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- (54) Benævnelse: **SAMMENSÆTNINGER OG FREMGANGSMÅDER TIL BEHANDLING AF CNS-FORSTYRRELSER**
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DESCRIPTION

Background of the Invention

[0001] 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, e.g., a change of potential 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.

[0002] In the case of the GABA receptor complex (GRC), the effect on brain excitability is mediated by 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.

[0003] 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.

[0004] Neuroactive steroids can occur endogenously. The most potent endogenous neuroactive steroids are 3 α -hydroxy-5-reducedpregnan-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)).

[0005] The ovarian hormone progesterone and its metabolites have been demonstrated to have profound effects on brain excitability (Backstrom, T. et al., Acta Obstet. Gynecol. Scand. Suppl. 130:19-24 (1985); Pfaff, D.W and McEwen, B. S., Science 219:808-814 (1983); Gyermek et al., J Med Chem. 11: 117 (1968); Lambert, J. et al., Trends Pharmacol. Sci. 8:224-227 (1987)). The levels of progesterone and its metabolites vary with the phases of the menstrual cycle. It has been well documented that the levels of progesterone and its metabolites decrease prior to the onset of menses. The monthly recurrence of certain physical symptoms prior to the onset of menses has also been well documented. These symptoms, which have become associated with premenstrual syndrome (PMS), include stress, anxiety, and migraine headaches (Dalton, K., Premenstrual Syndrome and Progesterone Therapy, 2nd edition, Chicago Yearbook, Chicago (1984)). Subjects with PMS have a monthly recurrence of symptoms that are present in premenses and absent in postmenses.

[0006] In a similar fashion, a reduction in progesterone has also been temporally correlated with an increase in seizure frequency in female epileptics, *i.e.*, catamenial epilepsy (Laidlaw, J., Lancet, 1235-1237 (1956)). A more direct correlation has been observed with a reduction in progesterone metabolites (Roszczewska et al., J. Neurol. Neurosurg. Psych. 49:47-51 (1986)). In addition, for subjects with primary generalized petit mal epilepsy, the temporal incidence of seizures has been correlated with the incidence of the symptoms of premenstrual syndrome (Backstrom, T. et al., J. Psychosom. Obstet. Gynaecol. 2:8-20 (1983)). The steroid deoxycorticosterone has been found to be effective in treating subjects with epileptic spells correlated with their menstrual cycles (Aird, R.B. and Gordan, G., J. Amer. Med. Soc. 145:715-719 (1951)).

[0007] A syndrome also related to low progesterone levels is postnatal depression (PND). Immediately after birth, progesterone levels decrease dramatically leading to the onset of PND. The symptoms of PND range from mild depression to psychosis requiring hospitalization. PND is also associated with severe anxiety and irritability. PND-associated depression is not amenable to treatment by classic antidepressants, and women experiencing PND show an increased incidence of PMS (Dalton, K., Premenstrual Syndrome and Progesterone Therapy, 2nd edition, Chicago Yearbook, Chicago (1984)).

[0008] Collectively, these observations imply a crucial role for progesterone and deoxycorticosterone and more specifically their metabolites in the homeostatic regulation of brain excitability, which is manifested as an increase in seizure activity or symptoms associated with catamenial epilepsy, PMS, and PND. The correlation between reduced levels of progesterone and the symptoms associated with PMS, PND, and catamenial epilepsy (Backstrom, T. et al., JPsychosom.Obstet. Gynaecol. 2:8-20 (1983)); Dalton, K., Premenstrual Syndrome and Progesterone Therapy, 2nd edition, Chicago Yearbook, Chicago (1984)) has prompted the use of progesterone in their treatment (Mattson et al., "Medroxyprogesterone therapy of catamenial epilepsy," in Advances in Epileptology: XVth Epilepsy International Symposium, Raven Press, New York (1984), pp. 279-282, and Dalton, K., Premenstrual

Syndrome and Progesterone Therapy, 2nd edition, Chicago Yearbook, Chicago (1984)). However, progesterone is not consistently effective in the treatment of the aforementioned syndromes. For example, no dose-response relationship exists for progesterone in the treatment of PMS (Maddocks et al., Obstet. Gynecol. 154:573-581 (1986); Dennerstein et al., Brit. Med J 290:16-17 (1986)). WO 2014/169831 relates to 19-nor-C3,3-disubstituted steroids contemplated for use in the treatment of CNS-related conditions. WO 2014/169832 relates to 3,3-disubstituted 19-nor-steroidal compounds contemplated for use in the treatment of CNS-related conditions.

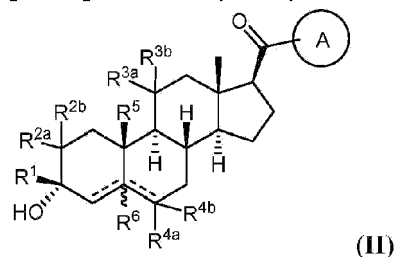
[0009] New and improved neuroactive steroids are needed that act as modulating agents for brain excitability, as well as agents for the prevention and treatment of CNS-related diseases. The compounds, compositions, and methods described herein are directed toward this end.

Summary of the Invention

[0010] The scope of the invention is defined by the claims. Any references in the description to methods of treatment refer to the compounds, pharmaceutical compositions and medicaments of the present invention for use in a method for treatment of the human (or animal) body by therapy (or for diagnosis).

[0011] Provided herein are C21-substituted neuroactive steroids designed, for example, to act as GABA modulators. In certain embodiments, such compounds are envisioned to be useful as therapeutic agents for the inducement of anesthesia and/or sedation in a subject. In some embodiments, such compounds are envisioned to be useful as therapeutic agents for treating a CNS-related disorder (e.g., 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, or tinnitus) in a subject in need (e.g., a subject with Rett syndrome, Fragile X syndrome, or Angelman syndrome).

[0012] In one aspect, provided is a compound of Formula (II):



or a pharmaceutically acceptable salt thereof; wherein: Ring A is substituted or unsubstituted aryl or heteroaryl; R¹ is hydrogen, or substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, or substituted or unsubstituted C₃₋₆ carbocyclyl; each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl,

substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₃₋₆ carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -N(R^A)(R^B), or -OR^{A2}, wherein each of R^A and R^B is independently hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₃₋₆ carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or R^A and R^B, together with the nitrogen atom to which they are attached form a ring (e.g., heteroaryl, heterocyclyl), or R^{2a} and R^{2b}, together with the carbon atom to which they are attached form a ring; R^{A2} is hydrogen or substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₃₋₆ carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3a} is hydrogen, -N(R^A)(R^B), or -OR^{A3}, wherein R^{A3} is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, or substituted or unsubstituted C₃₋₆ carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and R^{3b} is hydrogen or -N(R^A)C(O)R^{A3}; or R^{3a} and R^{3b} are joined to form an oxo (=O) group; each of R^{4a} and R^{4b} is independently selected from hydrogen or halogen; R⁵ is hydrogen, unsubstituted C₁₋₆ alkyl, or -CH₂OR^{A5}, wherein R^{A5} is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, or substituted or unsubstituted C₃₋₆ carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R⁶ is absent or hydrogen; and ----- represents a single or double bond, wherein when one of ----- is a double bond, the other ----- is a single bond; and when one of the ----- is a double bond, R⁶ is absent.

[0013] Also provided herein are pharmaceutical compositions comprising a compound of the present invention and methods of use and treatment, e.g., such as for inducing sedation and/or anesthesia, for treating a CNS-related disorder.

[0014] Steroids of Formula (I), sub-genera thereof, and pharmaceutically acceptable salts thereof are collectively referred to herein as "compounds of the present invention."

[0015] In another aspect, provided is a pharmaceutical composition comprising a compound of the present invention 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. In certain embodiments, the compound of the present invention is provided in a prophylactically effective amount.

[0016] Compounds of the present invention as described herein, act, in certain embodiments, as GABA modulators, e.g., effecting the GABA_A receptor in either a positive or negative

manner. As modulators of the excitability of the central nervous system (CNS), as mediated by their ability to modulate GABA_A receptor, such compounds are expected to have CNS-activity.

[0017] Thus, in another aspect, provided are methods of treating a CNS-related disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present invention. In certain embodiments, the CNS-related disorder is selected from the group consisting of 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, and tinnitus. In certain embodiments, the compound is administered orally, subcutaneously, intravenously, or intramuscularly. In certain embodiments, the compound is administered chronically. In certain embodiments, the compound is administered continuously, e.g., by continuous intravenous infusion.

[0018] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Detailed Description, Examples, and Claims**.

Definitions

Chemical definitions

[0019] 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.

[0020] Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure 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).

[0021] 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-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.

[0022] Compound described herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D or deuterium), and ^3H (T or tritium); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; and the like.

[0023] 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.

[0024] 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.

[0025] 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.

[0026] "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 8 carbon atoms ("C₁₋₈ 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), isobutyl (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).

[0027] "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, and no triple bonds ("C₂₋₂₀ alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C₂₋₁₀ 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 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.*, for instance 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.

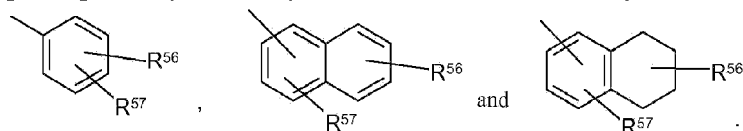
[0028] "Alkynyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon triple bonds, and optionally one or more double bonds ("C₂₋₂₀ alkynyl"). In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C₂₋₁₀ alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C₂₋₈ alkynyl"). In some embodiments, an alkynyl group has 2 to 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-butylnyl (C₄), 2-butylnyl (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.*, for instance 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.

[0029] "Aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C₆₋₁₄ aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C₆ aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C₁₀ aryl"; *e.g.*, naphthyl such as 1-naphthyl and 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. Aryl groups include, but are not limited to, 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.

[0030] In certain embodiments, an aryl group substituted with one or more of groups selected from halo, C₁-C₈ alkyl, C₁-C₈ haloalkyl, cyano, hydroxy, C₁-C₈ alkoxy, and amino.

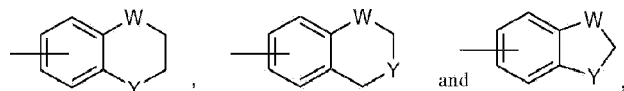
[0031] Examples of representative substituted aryls include the following



wherein one of R⁵⁶ and R⁵⁷ may be hydrogen and at least one of R⁵⁶ and R⁵⁷ is each independently selected from C₁-C₈ alkyl, C₁-C₈ haloalkyl, 4-10 membered heterocyclyl, alkanoyl, C₁-C₈ alkoxy, heteroaryloxy, alkylamino, arylamino, heteroaryl amino, NR⁵⁸COR⁵⁹, NR⁵⁸SOR⁵⁹, NR⁵⁸SO₂R⁵⁹, COOalkyl, COOaryl, CONR⁵⁸R⁵⁹, CONR⁵⁸OR⁵⁹, NR⁵⁸R⁵⁹, SO₂NR⁵⁸R⁵⁹, S-alkyl, SOalkyl, SO₂alkyl, Saryl, SOaryl, SO₂aryl; or R⁵⁶ and R⁵⁷ may be joined to form a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group N, O, or S. R⁶⁰ and R⁶¹ are independently

hydrogen, C₁-C₈ alkyl, C₁-C₄ haloalkyl, C₃-C₁₀ cycloalkyl, 4-10 membered heterocyclyl, C₆-C₁₀ aryl, substituted C₆-C₁₀ aryl, 5-10 membered heteroaryl, or substituted 5-10 membered heteroaryl.

[0032] Other representative aryl groups having a fused heterocyclyl group include the following:



wherein each W is selected from C(R⁶⁶)₂, NR⁶⁶, O, and S; and each Y is selected from carbonyl, NR⁶⁶, O and S; and R⁶⁶ is independently hydrogen, C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4-10 membered heterocyclyl, C₆-C₁₀ aryl, and 5-10 membered heteroaryl.

[0033] "Halo" or "halogen," independently or as part of another substituent, mean, unless otherwise stated, a fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) atom. The term "halide" by itself or as part of another substituent, refers to a fluoride, chloride, bromide, or iodide atom. In certain embodiments, the halo group is either fluorine or chlorine.

[0034] "Haloalkyl" and "haloalkoxy" can include alkyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

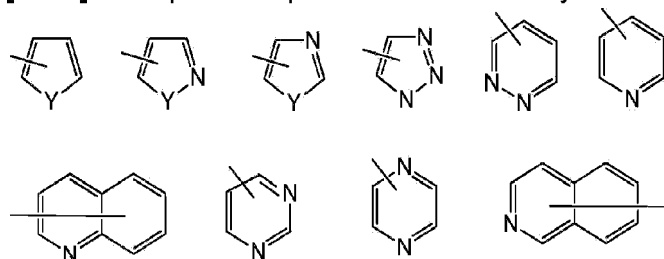
[0035] "Heteroaryl" refers to a radical of a 5-10 membered monocyclic or bicyclic 4n+2 aromatic ring system (e.g., having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5-10 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, i.e., either the ring bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl).

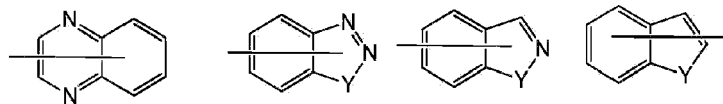
[0036] In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system,

wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-8 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5-14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5-14 membered heteroaryl.

[0037] 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, indoliziny, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0038] Examples of representative heteroaryls include the following formulae:





wherein each Y is selected from carbonyl, N, NR⁶⁵, O, and S; and R⁶⁵ is independently hydrogen, C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4-10 membered heterocyclyl, C₆-C₁₀ aryl, and 5-10 membered heteroaryl.

[0039] "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.

[0040] 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

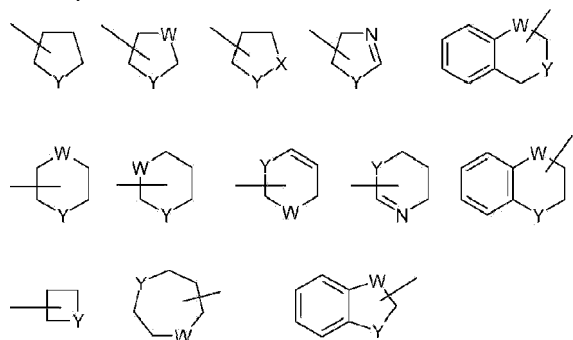
group has 5 to 10 ring carbon atoms ("C₅₋₁₀ cycloalkyl"). Examples of C₅₋₆ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃₋₆ cycloalkyl groups include the aforementioned C₅₋₆ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ cycloalkyl 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.

[0041] "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.

[0042] 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.

[0043] 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.

[0044] Particular examples of heterocyclyl groups are shown in the following illustrative examples:



wherein each W is selected from CR⁶⁷, C(R⁶⁷)₂, NR⁶⁷, O, and S; and each Y is selected from NR⁶⁷, O, and S; and R⁶⁷ is independently hydrogen, C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4-10 membered heterocyclyl, C₆-C₁₀ aryl, and 5-10-membered heteroaryl. These heterocyclyl rings may be optionally substituted with one or more groups selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl (e.g., amido), aminocarbonylamino, aminosulfonyl, sulfonylamino, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, halogen, hydroxy, keto, nitro, thiol, -S-alkyl, -S-aryl, -S(O)-alkyl, -S(O)-aryl, -S(O)₂-alkyl, and -S(O)₂-aryl. Substituting groups include carbonyl or thiocarbonyl which provide, for example, lactam and urea derivatives.

[0045] "Acyl" refers to a radical $-C(O)R^{20}$, where R^{20} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, as defined herein. "Alkanoyl" is an acyl group wherein R^{20} is a group other than hydrogen. Representative acyl groups include, but are not limited to, formyl ($-CHO$), acetyl ($-C(=O)CH_3$), cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl ($-C(=O)Ph$), benzylcarbonyl ($-C(=O)CH_2Ph$), $-C(O)-C_1-C_8$ alkyl, $-C(O)-(CH_2)_t(C_6-C_{10}$ aryl), $-C(O)-(CH_2)_t(5-10$ membered heteroaryl), $-C(O)-(CH_2)_t(C_3-C_{10}$ cycloalkyl), and $-C(O)-(CH_2)_t(4-10$ membered heterocyclyl), wherein t is an integer from 0 to 4. In certain embodiments, R^{21} is C_1-C_8 alkyl, substituted with halo or hydroxy; or C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy.

[0046] "Acylamino" refers to a radical $-NR^{22}C(O)R^{23}$, where each instance of R^{22} and R^{23} is independently 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, or R^{22} is an amino protecting group. Exemplary "acylamino" groups include, but are not limited to, formylamino, acetylamino, cyclohexylcarbonylamino, cyclohexylmethyl-carbonylamino, benzoylamino and benzylcarbonylamino. Particular exemplary "acylamino" groups are $-NR^{24}C(O)-C_1-C_8$ alkyl, $-NR^{24}C(O)-(CH_2)_t(C_6-C_{10}$ aryl), $-NR^{24}C(O)-(CH_2)_t(5-10$ membered heteroaryl), $-NR^{24}C(O)-(CH_2)_t(C_3-C_{10}$ cycloalkyl), and $-NR^{24}C(O)-(CH_2)_t(4-10$ membered heterocyclyl), wherein t is an integer from 0 to 4, and each R^{24} independently represents hydrogen or C_1-C_8 alkyl. In certain embodiments, R^{25} is H, C_1-C_8 alkyl, substituted with halo or hydroxy; C_3-C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6-C_{10} aryl, arylalkyl, 5-10 membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy; and R^{26} is H, C_1-C_8 alkyl, substituted with halo or hydroxy; C_3-C_{10} cycloalkyl, 4-10-membered heterocyclyl, C_6-C_{10} aryl, arylalkyl, 5-10-membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1-C_4 alkyl, halo, unsubstituted C_1-C_4 alkoxy, unsubstituted C_1-C_4 haloalkyl, unsubstituted C_1-C_4 hydroxyalkyl, or unsubstituted C_1-C_4 haloalkoxy or hydroxy; provided at least one of R^{25} and R^{26} is other than H.

[0047] "Acyloxy" refers to a radical $-OC(O)R^{27}$, where R^{27} 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. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl, and benzylcarbonyl. In certain embodiments, R^{28} is C_1 - C_8 alkyl, substituted with halo or hydroxy; C_3 - C_{10} cycloalkyl, 4-10-membered heterocyclyl, C_6 - C_{10} aryl, arylalkyl, 5-10-membered heteroaryl or heteroarylalkyl, each of which is substituted with unsubstituted C_1 - C_4 alkyl, halo, unsubstituted C_1 - C_4 alkoxy, unsubstituted C_1 - C_4 haloalkyl, unsubstituted C_1 - C_4 hydroxyalkyl, or unsubstituted C_1 - C_4 haloalkoxy or hydroxy.

[0048] "Alkoxy" refers to the group $-OR^{29}$ where R^{29} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, *i.e.*, with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

[0049] In certain embodiments, R^{29} is a group that has 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent, selected from the group consisting of amino, substituted amino, C_6 - C_{10} aryl, aryloxy, carboxyl, cyano, C_3 - C_{10} cycloalkyl, 4-10 membered heterocyclyl, halogen, 5-10 membered heteroaryl, hydroxy, nitro, thioalkoxy, thioaryloxy, thiol, alkyl-S(O)-, aryl-S(O)-, alkyl-S(O)₂- and aryl-S(O)₂-. Exemplary "substituted alkoxy" groups include, but are not limited to, $-O-(CH_2)_t(C_6-C_{10}$ aryl), $-O-(CH_2)_t(5-10$ membered heteroaryl), $-O-(CH_2)_t(C_3-C_{10}$ cycloalkyl), and $-O-(CH_2)_t(4-10$ membered heterocyclyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocyclyl groups present, may themselves be substituted by unsubstituted C_1 - C_4 alkyl, halo, unsubstituted C_1 - C_4 alkoxy, unsubstituted C_1 - C_4 haloalkyl, unsubstituted C_1 - C_4 hydroxyalkyl, or unsubstituted C_1 - C_4 haloalkoxy or hydroxy. Particular exemplary 'substituted alkoxy' groups are $-OCF_3$, $-OCH_2CF_3$, $-OCH_2Ph$, $-OCH_2$ -cyclopropyl, $-OCH_2CH_2OH$, and $-OCH_2CH_2NMe_2$.

[0050] "Amino" refers to the radical $-NH_2$.

[0051] "Substituted amino" refers to an amino group of the formula $-N(R^{38})_2$ wherein R^{38} is hydrogen, substituted or unsubstituted alkyl, substituted or 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 R^{38} is not a hydrogen. In certain embodiments, each R^{38} is independently selected from hydrogen, C_1 - C_8 alkyl, C_3 - C_8 alkenyl, C_3 - C_8 alkynyl, C_6 - C_{10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocyclyl, or C_3 - C_{10} cycloalkyl; or

C₁-C₈ alkyl, substituted with halo or hydroxy; C₃-C₈ alkenyl, substituted with halo or hydroxy; C₃-C₈ alkynyl, substituted with halo or hydroxy, or -(CH₂)_t(C₆-C₁₀ aryl), -(CH₂)_t(5-10 membered heteroaryl), -(CH₂)_t(C₃-C₁₀ 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-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxy; or both R³⁸ groups are joined to form an alkylene group.

[0052] Exemplary "substituted amino" groups include, but are not limited to, -NR³⁹-C₁-C₈ alkyl, -NR³⁹-(CH₂)_t(C₆-C₁₀ aryl), -NR³⁹-(CH₂)_t(5-10 membered heteroaryl), -NR³⁹-(CH₂)_t(C₃-C₁₀ 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 hydrogen or C₁-C₈ 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-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ 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.

[0053] "Azido" refers to the radical -N₃.

[0054] "Carbamoyl" or "amido" refers to the radical -C(O)NH₂.

[0055] "Substituted carbamoyl" or "substituted amido" refers to the radical -C(O)N(R⁶²)₂ wherein each R⁶² is independently 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 R⁶² is not a hydrogen. In certain embodiments, R⁶² is selected from H, C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4-10 membered heterocyclyl, C₆-C₁₀ aryl, and 5-10 membered heteroaryl; or C₁-C₈ alkyl substituted with halo or hydroxy; or C₃-C₁₀ cycloalkyl, 4-10 membered heterocyclyl, C₆-C₁₀ aryl, or 5-10 membered heteroaryl, each of which is substituted by unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxy; provided that at least one R⁶² is other than H.

[0056] "Carboxy" refers to the radical -C(O)OH.

[0057] "Cyano" refers to the radical -CN.

[0058] "Hydroxy" refers to the radical -OH.

[0059] "Nitro" refers to the radical -NO₂.

[0060] "Ethenyl" refers to substituted or unsubstituted -(C=C)-. "Ethylene" refers to substituted or unsubstituted -(C-C)-. "Ethynyl" refers to -(C≡C)-.

[0061] "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.

[0062] 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.

[0063] Exemplary carbon atom substituents include, but are not limited to, halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{aa}, -ON(R^{bb})₂, -N(R^{bb})₂, N(R^{bb})₃⁺X⁻, -N(OR^{cc})R^{bb}, -SH, -SR^{aa}, -SSR^{cc}, -C(=O)R^{aa}, -CO₂H, -CHO, -C(OR^{cc})₂, -CO₂R^{aa}, -OC(=O)R^{aa}, -OCO₂R^{aa}, -C(=O)N(R^{bb})₂, -OC(=O)N(R^{bb})₂, -NR^{bb}C(=O)R^{aa}, -NR^{bb}CO₂R^{aa}, -NR^{bb}C(=O)N(R^{bb})₂, -C(=NR^{bb})R^{aa}, -C(=NR^{bb})OR^{aa}, -OC(=NR^{bb})R^{aa}, -OC(=NR^{bb})OR^{aa}, -C(=NR^{bb})N(R^{bb})₂, -OC(=NR^{bb})N(R^{bb})₂, -NR^{bb}C(=NR^{bb})N(R^{bb})₂, -C(=O)NR^{bb}SO₂R^{aa}, -NR^{bb}SO₂R^{aa}, -SO₂N(R^{bb})₂, -

SO₂R^{aa}, -SO₂OR^{aa}, -OSO₂R^{aa}, -S(=O)R^{aa}, -OS(=O)R^{aa}, -Si(R^{aa})₃, -OSi(R^{aa})₃, -C(=S)N(R^{bb})₂, -C(=O)SR^{aa}, -C(=S)SR^{aa}, -SC(=S)SR^{aa}, -SC(=O)SR^{aa}, -OC(=O)SR^{aa}, -SC(=O)OR^{aa}, -SC(=O)R^{aa}, -P(=O)₂R^{aa}, -OP(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -OP(=O)(R^{aa})₂, -OP(=O)(OR^{cc})₂, -P(=O)₂N(R^{bb})₂, -OP(=O)₂N(R^{bb})₂, -OP(=O)₂N(R^{bb})₂, -OP(=O)(NR^{bb})₂, -NR^{bb}P(=O)(OR^{cc})₂, -NR^{bb}P(=O)(NR^{bb})₂, -P(R^{cc})₂, -P(R^{cc})₃, -OP(R^{cc})₂, -OP(R^{cc})₃, -B(R^{aa})₂, -B(OR^{cc})₂, -BR^{aa}(OR^{cc}), C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ 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;

each instance of R^{aa} is, independently, selected from C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ 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, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{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, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ 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, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ 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, -NO₂, -N₃, -SO₂H, -SO₃H, -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}, -CO₂H, -CO₂R^{ee}, -OC(=O)R^{ee}, -OCO₂R^{ee}, -C(=O)N(R^{ff})₂, -OC(=O)N(R^{ff})₂, -NR^{ff}C(=O)R^{ee}, -NR^{ff}CO₂R^{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}SO₂R^{ee}, -SO₂N(R^{ff})₂, -SO₂R^{ee}, -SO₂OR^{ee}, -OSO₂R^{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, C₁₋₆

alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, 3-10 membered heterocyclyl, C₆₋₁₀ 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;

each instance of R^{ee} is, independently, selected from C₁₋₆ alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, C₆₋₁₀ 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, C₁₋₆ alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, 3-10 membered heterocyclyl, C₆₋₁₀ 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, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OC₁₋₆ alkyl, -ON(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₃⁺X⁻, -NH(C₁₋₆ alkyl)₂⁺X⁻, -NH₂(C₁₋₆ alkyl)⁺X⁻, -NH₃⁺X⁻, -N(OC₁₋₆ alkyl)(C₁₋₆ alkyl), -N(OH)(C₁₋₆ alkyl), -NH(OH), -SH, -SC₁₋₆ alkyl, -SS(C₁₋₆ alkyl), -C(=O)(C₁₋₆ alkyl), -CO₂H, -CO₂(C₁₋₆ alkyl), -OC(=O)(C₁₋₆ alkyl), -OCO₂(C₁₋₆ alkyl), -C(=O)NH₂, -C(=O)N(C₁₋₆ alkyl)₂, -OC(=O)NH(C₁₋₆ alkyl), -NHC(=O)(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)C(=O)(C₁₋₆ alkyl), -NHCO₂(C₁₋₆ alkyl), -NHC(=O)N(C₁₋₆ alkyl)₂, -NHC(=O)NH(C₁₋₆ alkyl), -NHC(=O)NH₂, -C(=NH)O(C₁₋₆ alkyl), -OC(=NH)(C₁₋₆ alkyl), -OC(=NH)OC₁₋₆ alkyl, -C(=NH)N(C₁₋₆ alkyl)₂, -C(=NH)NH(C₁₋₆ alkyl), -C(=NH)NH₂, -OC(=NH)N(C₁₋₆ alkyl)₂, -OC(NH)NH(C₁₋₆ alkyl), -OC(NH)NH₂, -NHC(NH)N(C₁₋₆ alkyl)₂, -NHC(=NH)NH₂, -NHCO₂(C₁₋₆ alkyl), -SO₂N(C₁₋₆ alkyl)₂, -SO₂NH(C₁₋₆ alkyl), -SO₂NH₂, -SO₂C₁₋₆ alkyl, -SO₂OC₁₋₆ alkyl, -OSO₂C₁₋₆ alkyl, -SOC₁₋₆ alkyl, -Si(C₁₋₆ alkyl)₃, -OSi(C₁₋₆ alkyl)₃, -C(=S)N(C₁₋₆ alkyl)₂, C(=S)NH(C₁₋₆ alkyl), C(=S)NH₂, -C(=O)S(C₁₋₆ alkyl), -C(=S)SC₁₋₆ alkyl, -SC(=S)SC₁₋₆ alkyl, -P(=O)₂(C₁₋₆ alkyl), -P(=O)(C₁₋₆ alkyl)₂, -OP(=O)(C₁₋₆ alkyl)₂, -OP(=O)(OC₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, C₆₋₁₀ aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; wherein X⁻ is a counterion.

