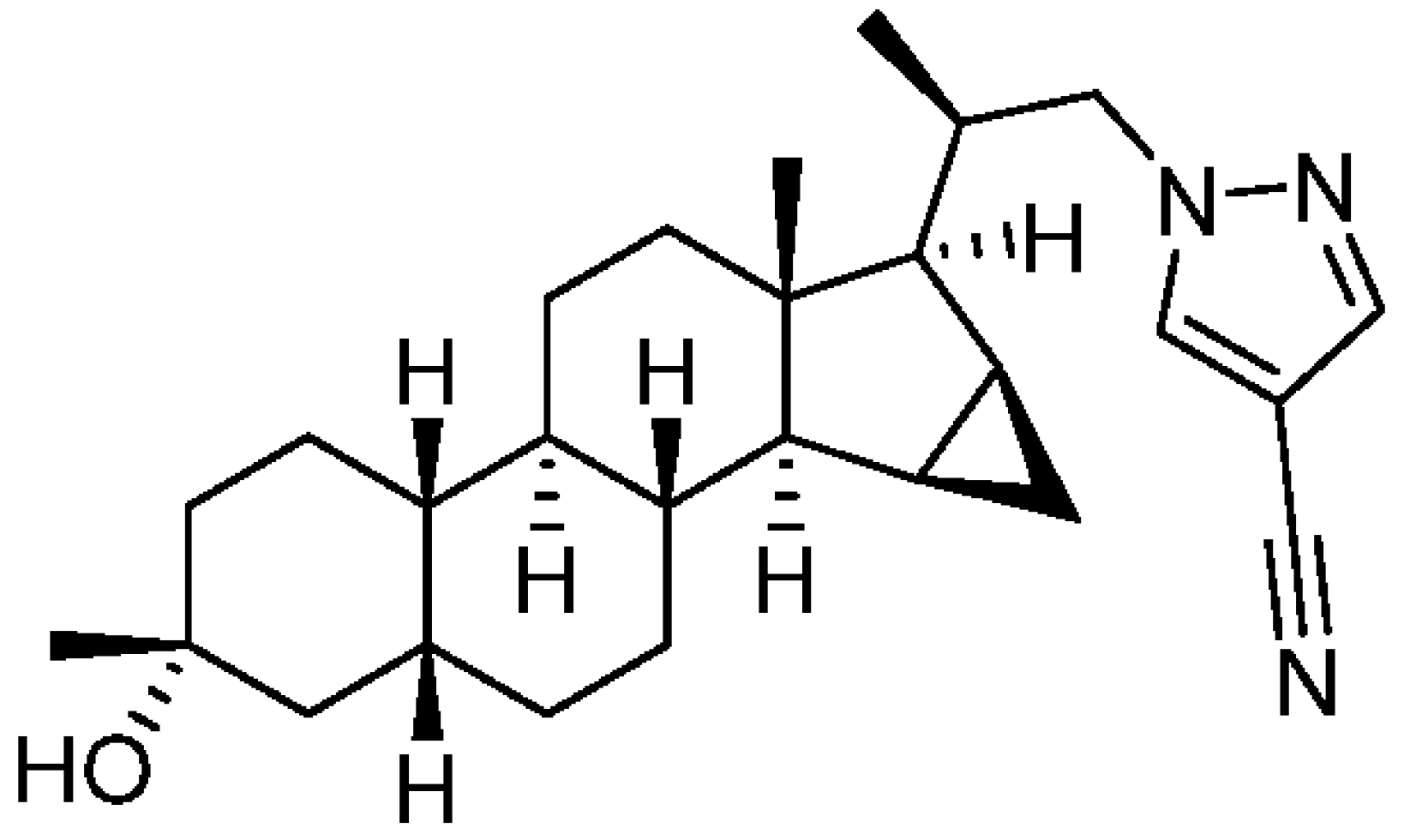
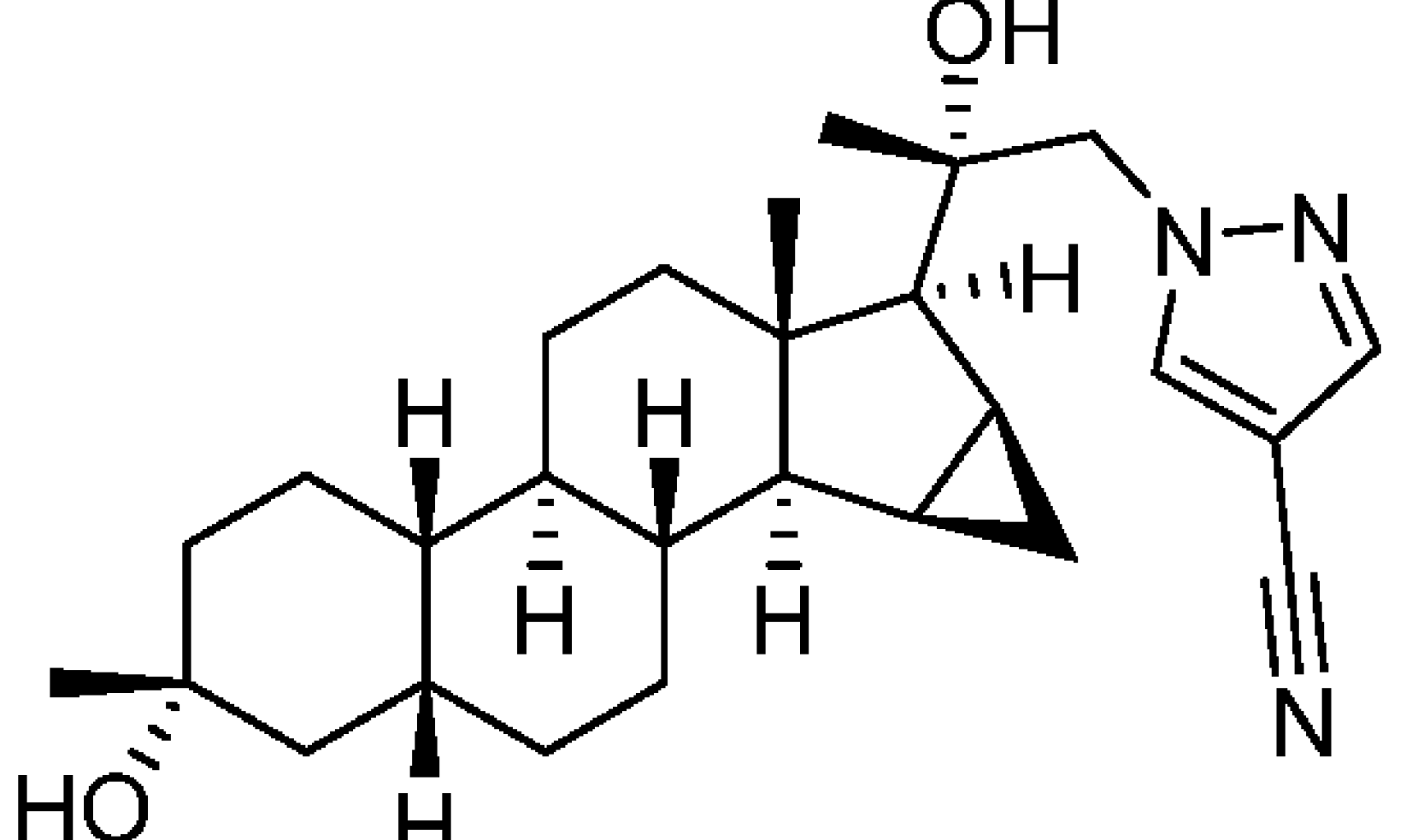
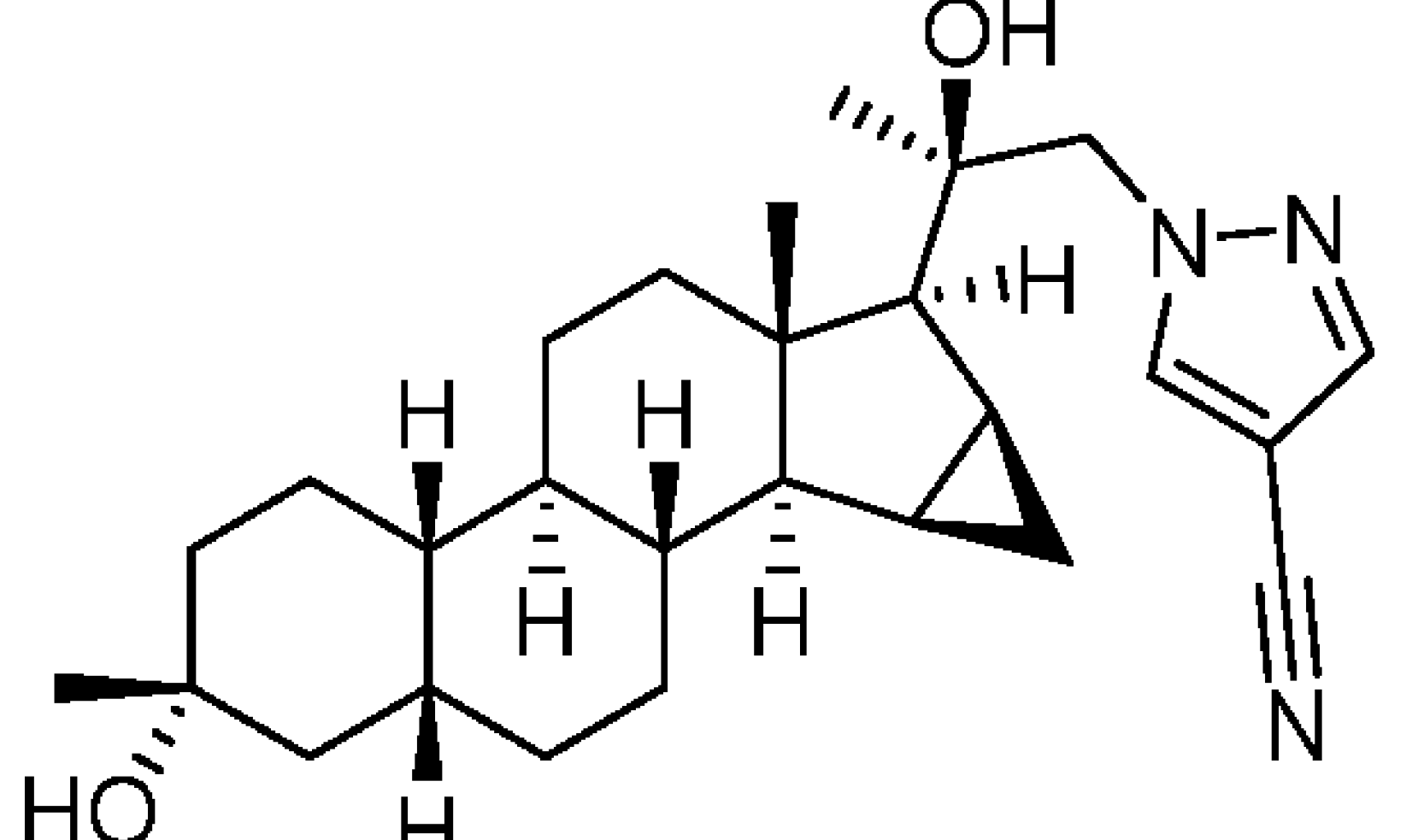
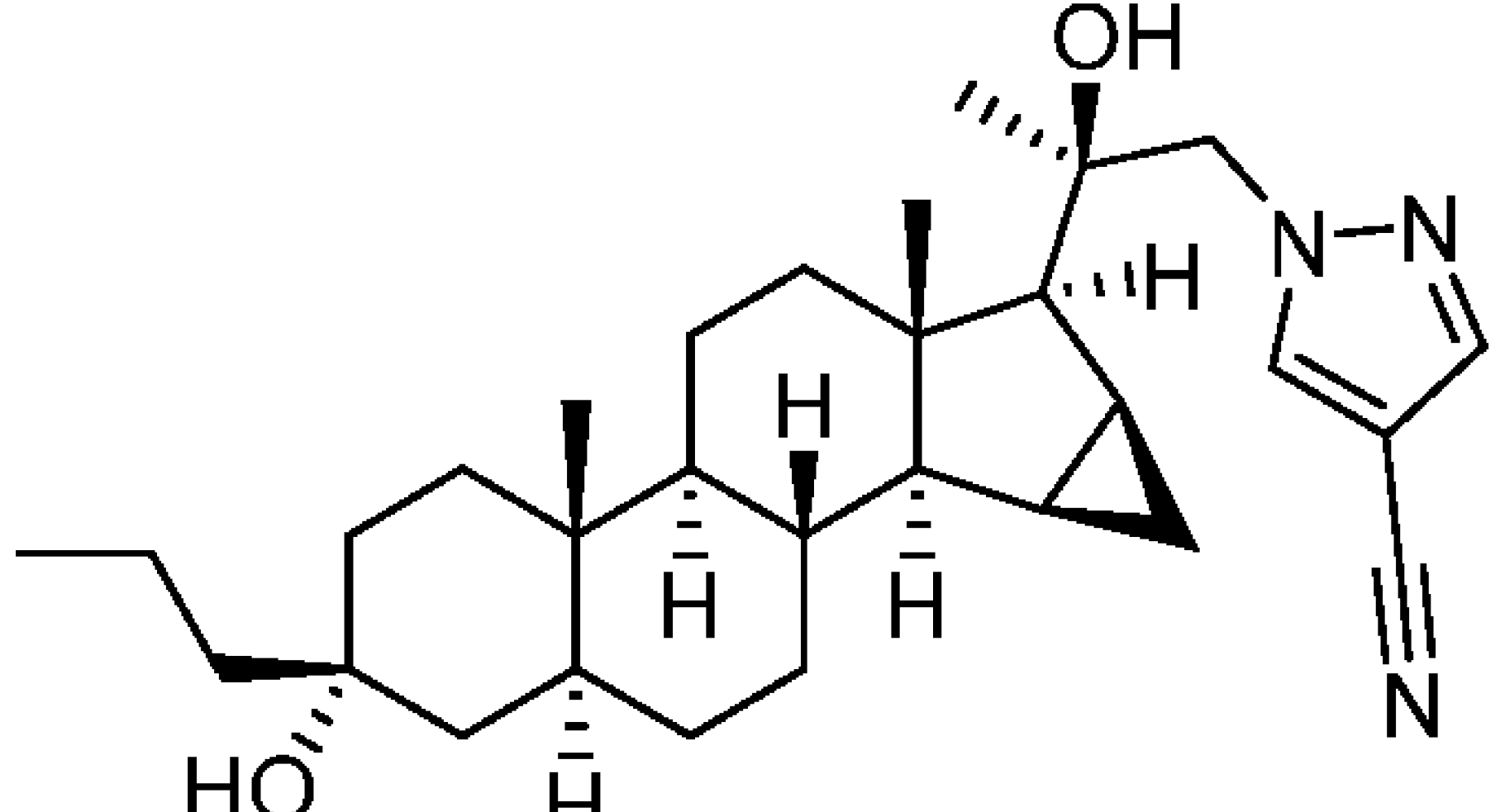
183. The compound or pharmaceutically acceptable salt of any one of claims 30-43, 80-90, 127-136, or 176-182, wherein R^{10} is $-H$, methyl, ethyl, propyl, iso-propyl, methoxymethyl, ethoxymethyl, propoxymethyl, methoxyethyl, ethoxyethyl, or propoxyethyl.