[0064] 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⁻), NO₃⁻, ClO₄⁻, OH⁻, H₂PO₄⁻, HSO₄⁻, 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).

[0065] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include

primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{bb})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{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, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14-membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom 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, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0066] 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, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14-membered heterocyclyl, C₆₋₁₄ 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.

[0067] Exemplary amino protecting groups include, but are not limited to amide groups (e.g., -C(=O)R^{aa}), which include, but are not limited to, formamide and acetamide; carbamate groups (e.g., -C(=O)OR^{aa}), which include, but are not limited to, 9-fluorenylmethyl carbamate (Fmoc), *t*-butyl carbamate (BOC), and benzyl carbamate (Cbz); sulfonamide groups (e.g., -S(=O)₂R^{aa}), which include, but are not limited to, *p*-toluenesulfonamide (Ts), methanesulfonamide (Ms), and *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM).

[0068] 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}, -CO₂R^{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}, -SO₂R^{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.

[0069] 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).

[0070] In certain embodiments, the substituent present on an sulfur atom is an sulfur protecting group (also referred to as a thiol protecting group). Sulfur protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999.

[0071] These and other exemplary substituents are described in more detail in the **Detailed Description, Examples, and Claims**. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other definitions

[0072] As used herein, the term "modulation" refers to the inhibition or potentiation of GABA receptor function. A "modulator" (e.g., a modulator compound) may be, for example, an agonist, partial agonist, antagonist, or partial antagonist of the GABA receptor.

[0073] "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.

[0074] "Pharmaceutically acceptable salt" refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid,

camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term "pharmaceutically acceptable cation" refers to an acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like. See, *e.g.*, Berge, et al., J. Pharm. Sci. (1977) 66(1): 1-79.

[0075] "Solvate" refers to forms of the compound that are associated with a solvent or water (also referred to as "hydrate"), usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid, and the like. The compounds of the invention may be prepared *e.g.* in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[0076] As used herein, the term "isotopic variant" refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an "isotopic variant" of a compound can contain one or more non-radioactive isotopes, such as for example, deuterium (^2H or D), carbon-13 (^{13}C), nitrogen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be $^2\text{H}/\text{D}$, any carbon may be ^{13}C , or any nitrogen may be ^{15}N , and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.*, ^3H , and carbon-14, *i.e.*, ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O , and ^{13}N , and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. All isotopic variants of the compounds provided herein, radioactive or not, are intended to be encompassed within the scope of the invention.

[0077] "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.

[0078] A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.* infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult or senior adult)) and/or a non-human animal, *e.g.*, a mammal such as primates (*e.g.*, cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal. The terms "human," "patient," and "subject" are used interchangeably herein.

[0079] Disease, disorder, and condition are used interchangeably herein.

[0080] 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 ("prophylactic treatment").

[0081] In general, the "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response, *e.g.*, to treat a CNS-related disorder, is sufficient to induce anesthesia or sedation. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of the invention may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the age, weight, health, and condition of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[0082] 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.

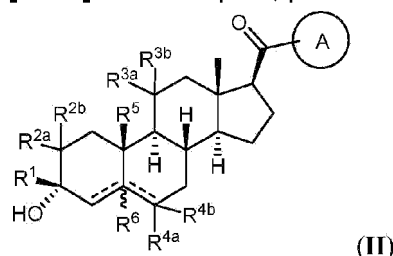
[0083] As used herein, and unless otherwise specified, a "prophylactically effective amount" of a compound is an amount sufficient to prevent a disease, disorder or condition, or one or more symptoms associated with the disease, disorder or condition, or prevent its recurrence. A prophylactically effective 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.

Detailed Description of Certain Embodiments of the Invention

[0084] As generally described herein, the present invention provides C21-substituted neuroactive steroids designed, for example, to act as GABA modulators. In certain embodiments, such compounds are envisioned to be useful as therapeutic agents for the inducement of anesthesia and/or sedation in a subject. In certain embodiments, such compounds are envisioned to be useful as therapeutic agents for treating a CNS-related disorder.

Compounds

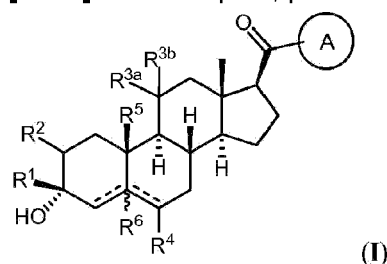
[0085] In one aspect, provided is a compound of Formula (II):



or a pharmaceutically acceptable salt thereof; wherein: Ring A is substituted or unsubstituted aryl or heteroaryl; R^1 is hydrogen, or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl; each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-N(R^A)(R^B)$, or $-OR^{A2}$, wherein each of R^A and R^B is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or R^A and R^B , together with the nitrogen atom to which they are attached form a ring (e.g., heteroaryl, heterocyclyl), or R^{2a} and

R^{2b} , together with the carbon atom to which they are attached form a ring; R^{A2} is hydrogen or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3a} is hydrogen, $-N(R^A)(R^B)$, or $-OR^{A3}$, wherein R^{A3} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and R^{3b} is hydrogen or $-N(R^A)C(O)R^{A3}$; or R^{3a} and R^{3b} are joined to form an oxo ($=O$) group; each of R^{4a} and R^{4b} is independently selected from hydrogen or halogen; R^5 is hydrogen, unsubstituted C_{1-6} alkyl, or $-CH_2OR^{A5}$, wherein R^{A5} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^6 is absent or hydrogen; and ----- represents a single or double bond, wherein when one of ----- is a double bond, the other ----- is a single bond; and when one of the ----- is a double bond, R^6 is absent.

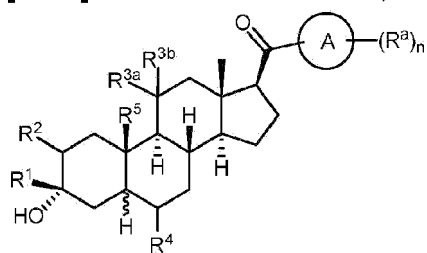
[0086] In one aspect, provided is a compound of Formula (I):



or a pharmaceutically acceptable salt thereof; wherein: Ring A is substituted or unsubstituted aryl or heteroaryl; R^1 is hydrogen, or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, or substituted or unsubstituted C_{3-6} carbocyclyl; R^2 is hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, $-N(R^A)(R^B)$, or $-OR^{A2}$, wherein each of R^A and R^B is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, or substituted or unsubstituted heterocyclyl, or R^A and R^B , together with the nitrogen atom to which they are attached form a ring (e.g., heteroaryl, heterocyclyl); R^{A2} is hydrogen or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl; R^{3a} is hydrogen, $-N(R^A)(R^B)$, or $-OR^{A3}$, wherein R^{A3} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6}

carbocyclyl, and R^{3b} is hydrogen or $-N(R^A)C(O)R^{A3}$; or R^{3a} and R^{3b} are joined to form an oxo ($=O$) group; R^4 is hydrogen or halogen; R^5 is hydrogen, unsubstituted C_{1-6} alkyl, or $-CH_2OR^{A5}$, wherein R^{A5} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl; R^6 is absent or hydrogen; and ----- represents a single or double bond, wherein when one of is a double bond, the other ----- is a single bond; and when one of the ----- is a double bond, R^6 is absent.

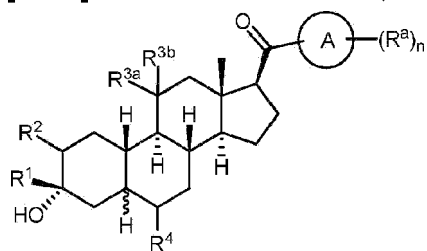
[0087] In some embodiments, the compound of Formula (I) is a compound of Formula (I-a):



(I-a)

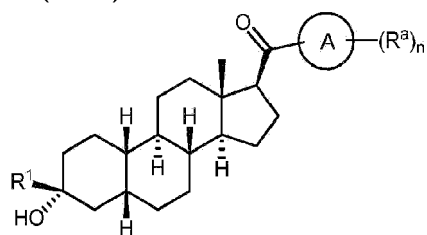
wherein: n is 0, 1, 2, 3, 4, 5, or 6; and each R^a is independently halogen, cyano, C_{1-6} alkyl, $-N(R^A)(R^B)$, $-N(R^A)C(O)R^{AA}$, $-N(R^A)C(O)OR^{AA}$, $-SR^{AA}$ or $-OR^{AA}$, wherein R^{AA} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two R^a groups, together with the atoms with which they are attached form a ring.

[0088] In some embodiments, the compound of Formula (I) is a compound of Formula (I-b):

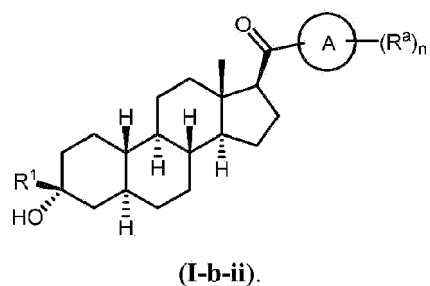


(I-b).

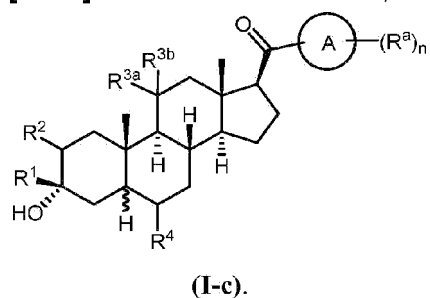
[0089] In some embodiments, the compound of Formula (I) is a compound of Formula (I-b-i) or (I-b-ii):



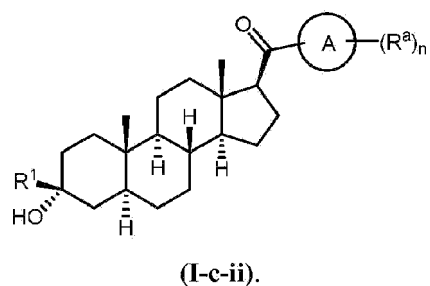
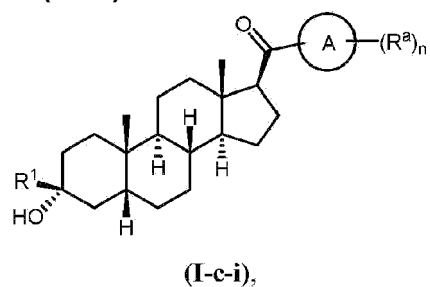
(I-b-i).



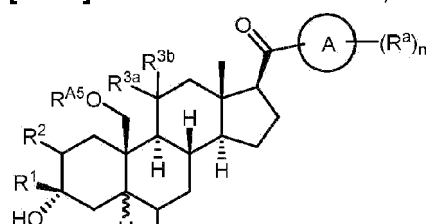
[0090] In some embodiments, the compound of Formula (I) is a compound of Formula (I-c):

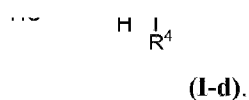


[0091] In some embodiments, the compound of Formula (I) is a compound of Formula (I-c-i) or (I-c-ii):

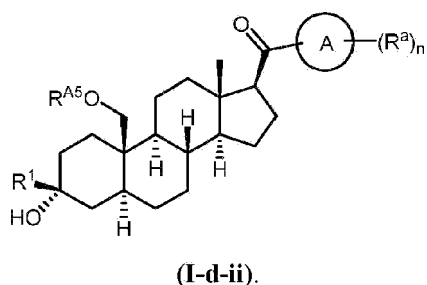
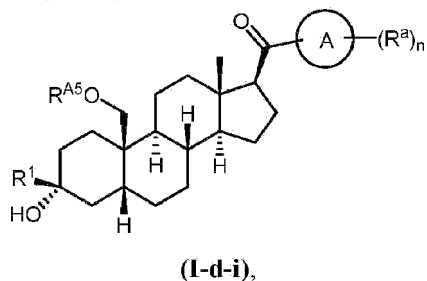


[0092] In some embodiments, the compound of Formula (I) is a compound of Formula (I-f):





[0093] In some embodiments, the compound of Formula (I) is a compound of Formula (I-d-i) or (I-d-ii):



[0094] In some embodiments, A is a 5-10-membered ring. In some embodiments, A is phenyl, naphthyl, furan, thiophene, thiazole, pyrrole, imidazole, pyrazole, or triazole.

[0095] In some embodiments, A is a fused bicyclic ring. In some embodiments, A is benzofuran, benzoimidazole, indole, benzothiazole, or benzothiophene.

[0096] In some embodiments, A is linked through a carbon atom.

[0097] In some embodiments, R¹ is hydrogen or substituted or unsubstituted C₁₋₆ alkyl.

[0098] In some embodiments, R¹ is unsubstituted C₁₋₆ alkyl. In some embodiments, R¹ is -CH₃.

[0099] In some embodiments, R¹ is hydrogen.

[0100] In some embodiments, R² is hydrogen or halogen. In some embodiments, R² is hydrogen.

[0101] In some embodiments, R^{3a} is -N(R^A)(R^B). In some aspects of these embodiments, each of R^A and R^B is independently hydrogen or substituted or unsubstituted C₁₋₆ alkyl. In

some embodiments, R^{3a} is $-NH_2$. In some embodiments, R^{3a} is $-NHCH_3$ or $-NHCH_2CH_3$. In some embodiments, R^{3a} is $-N(CH_3)(CH_2CH_3)$, $-N(CH_2CH_3)_2$ or $-N(CH_3)_2$. In some aspects of these embodiments, R^A and R^B , together with the nitrogen atom to which they are attached form a ring (e.g., heteroaryl, heterocyclyl). In some embodiments, R^A and R^B , together with the nitrogen atom to which they are attached form a 3-7-membered ring (e.g., pyrrolidine, imidazolidine, piperidine, piperazine, morpholine, pyrrole, imidazole, triazole, tetrazole).

[0102] In some embodiments, R^{3b} is hydrogen.

[0103] In some embodiments, R^{3b} is $-N(R^A)C(O)R^{A3}$. In some aspects of these embodiments, R^A is hydrogen or substituted or unsubstituted C_{1-6} alkyl. In some aspects of these embodiments, R^{A3} is hydrogen or substituted or unsubstituted C_{1-6} alkyl.

[0104] In some embodiments, R^4 is hydrogen.

[0105] In some embodiments, R^5 is hydrogen or unsubstituted C_{1-6} alkyl. In some embodiments, R^5 is $-CH_2OR^{A5}$. In some aspects of these embodiments, R^{A5} is hydrogen or substituted or unsubstituted C_{1-6} alkyl.

[0106] In some embodiments, n is 0, 1, or 2. In some embodiments, n is 0 or 1.

[0107] In some embodiments, n is 0, 1, or 2, and each R^a is independently halogen, C_{1-6} alkyl, or $-OR^{AA}$. In some aspects of these embodiments, R^{AA} is hydrogen, or substituted or unsubstituted C_{1-6} alkyl. In some embodiments, R^a is $-CH_3$.

[0108] In some embodiments, R^a is C_{1-6} alkyl.

[0109] In some embodiments, R^a is $-N(R^A)(R^B)$. In some aspects of these embodiments, each of R^A and R^B is independently hydrogen or substituted or unsubstituted C_{1-6} alkyl. In some embodiments, R^a is $-NH_2$. In some embodiments, R^a is $-NHCH_3$ or $-NHCH_2CH_3$. In some embodiments, R^a is $-N(CH_3)(CH_2CH_3)$, $-N(CH_2CH_3)_2$ or $-N(CH_3)_2$. In some aspects of these embodiments, R^A and R^B , together with the nitrogen atom to which they are attached form a ring (e.g., heteroaryl, heterocyclyl). In some embodiments, R^A and R^B , together with the nitrogen atom to which they are attached form a 3-7-membered ring (e.g., pyrrolidine, imidazolidine, piperidine, piperazine, morpholine, pyrrole, imidazole, triazole, tetrazole).

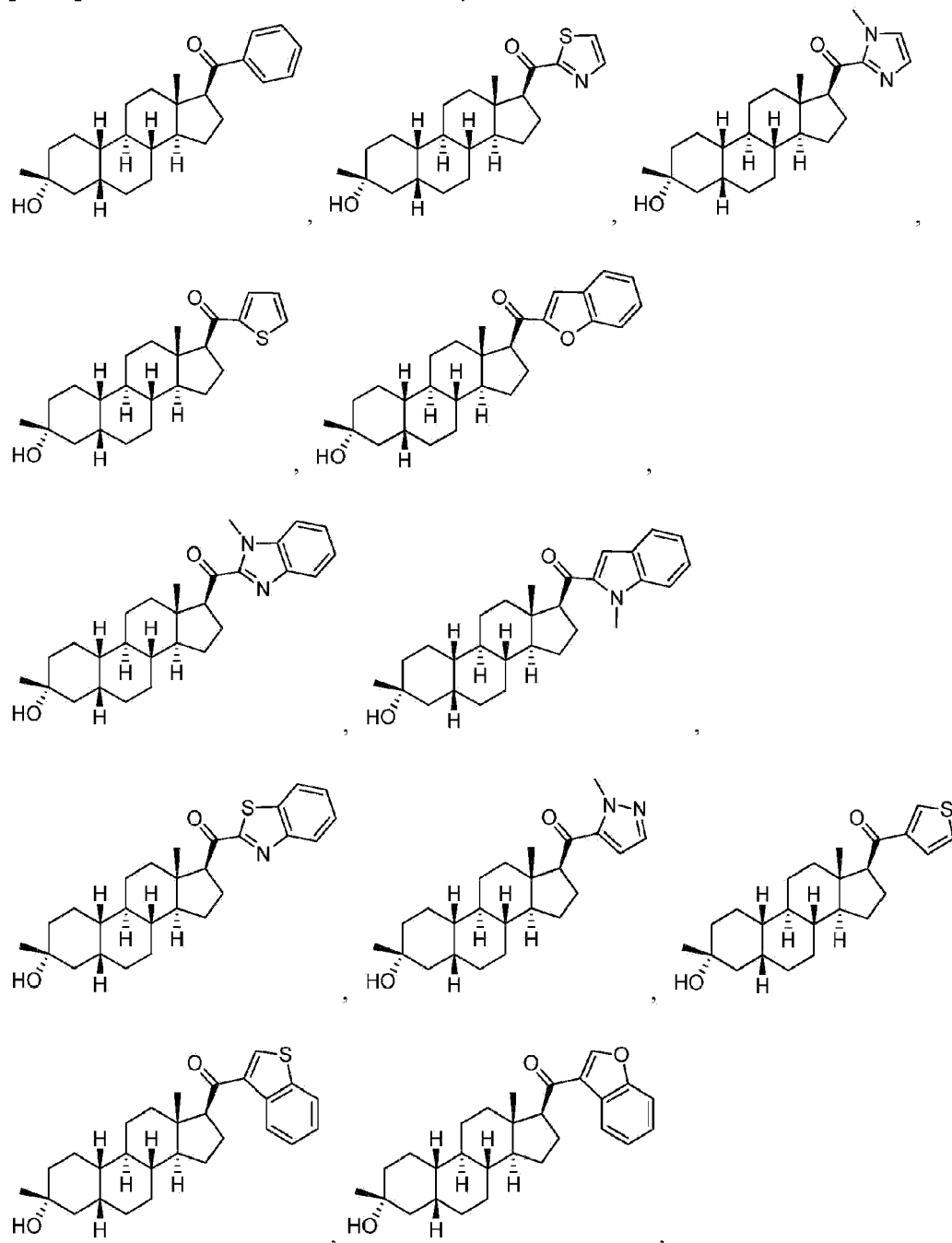
[0110] In some embodiments, R^a is $-N(R^A)C(O)R^{AA}$. In some aspects of these embodiments,

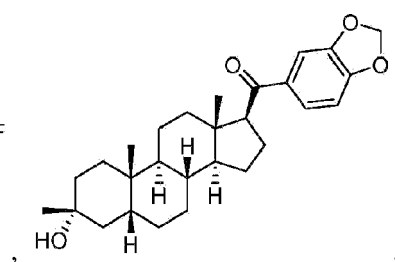
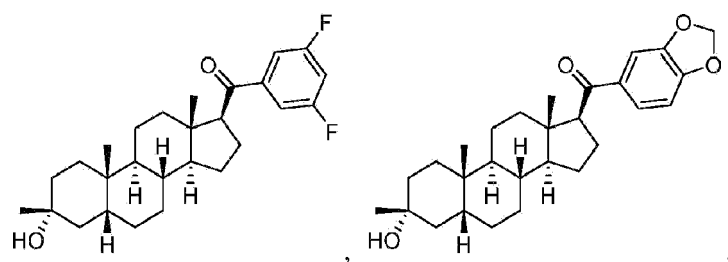
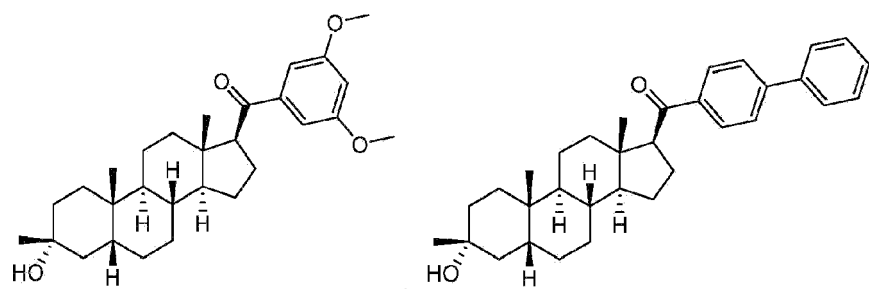
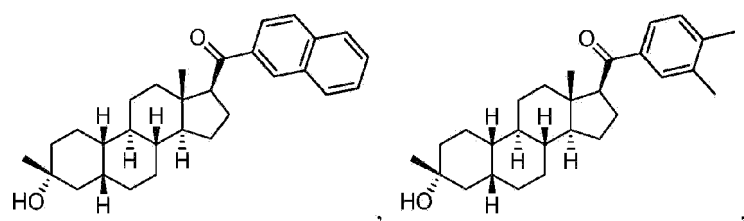
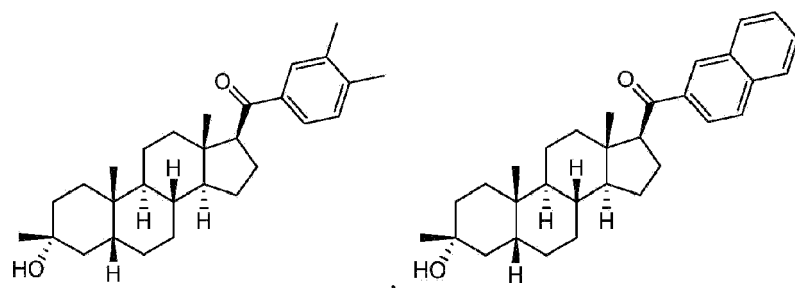
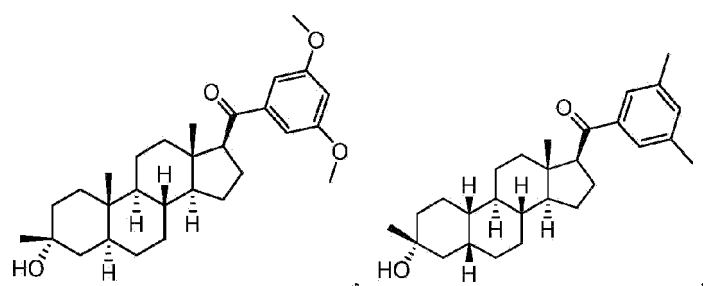
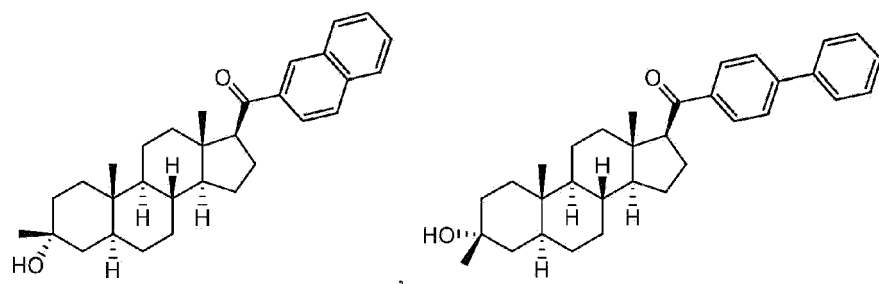
R^A is hydrogen or substituted or unsubstituted C_{1-6} alkyl. In some aspects of these embodiments, R^{AA} is hydrogen or substituted or unsubstituted C_{1-6} alkyl.

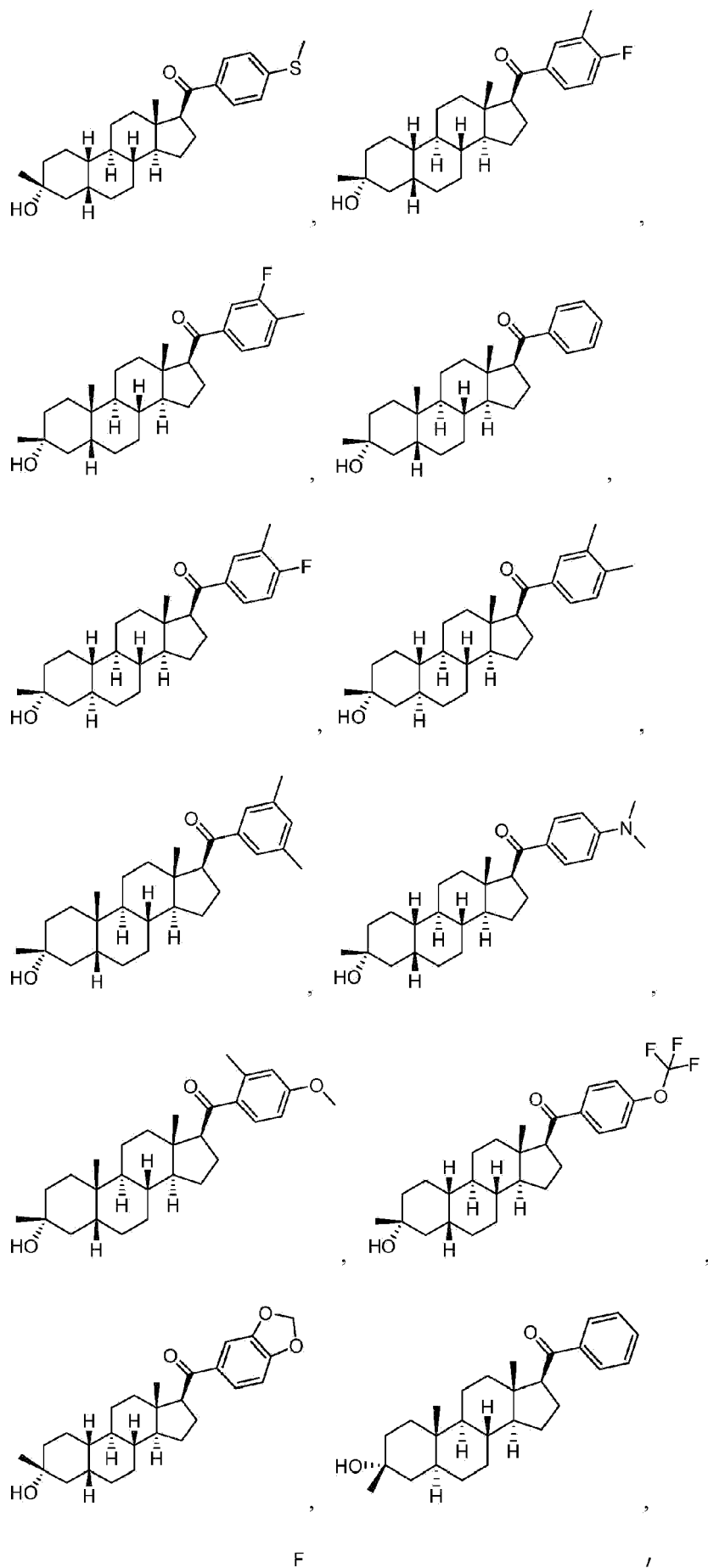
[0111] In some embodiments, R^a is $-N(R^A)C(O)OR^{AA}$. In some aspects of these embodiments, R^A is hydrogen or substituted or unsubstituted C_{1-6} alkyl. In some aspects of these embodiments, R^{AA} is hydrogen or substituted or unsubstituted C_{1-6} alkyl.

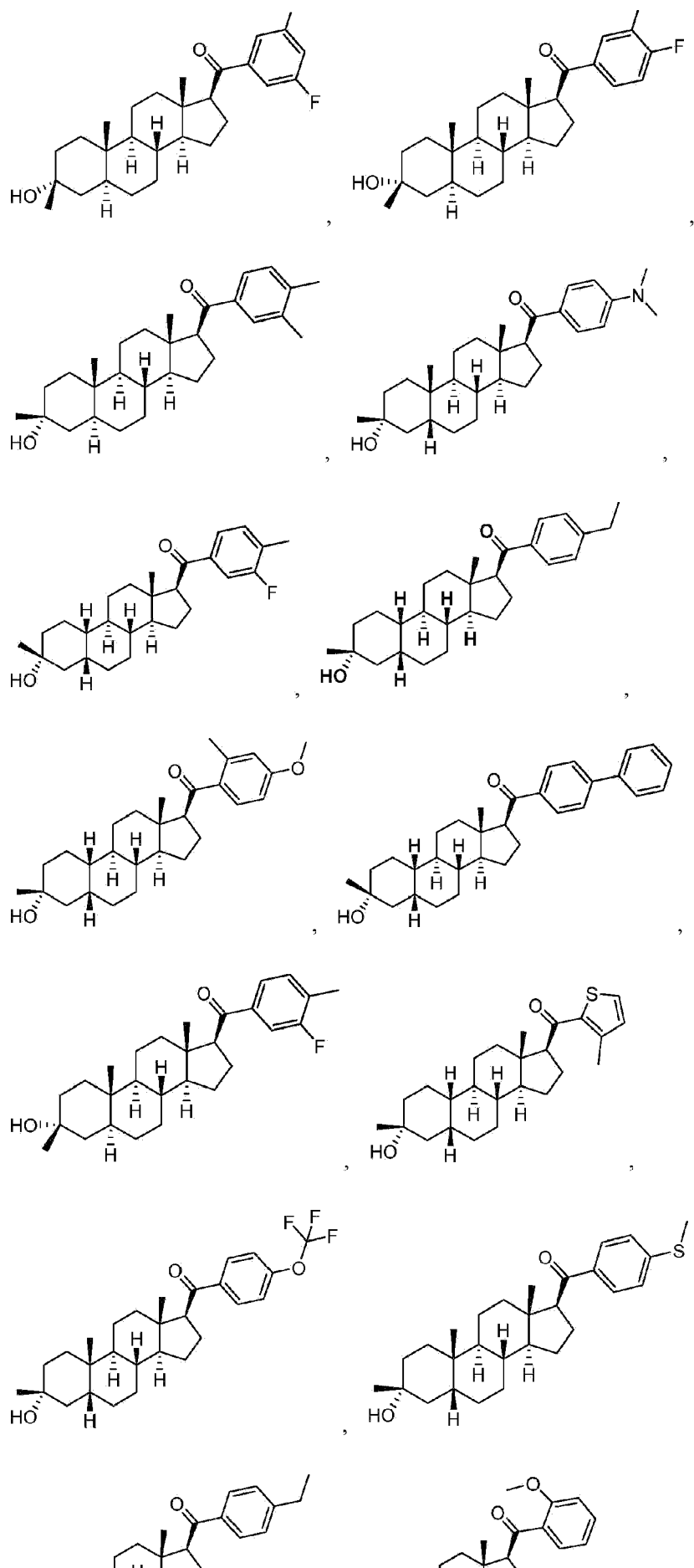
[0112] In some embodiments, R^a is $-OR^{AA}$. In some embodiments, R^a is $-OCH_3$, $-OCH_2CH_3$.

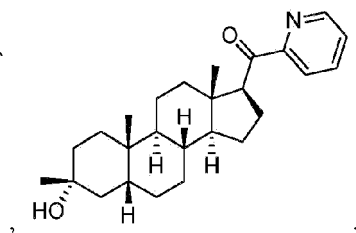
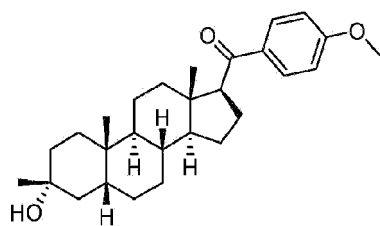
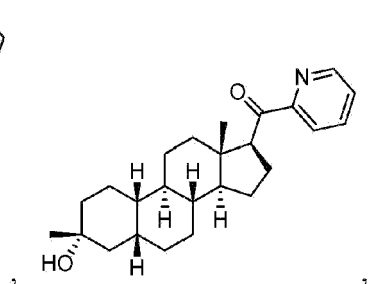
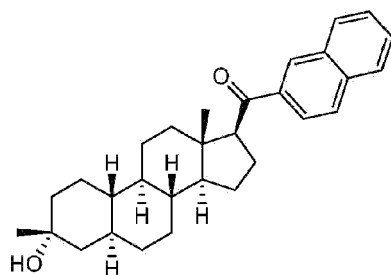
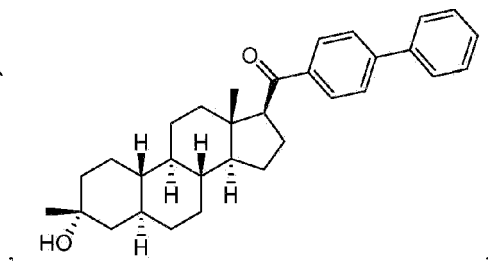
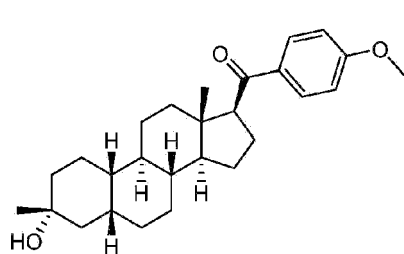
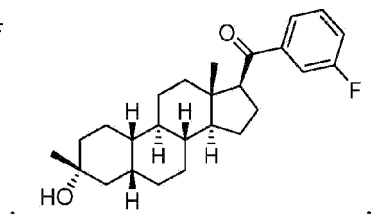
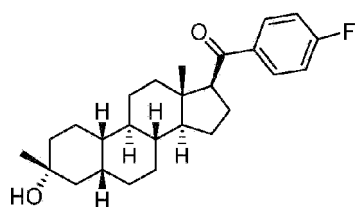
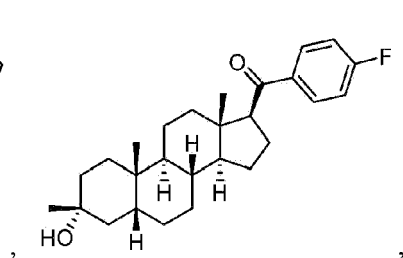
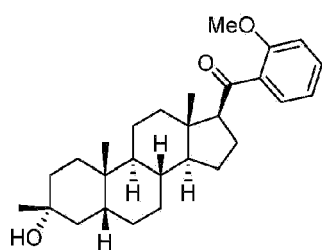
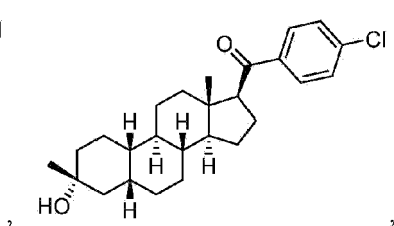
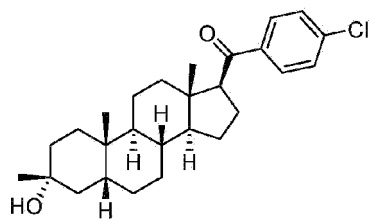
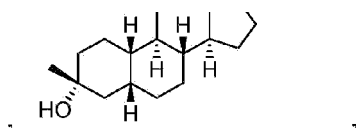
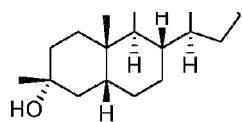
[0113] In some embodiments, the compound is:

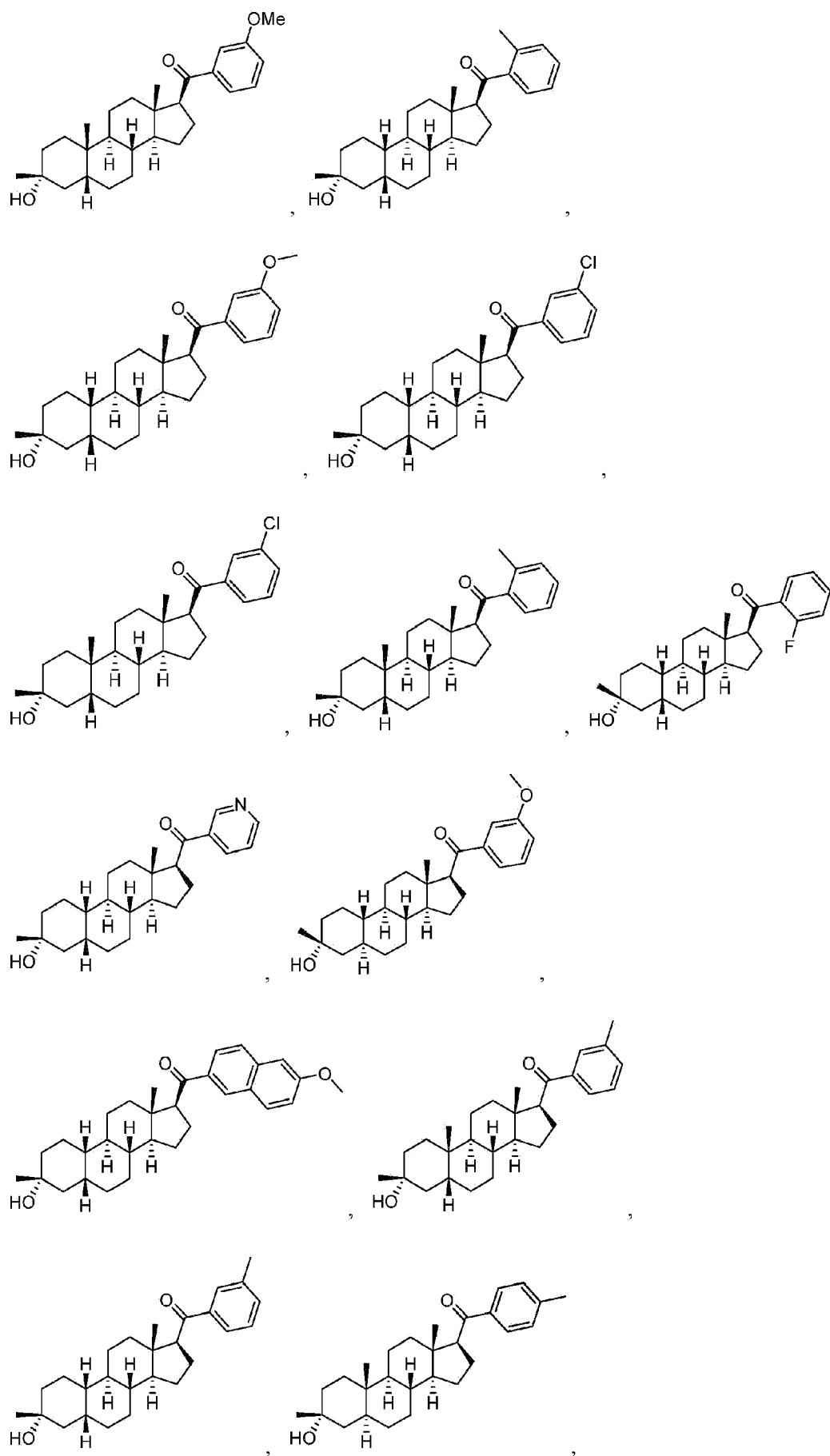


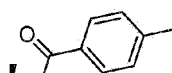
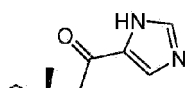
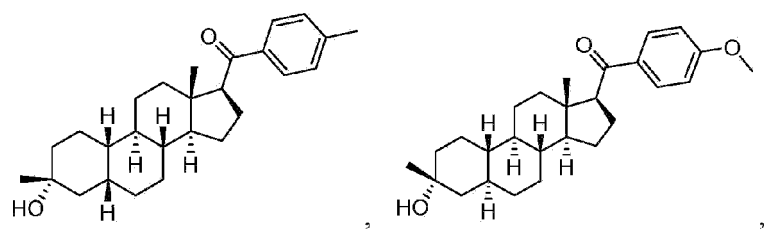
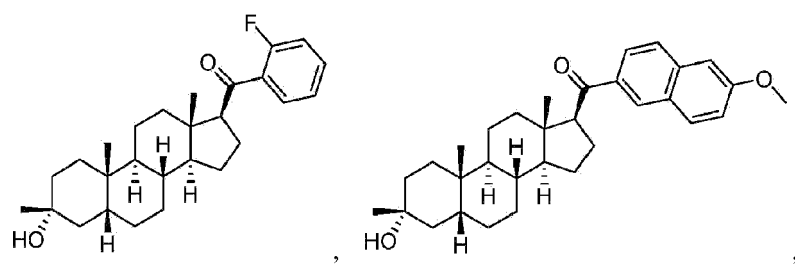
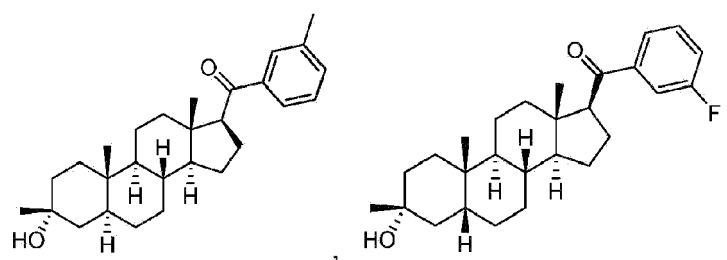
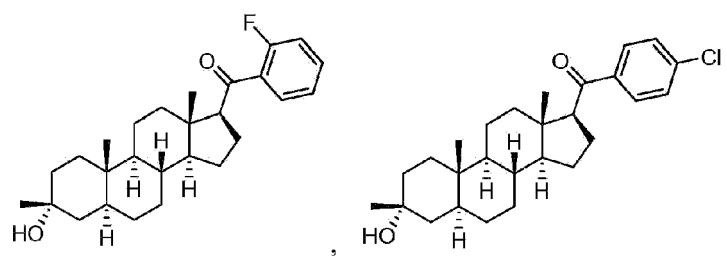
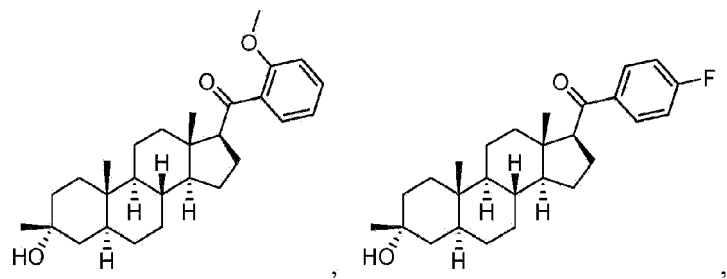
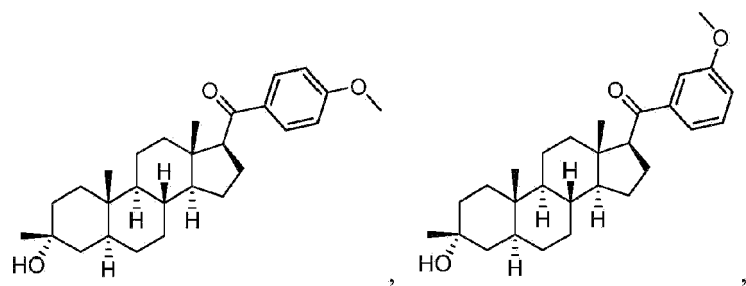


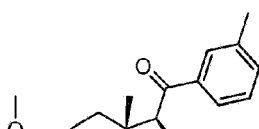
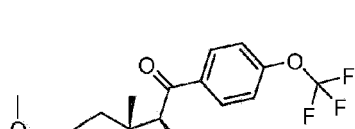
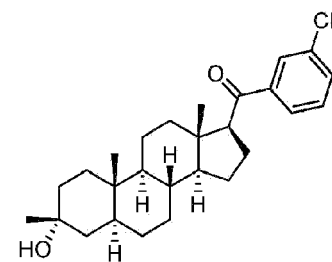
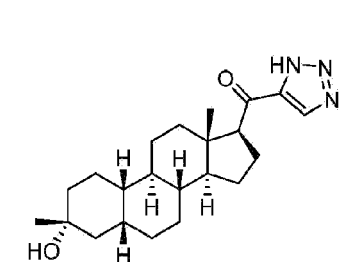
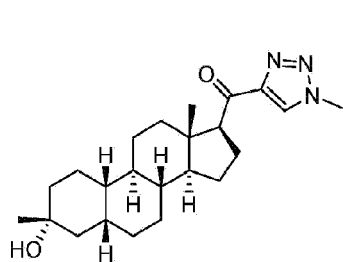
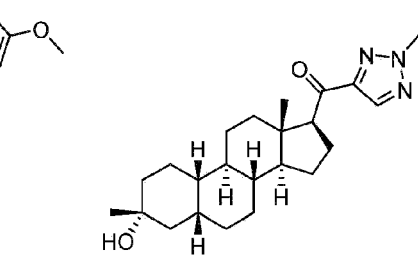
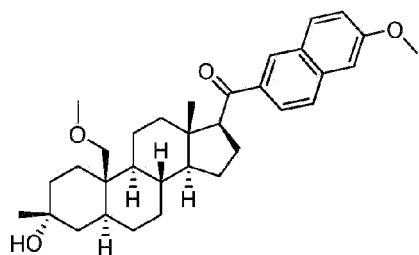
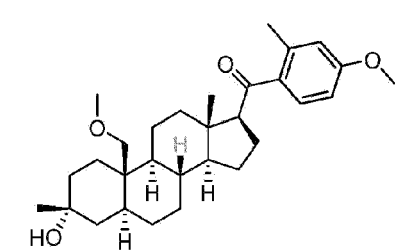
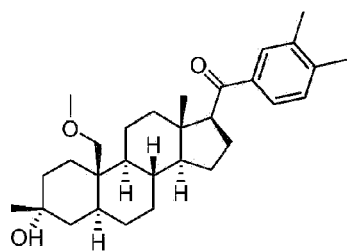
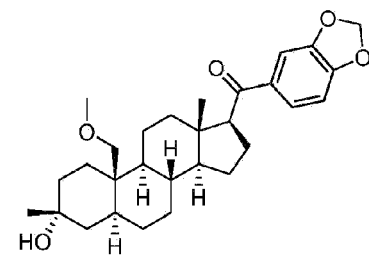
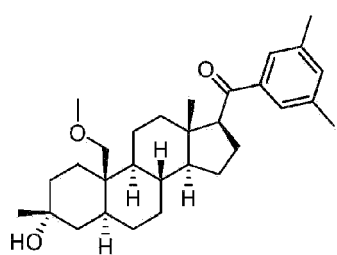
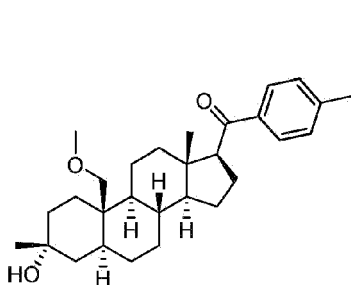
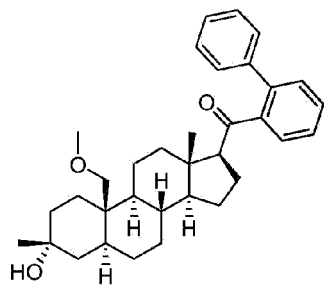
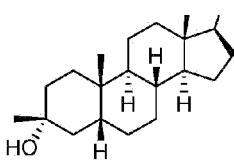
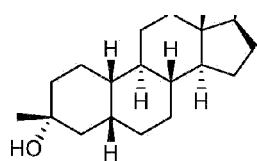


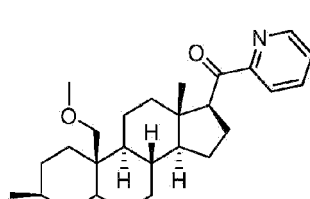
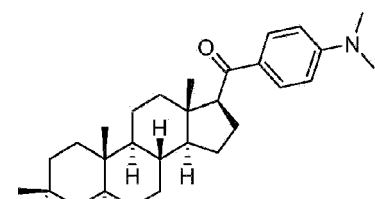
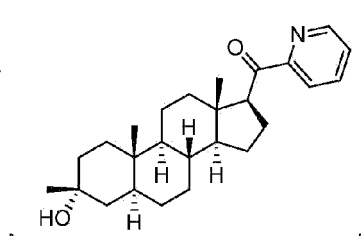
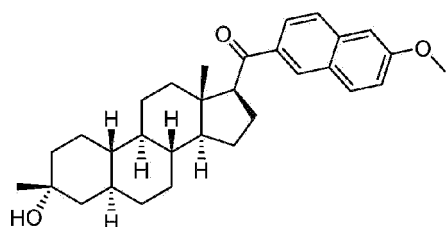
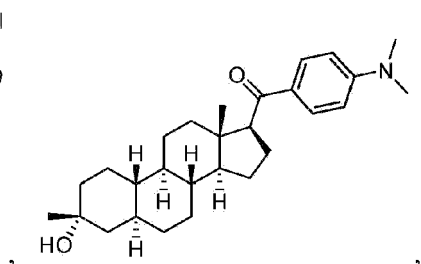
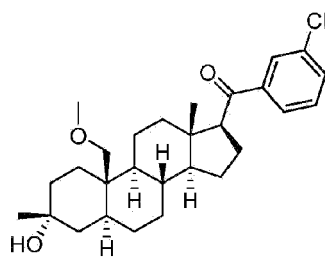
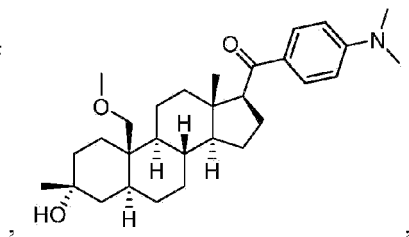
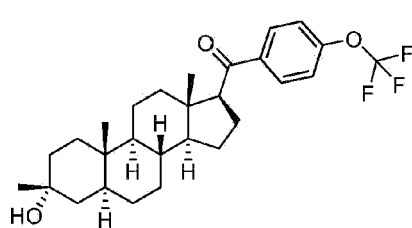
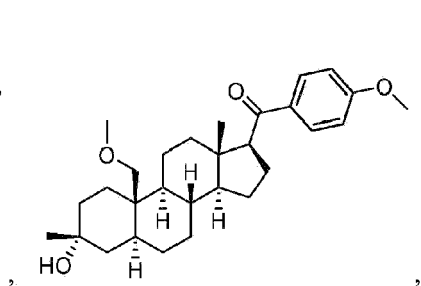
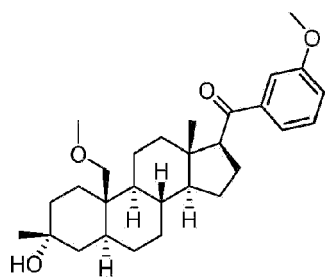
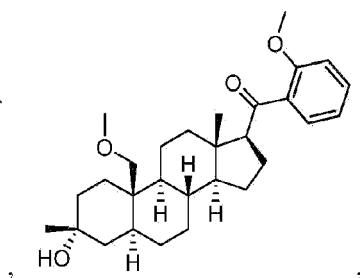
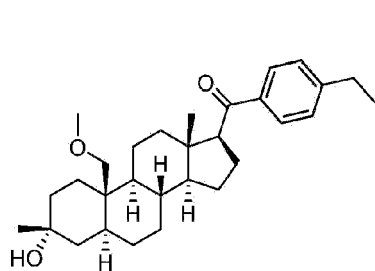
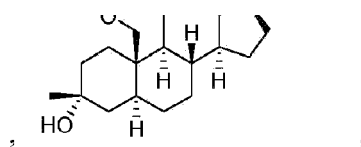
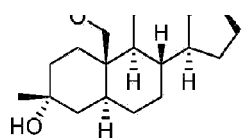