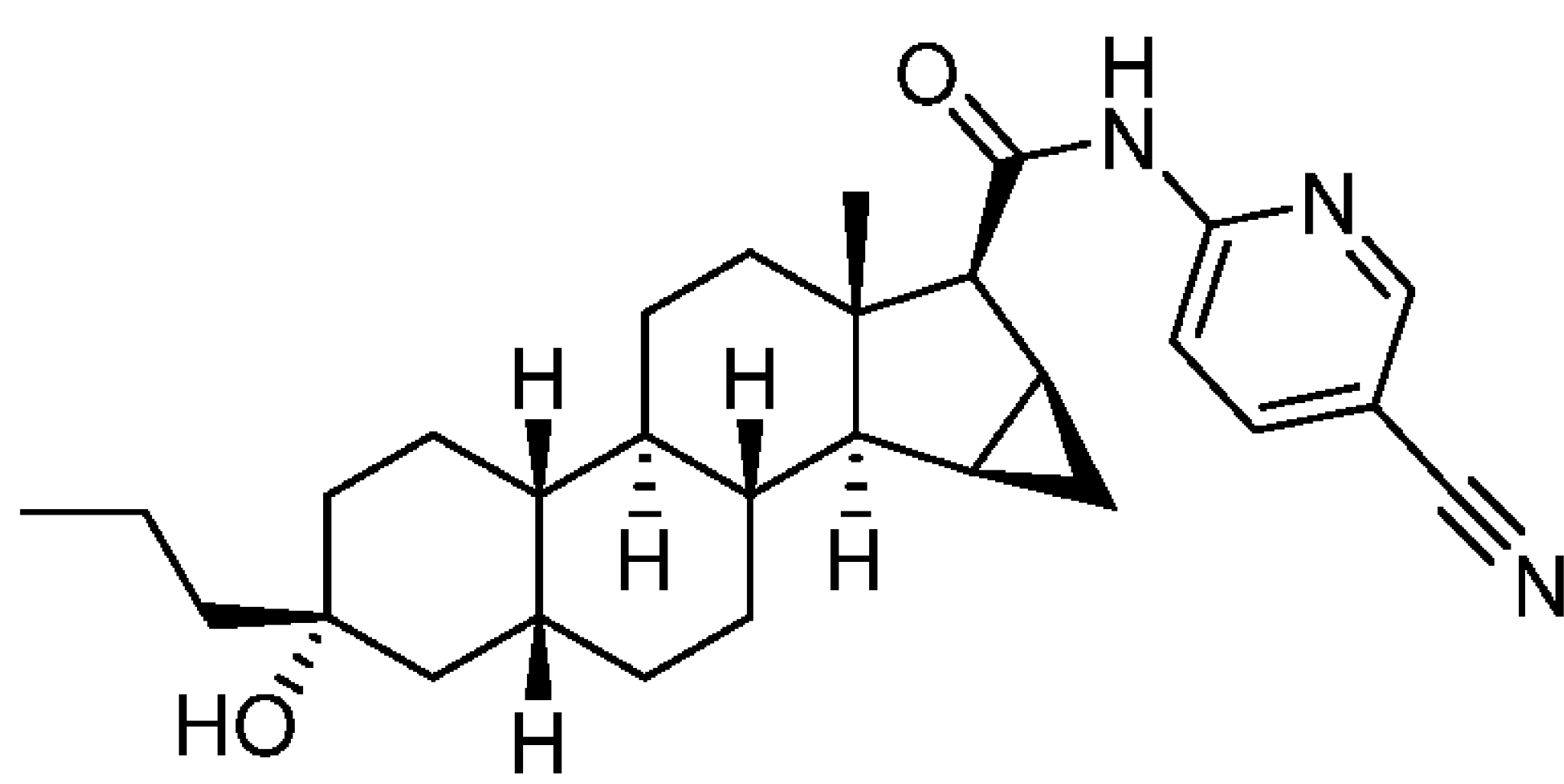
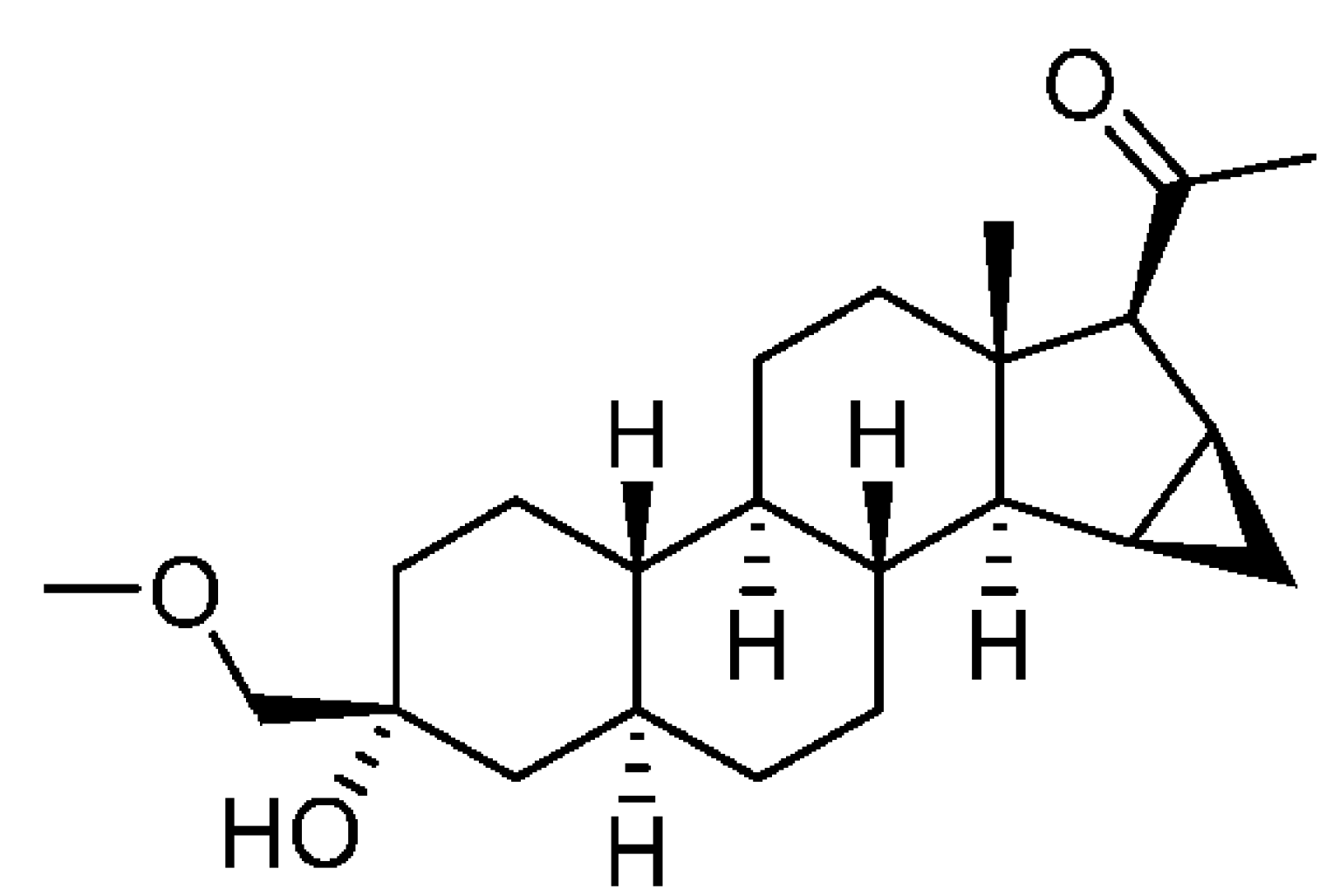
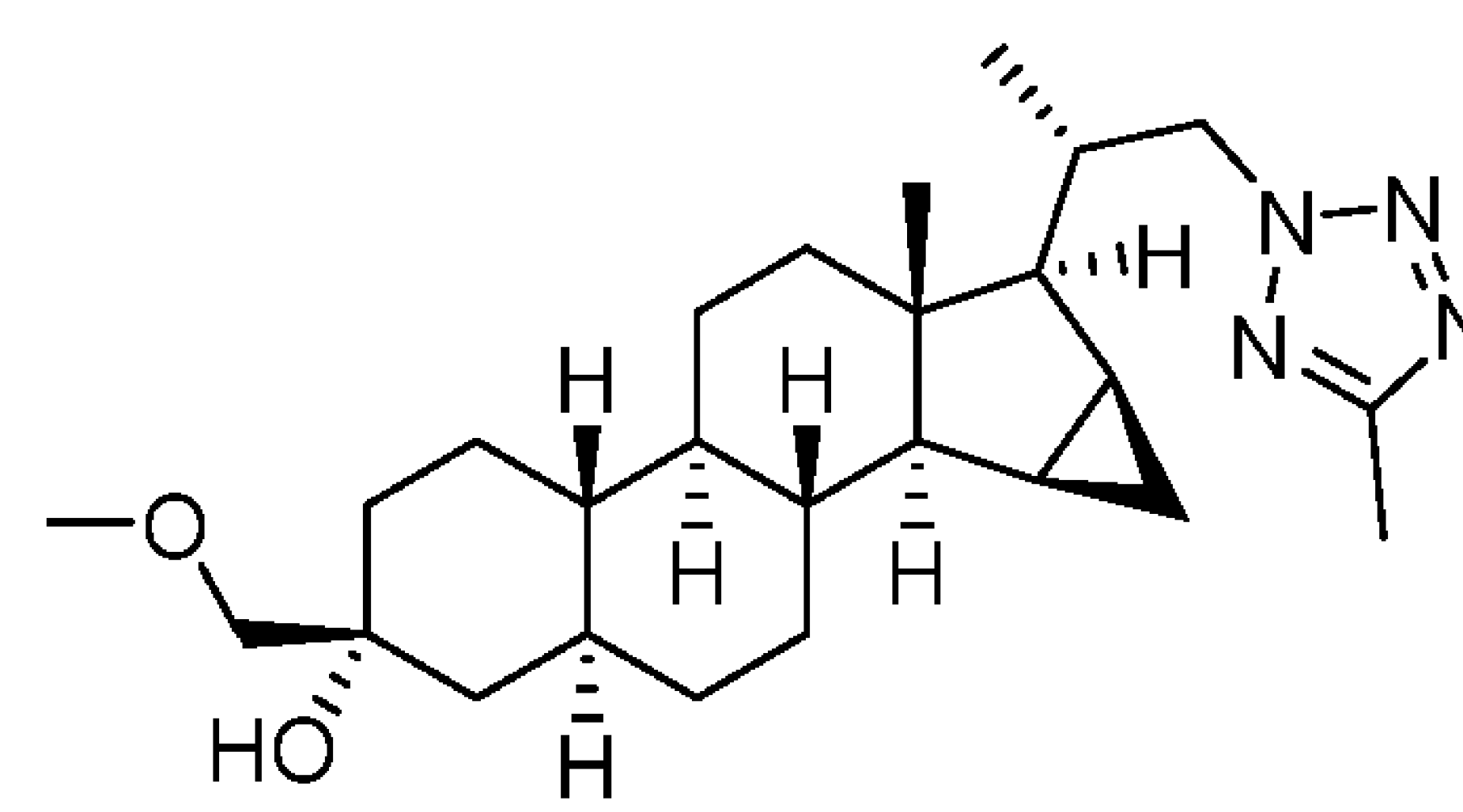