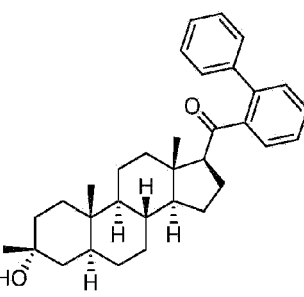
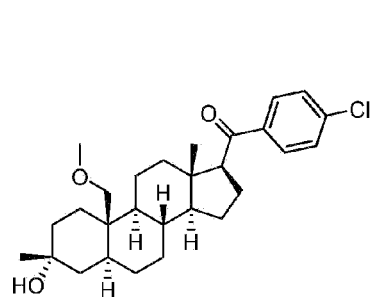
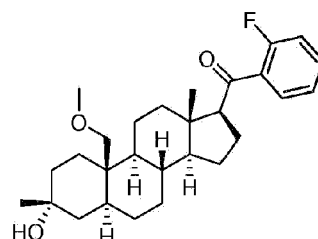
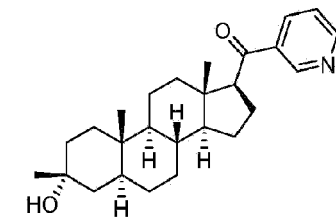
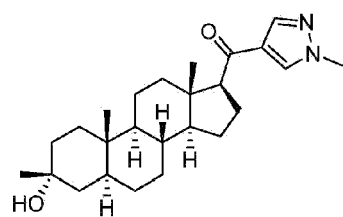
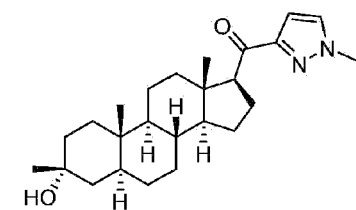
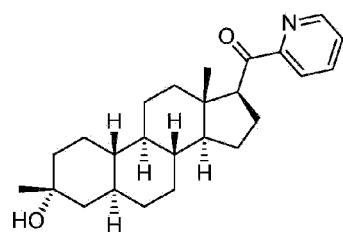
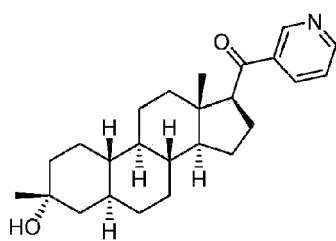
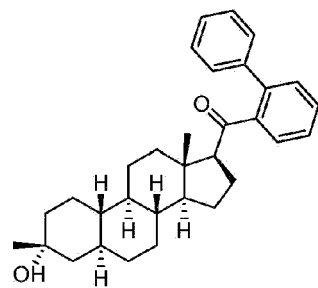
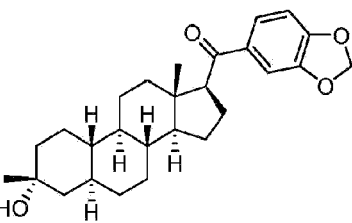
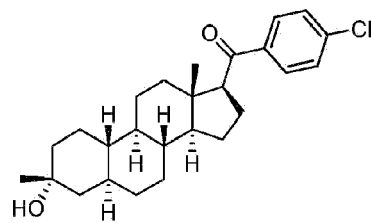
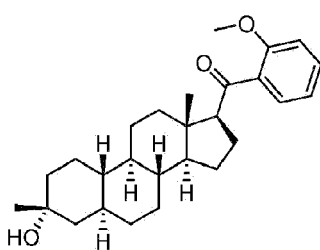
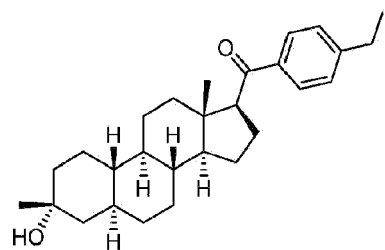


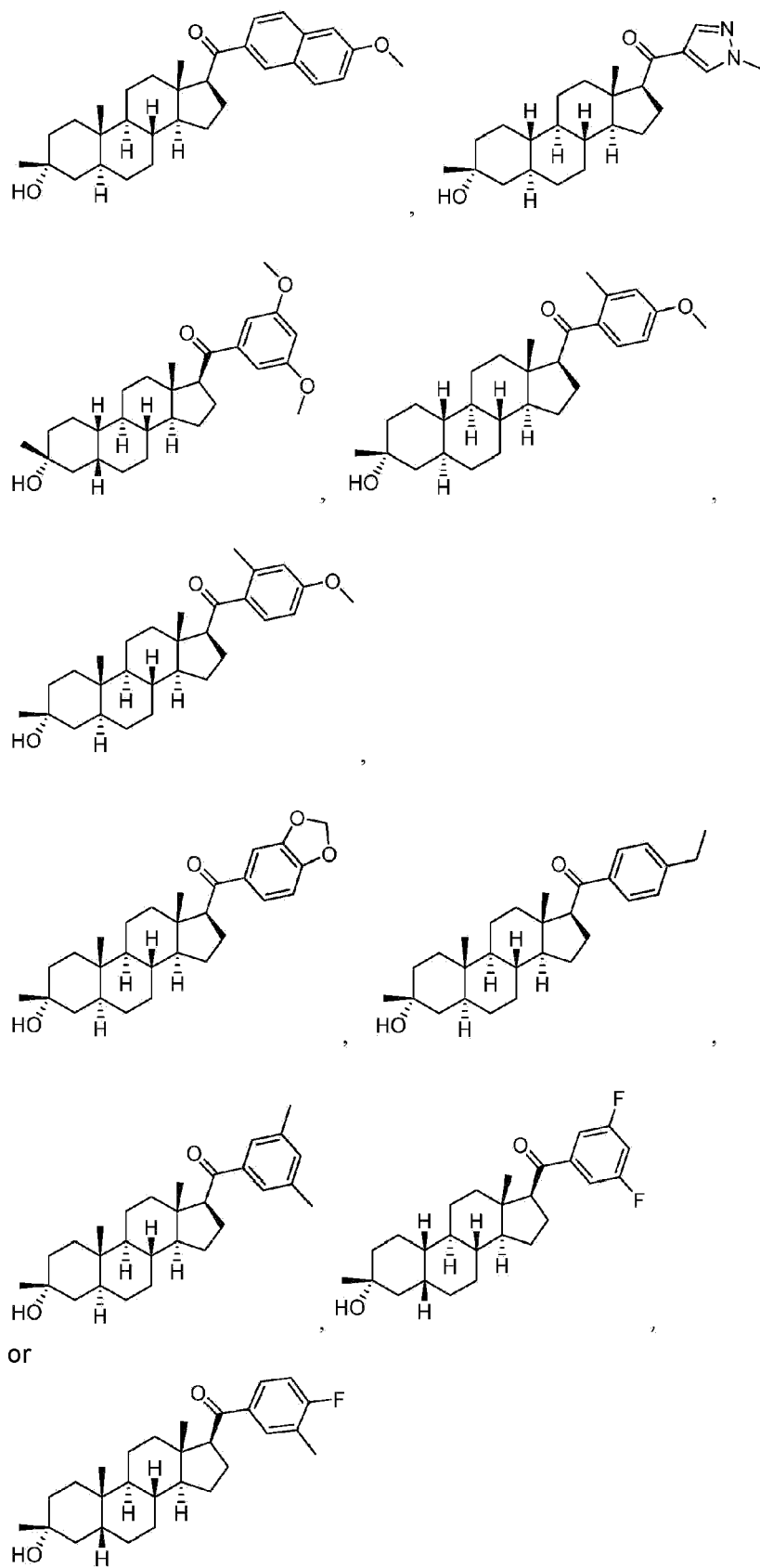








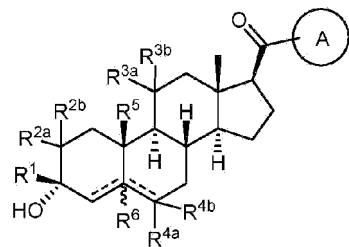




[0114] In one aspect, provided is a pharmaceutical composition comprising a compound of

Formula (I) and a pharmaceutically acceptable excipient.

[0115] In one aspect, provided is a method of inducing sedation and/or anesthesia in a subject, comprising administering to the subject an effective amount of a compound of the Formula (II):



(II)

or a pharmaceutically acceptable salt thereof; wherein: Ring A is substituted or unsubstituted aryl or heteroaryl; R^1 is hydrogen, or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl; each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-N(R^A)(R^B)$, or $-OR^{A2}$, wherein each of R^A and R^B is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or R^A and R^B , together with the nitrogen atom to which they are attached form a ring (e.g., heteroaryl, heterocyclyl), or R^{2a} and R^{2b} , together with the carbon atom to which they are attached form a ring; R^{A2} is hydrogen or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3a} is hydrogen, $-N(R^A)(R^B)$, or $-OR^{A3}$, wherein R^{A3} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and R^{3b} is hydrogen or $-N(R^A)C(O)R^{A3}$; or R^{3a} and R^{3b} are joined to form an oxo ($=O$) group; each of R^{4a} and R^{4b} is independently selected from hydrogen or halogen; R^5 is hydrogen, unsubstituted C_{1-6} alkyl, or $-CH_2OR^{A5}$, wherein R^{A5} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^6 is absent or hydrogen; and ----- represents a single or double bond, wherein when one of ----- is a double bond, the other ----- is a single bond; and when one of the ----- is a double bond, R^6 is absent.

[0116] In one aspect, provided is a method of administering an effective amount of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of a compound of Formula (I), to a subject in need thereof, wherein the subject experiences sedation and/or anesthesia within two hours of administration.

[0117] In some embodiments, the subject experiences sedation and/or anesthesia within one hour of administration. In some embodiments, the subject experiences sedation and/or anesthesia instantaneously.

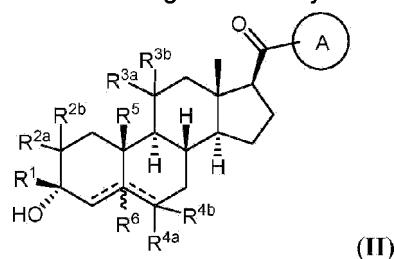
[0118] In some embodiments, compound is administered by intravenous administration.

[0119] In some embodiments, compound is administered chronically.

[0120] In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

[0121] In some embodiments, the compound is administered in combination with another therapeutic agent.

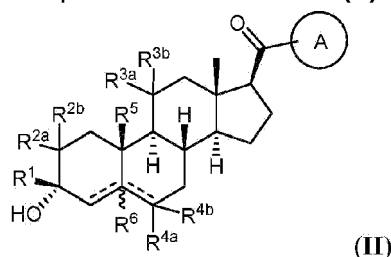
[0122] In one aspect, provided is a method for treating seizure in a subject, comprising administering to the subject an effective amount of a compound of the Formula (II):



or a pharmaceutically acceptable salt thereof; wherein: Ring A is substituted or unsubstituted aryl or heteroaryl; R^1 is hydrogen, or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl; each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-N(R^A)(R^B)$, or $-OR^{A2}$, wherein each of R^A and R^B is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or R^A and R^B , together with the nitrogen atom to which they are attached form a ring (e.g., heteroaryl, heterocyclyl), or R^{2a} and R^{2b} , together with the carbon atom to which they are attached form a ring; R^{A2} is hydrogen or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or

unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₃₋₆ carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3a} is hydrogen, -N(R^A)(R^B), or -OR^{A3}, wherein R^{A3} is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, or substituted or unsubstituted C₃₋₆ carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and R^{3b} is hydrogen or -N(R^A)C(O)R^{A3}; or R^{3a} and R^{3b} are joined to form an oxo (=O) group; each of R^{4a} and R^{4b} is independently selected from hydrogen or halogen; R⁵ is hydrogen, unsubstituted C₁₋₆ alkyl, or -CH₂OR^{A5}, wherein R^{A5} is hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, or substituted or unsubstituted C₃₋₆ carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R⁶ is absent or hydrogen; and ----- represents a single or double bond, wherein when one of ----- is a double bond, the other ----- is a single bond; and when one of the ----- is a double bond, R⁶ is absent.

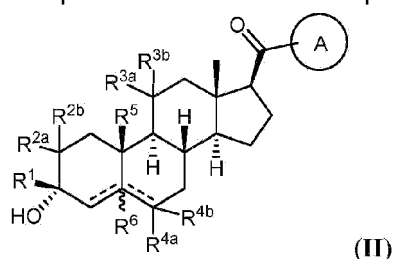
[0123] In one aspect, provided is a method for treating epilepsy or status or status epilepticus in a subject, the method comprising administering to the subject an effective amount of a compound of the Formula (II):



or a pharmaceutically acceptable salt thereof; wherein: Ring A is substituted or unsubstituted aryl or heteroaryl; R¹ is hydrogen, or substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, or substituted or unsubstituted C₃₋₆ carbocyclyl; each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₃₋₆ carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -N(R^A)(R^B), or -OR^{A2}, wherein each of R^A and R^B is independently hydrogen, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₃₋₆ carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or R^A and R^B, together with the nitrogen atom to which they are attached form a ring (e.g., heteroaryl, heterocyclyl), or R^{2a} and R^{2b}, together with the carbon atom to which they are attached form a ring; R^{A2} is hydrogen or substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₂₋₆ alkynyl, substituted or unsubstituted C₃₋₆ carbocyclyl, substituted or

unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3a} is hydrogen, $-N(R^A)(R^B)$, or $-OR^{A3}$, wherein R^{A3} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and R^{3b} is hydrogen or $-N(R^A)C(O)R^{A3}$; or R^{3a} and R^{3b} are joined to form an oxo ($=O$) group; each of R^{4a} and R^{4b} is independently selected from hydrogen or halogen; R^5 is hydrogen, unsubstituted C_{1-6} alkyl, or $-CH_2OR^{A5}$, wherein R^{A5} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^6 is absent or hydrogen; and ----- represents a single or double bond, wherein when one of ----- is a double bond, the other ----- is a single bond; and when one of the ----- is a double bond, R^6 is absent.

[0124] In one aspect, provided is a method for treating disorders related to GABA function in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of one of a compound of Formula (II):



or a pharmaceutically acceptable salt thereof; wherein: Ring A is substituted or unsubstituted aryl or heteroaryl; R^1 is hydrogen, or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl; each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-N(R^A)(R^B)$, or $-OR^{A2}$, wherein each of R^A and R^B is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or R^A and R^B , together with the nitrogen atom to which they are attached form a ring (e.g., heteroaryl, heterocyclyl), or R^{2a} and R^{2b} , together with the carbon atom to which they are attached form a ring; R^{A2} is hydrogen or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or

unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3a} is hydrogen, $-N(R^A)(R^B)$, or $-OR^{A3}$, wherein R^{A3} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and R^{3b} is hydrogen or $-N(R^A)C(O)R^{A3}$; or R^{3a} and R^{3b} are joined to form an oxo ($=O$) group; each of R^{4a} and R^{4b} is independently selected from hydrogen or halogen; R^5 is hydrogen, unsubstituted C_{1-6} alkyl, or $-CH_2OR^{A5}$, wherein R^{A5} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^6 is absent or hydrogen; and $-----$ represents a single or double bond, wherein when one of $-----$ is a double bond, the other $-----$ is a single bond; and when one of the $-----$ is a double bond, R^6 is absent.

[0125] In one aspect, provided is a method for treating a CNS-related disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0126] In some embodiments, the CNS-related disorder is a sleep disorder, a mood disorder, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, or tinnitus.

[0127] In some embodiments, the disorder is tremor (e.g., essential tremor).

[0128] In some embodiments, the disorder is depression (e.g., postpartum depression).

[0129] In some embodiments, the compound is administered orally. In some embodiments, the compound is administered parenterally. In some embodiments, the compound is administered intravenously. In some embodiments, the compound is administered intramuscularly.

[0130] In some embodiments, the subject is a subject with Rett syndrome, Fragile X syndrome, or Angelman syndrome.

[0131] In one aspect, provided is a method for treating a subject having an injury resulting from exposure to a warfare agent (e.g., a chemical warfare agent), the method comprising administering to the subject a compound described herein (e.g., a GABA modulator such as a compound (e.g., neuroactive steroid) described herein).

[0132] In one aspect, provided is a compound described herein (e.g., GABA modulator such as a compound (e.g., neuroactive steroid) described herein), for use in a method of treating an injury in a subject who has been exposed to a chemical warfare agent, the method comprising

administering said compound to the subject.

[0133] In one aspect, provided is a compound described herein (e.g., GABA modulator such as a neuroactive steroid described herein), for use in a method of treating a subject, the method comprising: identifying a subject that has been exposed to a chemical warfare agent such as a nerve agent or toxin; and administering said compound to the subject.

[0134] In some embodiments, the injury is a seizure. In some embodiments, the injury is a myoclonic seizure (e.g., sporadic jerks).

[0135] In some embodiments, the injury is status epilepticus.

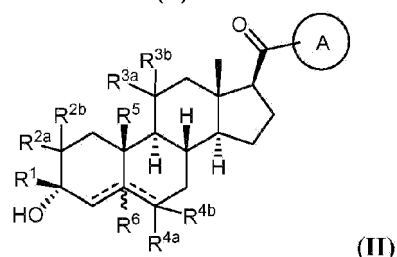
[0136] In some embodiments, the administration is within 1 week; 6, 5, 4, 3, 2, 1 day; 24, 22, 20, 18, 16, 14, 12, 10, 8, 7, 6, 5, 4, 3, 2, 1 hour, 45, 30, 20, 10, or 5 minutes of exposure to the chemical warfare agent.

[0137] In some embodiments, the compound is administered parenterally. In some embodiments, the compound is administered by intravenous administration.

[0138] In some embodiments, the subject is a human.

[0139] In some embodiments, the chemical warfare agent is a nerve agent or toxin. In some embodiments, the chemical warfare agent is a nerve agent. In some embodiments, the nerve agent is a phosphorus-containing organic chemical. In some embodiments, the nerve agent is a G agent (e.g., tabun (GA), sarin (GB), soman (GD), cyclosarin (GF), and GV). In some embodiments, the nerve agent is a V agent (e.g., VE, VG, VM, VX, and Novichok agents). In some embodiments, the toxin is abrin, ricin, or saxitoxin.

[0140] In one aspect, provided is a kit comprising a solid composition comprising a compound of Formula (II):



or a pharmaceutically acceptable salt thereof; wherein: Ring A is substituted or unsubstituted aryl or heteroaryl; R^1 is hydrogen, or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl; each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-N(R^A)(R^B)$, or $-OR^{A2}$, wherein each of R^A and R^B is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or R^A and R^B , together with the nitrogen atom to which they are attached form a ring (e.g., heteroaryl, heterocyclyl), or R^{2a} and R^{2b} , together with the carbon atom to which they are attached form a ring; R^{A2} is hydrogen or substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3a} is hydrogen, $-N(R^A)(R^B)$, or $-OR^{A3}$, wherein R^{A3} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and R^{3b} is hydrogen or $-N(R^A)C(O)R^{A3}$; or R^{3a} and R^{3b} are joined to form an oxo ($=O$) group; each of R^{4a} and R^{4b} is independently selected from hydrogen or halogen; R^5 is hydrogen, unsubstituted C_{1-6} alkyl, or $-CH_2OR^{A5}$, wherein R^{A5} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, or substituted or unsubstituted C_{3-6} carbocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^6 is absent or hydrogen; and $-----$ represents a single or double bond, wherein when one of $-----$ is a double bond, the other $-----$ is a single bond; and when one of the $-----$ is a double bond, R^6 is absent.

Pharmaceutical Compositions

[0141] In one aspect, the invention provides a pharmaceutical composition comprising a compound of the present invention (also referred to as the "active ingredient") and a pharmaceutically acceptable excipient. 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. In certain embodiments, the pharmaceutical composition comprises a prophylactically effective amount of the active ingredient.

[0142] 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.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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.

[0147] 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.

[0148] 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.

[0149] 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.

[0150] 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.

[0151] 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.

[0152] 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.

[0153] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s). When formulated as a ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or Formulation. All such known transdermal formulations and ingredients are included within the scope provided herein.

[0154] 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.

[0155] 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.

[0156] 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*.

[0157] 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.

[0158] 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.

[0159] 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).

[0160] 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.

[0161] 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).

[0162] 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.

[0163] 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.

[0164] 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.

[0165] 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.

[0166] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation. General considerations in the formulation and/or manufacture of pharmaceutical compositions can be found, for example, in Remington: The Science and Practice of Pharmacy 21st ed., Lippincott Williams & Wilkins, 2005.

Methods of Use and Treatment

[0167] As generally described herein, the present invention is directed to C21-substituted

neuroactive steroids designed, for example, to act as GABA modulators. In certain embodiments, such compounds are envisioned to be useful as therapeutic agents for the inducement of anesthesia and/or sedation in a subject. In some embodiments, such compounds are envisioned to be useful as therapeutic agents for treating a CNS-related disorder (e.g., 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, or tinnitus) in a subject in need (e.g., a subject with Rett syndrome, Fragile X syndrome, or Angelman syndrome).

[0168] Thus, in one aspect, the present invention provides a method of inducing sedation and/or anesthesia in a subject, comprising administering to the subject an effective amount of a compound of the present invention or a composition thereof. In certain embodiments, the compound is administered by intravenous administration.

[0169] Earlier studies (see, e.g., Gee et al., *European Journal of Pharmacology*, 136:419-423 (1987)) demonstrated that certain 3 α -hydroxylated steroids are orders of magnitude more potent as modulators of the GABA receptor complex (GRC) than others had reported (see, e.g., Majewska et al., *Science* 232:1004-1007 (1986); Harrison et al., *J Pharmacol. Exp. Ther.* 241:346-353 (1987)). Majewska *et al.* and Harrison *et al.* taught that 3 α -hydroxylated-5-reduced steroids are only capable of much lower levels of effectiveness. *In vitro* and *in vivo* experimental data have now demonstrated that the high potency of these steroids allows them to be therapeutically useful in the modulation of brain excitability via the GRC (see, e.g., Gee et al., *European Journal of Pharmacology*, 136:419-423 (1987); Wieland et al., *Psychopharmacology* 118(1):65-71 (1995)).

[0170] Various synthetic steroids have also been prepared as neuroactive steroids. See, for example, U.S. Patent 5,232,917, which discloses neuroactive steroid compounds useful in treating stress, anxiety, insomnia, seizure disorders, and mood disorders, that are amenable to GRC-active agents, such as depression, in a therapeutically beneficial manner. Furthermore, it has been previously demonstrated that these steroids interact at a unique site on the GRC which is distinct from other known sites of interaction (e.g., barbiturates, benzodiazepines, and GABA) where therapeutically beneficial effects on stress, anxiety, sleep, mood disorders and seizure disorders have been previously elicited (see, e.g., Gee, K.W. and Yamamura, H.I., "Benzodiazepines and Barbiturates: Drugs for the Treatment of Anxiety, Insomnia and Seizure Disorders," in *Central Nervous System Disorders*, Horvell, ed., Marcel-Dekker, New York (1985), pp. 123-147; Lloyd, K.G. and Morselli, P.L., "Psychopharmacology of GABAergic Drugs," in *Psychopharmacology: The Third Generation of Progress*, H.Y. Meltzer, ed., Raven Press, N.Y. (1987), pp. 183-195; and Gee et al., *European Journal of Pharmacology*, 136:419-423 (1987). These compounds are desirable for their duration, potency, and oral activity (along with other forms of administration).

[0171] Compounds of the present invention, as described herein, are generally designed to modulate GABA function, and therefore to act as neuroactive steroids for the treatment and

prevention of CNS-related conditions in a subject. Modulation, as used herein, refers to the inhibition or potentiation of GABA receptor function. Accordingly, the compounds and pharmaceutical compositions provided herein find use as therapeutics for preventing and/or treating CNS conditions in mammals including humans and non-human mammals. Thus, and as stated earlier, the present invention includes within its scope, and extends to, the recited methods of treatment, as well as to the compounds for such methods, and to the use of such compounds for the preparation of medicaments useful for such methods.

[0172] Exemplary CNS conditions related to GABA-modulation include, but are not limited to, sleep disorders [e.g., insomnia], mood disorders [e.g., depression, 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.

[0173] 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.

[0174] In another aspect, provided is a compound of the present invention to the subject for use in a method of treating or preventing brain excitability in a subject susceptible to or afflicted with a condition associated with brain excitability.

[0175] In yet another aspect, provided is a compound of the present invention, or a composition thereof, for use in a method of treating or preventing stress or anxiety in a subject.

[0176] In yet another 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.

[0177] 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.

[0178] 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.

[0179] In yet another aspect, provided is a method of alleviating or preventing PMS or PND in a subject, comprising administering to the subject in need of such treatment an effective amount of a compound of the present invention.

[0180] In yet another aspect, provided is a compound of the present invention for use in a method of treating or preventing mood disorders in a subject. In certain embodiments the mood disorder is depression.

[0181] In yet another aspect, provided is a method of inducing anesthesia in a subject, comprising administering to the subject an effective amount of a compound of the present invention.

[0182] 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.

[0183] In yet another aspect, provided is a compound of the present invention for use in a method of treating attention disorders. In certain embodiments, the attention disorder is ADHD.

[0184] 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.

Anesthesia/Sedation

[0185] 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.

[0186] Sedation is the reduction of irritability or agitation by administration of a pharmacological agent, generally to facilitate a medical procedure or diagnostic procedure.

[0187] Sedation and analgesia include a continuum of states of consciousness ranging from minimal sedation (anxiolysis) to general anesthesia.

[0188] 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.

[0189] 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.

[0190] 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.

[0191] 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.

[0192] 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.

[0193] 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.

[0194] 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.

Anxiety Disorders

[0195] 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.

[0196] 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.

[0197] 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).

[0198] 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.

[0199] 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.

[0200] 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.

Neurodegenerative Diseases and Disorders

[0201] The term "neurodegenerative disease" includes diseases and disorders that are associated with the progressive loss of structure or function of neurons, or death of neurons. Neurodegenerative diseases and disorders include, but are not limited to, Alzheimer's disease (including the associated symptoms of mild, moderate, or severe cognitive impairment); amyotrophic lateral sclerosis (ALS); anoxic and ischemic injuries; ataxia and convulsion (including for the treatment and prevention and prevention of seizures that are caused by schizoaffective disorder or by drugs used to treat schizophrenia); benign forgetfulness; brain edema; cerebellar ataxia including McLeod neuroacanthocytosis syndrome (MLS); closed head injury; coma; contusive injuries (e.g., spinal cord injury and head injury); dementias including multi-infarct dementia and senile dementia; disturbances of consciousness; Down syndrome; drug-induced or medication-induced Parkinsonism (such as neuroleptic-induced acute akathisia, acute dystonia, Parkinsonism, or tardive dyskinesia, neuroleptic malignant syndrome, or medication-induced postural tremor); epilepsy; fragile X syndrome; Gilles de la Tourette's syndrome; head trauma; hearing impairment and loss; Huntington's disease; Lennox syndrome; levodopa-induced dyskinesia; mental retardation; movement disorders including akinesias and akinetic (rigid) syndromes (including basal ganglia calcification, corticobasal degeneration, multiple system atrophy, Parkinsonism-ALS dementia complex, Parkinson's disease, postencephalitic parkinsonism, and progressively supranuclear palsy); muscular spasms and disorders associated with muscular spasticity or weakness including chorea (such as benign hereditary chorea, drug-induced chorea, hemiballism, Huntington's disease, neuroacanthocytosis, Sydenham's chorea, and symptomatic chorea), dyskinesia (including tics such as complex tics, simple tics, and symptomatic tics), myoclonus (including generalized myoclonus and focal cyloclonus), tremor (such as rest tremor, postural tremor, and intention tremor) and dystonia (including axial dystonia, dystonic writer's cramp, hemiplegic dystonia, paroxysmal dystonia, and focal dystonia such as blepharospasm, oromandibular dystonia, and spasmodic dysphonia and torticollis); neuronal damage including ocular damage, retinopathy or macular degeneration of the eye; neurotoxic injury which follows cerebral stroke, thromboembolic stroke, hemorrhagic stroke, cerebral ischemia, cerebral vasospasm, hypoglycemia, amnesia, hypoxia, anoxia, perinatal asphyxia and cardiac arrest; Parkinson's disease; seizure; status 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.

Epilepsy

[0202] 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.

Status epilepticus (SE)

[0203] 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.

[0204] 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.

[0205] Compositions described herein 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.

Epileptogenesis

[0206] 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).

Seizure

[0207] 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.

[0208] 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.

[0209] 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.

[0210] 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.

[0211] 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."

[0212] 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.

[0213] Clonic seizures are repetitive, rhythmic jerks that involve both sides of the body at the same time.

[0214] Tonic seizures are characterized by stiffening of the muscles.

[0215] Atonic seizures consist of a sudden and general loss of muscle tone, particularly in the arms and legs, which often results in a fall.

[0216] 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; Sylvian seizures; visual reflex seizures; or withdrawal seizures.

Chemical warfare agents

[0217] A subject may be exposed to a chemical warfare agent. If a compound described herein is administered, the symptoms or injuries resulting from the exposure to the chemical warfare agents can be reduced, prevented, or both. The compounds described herein can be administered to a subject before, during, or following such exposure and is therefore administered within 1 week; 6, 5, 4, 3, 2, 1 day; 24, 22, 20, 18, 16, 14, 12, 10, 8, 7, 6, 5, 4, 3, 2, 1 hour, 45, 30, 20, 10, or 5 minutes before or after such exposure. The compounds described herein can be administered prophylactically, when exposure to an agent is anticipated. It can also be administered after exposure to the chemical warfare agent (e.g., before or after symptoms of injury present in a subject).

[0218] Injuries resulting from the exposure to chemical warfare agents are known in the art and include any physical injuries, such as injuries to the central nervous system and peripheral nervous system. Exemplary symptoms or injuries resulting from the exposure to chemical warfare agents include inflammation, burn, itch, pain, rash, blisters, sweating, muscle twitching, nausea, vomiting, diarrhea, weakness, loss of consciousness, convulsions, muscular twitching, paralysis, secretions (from the mouth, nose, or lung for example), difficulty breathing, blurred

vision, eye pain, lacrimation, red eyes, shortness of breath, coughing, phlegm production and narrowing of the airways, headaches, tremors, dizziness, numbness or tingling, anxiety, insomnia, depression, emotional instability, and even death. The term "chemical warfare agent" includes all of those agents classified as schedule 1, 2, and 3 agents under the Chemical Weapons Convention of 1993 and may be in liquid form, gas form, solid form, or combinations thereof. Exemplary agents are described in further detail below and include, for example, nerve agents and toxins.

[0219] Nerve agents. Nerve agent poisoning typically leads to contraction of pupils, profuse salivation, convulsions, involuntary urination and defecation, and eventual death by asphyxiation as control is lost over respiratory muscles. For example, nerve agents can be phosphorus-containing organic chemicals (organophosphates) that disrupt the mechanism by which nerves transfer messages to organs. Exemplary agents include G agents such as tabun (GA), sarin (GB), soman (GD), cyclosarin (GF), and GV; V agents such as VE, VG, VM, VX, and Novichok agents.

[0220] Toxins. Exemplary toxins are abrin, ricin, and saxitoxin.

Equivalents and Scope

[0221] 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.

Examples

[0222] In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions and methods provided herein and are not to be construed in any way as limiting their scope.

Materials and Methods

[0223] 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.

[0224] 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.

[0225] The compounds provided herein may be isolated and purified by known standard procedures. Such procedures include (but are not limited to) recrystallization, column chromatography, HPLC, or supercritical fluid chromatography (SFC). The following schemes are presented with details as to the preparation of representative heteroaryls and heterocyclyls 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.

[0226] The stereochemistry assigned herein (*e.g.*, the assignment of "R" or "S" to the C21 position of the steroid) may be tentatively (*e.g.*, randomly) assigned. For example, a C21 position may be drawn in the "R" configuration when the C21 position is in the "S" configuration.

[0227] ¹H-NMR reported herein (*e.g.*, for intermediates) may be a partial representation of the full NMR spectrum of a compound, *e.g.*, a compound described herein. For example, the reported ¹H NMR may exclude the region between δ (ppm) of about 1 to about 2.5 ppm.

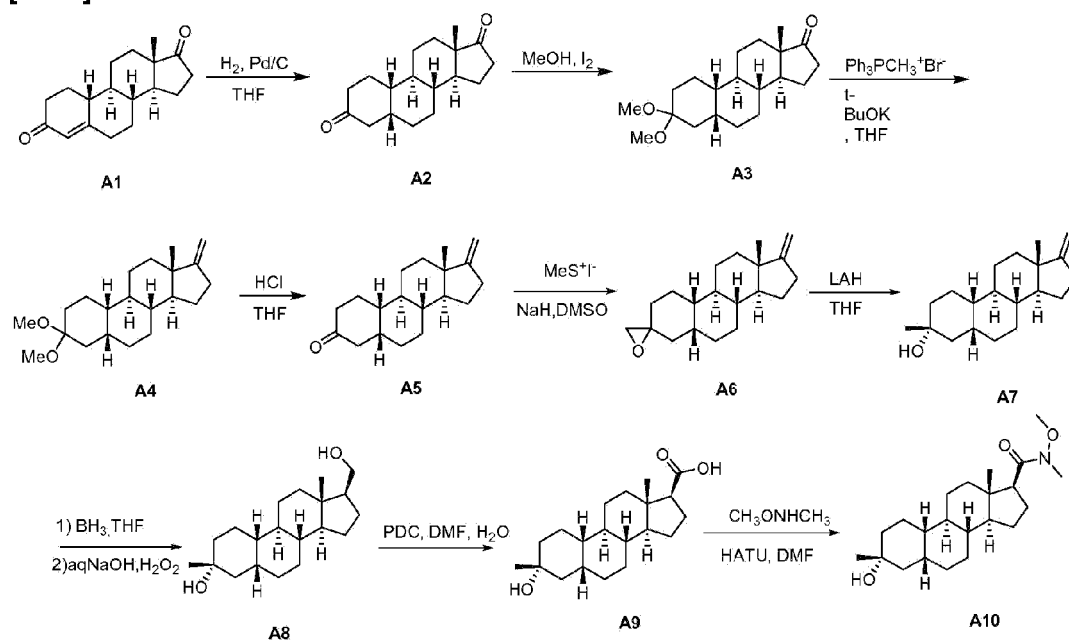
[0228] Exemplary general method for preparative HPLC: Column: Waters RBridge prep 10 μm C18, 19*250 mm. Mobile phase: acetonitrile, water (NH₄HCO₃) (30 L water, 24 g NH₄HCO₃, 30 mL NH₃.H₂O). Flow rate: 25 mL/min

[0229] Exemplary general method for analytical HPLC: Mobile phase: A: water (10 mM NH₄HCO₃), B: acetonitrile Gradient: 5%-95% B in 1.6 or 2 min Flow rate: 1.8 or 2 mL/min; Column: XBridge C18, 4.6*50mm, 3.5 μm at 45 C.

Synthetic Methods

Example 1. Synthesis of Intermediate A10.

[0230]



Step 1. Synthesis of compound A2. Compound **A1** (500 mg, 1.84 mmol) and 10% Pd/black (20mg) in tetrahydrofuran (5 mL) and concentrated hydrobromic acid (0.02 mL) was hydrogenated with a hydrogen balloon at 1 atm. After stirring at room temperature for 24h, the mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo*. Recrystallization from acetone to give compound **A2** (367 mg, 1.34 mmol, 73%). ^1H NMR (400 MHz, CDCl_3), δ (ppm), 2.61-2.54 (m, 1H), 2.58 (t, 1H, $J=14$ Hz), 2.45 (dd, 1H, $J=19$ Hz, 9 Hz), 0.98 (s, 3H).

Step 2. Synthesis of compound A3. To a solution of compound **A2** (274mg, 1 mmol) in methanol (4 mL) was added iodine (0.1 mmol). After stirring at 60°C for 12h, TLC showed no SM and the solvent was removed *in vacuo*. The crude product was dissolved in dichloromethane (20 mL) and washed with saturated NaHCO_3 (15 mL), brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by chromatography on basic alumina (petroleum ether/ethyl acetate = 9:1) to give compound **A3** (280 mg, 0.88 mmol, 88%), ^1H NMR (400 MHz, CDCl_3), δ (ppm), 3.19 (s, 3H), 3.13 (s, 3H), 2.43 (dd, 1H, $J=19.2$ Hz, 8.8 Hz), 0.83 (s, 3H).

Step 3. Synthesis of compound A4. To a solution of methyltriphenylphosphonium bromide (10.26 g, 28.84 mmol) in 30 mL THF, was added $\text{KO}^t\text{-Bu}$ (3.23 g, 28.80 mmol). The reaction was heated to 60°C for 1 h. **A3** (3.23 g, 9.6 mmol) was added to the mixture, stirred at 60°C

for 15 h. The reaction mixture was extracted 500 ml EtOAc, washed with brine and evaporated *in vacuo* then purified by chromatography (PE:EA = 3:1) to afford **A4** as a solid (2.1 g).

Step 4. Synthesis of compound A5. To a solution of **A4** (1 g, 3.1 mmol) in 20 ml THF, was added 2 mL of 2 M HCl and reaction stirred at rt for 1 h. The reaction mixture was quenched with 5 mL H₂O and extracted with 100 mL EtOAc, washed with brine and evaporated *in vacuo*, then purified by chromatography (PE:EtOAc = 10:1) to afford **A5** as a solid (710 mg). ¹H NMR (400 MHz, CDCl₃), δ (ppm), 4.65 (s, 1H), 4.63 (s, 1H), 0.82 (s, 3H).

Step 5. Synthesis of compound A6. To a stirred solution of trimethylsulfonium iodide (6.4 g, 31.5 mmol) in 10 mL of DMSO was added NaH (60%;800 mg, 31.5 mmol).After stirring at room temperature for 1h,a suspension of **A5** (870 mg, 3.2 mmol) in 5 mL of DMSO was added dropwise. After 15 h, the reaction mixture was poured into ice-cold water and extracted with 300 mL EtOAc, washed with 100 mL brine solution, dried and evaporated *in vacuo*, then purified by chromatography (PE:EtOAc = 10:1) to afford **A6** and its isomer as a solid (695 mg).

Step 6. Synthesis of compound A7. To a solution of **A6** and its isomer (129 mg, 0.45 mmol) in 10 mL THF, was added LiAlH₄ (50 mg, 1.35 mmol), stirred at rt for 1 h. The reaction mixture was quenched with 5 mL H₂O and extracted with 100 ml EtOAc, washed with brine solution and evaporated *in vacuo* then purified by chromatography (PE:EtOAc = 3:1) to afford **A7** as a solid (62 mg). ¹H NMR (400 MHz, CDCl₃), δ (ppm), 4.63 (s, 1H), 4.61 (s, 1H), 0.82 (s, 3H), 1.25 (s, 3H).

Step 7. Synthesis of compound A8. To a solution of **A7** (86 mg, 0.3 mmol) in dry THF (5 mL) was added borane-tetrahydrofuran complex (1 mL; 1.0 M solution in THF). After stirring at room temperature for 1 hour, the reaction mixture was cooled in an ice bath then quenched slowly with 10% aqueous NaOH (1 mL) followed by 30% aqueous solution of H₂O₂ (1 mL). After stirring at room temperature for one hour, the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with 10% aqueous Na₂S₂O₃ (100 mL), brine (aq., 100 mL), dried over MgSO₄, filtered and concentrated to afford **A8** as a solid (83 mg, 91%). The crude product was used in the next step without further purification.

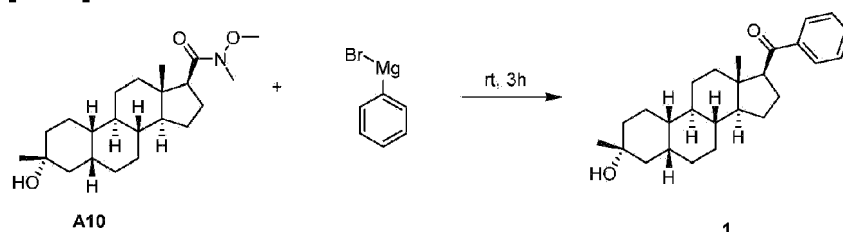
Step 8. Synthesis of compound A9. To a solution of **A8** (300 mg, 0.80 mmol) in 15 mL DMF, was added PDC (2.7 g, 7.2 mmol) and 1 mL H₂O, stirred at rt for 15 h. The reaction mixture was extracted 100 mL EtOAc, washed with brine and evaporated *in vacuo* then purified by chromatography (PE:EtOAc = 1:1) to afford **A9** as a solid 128 mg. ¹H NMR (400 MHz, DMSO-d₆), δ (ppm), 11.90 (s, 1H), 4.22 (s, 1H), 2.28 (1H,t, J=7 Hz), 1.28 (s, 3H), 0.68 (s, 3H).

Step 9. Synthesis of compound A10. To a solution of **A9** (200 mg, 0.61 mmol) in 5 mL DMF, was added N,O-dimethylhydroxylamine HCl salt (60 mg, 0.62 mmol), HATU (236 mg, 0.62 mmol) and DIPEA 1 mL, stirred at rt for 3h, The reaction mixture was extracted 100 mL EtOAc, washed with brine solution and evaporated *in vacuo* then purified by chromatography (PE:EtOAc = 1:1) to afford **A10** as a solid 110 mg. ¹H NMR (400 MHz, DMSO-d₆), δ (ppm),

3.64 (s, 3H), 3.19 (s, 3H), 2.70 (bs, 1H), 2.17 (t, J=7 Hz, 1H), 1.32 (s, 3H), 0.73 (s, 3H).

Example 2. Synthesis of compound 1.

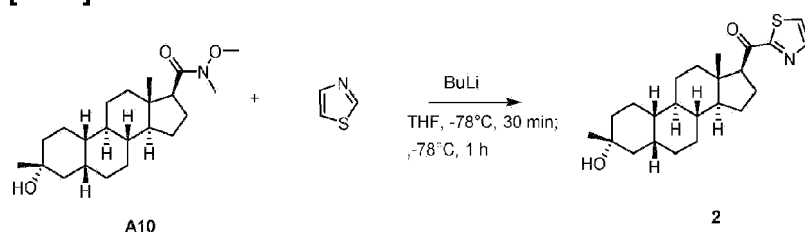
[0231]



[0232] To a stirred solution of **A10** (0.1 g, 0.275 mmol) in 5 mL of THF was added phenylmagnesium bromide (1 M; 1.375 mL, 1.375 mmol) dropwise at rt. After stirring at rt for 3 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3), washed with brine (100 mL x 3), dried (MgSO₄), filtered, and evaporated *in vacuo*, then purified by prep-HPLC to afford **1** as a solid 24 mg. ¹H NMR (500 MHz, CDCl₃), δ (ppm), 7.86 (d, 2H, J=6.8 Hz), 7.52 (t, 1H, J=7.2 Hz), 7.43 (t, 2H, J=7.2 Hz), 3.49 (t, 1H, J=7.8 Hz), 2.43 (q, 1H, J=8.6 Hz), 1.25 (s, 3H), 0.60 (s, 3H). LCMS: Rt = 2.618 min, MS (ESI) m/z: 381 [M+H]⁺.

Example 3. Synthesis of compound 2.

[0233]

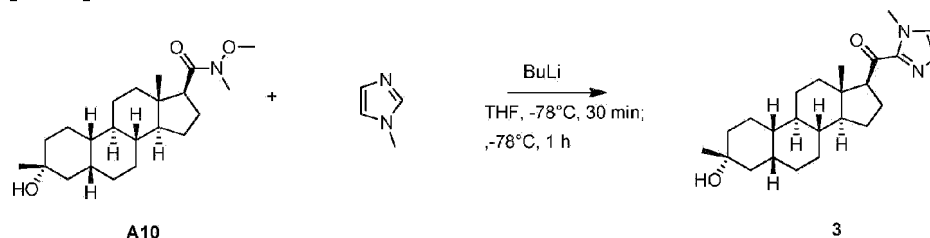


[0234] To a stirred solution of thiazole (117 mg, 1.375 mmol) in 10 mL of THF was added n-BuLi (2.5 M; 0.55 mL, 1.375 mmol) at -78°C. After stirring at -78°C for 30 min, a solution of **A10** (0.1 g, 0.275 mmol) in 5 mL of THF was added dropwise at -78°C. After stirring at -78°C for 1 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3), washed with brine (100 mL x 3), dried (MgSO₄), filtered, and evaporated *in vacuo*, purified by prep-HPLC to afford **2** as a solid 44 mg. ¹H NMR (500 MHz, CDCl₃), δ (ppm), 7.97 (d, 1H, J=3.0 Hz), 7.63 (d, 1H, J=3.0 Hz), 3.87 (t, 1H, J=9.0 Hz), 1.26 (s, 3H), 0.69 (s, 3H).

LCMS: Rt = 2.564 min, MS (ESI) m/z: 388 [M+H]⁺.

Example 4. Synthesis of compound 3.

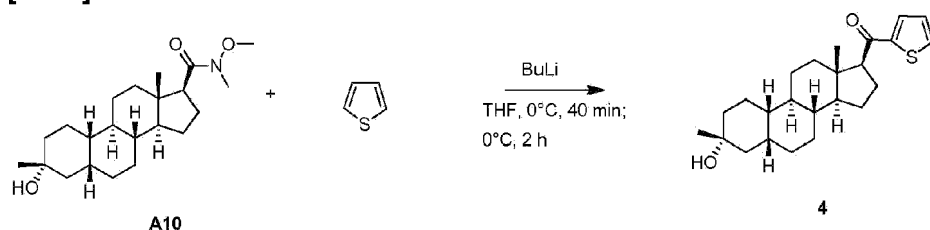
[0235]



[0236] To a stirred solution of 1-methyl-1H-imidazole (113 mg, 1.375 mmol) in 10 mL of THF was added nBuLi (2.5 M; 0.55 mL, 1.375 mmol) at -78°C. After stirring at -78°C for 30 min, a solution of A10 (0.1 g, 0.275 mmol) in 5 mL of THF was added dropwise at -78°C. After stirring at -78°C for 1 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3), washed with brine (100 mL x 3), dried (MgSO₄), filtered, and evaporated *in vacuo*, then purified by prep-HPLC to afford 3 as a solid 20 mg. ¹H NMR (500 MHz, CDCl₃), δ_H (ppm), 7.09 (d, 1H, J=0.5 Hz), 6.98 (d, 1H, J=0.5 Hz), 3.97 (s, 3H), 3.96 (t, 1H, J=8.6 Hz), 1.25 (s, 3H), 0.67 (s, 3H). LCMS: Rt = 2.393 min, MS (ESI) m/z: 385 [M+H]⁺.

Example 5. Synthesis of compound 4.

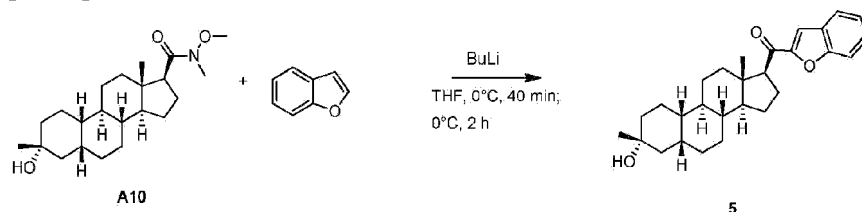
[0237]



[0238] To a stirred solution of thiophene (115 mg, 1.375 mmol) in 10 mL of THF was added nBuLi (2.5 M; 0.55 mL, 1.375 mmol) at 0°C. After stirring at 0°C for 40 min, a solution of A10 (0.1 g, 0.275 mmol) in 5 mL of THF was added dropwise at 0°C. After stirring at 0°C for 2 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3), washed with brine (100 mL x 3), dried (MgSO₄), filtered, and evaporated *in vacuo*, then purified by prep-HPLC to afford 4 as a solid 31 mg. ¹H NMR (500 MHz, CDCl₃), δ (ppm), 7.66 (d, 1H), 7.61 (d, 1H), 7.11 (t, 1H), 3.27 (t, 1H), 1.26 (s, 3H), 0.67 (s, 3H). LCMS: Rt = 2.541 min, MS (ESI) m/z: 387 [M+H]⁺.

Example 6. Synthesis of compound 5.

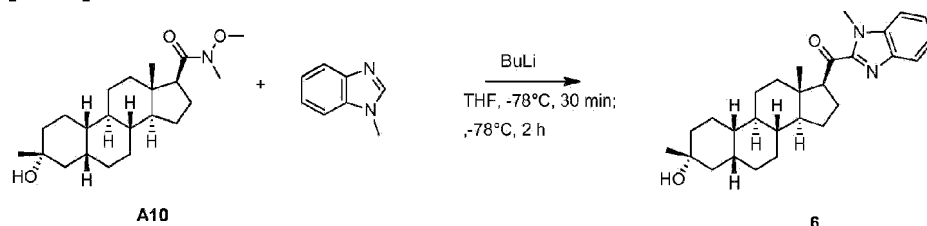
[0239]



[0240] To a stirred solution of benzofuran (162 mg, 1.375 mmol) in 10 mL of THF was added nBuLi (2.5 M; 0.55 mL, 1.375 mmol) at 0°C. After stirring at 0°C for 40 min, a solution of **A10** (0.1 g, 0.275 mmol) in 5 mL of THF was added dropwise at 0°C. After stirring at 0°C for 2 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3), washed with brine (100 mL x 3), dried (MgSO₄), filtered, and evaporated *in vacuo*, then purified by prep-HPLC to afford **5** as a solid 47 mg. ¹H NMR (500 MHz, CDCl₃), δ (ppm), 7.71 (d, 1H, J=7.8 Hz), 7.58 (d, 1H, J=7.8 Hz), 7.46 (t, 1H, J=7.8 Hz), 7.45 (s, 1H), 7.30 (t, 1H, J=7.8 Hz), 3.40 (t, 1H, J=8.2 Hz), 1.27 (s, 3H), 0.69 (s, 3H). LCMS: Rt = 2.621 min, MS (ESI) m/z: 421 [M+H]⁺.

Example 7. Synthesis of compound 6.

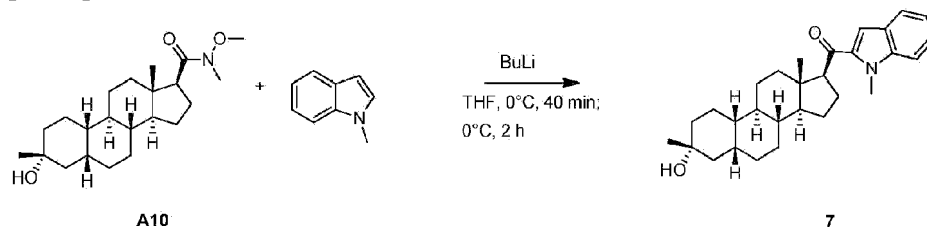
[0241]



[0242] To a stirred solution of 1-methyl-1H-benzodimidazole (181 mg, 1.375 mmol) in 10 mL of THF was added nBuLi (2.5 M; 0.55 mL, 1.375 mmol) at -78°C. After stirring at -78°C for 30 min, a solution of **A10** (0.1 g, 0.275 mmol) in 5 mL of THF was added dropwise at -78°C. After stirring at -78°C for 2 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3), washed with brine (100 mL x 3), dried (MgSO₄), filtered, and evaporated *in vacuo*, then purified by prep-HPLC to afford **6** as a solid 65 mg. ¹H NMR (500 MHz, CDCl₃), δ (ppm), 7.89 (d, 1H, J=7.8 Hz), 7.44-7.40 (m, 2H), 7.36-7.33 (m, 1H), 4.19 (t, 1H, J=8.6 Hz), 4.10 (s, 3H), 1.25 (s, 3H), 0.69 (s, 3H). LCMS: Rt = 2.607 min, MS (ESI) m/z: 435 [M+H]⁺.

Example 8. Synthesis of compound 7.

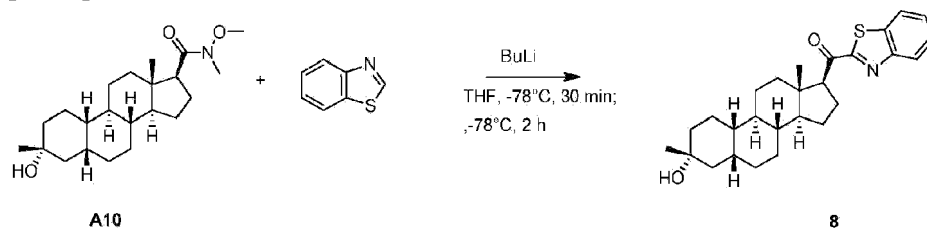
[0243]



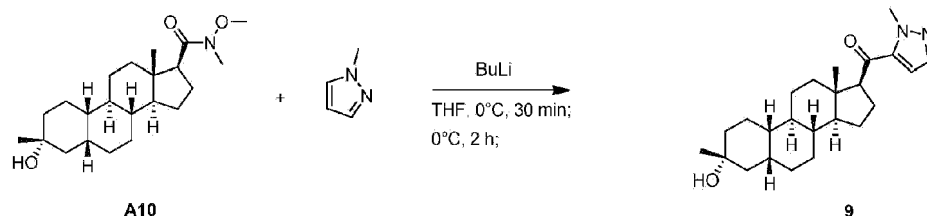
[0244] To a stirred solution of 1-methyl-1H-indole (180 mg, 1.375 mmol) in 10 mL of THF was added nBuLi (2.5 M; 0.55 mL, 1.375 mmol) at 0°C. After stirring at 0°C for 40 min, a solution of **A10** (0.1 g, 0.275 mmol) in 5 mL of THF was added dropwise at 0°C. After stirring at 0°C for 2 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3), washed with brine (100 mL x 3), dried (MgSO₄), filtered, and evaporated *in vacuo*, then purified by prep-HPLC to afford **7** as a solid 36 mg. ¹H NMR (500 MHz, CDCl₃), δ (ppm), 7.70 (d, 1H, J=7.8 Hz), 7.38-7.34 (m, 2H), 7.23 (s, 1H), 7.15-7.13 (m, 1H), 4.06 (s, 3H), 3.40 (t, 1H, J=8.2 Hz), 1.26 (s, 3H), 0.68 (s, 3H). LCMS: Rt = 2.742 min, MS (ESI) m/z: 434 [M+H]⁺.

Example 9. Synthesis of compound 8.

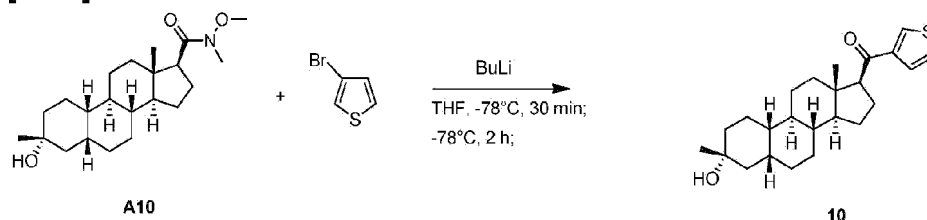
[0245]



[0246] To a stirred solution of benzo[d]thiazole (185 mg, 1.375 mmol) in 10 mL of THF was added nBuLi (2.5 M; 0.55 mL, 1.375 mmol) at -78°C. After stirring at -78°C for 30 min, a solution of **A10** (0.2 g, 0.55 mmol) in 5 mL of THF was added dropwise at -78°C. After stirring at -78°C for 2 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3), washed with brine (100 mL x 3), dried (MgSO₄), filtered, and evaporated *in vacuo*, purified by prep-HPLC to afford **8** as a solid 100 mg. ¹H NMR (500 MHz, CDCl₃), δ (ppm), 8.09 (d, 1H, J=7.8 Hz), 7.87 (d, 1H, J=7.8 Hz), 7.45 (t, 1H, J=7.8 Hz), 7.40 (t, 1H, J=7.8 Hz), 3.94 (t, 1H, J=8.6 Hz), 1.17 (s, 3H), 0.61 (s, 3H). LCMS: Rt = 2.829 min, MS (ESI) m/z: 438 [M+H]⁺.