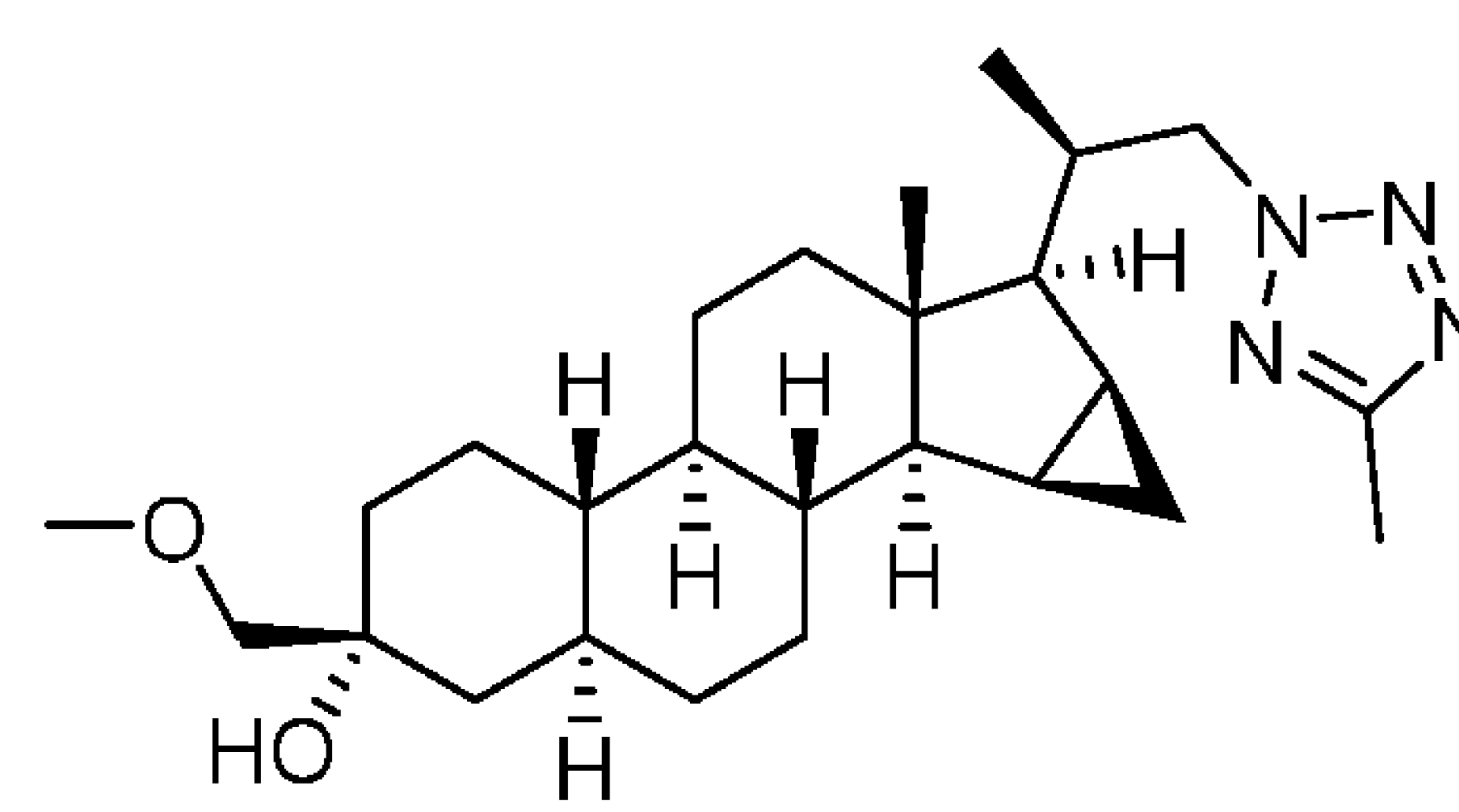
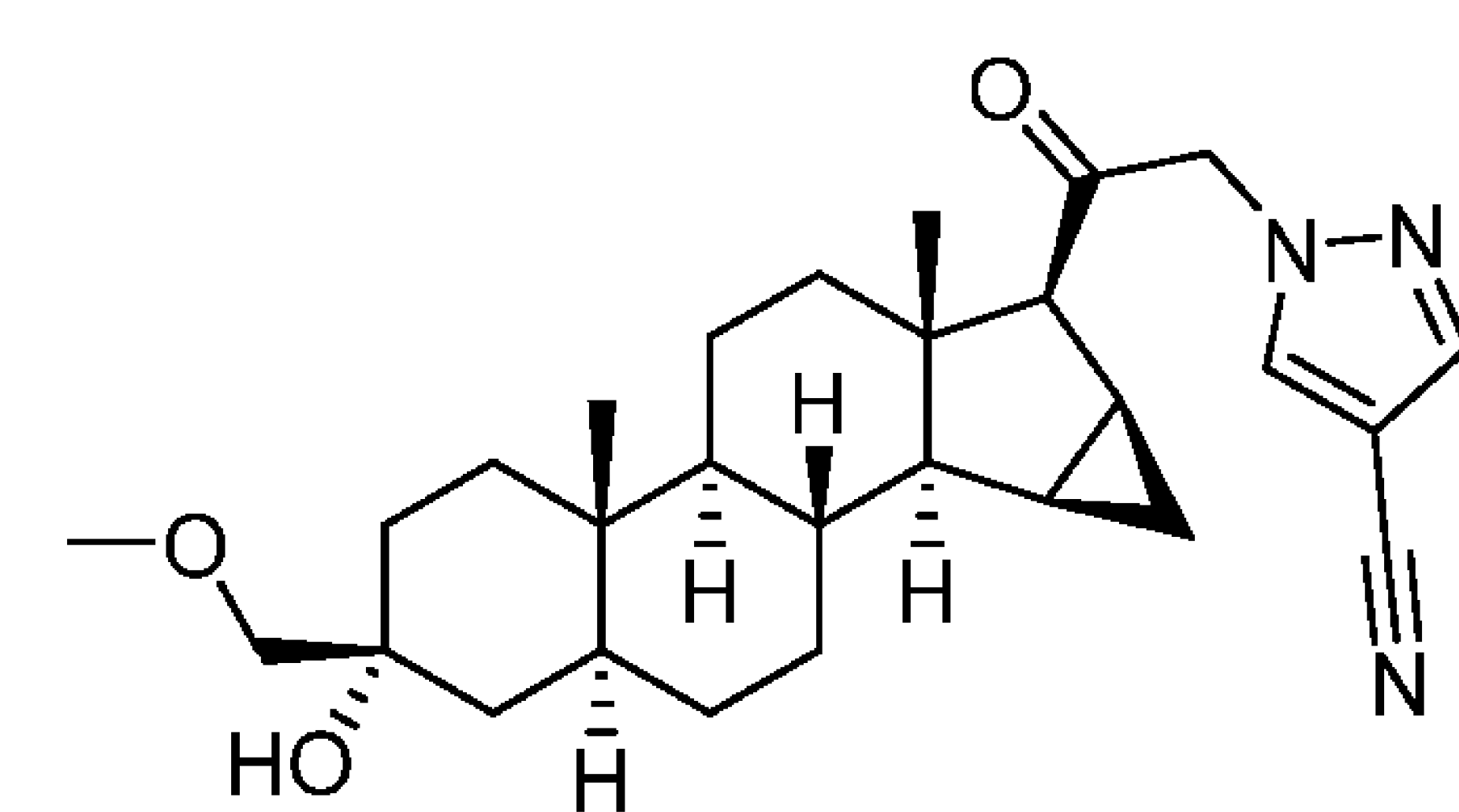
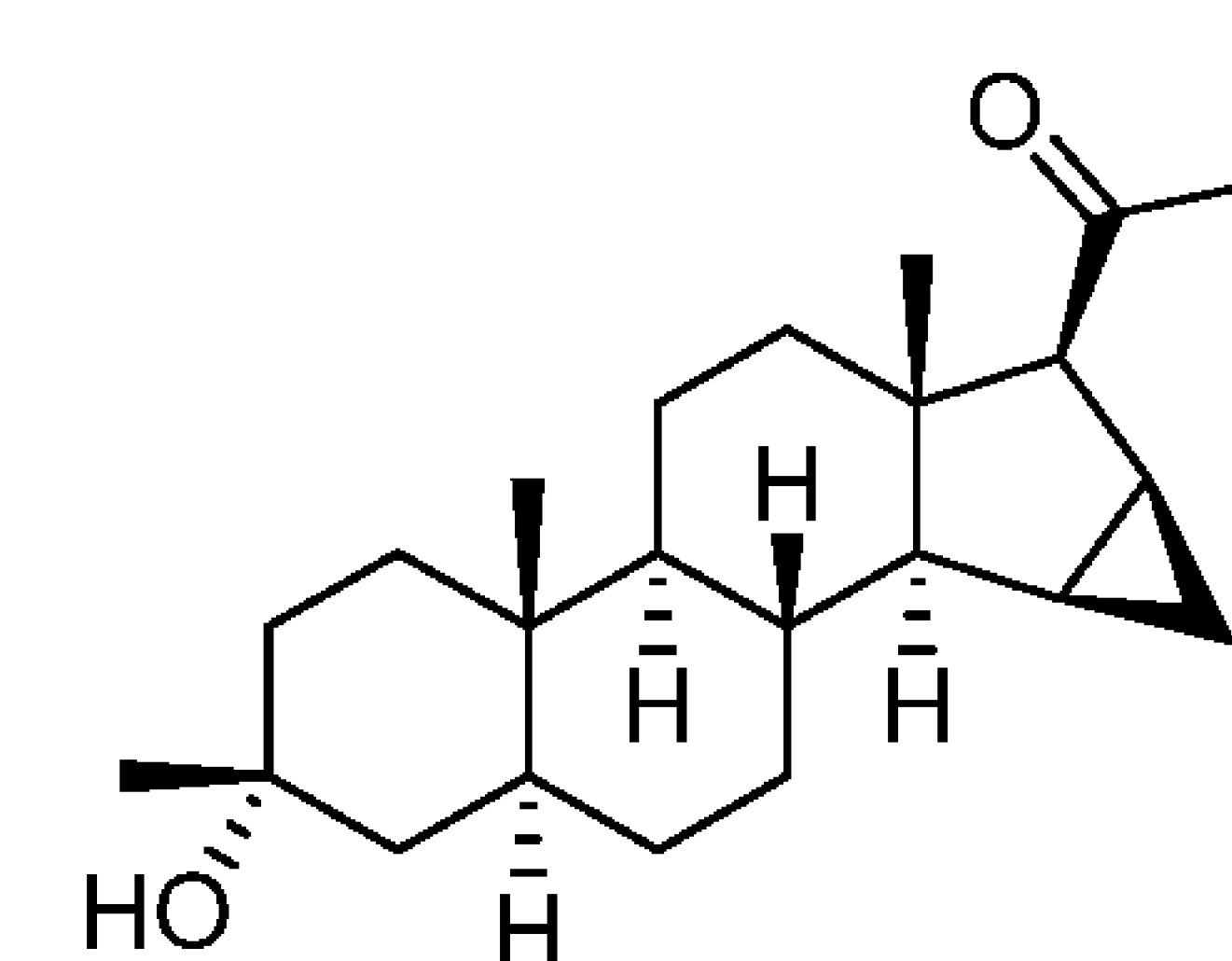
184. The compound or pharmaceutically acceptable salt of any one of claims 30-43, 80-90, 127-136, or 176-183, wherein R^{10} is $-H$ or methyl.