Example 10. Synthesis of compound 9.**[0247]**

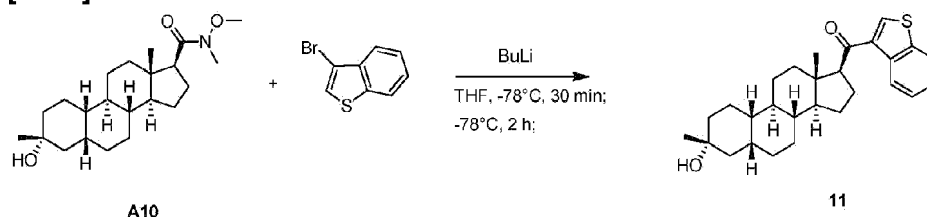
[0248] To a stirred solution of 1-methyl-1H-pyrazole (60 mg, 0.7 mmol) in 10 mL THF was added BuLi (2.5 M; 0.3 mL, 0.7 mmol) at 0°C. After stirring at 0°C for 30 min, a solution of **A10** (50 mg, 0.14 mmol) in 3 mL THF was added dropwise at -78°C. After stirring at 0°C for 2 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3). The combined extracts were washed with brine (100 mL x 3), dried (MgSO₄), filtered, evaporated *in vacuo*, and purified by prep-HPLC to afford **9** as a solid (23 mg, 0.06 mmol). ¹H NMR (500 MHz, CDCl₃), δ(ppm), 7.44(1H, d, J=2Hz), 6.77 (1H, d, J=2Hz), 4.15 (3H, s), 3.17 (1H, t, J=9Hz), 2.35 (1H, dd, J=9Hz, 8Hz), 1.27 (s, 3H), 0.64 (s, 3H). LCMS: Rt=2.45min, m/z=385.2 [M+H]

Example 11. Synthesis of compound 10.**[0249]**

[0250] To a stirred solution of 3-bromothiophene (110 mg, 0.7 mmol) in 10 mL of THF was added BuLi (2.5 M; 0.3 mL, 0.7 mmol) at -78°C. After stirring at -78°C for 30 min, a solution of **A10** (50 mg, 0.14 mmol) in 3 mL of THF was added dropwise at -78°C. After stirring at -78°C for 2 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3), washed with brine (100 mL x 3), dried (MgSO₄), filtered, evaporated *in vacuo*, and purified by prep-HPLC to afford **10** as a solid (15 mg, 0.039 mmol). ¹H NMR (500 MHz, CDCl₃), δ(ppm), 7.66(1H, d, J=4Hz), 7.61 (1H, dd, J=1Hz), 7.11 (1H, t, J=4Hz), 3.28 (1H, t, J=9 Hz), 2.42-2.36 (1H, m), 1.27 (s, 3H), 0.68 (s, 3H). LCMS: Rt=2.54min, m/z=387.1 [M+H]

Example 12. Synthesis of compound 11.

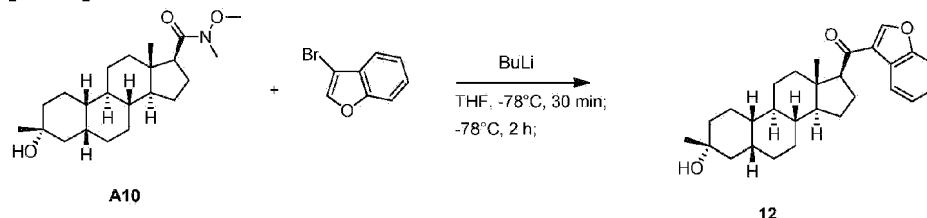
[0251]



[0252] To a stirred solution of 3-bromobenzo[b]thiophene (230 mg, 1.1 mmol) in 10 mL THF was added BuLi (2.5 M; 0.45 mL, 1.1 mmol) at -78°C . After stirring at -78°C for 30 min, a solution of **A10** (80 mg, 0.22 mmol) in 3 mL THF was added dropwise at -78°C . After stirring at -78°C for 2 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3). The combined extracts were washed with brine (100 mL x 3), dried (MgSO_4), filtered, evaporated *in vacuo*, and purified by prep-HPLC to afford **11** as a solid (52 mg, 0.12 mmol). $^1\text{H NMR}$ (500 MHz, CDCl_3), δ (ppm), 7.90-7.89 (2H, s), 7.85 (1H, d, $J=9\text{ Hz}$), 7.44 (1H, t, $J=7\text{ Hz}$), 7.39 (1H, t, $J=7\text{ Hz}$), 3.40 (1H, t, $J=9\text{ Hz}$), 2.43-2.39 (1H, m), 1.27 (s, 3H), 0.69 (s, 3H). **LCMS**: : $t_r=2.73\text{ min}$, $m/z=437.2$ [$\text{M}+\text{H}$]

Example 13. Synthesis of compound 12.

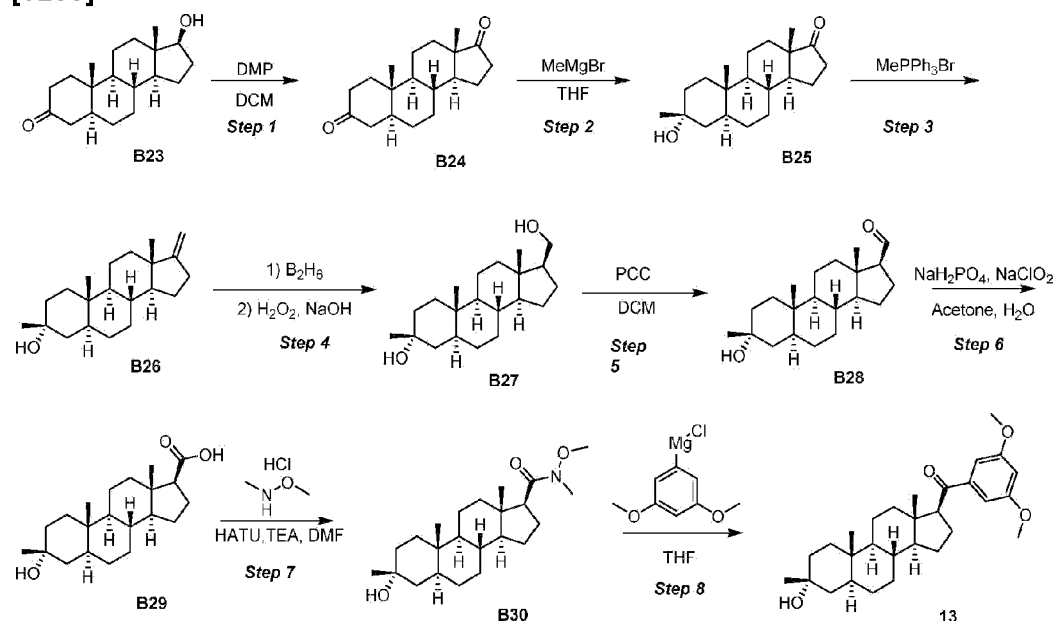
[0253]



[0254] To a stirred solution of 3-bromobenzofuran (140 mg, 0.7 mmol) in 10 mL THF was added BuLi (2.5 M; 0.3 mL, 0.7 mmol) at -78°C . After stirring at -78°C for 30 min, a solution of **A10** (50 mg, 0.14 mmol) in 3 mL of THF was added dropwise at -78°C . After stirring at -78°C for 2 h, the reaction mixture was poured into ice-cold water and extracted with EtOAc (100 mL x 3). The combined extracts were washed with brine (100 mL x 3), dried (MgSO_4), filtered, evaporated *in vacuo*, and purified by prep-HPLC to afford **12** as a solid (25 mg, 0.06 mmol). $^1\text{H NMR}$ (500 MHz, CDCl_3), δ (ppm), 7.71 (1H, d, $J=8\text{ Hz}$), 7.58 (1H, d, $J=9\text{ Hz}$), 7.46 (1H, s), 7.46 (1H, t, $J=5\text{ Hz}$), 7.30 (1H, t, $J=7\text{ Hz}$), 3.41 (1H, t, $J=9\text{ Hz}$), 2.45-2.37 (1H, m), 1.27 (s, 3H), 0.69 (s, 3H). **LCMS**: : $t_r=2.53\text{ min}$, $m/z=421.3$ [$\text{M}+\text{H}$].

Example 14. Synthesis of compound 13.

[0255]



Step 1. To a solution of **B23** (55 g, 198 mmol) in DCM (2000 mL) was added Dess-Martin (167 g, 396 mmol) in portions at 15°C. After addition was completed, the mixture was stirred at 15°C for 2 hours. TLC (PE: EA = 3:1, PMA) indicated the reaction was finished and one main spot was found. To the mixture was added a saturated mixed solution of NH_4Cl and NaHCO_3 (v:v = 1:1) (1.5 L) until the reaction solution became clear and starch potassium iodide paper did not turn blue. The mixture was extracted with DCM (1 L X 2). The combined organic phase was dried over Na_2SO_4 and concentrated to give crude **B24** (60 g, crude) as solid.

Step 2. To a solution of **B24** (60 g, 208 mmol) in THF (1000 mL) was added methylmagnesium bromide (624 mmol, 208 mL, 3M in ether) at -70°C. The mixture was stirred at -70°C for 3 hours. TLC (PE: EA = 3:1, PMA) indicated the reaction was finished. The reaction mixture was quenched with saturated NH_4Cl solution (1500 mL) and then concentrated to give a residue, which was extracted with DCM (1000 mL X 3). The organic phase was dried, concentrated to give crude **B25** (50 g) as a solid.

Step 3. To a solution of Ph_3PMeBr (280 g, 785 mmol) in THF (500 mL) was added a slurry of $t\text{-BuOK}$ (87.9 g, 785 mmol) in THF (200 mL) under N_2 . The mixture turned red and the mixture was stirred at 60°C for 1 hour. A solution of **B25** (48 g, 157 mmol) was added in one portion. The final reaction mixture was stirred at this temperature (60°C) for 2 hours. TLC (PE: EA = 3:1, PMA) indicated the reaction was finished. The reaction was worked up. To the combined reaction mixture was added saturated NH_4Cl solution (1000 mL) and then extracted with EtOAc (1000 mL X 2). The combined organic phase was dried, concentrated and purified on silicon gel column (PE: EA = 50/1-20/1) to give **B26** (15 g, 31.6%) as a solid.

^1H NMR (400 MHz, CDCl_3) δ = 4.65 - 4.57 (m, 2H), 2.53 - 2.42 (m, 1H), 2.27 - 2.16 (m, 1H), 1.85 - 1.10 (m, 21H), 1.05 - 0.78 (m, 2H), 0.77 (s, 7H)

Step 4. To a solution of **B26** (15 g, 49.5 mmol) in THF (500 mL) was added dropwise a solution of BH₃-Me₂S (49.5 mL, 495 mmol) at 0 °C. The solution was stirred at 15°C for 3h. TLC (PE/EtOAc = 3/1) showed the reaction was completed. After cooling to 0°C, a solution of NaOH (250 mL, 3M) was added very slowly. After addition, H₂O₂ (67 g, 594 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. The resulting solution was stirred at 15°C for 2h. Then saturated aqueous Na₂S₂O₃ (500 mL) was added until the reaction solution became clear. The mixture was extracted with EtOAc (200 x3). The combined organic solution was washed with saturated aqueous Na₂S₂O₃ (100 mL x 3), brine (200 mL), dried over Na₂SO₄ and concentrated in vacuum to give the crude product **B27** (20 g) as a solid, which was used for the next step without further purification.

Step 5. To a solution of **B27** (20 g, 62.4 mmol) in DCM (400 mL) was added PCC (26.7 g, 123 mmol) and SiO₂ (26.7 g). The final reaction mixture was stirred at 15°C for 3 hours. After TLC (PE: EA = 3:1) indicated the reaction was finished and one main spot was found, the mixture was concentrated and purified by combi-flash (PE: EA= 100%-70%) to give **B28** (10 g, 51.2%) as a solid.

Step 6. To a solution of **B28** (10 g, 31.3 mmol) in acetone (150 mL) and 2-methyl-2-butene (35 mL) was added slowly drop wise aqueous NaH₂PO₄ (18.7 g, 156 mmol) and NaClO₂ (14.1 g, 156 mmol) in water (100 mL) at 0°C. The mixture was stirred at 15°C for 2 h. TLC (PE/EA=1/1) showed the reaction was completed and two main spots were found. Then, the reaction was poured in to water (400 mL) and filtered. The filtered cake was washed with water (100 mL) and concentrated to afford a mixture (8 g) as a solid.

Step 7. To a solution of **B29** (8 g, 23.9 mmol) in DMF (200 mL) was added HATU (18.1 g, 47.8 mmol), TEA (5.25 g, 47.8 mmol) and N,O-dimethylhydroxylamine (2.18 g, 35.8 mmol) at 15°C. The mixture was stirred at 15°C for 16 hrs. TLC (PE/EA=1/1) showed the reaction was completed. The reaction was poured into water (500 mL) and extracted with EtOAc (100 mL X 2). The combined organic phase was washed with saturated brine (200 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, Petroleum ether/Ethyl acetate=4/1) to afford **B30** (3 g) as a solid.

¹H NMR (400 MHz, CDCl₃) δ = 3.64 (s, 3H), 3.20 (s, 3H), 2.85 - 2.71 (m, 1H), 2.28 - 2.08 (m, 1H), 1.80-0.70 (m, 31H)

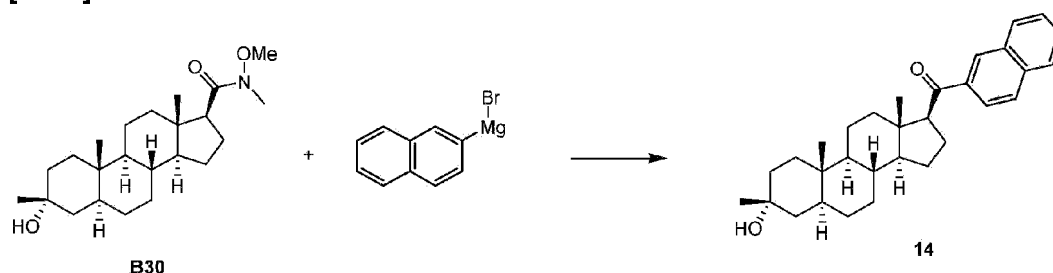
Step 8. To a solution of **B30** (0.1 g, 0.264 mmol) in THF (2 mL) was added (3,5-dimethoxyphenyl)magnesium chloride (2.63 mL, 2.63 mmol, 1.0M in THF) under N₂. The reaction mixture was stirred at 15°C for 1.5 hours. LCMS indicated the reaction was finished and desired MS peak was found. To the reaction mixture was added saturated NH₄Cl solution (5 mL) and then extracted with EtOAc (2 mL X 3). The combined organic phase was concentrated and purified by prep-HPLC to give **13** (47.8 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.01 (d, J=2.3 Hz, 2H), 6.65 - 6.59 (m, 1H), 3.83 (s, 6H), 3.46 - 3.36 (m, 1H), 2.49 - 2.34 (m, 1H), 1.84 - 1.66 (m, 3H), 1.19 (s, 20H), 1.04 - 0.89 (m, 1H), 0.71 (s, 4H), 0.60 (s, 3H). **LCMS** Rt = 1.489 min in 2 min chromatography, 10-80AB, MS ESI calcd.

for $C_{29}H_{43}O_4$ $[M+H]^+$ 455, found 455.

Example 15. Synthesis of compound 14.

[0256]

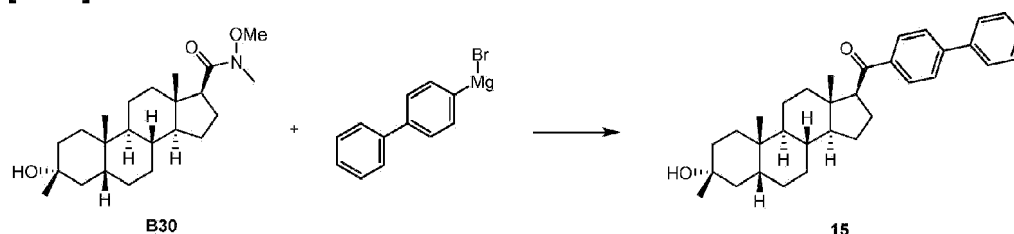


[0257] To a solution of **B30** (0.1 g, 0.264 mmol) in THF (2 mL) was added naphthalen-2-ylmagnesium bromide (5.26 mL, 2.63 mmol, 0.5M in THF) under N_2 . The reaction mixture was stirred at 15°C for 4 hours. LCMS indicated the reaction was finished and desired MS peak was found. To the reaction mixture was added saturated NH_4Cl solution (5 mL) and then extracted with EtOAc (2 mL X 3). The combined organic phase was concentrated and purified by prep-HPLC to give **14** (36.1 mg) as a solid.

1H NMR (400 MHz, $CDCl_3$) δ 8.42 - 8.37 (m, 1H), 8.00 - 7.94 (m, 2H), 7.91 - 7.84 (m, 2H), 7.62 - 7.51 (m, 2H), 3.70 - 3.62 (m, 1H), 2.56 - 2.42 (m, 1H), 1.87 - 1.69 (m, 3H), 1.19 (s, 21H), 0.84 - 0.75 (m, 1H), 0.70 (s, 3H), 0.63 (s, 3H). LCMS R_t = 1.553 min in 2 min chromatography, 10-80AB, MS ESI calcd. for $C_{31}H_{41}O_2$ $[M+H]^+$ 445, found 445.

Example 16. Synthesis of compound 15.

[0258]



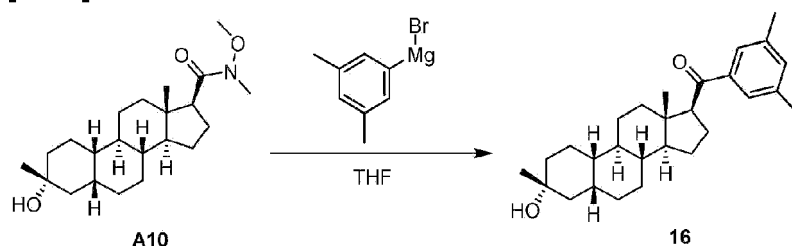
[0259] To a solution of **B30** (0.1 g, 0.264 mmol) in THF (2 mL) was added [1,1'-biphenyl]-4-ylmagnesium bromide (5.26 mL, 2.63 mmol, 0.5M in THF) under N_2 . The reaction mixture was stirred at 15°C for 4 hours. LCMS indicated the reaction was finished and desired MS peak

was found. To the reaction mixture was added saturated NH_4Cl solution (5 mL) and then extracted with EtOAc (2 mL X 3). The combined organic phase was concentrated and purified by preparative HPLC to give **15** (41.4 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.96 (d, $J=8.3$ Hz, 2H), 7.65 (dd, $J=7.9, 11.9$ Hz, 4H), 7.50 - 7.33 (m, 3H), 3.59 - 3.47 (m, 1H), 2.51 - 2.38 (m, 1H), 1.86 - 1.68 (m, 3H), 1.19 (s, 20H), 1.05 - 0.91 (m, 1H), 0.84 - 0.75 (m, 1H), 0.72 (s, 3H), 0.62 (s, 3H). LCMS Rt = 1.645 min in 2 min chromatography, 10-80AB, MS ESI calcd. for $\text{C}_{33}\text{H}_{43}\text{O}_2$ $[\text{M}+\text{H}]^+$ 471, found 471.

Example 17. Synthesis of compound 16.

[0260]

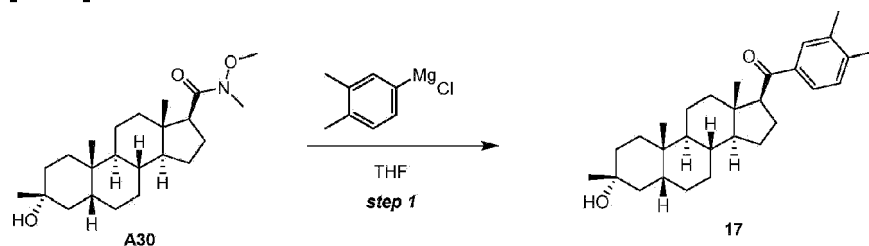


[0261] To a solution of **A10** (100 mg, 0.275 mmol) in THF (3 mL) was added (3,5-dimethylphenyl)magnesium bromide (5.5 mL, 95%). The mixture was stirred at 20 °C for 3.5h. When TLC showed starting material was consumed and new spot was produced, to the mixture was added sat. aq. NH_4Cl (5 mL). The organic phase was extracted with DCM (5 mL * 2), washed with sat. aq. NaCl (8 mL * 2), concentrated in vacuum. The residue was purified by prep. HPLC to give **16** (48.3 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.47 (s, 2H), 7.16 (s, 1H), 3.47 (t, $J = 8.8$ Hz, 1H), 2.36 (s, 7H), 1.84-1.70 (m, 5H), 1.66-1.58 (m, 2H), 1.49-1.24 (m, 16H), 1.17-1.04 (m, 2H), 0.98-0.85 (m, 1H), 0.60 (s, 3H). LCMS Rt = 1.500 min in 2 min chromatography, 10-80AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{41}\text{O}_2$ $[\text{M}+\text{H}]^+$ 409, found 391 $[\text{M}-\text{H}_2\text{O}]$.

Example 18. Synthesis of compound 17.

[0262]



[0263] The synthesis of **A30** can be found in **Example 37**, below.

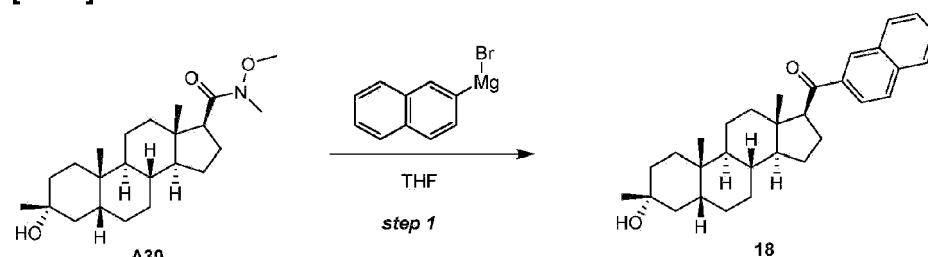
[0264] To a solution of **A30** (100 mg, 264 μ mol) in anhydrous THF (2 mL) was added (3,4-dimethylphenyl)magnesium chloride (5.26 mL, 0.5 M, 2.63 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 hours. LCMS showed the starting material was consumed completely. The reaction was quenched with saturated NH_4Cl aqueous (1 mL), concentrated under vacuum to give a residue, which was purified by Prep-HPLC (0.05% HCl-ACN) to afford **17** (61.8 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ = 7.67 (s, 1H), 7.61 (d, J =7.5 Hz, 1H), 7.18 (d, J =8.0 Hz, 1H), 3.47 (t, J =8.8 Hz, 1H), 2.48 - 2.36 (m, 1H), 2.31 (s, 6H), 2.04 - 1.92 (m, 1H), 1.90 - 1.80 (m, 1H), 1.79 - 1.63 (m, 3H), 1.54 - 0.97 (m, 21H), 0.91 (s, 3H), 0.58 (s, 3H)

LCMS R_t = 1.475 min in 2 min chromatography, 10-80AB, MS ESI calcd. for $\text{C}_{33}\text{H}_{42}\text{O}_2$ $[\text{M}+\text{H}]^+$ 423, found 423.3.

Example 19. Synthesis of compound 18.

[0265]



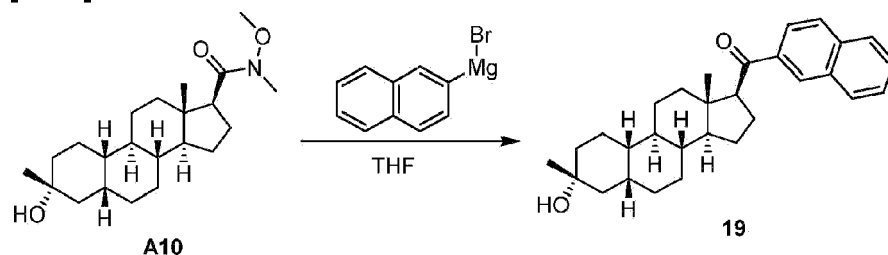
[0266] To a solution of **A30** (100 mg, 264 μ mol) in anhydrous THF (2 mL) was added naphthalen-2-ylmagnesium bromide (5.26 mL, 0.5 M, 2.63 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 hours. LCMS showed the starting material was consumed completely. The reaction was quenched with saturated NH_4Cl aqueous (1 mL), concentrated under vacuum to give a residue, which was purified by Prep-HPLC (0.05% HCl-ACN) to afford **18** (8.4 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ = 8.39 (s, 1H), 8.02 - 7.92 (m, 2H), 7.88 (d, J =8.5 Hz, 2H), 7.65 - 7.51 (m, 2H), 3.67 (t, J =8.5 Hz, 1H), 2.55 - 2.43 (m, 1H), 2.07 - 1.75 (m, 5H), 1.66 (d, J =14.6 Hz, 2H), 1.58 - 1.23 (m, 19H), 1.21 - 0.97 (m, 3H), 0.90 (s, 3H), 0.63 (s, 3H)

LCMS R_t = 1.496 min in 2 min chromatography, 10-80AB, MS ESI calcd. for $\text{C}_{31}\text{H}_{41}\text{O}_2$ $[\text{M}+\text{H}]^+$ 445, found 445.3.

Example 20. Synthesis of compound 19.

[0267]

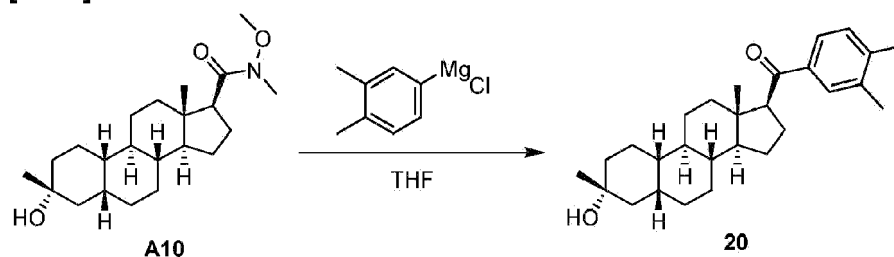


[0268] To a solution of **A10** (100 mg, 0.275 mmol) in THF (3 mL) was added naphthalen-2-ylmagnesium bromide (5.5 mL, 0.5 M in THF). The mixture was stirred at 20 °C for 3.5h. When TLC showed starting material was consumed and new spot was produced, to the mixture was added *sat. aq.* NH_4Cl (5 mL). The organic phase was extracted with DCM (5 mL * 2), washed with *sat. aq.* NaCl (8 mL * 2), concentrated in vacuum. The residue was purified by preparative HPLC to give **19** (37 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 8.39 (s, 1H), 8.01-7.93 (m, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.62-7.52 (m, 2H), 3.67 (t, J = 8.7 Hz, 1H), 2.57-2.43 (m, 1H), 1.91-1.71 (m, 5H), 1.68-1.56 (m, 2H), 1.50-1.23 (m, 16H), 1.19-1.04 (m, 2H), 0.95-0.83 (m, 1H), 0.64 (s, 3H). LCMS R_t = 1.495 min in 2 min chromatography, 10-80AB, MS ESI calcd. for $\text{C}_{30}\text{H}_{39}\text{O}_2$ $[\text{M}+\text{H}]^+$ 430, found 413 $[\text{M}-\text{H}_2\text{O}]$.

Example 21. Synthesis of compound 20.

[0269]



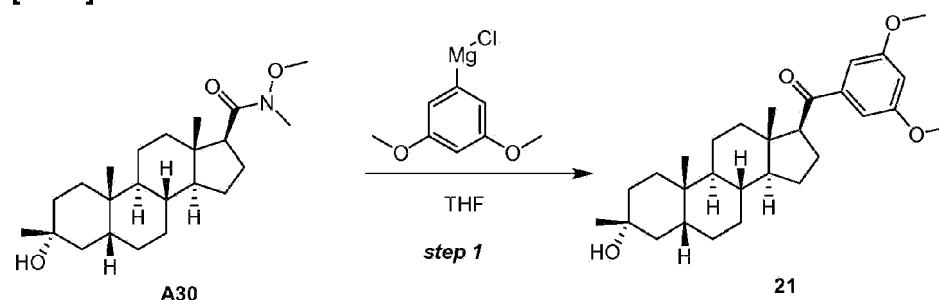
[0270] To a solution of **A10** (100 mg, 0.275 mmol) in THF (3 mL) was added (3,4-dimethylphenyl)magnesium chloride (5.5 mL, 0.5 M in THF). The mixture was stirred at 20°C for 3.5 h. When TLC showed starting material was consumed and new spot was produced. To the mixture was added *Sat.* NH_4Cl (5 mL). The aqueous layer was extracted with DCM (5 mL * 2), washed with *Sat.* NaCl (8 mL * 2), filtered and concentrated in vacuum. The residue was purified by prep-HPLC to give **20** (45 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.66 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 3.47 (t, J = 8.7 Hz, 1H), 2.48-2.36 (m, 1H), 2.31 (s, 6H), 1.82-1.60 (m, 6H), 1.51-1.23 (m,

17H), 1.19-1.02 (m, 2H), 0.98-0.85 (m, 1H), 0.60 (s, 3H). LCMS t_R = 1.491 min in 2 min chromatography, 10-80AB, MS ESI calcd. for $C_{28}H_{41}O_2$ $[M+H]^+$ 409, found 391 $[M-H_2O]^+$.

Example 22. Synthesis of compound 21.

[0271]

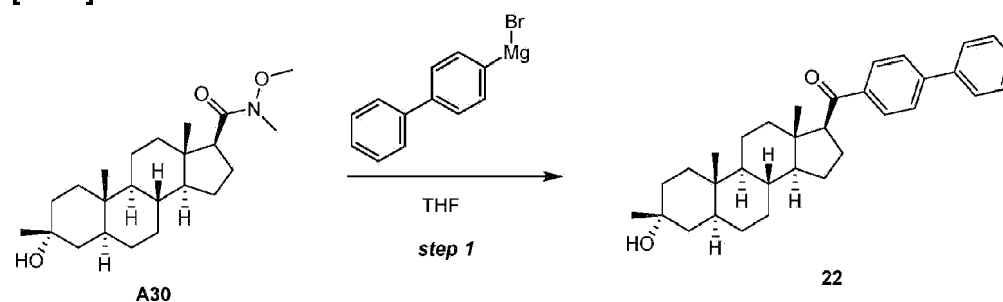


[0272] To a solution of **A30** (100 mg, 264 μmol) in anhydrous THF (2 mL) was added (3,5-dimethoxyphenyl)magnesium chloride (2.63 mL, 1.0 M, 2.63 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 2 hours. LCMS showed the starting material was consumed completely. The reaction was quenched with saturated NH_4Cl aqueous (1 mL), concentrated under vacuum to give a residue, which was purified by Prep-HPLC (0.05% HCl-ACN) to afford **21** (68.8 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ = 7.02 (d, J =2.0 Hz, 2H), 6.63 (s, 1H), 3.84 (s, 6H), 3.41 (t, J =8.8 Hz, 1H), 2.46 - 2.35 (m, 1H), 2.03 - 1.93 (m, 1H), 1.90 - 1.64 (m, 4H), 1.53 - 1.28 (m, 12H), 1.28 - 1.20 (m, 5H), 1.18 - 0.97 (m, 3H), 0.91 (s, 3H), 0.59 (s, 3H). LCMS R_t = 1.474 min in 2 min chromatography, 10-80AB, MS ESI calcd. for $C_{33}H_{43}O_2$ [455, found 437 ($[M-H_2O]^+$).

Example 23. Synthesis of compound 22.

[0273]



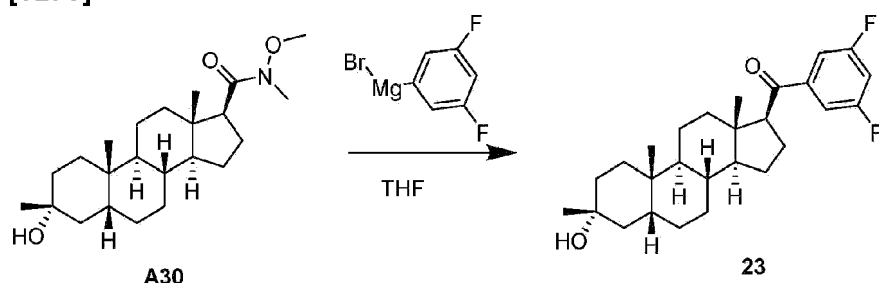
[0274] To a solution of **A30** (100 mg, 264 μmol) in anhydrous THF (2 mL) was added [1,1'-biphenyl]-4-ylmagnesium bromide (5.26 mL, 0.5 M, 2.63 mmol) at 25 °C. The reaction mixture

was stirred at 25 °C for 2 hours. LCMS showed the starting material was consumed completely. The reaction was quenched with saturated NH_4Cl aqueous (1 mL), concentrated under vacuum to give a residue, which was purified by Prep-HPLC (0.05% HCl -ACN) to afford **22** (76 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ = 7.96 (d, J =8.0 Hz, 2H), 7.72 - 7.60 (m, 4H), 7.51 - 7.43 (m, 2H), 7.43 - 7.36 (m, 1H), 3.53 (t, J =8.5 Hz, 1H), 2.52 - 2.40 (m, 1H), 1.98 (t, J =13.3 Hz, 1H), 1.91 - 1.63 (m, 4H), 1.55 - 1.29 (m, 12H), 1.28 - 0.96 (m, 9H), 0.92 (s, 3H), 0.62 (s, 3H). LCMS Rt = 1.556 min in 2 min chromatography, 10-80AB, MS ESI calcd. for $\text{C}_{33}\text{H}_{43}\text{O}_2$ $[\text{M}+\text{H}]^+$ 471, found 471.3.

Example 24. Synthesis of compound 23.

[0275]



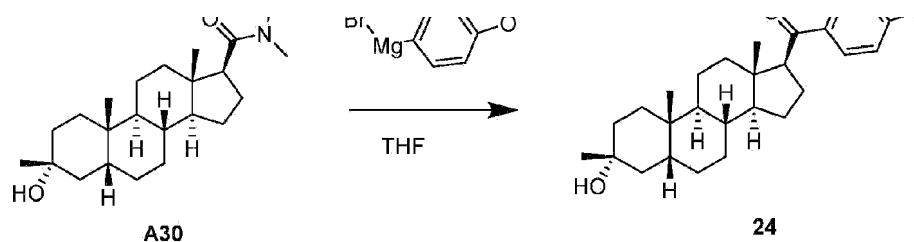
[0276] To a stirred solution of **A30** (110 mg, 291 μmol) in 3 mL of THF was added (3,5-difluorophenyl)magnesium bromide (0.5 M; 5.8 mL, 2.9 mmol) dropwise at 25°C. After stirring at 25°C for 12 hrs, LCMS showed the reaction was complete. The reaction mixture was poured into ice-cold water and extracted with EtOAc (50 mL x 2), washed with brine (30 mL x 2), dried (Na_2SO_4), filtered, and evaporated in vacuo to give crude product. The reaction mixture was purified by HPLC separation (column: Phenomenex Synergi C18 150*25*10 μm , gradient: 80-100% B (A= 0.05% HCl -ACN, B=acetonitrile), flow rate: 25 mL/min) for further purification to obtain **23** (28.4 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz): δ = 7.38 (d, J =6.0 Hz, 2H), 6.99 (t, J =8.4 Hz, 1H), 3.35 (t, J =8.8 Hz, 1H), 2.35-2.45 (m, 1H), 1.96 (t, J =13.2 Hz, 1H), 1.73-1.90 (m, 3H), 1.69 (d, J =14.6 Hz, 1H), 1.33-1.54 (m, 12H), 1.21-1.28 (m, 5H), 1.10-1.19 (m, 2H), 1.01-1.08 (m, 1H), 0.92 (s, 3H), 0.59 (s, 3H). LCMS Rt = 3.417 min in 4.0 min chromatography, 10-80 AB, MS ESI calcd. for $\text{C}_{27}\text{H}_{36}\text{F}_2\text{O}_2$ $[\text{M}-\text{H}]^+$ 430.3, found 413.0 $[\text{M}-\text{H}_2\text{O}]^+$.

Example 25. Synthesis of compound 24.

[0277]



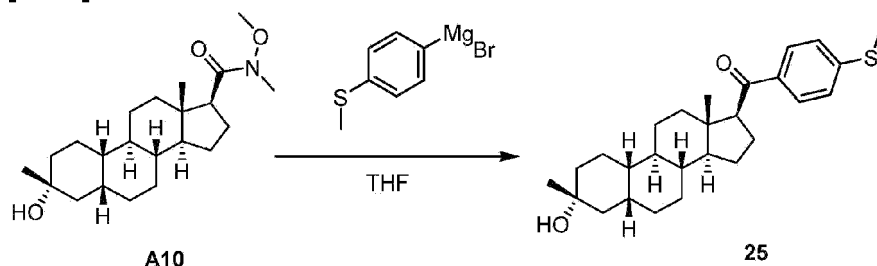


[0278] To a stirred solution of **A30** (110 mg, 291 μmol) in 3 mL of THF was added benzo[d][1,3]dioxol-5-ylmagnesium bromide (0.5 M; 5.8 mL, 2.9 mmol) dropwise at 25°C. After stirring at 25°C for 12 hrs, LCMS showed the reaction was complete. The reaction mixture was poured into ice-cold water and extracted with EtOAc (50 mL x 2), washed with brine (30 mL x 2), dried (Na_2SO_4), filtered, and evaporated in vacuo to give crude product. The reaction mixture was purified by HPLC separation (column: Phenomenex Synergi C18 150*25*10 μm , gradient: 80-100% B (A= 0.05% HCl-ACN, B=acetonitrile), flow rate: 25 mL/min) for further purification to obtain **24** (21.1 mg) as a solid.

^1H NMR (CDCl_3 , 400 MHz): δ = 7.50 (d, J =8.0 Hz, 1H), 7.41 (s, 1H), 6.84 (d, J =8.0 Hz, 1H), 6.04 (s, 2H), 3.40 (t, J =8.6 Hz, 1H), 2.37-2.45 (m, 1H), 1.97 (t, J =13.6 Hz, 1H), 1.81-1.90 (m, 1H), 1.64-1.79 (m, 3H), 1.29-1.55 (m, 12H), 1.27 (s, 3H), 1.23 (br. s, 2H), 1.10-1.19 (m, 2H), 1.00-1.08 (m, 1H), 0.92 (s, 3H), 0.59 (s, 3H). **LCMS** Rt = 3.309 min in 4.0 min chromatography, 10-80 AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{39}\text{O}_4$ $[\text{M}+\text{H}]^+$ 439.3, found 439.1.

Example 26. Synthesis of compound 25.

[0279]



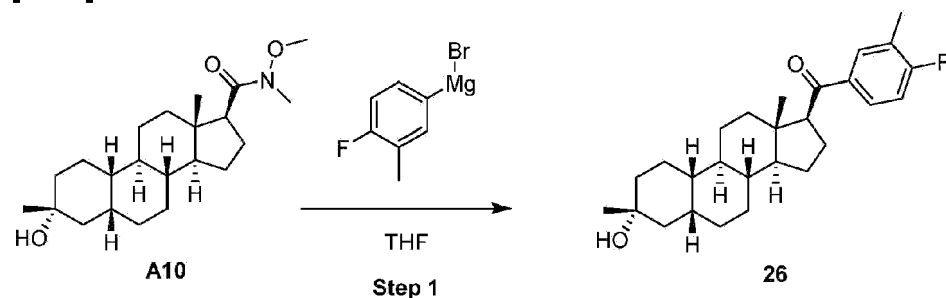
[0280] To a solution of **A10** (100 mg, 0.275 mmol) in THF (3 mL) was added (4-(methylthio)phenyl)magnesium bromide (5.5 mL, 0.5 M in THF). The mixture was stirred at 20°C for 3.5h. To the mixture was added *Sat.* NH_4Cl (5 mL). The organic phase was extracted with DCM (5 mL * 2), washed with *Sat.* NaCl (8 mL * 2), concentrated in vacuum. The residue was purified by *prep.* HPLC¹ to give **25** (32 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.81 (d, J =8.5 Hz, 2H), 7.25-7.22 (m, 2H), 3.45 (t, J =8.8 Hz, 1H), 2.56 - 2.35 (m, 4H), 1.84 - 1.72 (m, 5H), 1.53 - 1.25 (m, 18H), 1.20 - 0.84 (m, 3H), 0.59 (s, 3H). **LCMS** Rt = 1.476 min in 2 min chromatography, 10-80AB, MS ESI calcd. for

$C_{27}H_{39}O_2S[M+H]^+$ 427.3, found 409 $[M-H_2O]^+$.

Example 27. Synthesis of compound 26.

[0281]

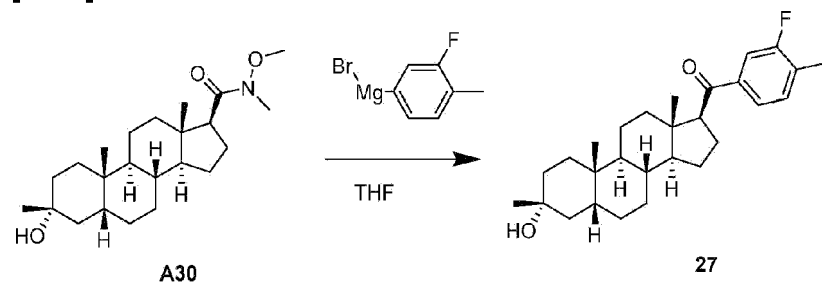


[0282] To a solution of **A10** (100 mg, 0.275 mmol) in THF (3 mL) was added (4-fluoro-3-methylphenyl)magnesium bromide (2.75 mL) at 25 °C for 2 hours, at which point the reaction was complete as shown by LC-MS. An aqueous solution of NH_4Cl (5 mL) was added drop wise into the reaction mixture at 25 °C, and extracted with EtOAc (10 mL x2). The combined organic solution was washed with brine (5 mL), dried over Na_2SO_4 . The organic layer was filtered and concentrated under reduced pressure to give the crude mixture which was purified by HPLC to give **26** (47.5 mg) as a solid.

¹H NMR ($CDCl_3$, 400MHz) δ = 7.83 - 7.70 (m, 2H), 7.06 (t, $J=8.9$ Hz, 1H), 3.46 (t, $J=8.7$ Hz, 1H), 2.48 - 2.31 (m, 4H), 1.89 - 1.73 (m, 5H), 1.71 - 1.60 (m, 2H), 1.61 - 1.60 (m, 1H), 1.54 - 1.45 (m, 3H), 1.43 - 1.33 (m, 7H), 1.33 - 1.24 (m, 6H), 1.22 - 1.05 (m, 2H), 1.03 - 0.88 (m, 1H), 0.62 (s, 3H). **LCMS** R_t = 1.285 min in 2 min chromatography, 30-90AB, MS ESI calcd, for $C_{27}H_{38}FO_2$ $[M+H]^+$ 413, found 413.

Example 28. Synthesis of compound 27.

[0283]



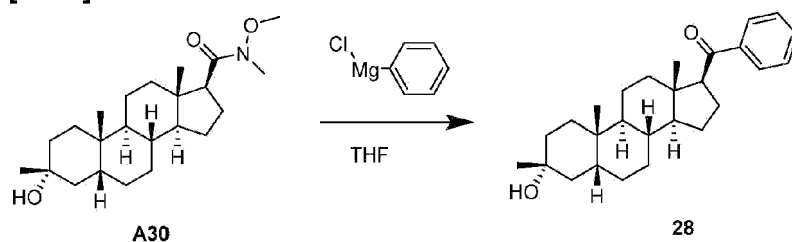
[0284] To a stirred solution of **A30** (110 mg, 291 μ mol) in 3 mL of THF was added (3-fluoro-4-methylphenyl)magnesium bromide (0.5 M, 5.8 mL, 2.9 mmol) dropwise at 25°C. After stirring

at 25°C for 12 hrs, LCMS showed the reaction was complete. The reaction mixture was poured into ice-cold water and extracted with EtOAc (50 mL x 2), washed with brine (30 mL x 2), dried (Na₂SO₄), filtered, and evaporated in vacuo to give crude product. The reaction mixture was purified by HPLC separation (column: Phenomenex Synergi C18 150*25*10um, gradient: 88-88% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to obtain **27** (42.4 mg) as a solid.

¹HNMR (CDCl₃, 400MHz): δ = 7.48-7.61 (m, 2H), 7.20-7.26 (m, 1H), 3.41 (t, J =8.8 Hz, 1H), 2.37-2.44 (m, 1H), 2.33 (d, J =1.4 Hz, 3H), 1.97 (t, J =13.2 Hz, 1H), 1.87 (ddd, J =13.8, 9.3, 4.5 Hz, 1H), 1.65-1.80 (m, 3H), 1.33-1.56 (m, 12H), 1.22-1.29 (m, 5H), 0.99-1.18 (m, 3H), 0.92 (s, 3H), 0.58 (s, 3H). LCMS Rt = 3.322 min in 4.0 min chromatography, 10-80 AB, MS ESI calcd. for C₂₈H₄₀FO₂ [M +H]⁺ 427.3, found 409.1 ([M-H₂O]⁺).

Example 29. Synthesis of compound 28.

[0285]

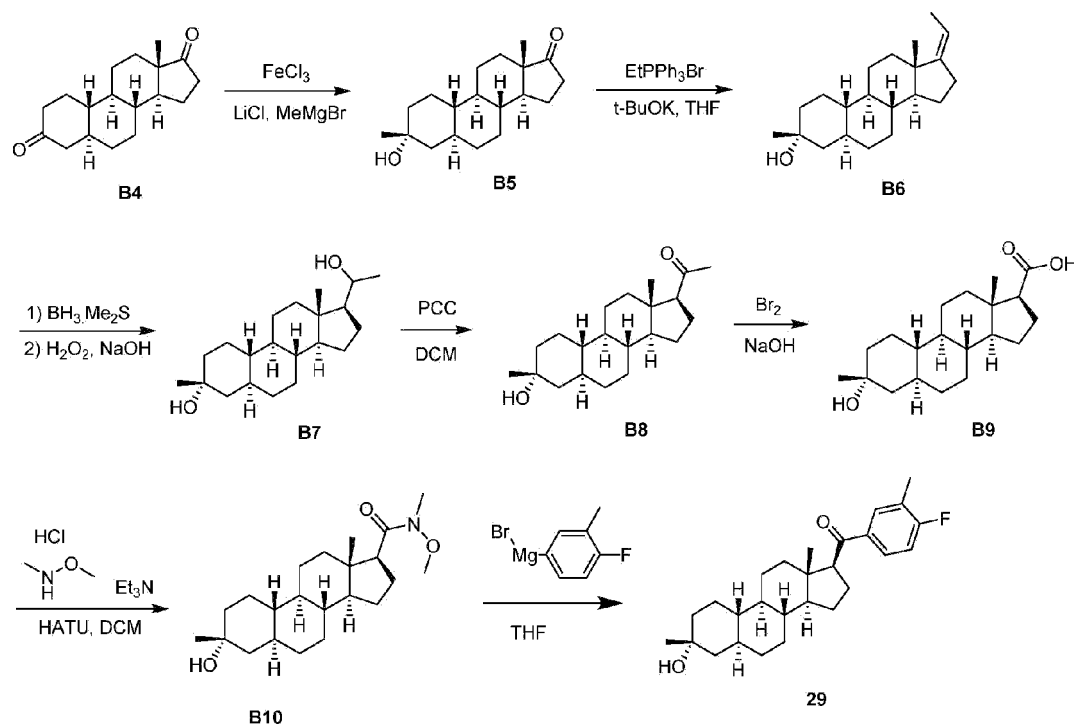


[0286] To a stirred solution of **A30** (110 mg, 291 μ mol) in 3 mL of THF was added phenylmagnesium chloride (0.5 M; 5.8 mL, 2.9 mmol) dropwise at 25°C. After stirring at 25°C for 12 hrs, LCMS showed the reaction was complete. The reaction mixture was poured into ice-cold water and extracted with EtOAc (50 mL x 2), washed with brine (30 mL x 2), dried (Na₂SO₄), filtered, and evaporated in vacuo to give crude product. The crude product was purified by HPLC separation (column: Gemini 150*25 5u, gradient: 69-94% B (A= 0.05%HCl-ACN, B=acetonitrile), flow rate: 30 mL/min) for further purification to obtain **28** (48.4 mg, 291 μ mol) as a solid.

¹HNMR (CDCl₃, 400MHz): δ = 7.88 (d, J =7.4 Hz, 1H), 7.50-7.58 (m, 1H), 7.39-7.48 (m, 2H), 3.50 (t, J =8.8 Hz, 1H), 2.36-2.52 (m, 1H), 1.98 (t, J =13.2 Hz, 1H), 1.85 (d, J =13.8 Hz, 1H), 1.74-1.81 (m, 2H), 1.68 (d, J =14.4 Hz, 1H), 1.32-1.55 (m, 13H), 1.21-1.29 (m, 5H), 0.99-1.17 (m, 3H), 0.91 (s, 3H), 0.60 (s, 3H). LCMS Rt = 3.253 min in 4.0 min chromatography, 10-80 AB, MS ESI calcd. for C₂₇H₃₉O₂ [M+H]⁺ 395.3, found 377.0 [M-H₂O]⁺.

Example 30. Synthesis of compound 29.

[0287]



Step 1. Under nitrogen atmosphere, anhydrous THF (400 mL) was cooled to 10°C and anhydrous LiCl (12.8 g, 304 mmol) was added in one portion. The mixture was stirred for 30 min after which a clear solution was obtained. To this mixture was added anhydrous FeCl_3 (25.7 g, 159 mmol) in one portion. The resulting mixture was stirred for additional 30 min. The reaction mixture was cooled to -35°C and methyl magnesium bromide (3 M in diethyl ether, 193 mL, 580 mmol) was added dropwise maintaining the internal temperature between -35°C and -30°C. The above mixture was stirred for 30 min at -30°C. **B4** (40 g, 145 mmol) was added in one portion. The internal temperature was allowed to -20°C and kept between -15°C and -20°C for 2 hours. TLC showed the reaction was completed. The reaction mixture was quenched with aqueous HCl (2 M, 200 mL), extracted with CH_2Cl_2 (500 mL x 2). The combined organic layer was washed with aqueous NaOH (10%, 300 mL x 2) and brine (300 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was triturated from EtOAc to give **B5** (25.0 g, 59.3%) as a solid.

^1H NMR (400MHz, CDCl_3) δ 2.44-2.40 (m, 1H), 2.09-2.00 (m, 1H), 1.89-1.57 (m, 7H), 1.54-1.03 (m, 16H), 0.87 (s, 3H), 0.73-0.70 (m, 2H).

Step 2. To a solution of ethyltriphenylphosphonium bromide (152 g, 412 mmol) in THF (600 mL), was added a solution of $t\text{-BuOK}$ (46.1 g, 412 mmol) at 25°C. The mixture was heated to 60°C and stirred for 1 h. **B5** (30.0 g, 103 mmol) was added. The mixture was stirred at 60°C for 2 hrs. TLC showed the reaction was completed. The mixture was poured into *Sat. aq* NH_4Cl (500 mL), extracted with EtOAc (300mL x 2). The combined organic phase was washed with brine (300 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated. The residue was purified by silica gel column (PE/EtOAc= 100/1) to afford **B6** (30 g, 96.4%) as a solid.

^1H NMR (400MHz, CDCl_3) δ 5.12-5.09 (m, 1H), 2.34-2.21 (m, 3H), 1.86-1.58 (m, 8H), 1.56-0.99 (m, 17H), 0.87 (s, 3H), 0.75-0.68 (m, 2H).

Step 3. To a solution of **B6** (40 g, 132 mmol) in THF (300 mL) was added dimethylsulfide borane (132 mL, 1.32 mol) dropwise at 0°C. The mixture was stirred at 25°C for 12 hrs. TLC showed the reaction was complete. After cooling to 0°C, a solution of NaOH (220 mL, 3M) was added very slowly. After the addition was complete, H₂O₂ (150 mL, 33%) was added slowly and the inner temperature was maintained below 10°C. The resulting solution was stirred at 25°C for 2 hrs. The resulting solution was filtered, and the filtrate was extracted with EtOAc (500 mL x3). The combined organic solution was washed with saturated aqueous Na₂S₂O₃ (500 mL x 2), brine (500 mL), dried over Na₂SO₄ and concentrated in vacuum to give **B7** (40 g, crude) as a solid. The crude product was used for the next step without further purification.

Step 4. To a solution of **B7** (40 g, 124 mmol) and silica gel (44 g) in CH₂Cl₂ (400 mL) was added Pyridinium chlorochromate (53.4 g, 248 mmol) at 25°C. The mixture was stirred at 25°C for 2 hrs. TLC showed the reaction was completed. The mixture was filtered and the filter cake was washed with CH₂Cl₂ (200 mL x 2). The combined filtrate was concentrated in vacuum. The residue was purified by silica gel column (eluted with PE/EtOAc = 10/1 to 1/1) to afford **B8** (34 g, 86.2%) as a solid.

¹H NMR (400MHz, CDCl₃) δ 2.55-2.51 (m, 1H), 2.20-2.10 (m, 4H), 2.00-1.64 (m, 4H), 1.60-0.99 (m, 20H), 0.75-0.69 (m, 3H), 0.60 (s, 3H).

Step 5. To a solution of **B8** (10.0 g, 31.3 mmol) in dioxane/H₂O (400 mL/120 mL) at 0 °C was added sodium hypobromide (1500 mL) [prepared from NaOH (163 g), dibromine (54.1 mL), dioxane (600 mL) and H₂O (800 mL)]. The resulting mixture was stirred at 25°C for 24 hours. After TLC showed the reaction was completed, sat. aq Na₂S₂O₃ (400 mL) was added followed by aq HCl (450 mL, 1M) was added into the mixture. The mixture was adjusted to pH = 6 and the white solid was precipitated. The solid was filtered and the filter cake was washed with water (300 mL x 2), dried in vacuum to give **B9** (9.5, 95.0%) as a solid.