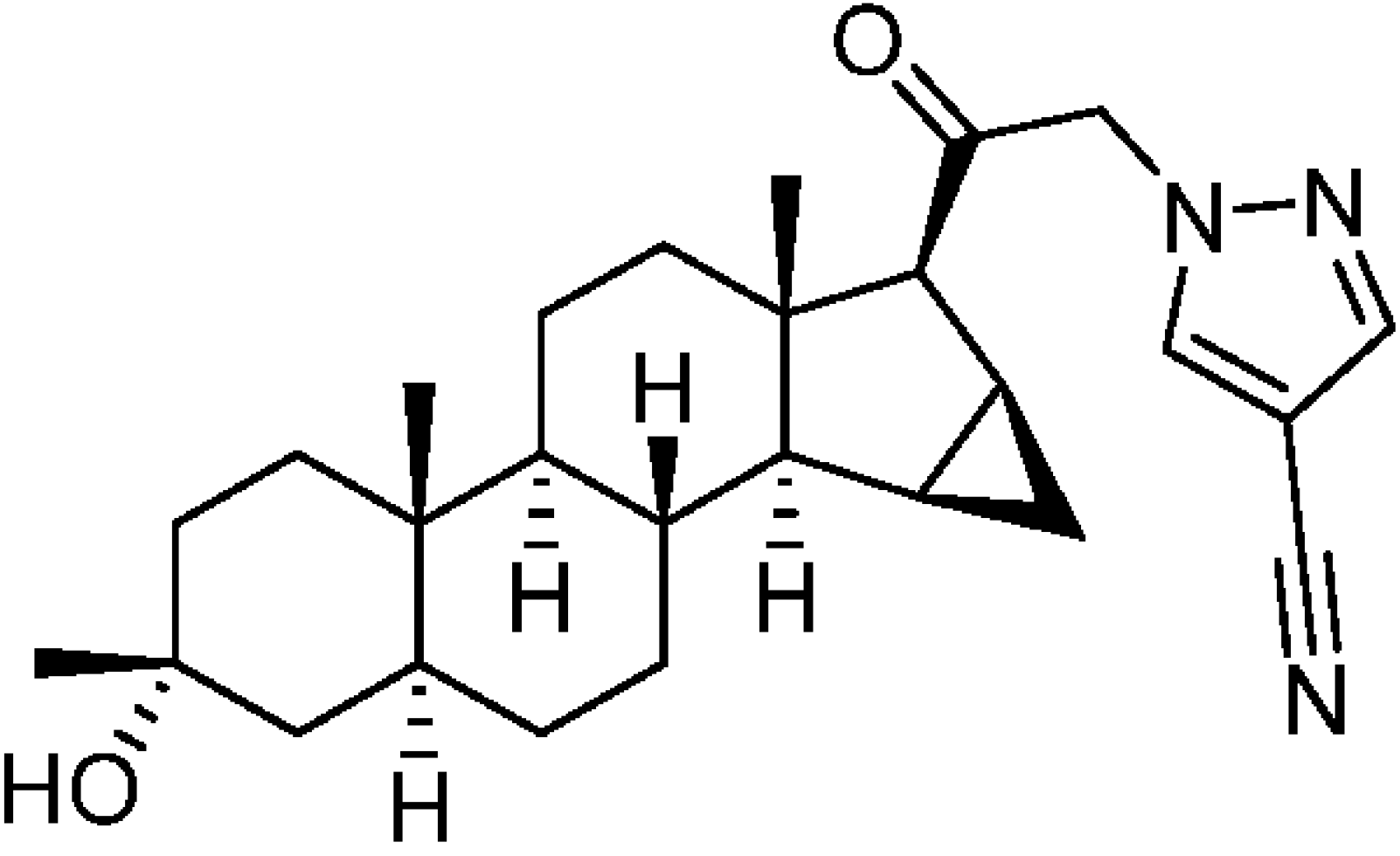
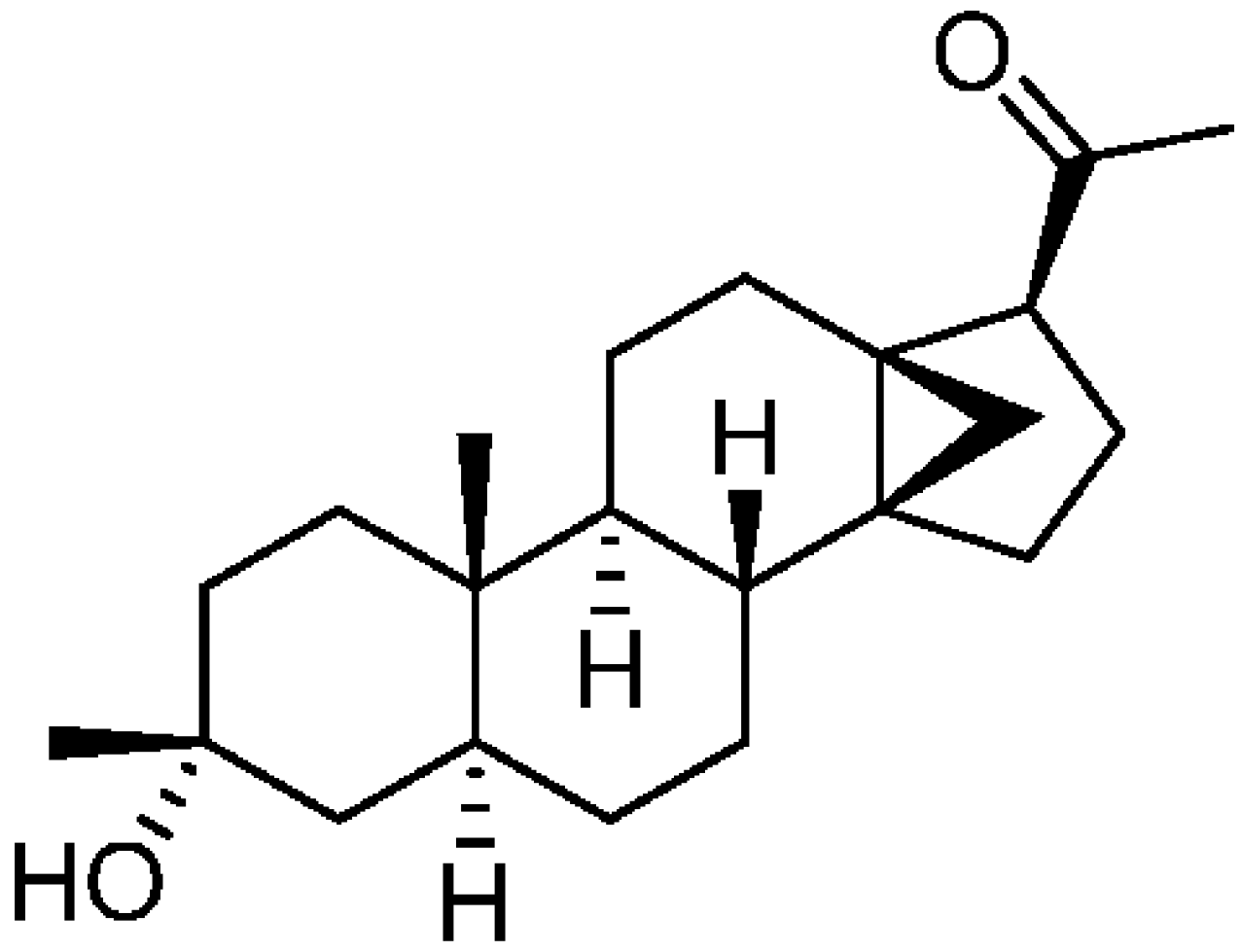
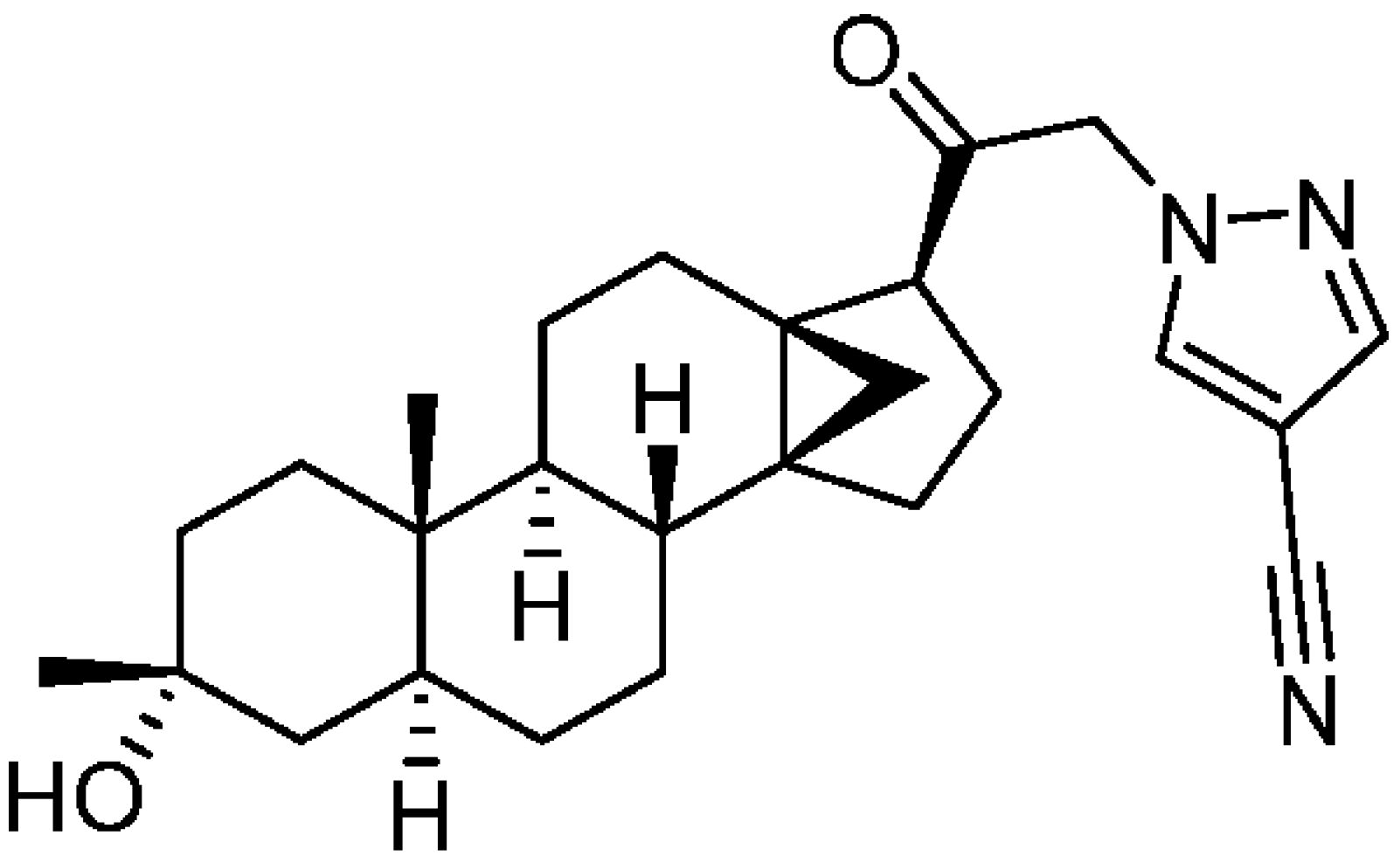
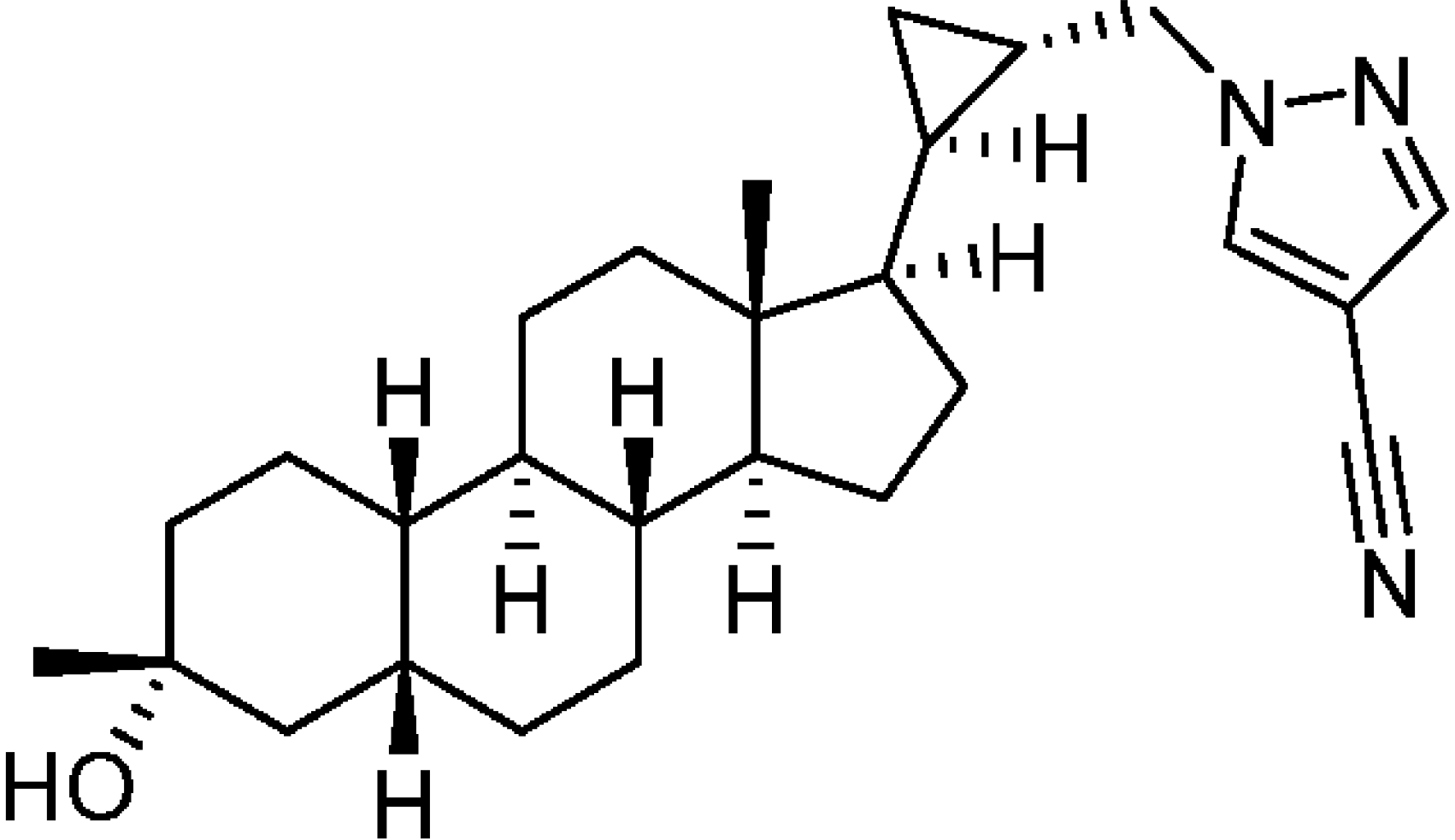
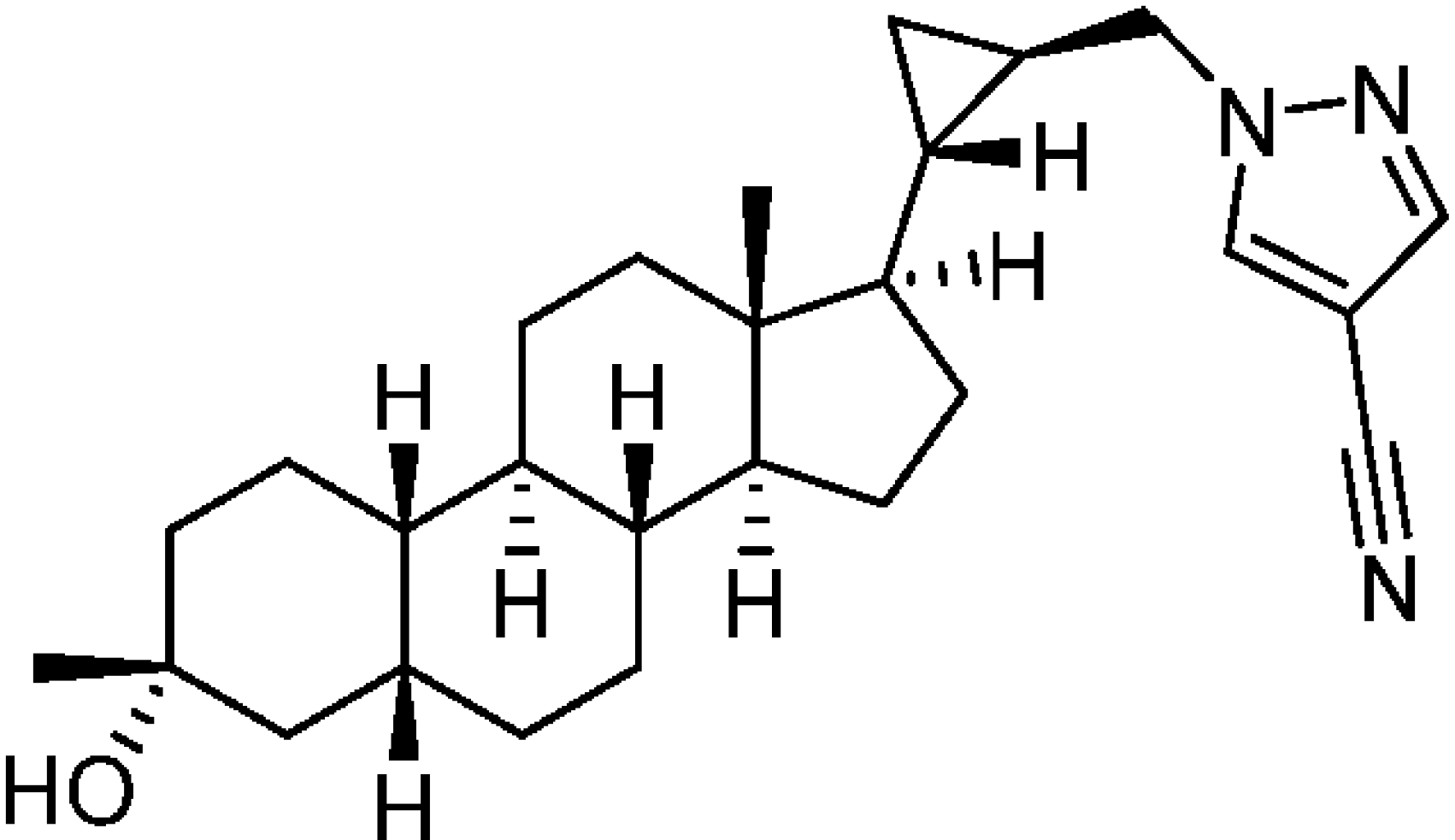
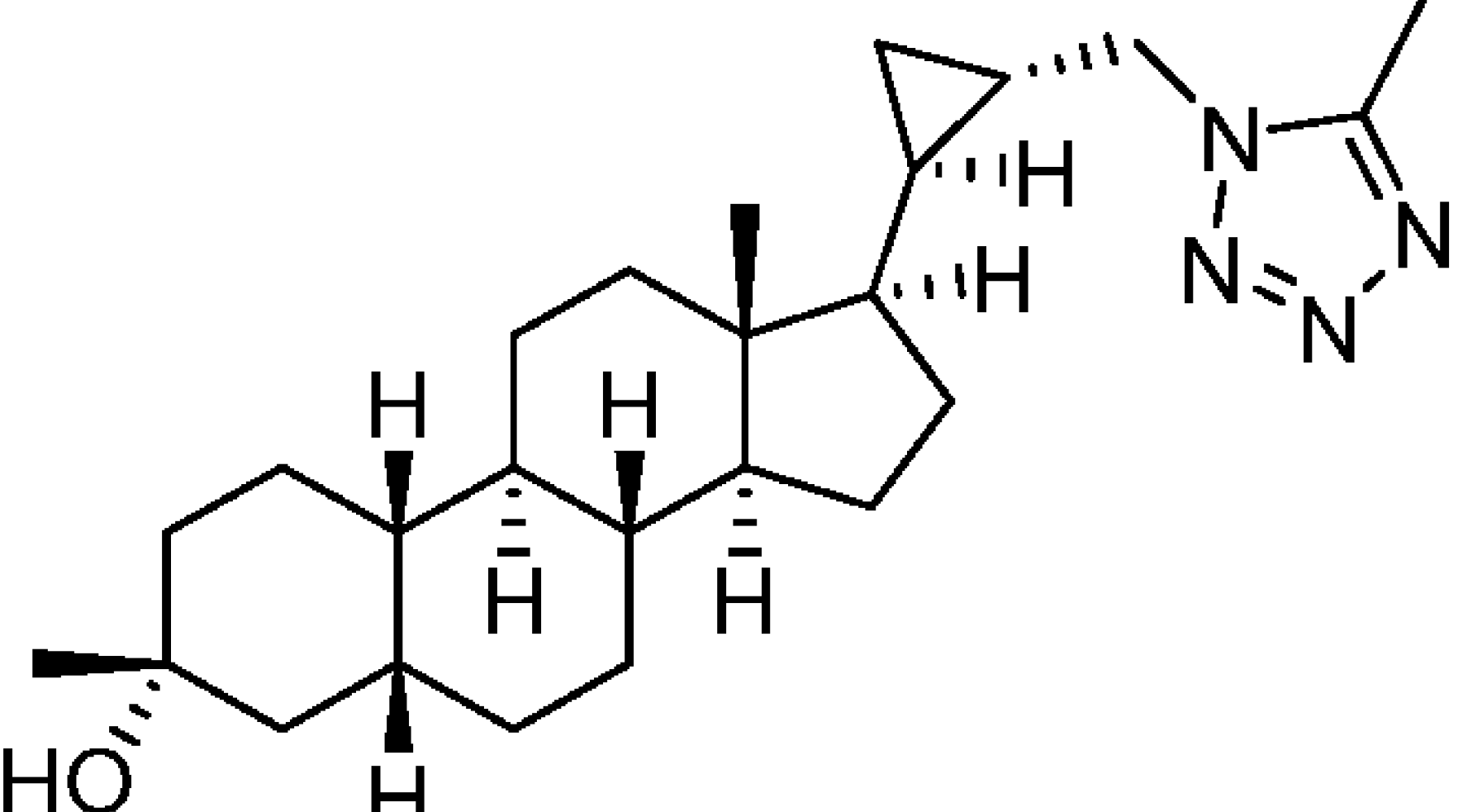
185. A compound selected from

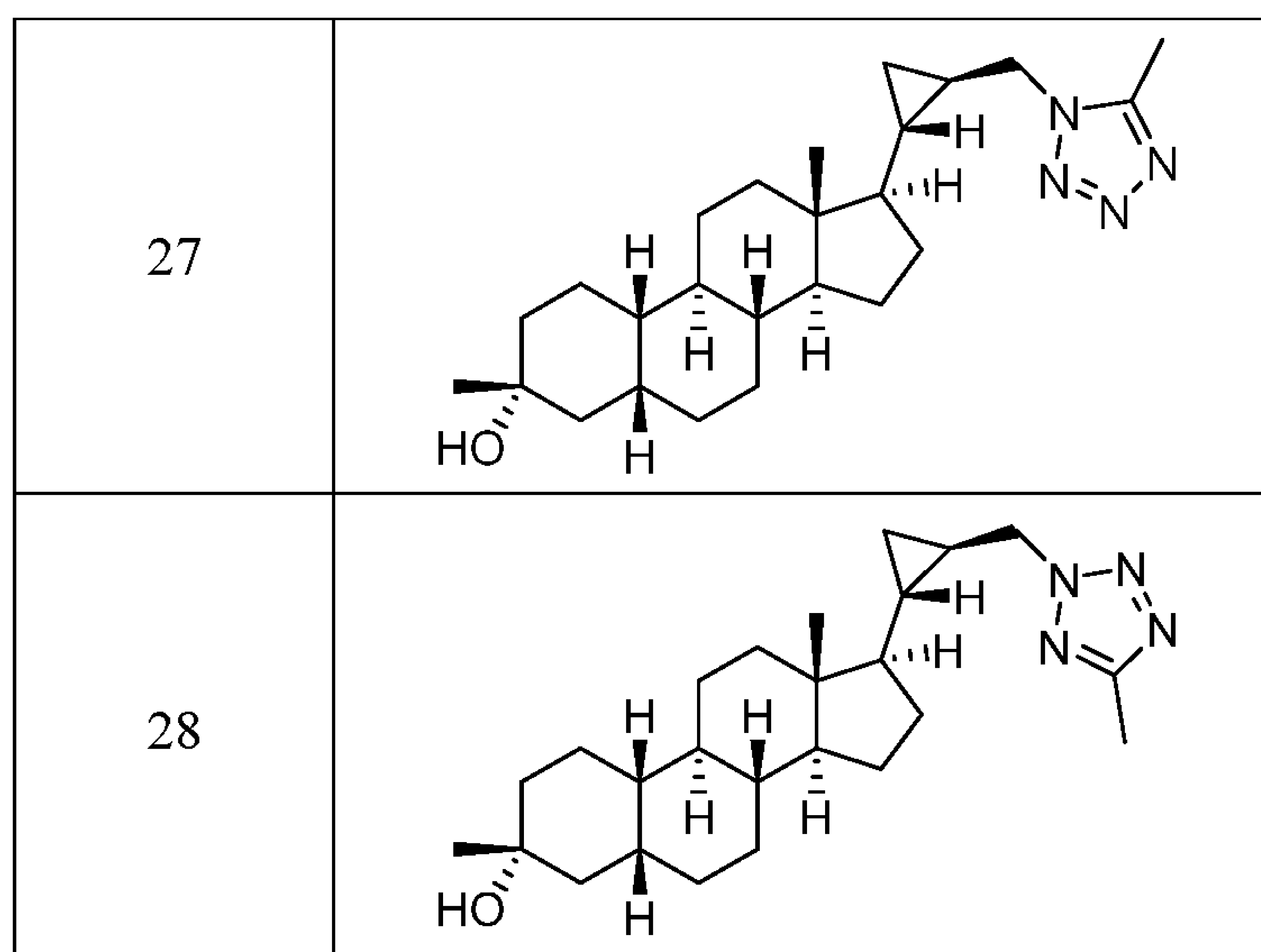


3	 <chem>N#Cc1ccnnc1CN[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>
4	 <chem>N#Cc1ccnnc1CN[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>
5	 <chem>N#Cc1ccnnc1CN[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>
6	 <chem>N#Cc1ccnnc1CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>
7	 <chem>N#Cc1ccnnc1CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>
8	 <chem>N#Cc1ccnnc1CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>

9	 <chem>CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>
10	 <chem>N#Cc1cc(CCN1C)ccn1</chem>
11	 <chem>CC1[C@H]2CC[C@@H]3[C@H]1CC=C4[C@@]3(CC[C@@H](C4)O)C</chem>
12	 <chem>O[C@H]1[C@H]2CC[C@@H]3[C@H]1CC=C4[C@@]3(CC[C@@H](C4)O)C</chem>
13	 <chem>CC1[C@H]2CC[C@@H]3[C@H]1CC=C4[C@@]3(CC[C@@H](C4)O)C</chem>
14	 <chem>CCCC1[C@H]2CC[C@@H]3[C@H]1CC=C4[C@@]3(CC[C@@H](C4)O)C</chem>

15	 <chem>CC[C@H](O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)C(=O)Nc5ccc(C#N)cc5)C)C</chem>
16	 <chem>CO[C@H](O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)C(=O)C)C)C</chem>
17	 <chem>CO[C@H](O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)C(=O)Nc5nn[nH]5)C)C</chem>
18	 <chem>CO[C@H](O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)C(=O)Nc5nn[nH]5)C)C</chem>
19	 <chem>CO[C@H](O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)C(=O)Nc5nn[nH]5)C)C</chem>
20	 <chem>CO[C@H](O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)C(=O)C)C)C</chem>

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or a pharmaceutically acceptable salt thereof.

186. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt of any one of claims 1-185, and a pharmaceutically acceptable carrier, vehicle, or excipient.

187. A method of modulating a GABA_A receptor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt of any one of claims 1-185 or a pharmaceutical composition of claim 186.

188. A method of modulating a GABA_A receptor mediated CNS-related disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt of any one of claims 1-185 or a pharmaceutical composition of claim 186.

189. A method of treating a CNS-related disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt of any one of claims 1-185 or a pharmaceutical composition of claim 186.

190. The method of claim 188 or claim 189, wherein 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, an autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, tinnitus, or status epilepticus.

191. The method of claim 190, wherein the CNS-related disorder is a mood disorder.

192. The method of claim 191, wherein the mood disorder is depression.

193. The method of claim 192, wherein the depression is postpartum depression.

194. The method of claim 192, wherein the depression is a major depressive disorder.

195. The method of claim 194, wherein the major depressive disorder is a moderate major depressive disorder.

196. The method of claim 195, wherein the major depressive disorder is a severe major depressive disorder.