¹H NMR (400MHz, DMSO-*d*₆) δ 11.89 (br, 1H), 3.87 (s, 1H), 2.29-2.26 (m, 1H), 2.00-1.93 (m, 2H), 1.65-1.15 (m, 9H), 1.13-0.91 (m, 13H), 0.85-0.75 (m, 5H).

Step 6. A mixture of **B9** (12.2 g, 38.0 mmol), N,O-dimethylhydroxylamine hydrochloride (7.41 g, 76.0 mmol), HATU (17.3 g, 45.5 mmol) and Et₃N (21.0 mL, 152 mmol) in 300 mL of anhydrous CH₂Cl₂ was stirred for 18 hrs at 25°C. TLC showed the reaction was completed. The mixture was treated with water (200 mL), extracted with CH₂Cl₂ (300 mL x 2). The combined organic phase was washed aq. HCl (200 mL, 1M), sat. aq NaHCO₃ (200 mL), and brine (300 mL), dried over anhydrous Na₂SO₄, filtered, concentrated in vacuum. The residue was purified by silica gel column (PE/EtOAc = 5/1) to afford **B10** (13.0 g, 94.2%) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 3.64 (s, 3H), 3.20 (s, 3H), 2.80 (br, 1H), 2.25-2.15 (m, 1H), 1.81-1.57 (m, 8H), 1.33-1.00 (m, 16H), 0.74 (s, 3H), 0.69-0.60 (m, 2H).

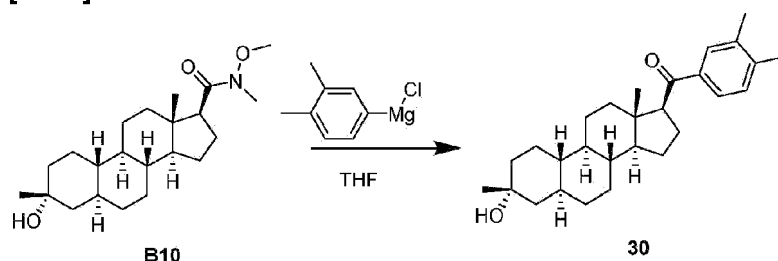
Step 7. To a solution of **B10** (100 mg, 275 μmol) in THF (3 mL) was added (4-fluoro-3-methylphenyl)magnesium bromide (2.74 mL, 1.37 mmol) dropwise at 25°C. The mixture was stirred at 25°C for 3 h. LCMS showed the reaction was complete. Then, the reaction was

concentrated in vacuum. The residue was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 80-95% B (A=0.05%HCl-acetonitrile, B=acetonitrile), flow rate: 25 mL/min) for further purification to obtain **29** (46.9 mg) as a solid.

¹H NMR (CDCl₃, CDC13 400MHz): δ=7.69-7.80 (m, 2H), 7.04 (t, *J*=8.8 Hz, 1H), 3.45 (t, *J*=8.6 Hz, 2H), 2.37-2.43 (m, 1H), 2.33 (s, 3H), 1.56-1.79 (m, 8H), 1.26-1.42 (m, 6H), 1.20 (s, 3H), 0.97-1.16 (m, 6H), 0.65-0.79 (m, 2H), 0.61 (s, 3H). LCMS Rt = 3.457 min in 4.0 min chromatography, 10-80 AB, MS ESI calcd. for C₂₇H₃₈FO₂ [M+H]⁺ 413.28, found 413.2 [M+H]⁺.

Example 31. Synthesis of compound 30.

[0288]

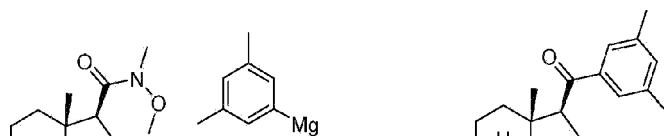


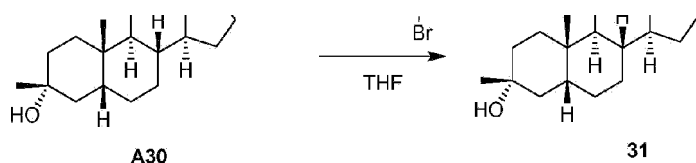
[0289] To a stirred solution of **B10** (100 mg, 275 umol) in 3 mL of THF was added (3,4-dimethylphenyl)magnesium chloride (0.5 M; 2.74 mL, 1.37 mmol) dropwise at 25°C. After stirring at 25°C for 12 hrs, LCMS showed the reaction was complete. The reaction mixture was poured into ice-cold water and extracted with EtOAc (50 mL x 2), washed with brine (30 mL x 2), dried (Na₂SO₄), filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 80-93% B (A= 0.05%HCl-ACN, B=acetonitrile), flow rate: 25 mL/min) for further purification to obtain **30** (28 mg) as a solid.

¹H NMR (CDCl₃, 400MHz): δ = 7.68 (s, 1H), 7.62 (d, *J*=8.0 Hz, 1H), 7.18 (d, *J*=7.6 Hz, 1H), 3.48 (t, *J*=8.6 Hz, 1H), 2.28-2.46 (m, 7H), 1.63-1.78 (m, 6H), 1.25-1.55 (m, 8H), 1.20 (s, 3H), 0.86-1.18 (m, 7H), 0.65-0.77 (m, 2H), 0.61 (s, 3H). LCMS Rt = 3.488 min in 4.0 min chromatography, 10-80 AB, MS ESI calcd. for C₂₈H₄₁O₂ [M +H]⁺ 409.3, found 409.1.

Example 32. Synthesis of compound 31.

[0290]



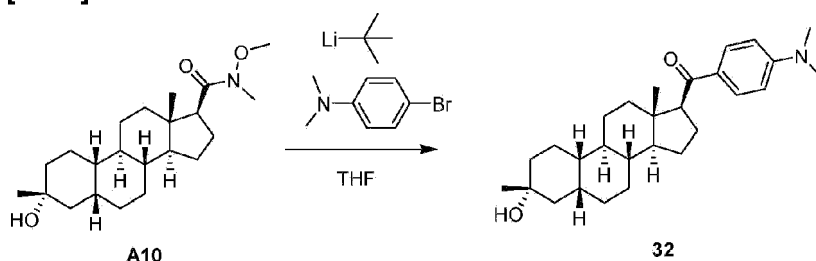


[0291] To a stirred solution of **A30** (100 mg, 264 μ mol) in 3 mL of THF was added (3,5-dimethylphenyl)magnesium bromide (0.5 M; 2.62 mL, 1.31 mmol) dropwise at 25°C. After stirring at 25°C for 12 hrs, LCMS showed the reaction was complete. The reaction mixture was poured into ice-cold water and extracted with EtOAc (50 mL x 2), washed with brine (30 mL x 2), dried (Na_2SO_4), filtered, and evaporated in vacuo to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4 μ m, gradient: 80-100% B (A= 0.05% HCl-ACN, B=acetonitrile), flow rate: 30 mL/min) to obtain **31** (15.3 mg) as a solid.

$^1\text{H NMR}$ (CDCl_3 , 400MHz): δ = 7.46 (s, 2H), 7.16 (s, 1H), 3.46 (t, J =8.8 Hz, 1H), 2.36 (s, 7H), 1.97 (t, J =13.2 Hz, 1H), 1.82-1.89 (m, 1H), 1.74 (br. s., 4H), 1.31-1.51 (m, 9H), 1.20-1.31 (m, 6H), 0.97-1.20 (m, 4H), 0.91 (s, 3H), 0.58 (s, 3H). **LCMS** Rt = 3.478 min in 4.0 min chromatography, 10-80 AB, MS ESI calcd. for $\text{C}_{29}\text{H}_{43}\text{O}_2$ $[\text{M} + \text{H}]^+$ 423.3, found 405.1 $[\text{M} - \text{H}_2\text{O}]^+$.

Example 33. Synthesis of compound 32.

[0292]



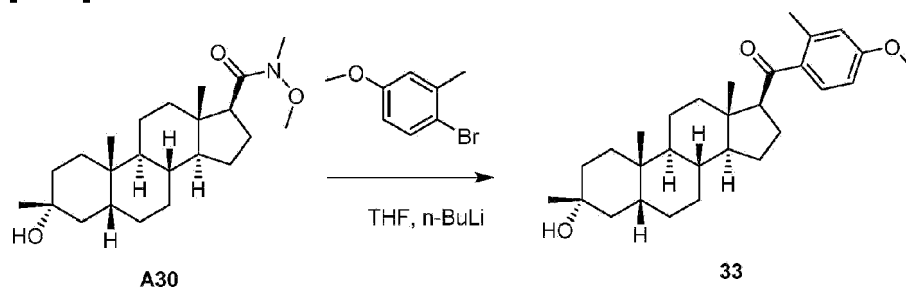
[0293] To a stirred solution of 4-bromo-N,N-dimethylaniline (1.3 M, 1.92 mL, 2.50 mmol) was added tert-butyllithium dropwise at -78°C. After stirring at -78°C for 2 hrs, **A10** (100 mg, 0.264 mmol) was added. The mixture was stirred at -78°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over (Na_2SO_4), filtered, and evaporated in vacuo to give crude product. The crude product was purified by HPLC separation (column: Boston Green ODS 150*30 5 μ , gradient: 85-100% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to afford **32** (11.9 mg) as a solid.

$^1\text{H NMR}$ (CDCl_3 , 400MHz): δ = 7.87 (d, J =9.0 Hz, 2H), 6.65 (d, J =9.0 Hz, 2H), 3.46 (t, J =8.6 Hz, 1H), 3.06 (s, 6H), 2.38-2.51 (m, 1H), 1.78-1.90 (m, 3H), 1.69-1.77 (m, 2H), 1.58-1.67 (m, 2H), 1.29-1.57 (m, 12H), 1.27 (s, 4H), 1.05-1.18 (m, 2H), 0.89-1.01 (m, 1H), 0.62 (s, 3H). **LCMS** Rt

= 2.443 min in 4.0 min chromatography, 30-90 AB,MS ESI calcd. for $C_{28}H_{42}NO_2$ $[M + H]^+$ 424.31, found 424.1.

Example 34. Synthesis of compound 33.

[0294]

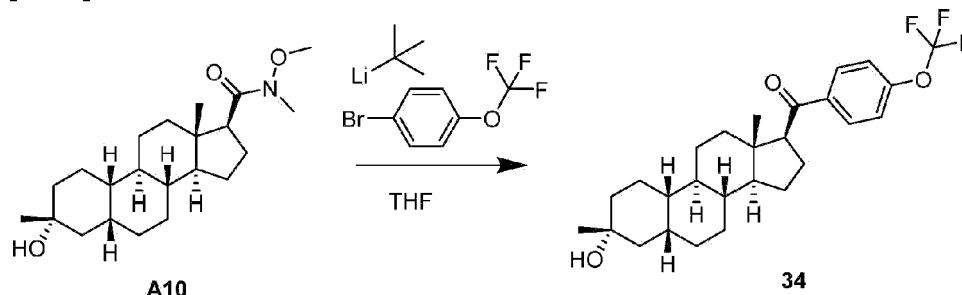


[0295] To a stirred solution of 1-bromo-4-methoxy-2-methylbenzene (2.5 M; 0.524 mL, 1.31 mmol) was added tert-butyllithium dropwise at -78°C . After stirring at -78°C for 2 hrs, **A30** (100 mg, 0.264 mmol) was added. The mixture was stirred at -78°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over (Na_2SO_4), filtered, and evaporated under vacuo to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 75-100% B (A= 0.05% HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to afford **33** (13.5 mg) as a solid.

$^1\text{H NMR}$ (CDCl_3 , 400MHz): δ = 7.53 (d, $J=8.0$ Hz, 1H), 6.69-6.75 (m, 2H), 3.83 (s, 3H), 3.49 (d, $J=5.6$ Hz, 1H), 3.33 (t, $J=8.8$ Hz, 1H), 2.46 (s, 3H), 2.34-2.40 (m, 1H), 1.93-1.98 (m, 1H), 1.63-1.76 (m, 4H), 1.32-1.50 (m, 8H), 1.22-1.30 (m, 7H), 0.96-1.17 (m, 5H), 0.87-0.92 (m, 3H), 0.60 (s, 3H). LCMS Rt = 3.478 min in 3.0 min chromatography, 30-90 CD. MS ESI calcd. for $C_{29}H_{43}O_3$ $[M + H]^+$ 439.31, found 439.3.

Example 35. Synthesis of compound 34.

[0296]

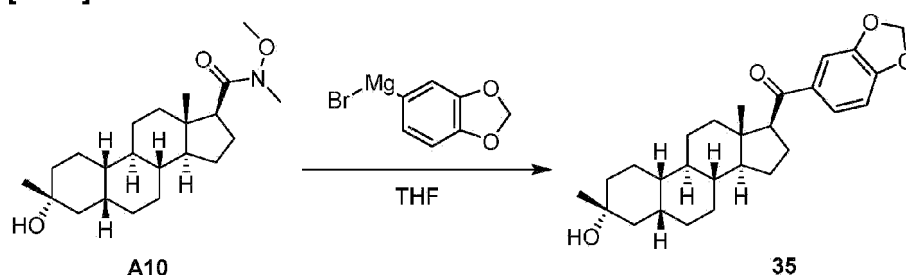


[0297] To a stirred solution of 1-bromo-4-(trifluoromethoxy)benzene (330 mg, 1.37 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 2.0 mL, 2.61 mmol) dropwise at -78°C. After stirring at -78°C for 2 hrs, **A10** (100 mg, 0.275 mmol) was added. The mixture was stirred at -78°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with NH₄Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over (Na₂SO₄), filtered, and evaporated in vacuo to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 80-100% B (A= 0.05% HCl-ACN, B=acetonitrile), flow rate: 30 mL/min) to obtain **34** (57 mg) as a solid.

¹H NMR (CDCl₃, 400MHz): δ = 7.93 (d, J=8.6 Hz, 2H), 7.26-7.29 (m, 2H), 3.45 (t, J=8.8 Hz, 1H), 2.37-2.46 (m, 1H), 1.73-1.86 (m, 5H), 1.58-1.65 (m, 2H), 1.41-1.50 (m, 3H), 1.37 (d, J=12.6 Hz, 6H), 1.24-1.33 (m, 7H), 1.06-1.17 (m, 2H), 0.87-0.97 (m, 1H), 0.60 (s, 3H). LCMS Rt = 3.467 min in 4.0 min chromatography, 10-80 AB, MS ESI calcd. for C₂₇H₃₆F₃O₃ [M +H]⁺ 465.26, found 447.2 [M-H₂O]⁺.

Example 36. Synthesis of compound 35.

[0298]

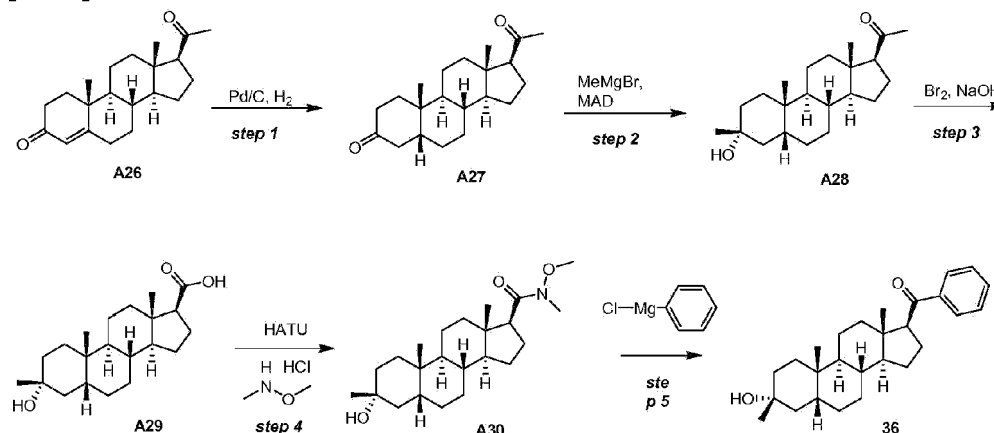


[0299] To a solution of **A10** (100 mg, 0.275 mmol) in THF (3 mL) was added benzo[d][1,3]dioxol-5-ylmagnesium bromide (5.5 mL, 95%). The mixture was stirred at 20 °C for 3.5h. When TLC showed starting material was consumed and new spot was produced, to the mixture was added *sat. aq.* NH₄Cl (5 mL). The organic phase was extracted with DCM (5 mL * 2), washed with *sat. aq.* NaCl (8 mL x 2), concentrated in vacuum. The residue was purified by preparative HPLC to give **35** (30 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.49 (dd, J=1.6, 8.2 Hz, 1H), 7.40 (d, J=1.5 Hz, 1H), 6.83 (d, J=8.0 Hz, 1H), 6.03 (s, 2H), 3.40 (t, J=8.5 Hz, 1H), 2.47 - 2.35 (m, 1H), 1.82 - 1.73 (m, 4H), 1.66 - 1.58 (m, 2H), 1.50 - 1.25 (m, 17H), 1.19 - 0.87 (m, 3H), 0.60 (s, 3H). LCMS Rt = 1.391 min in 2 min chromatography, 10-80AB, MS ESI calcd. for C₂₇H₃₇O₄ [M+H]⁺ 425.26, found 407 [M-H₂O]⁺.

Example 37. Synthesis of compound 36.

[0300]



Step 1. The mixture of **A26** (40 g, 127 mmol) and Pd/C (4 g) in ethyl acetate (200 mL) and THF (200 mL) was stirred at 25 °C under H₂ (103421 Pa; 15 psi) for 4 hours. TLC (PE:EA=5:1) showed the starting material was consumed completely. The reaction mixture was filtered, and the filtered cake was washed with ethyl acetate (40 mL x 5). The combined organic phase was concentrated under vacuum to give **A27** (41 g, crude) as a solid

¹H NMR (400 MHz, CDCl₃) δ = 2.69 (t, J=14.1 Hz, 1H), 2.61 - 2.48 (m, 1H), 2.43 - 2.25 (m, 1H), 2.24 - 1.96 (m, 8H), 1.95 - 1.78 (m, 2H), 1.75 - 1.07 (m, 15H), 1.03 (s, 3H), 0.64 (s, 3H)

Step 2. To a solution of 2,6-di-tert-butyl-4-methylphenol (170 g, 774 mmol) in toluene (150 mL) was added trimethylaluminum (193 mL, 387 mmol, 2.0 M in toluene) drop-wise blew 25°C under N₂ atmosphere. The resulting mixture was stirred at 25°C for 1 hour. **A27** (41 g, 129 mmol) in toluene (50 mL) was added at -78 °C. The mixture was stirred at -78 °C for 1 hour. Methylmagnesium bromide (129 mL, 387 mmol, 3.0 M in diethyl ether) was added at -78 °C. The reaction mixture was stirred at -78 °C for 4 hours. TLC (PE: EA =2:1) showed the starting material was consumed completely. The mixture was quenched by saturated aqueous NH₄Cl (20 mL), extracted with ethyl acetate (150mL x 2). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na₂SO₄. The ethyl acetate solvent was evaporated to afford crude solid, which was purified by chromatography on silica gel (PE/EtOAc=7/1) to afford desired product **A28** (36 g) as light solid.

¹H NMR (400 MHz, CDCl₃) δ = 2.58 - 2.46 (m, 1H), 2.22 - 2.09 (m, 4H), 2.06 - 1.79 (m, 3H), 1.78 - 0.99 (m, 25H), 0.94 (s, 3H), 0.59 (s, 3H).

Step 3. Liquid bromine (5.76 g, 36.0 mmol) was added slowly to a vigorously stirred sodium hydroxide aqueous (48.0 mL, 3 M, 144 mmol) at 0 °C. When all the bromine was dissolved, the mixture was diluted with cold dioxane (10 mL) and was added slowly to a stirred solution of 1 **A28** (4 g, 12.0 mmol) in dioxane (15 mL) and water (10 mL). The homogeneous yellow solution became colorless slowly and a white precipitate was formed. The reaction mixture was stirred at 25 °C for 16 hours. The remaining oxidizing reagent was quenched by Na₂S₂O₃ aqueous (30 mL) and the mixture was then heated at 80 °C until the solid material was

dissolved. Acidification of the solution with hydrochloride acid (3 N) furnished a white precipitate. The solid was filtered and washed with water (100 mL x 3) to give a white solid, which was dried under vacuum to afford **A29** (4.01 g, 100%) as a solid.

¹H NMR (400 MHz, CDCl₃) δ = 11.90 (br. s., 1H), 4.24 (s, 1H), 2.28 (t, J=9.0 Hz, 1H), 2.01 - 1.54 (m, 8H), 1.50 - 1.28 (m, 6H), 1.26 - 0.92 (m, 13H), 0.91 (s, 3H), 0.61 (s, 3H)

Step 4. To a suspension of **A29** (4.01 g, 11.9 mmol) and N,O-dimethylhydroxylamine hydrochloride (4.64 g, 47.6 mmol) in DMF (40 mL) was added HATU (9.04 g, 23.8 mmol) at 25 °C. DIPEA (15.3 g, 119 mmol) was added to the resulting mixture. The reaction mixture was stirred at 25 °C for 2 hours. TLC (PE:EA=2:1) showed the starting material was consumed completely. H₂O (500 mL) was added to the reaction mixture at 25 °C. A precipitate in the mixture was filtrated to give a light solid, which was washed with water (40 mL x 3), dried under vacuum to afford **A30** (4.31 g, 95.9 %) as a solid.

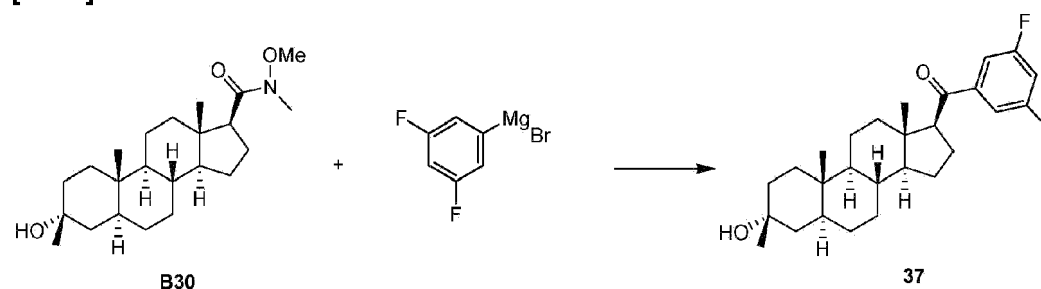
¹H NMR (400 MHz, CDCl₃) δ = 11.90 (br. s., 1H), 4.24 (s, 1H), 2.28 (t, J=9.0 Hz, 1H), 2.01 - 1.54 (m, 8H), 1.50 - 1.28 (m, 6H), 1.26 - 0.92 (m, 13H), 0.91 (s, 3H), 0.61 (s, 3H)

Step 5. To a solution of **B30** (0.1 g, 0.264 mmol) in THF (2 mL) was added phenylmagnesium chloride (5.26 mL, 2.63 mmol, 0.5M in THF) under N₂. The reaction mixture was stirred at 15°C for 16 hours. LCMS indicated the reaction was finished and desired MS peak was found. To the reaction mixture was added saturated NH₄Cl solution (5 mL) and then extracted with EtOAc (2 mL X 3). The combined organic phase was concentrated and purified by prep-HPLC to give **36** (20.6 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.88-7.86 (m, 2H), 7.54-7.51 (m, 1H), 7.45-7.41 (m, 2H), 3.50-3.46 (m, 1H), 2.45-2.38 (m, 1H), 1.80-0.72 (m, 25H), 0.70 (s, 3H), 0.59 (s, 3H). LCMS Rt = 1.466 min in 2 min chromatography, 10-80AB, MS ESI calcd. for C₂₇H₃₉O₂ [M+H]⁺ 395.29, found 377 [M-H₂O]⁺.

Example 38. Synthesis of compound 37.

[0301]



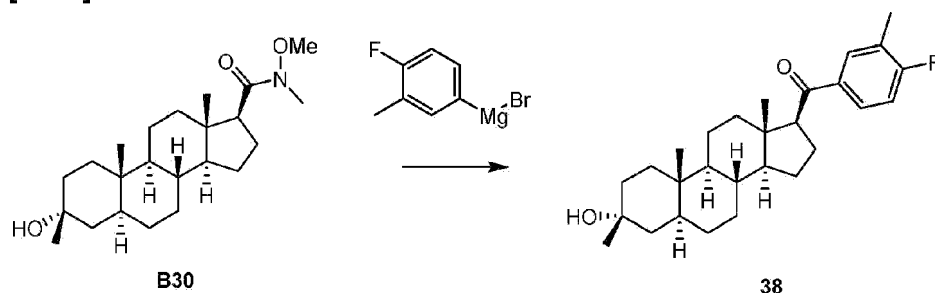
[0302] To a solution of **B30** (0.1 g, 0.264 mmol) in THF (2 mL) was added (3,5-

difluorophenyl)magnesium bromide (5.26 mL, 2.63 mmol, 0.5M in THF) under N₂. The reaction mixture was stirred at 15°C for 16 hours. LCMS indicated the reaction was finished and desired MS peak was found. To the reaction mixture was added saturated NH₄Cl solution (5 mL) and then extracted with EtOAc (2 mL X 3). The combined organic phase was concentrated and purified by prep-HPLC to give **37** (14.2 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, J=6.0 Hz, 2H), 7.04 - 6.89 (m, 1H), 3.40 - 3.28 (m, 1H), 2.47 - 2.30 (m, 1H), 1.87 - 1.65 (m, 3H), 1.19 (s, 19H), 0.72 (s, 4H), 0.59 (s, 3H). LCMS Rt = 1.540 min in 2 min chromatography, 10-80AB, MS ESI calcd. for C₂₇H₃₇F₂O₂ [M+H]⁺ 431.27, found 413 [M-H₂O]⁺.

Example 39. Synthesis of compound 38.

[0303]

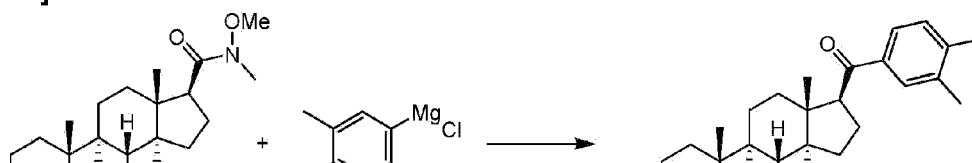


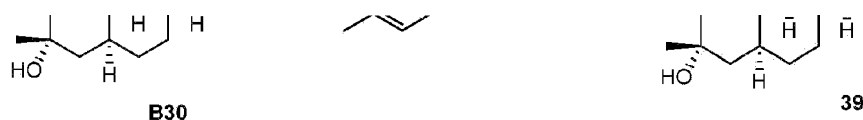
[0304] To a solution of **B30** (0.1 g, 0.264 mmol) in THF (2 mL) was added (4-fluoro-3-methylphenyl)magnesium bromide (5.26 mL, 2.63 mmol, 0.5M in THF) under N₂. The reaction mixture was stirred at 15°C for 1.5 hours. LCMS indicated the reaction was finished and desired MS peak was found. To the reaction mixture was added saturated NH₄Cl solution (5 mL) and then extracted with EtOAc (2 mL X 3). The combined organic phase was concentrated and purified by prep-HPLC to give **38** (38.6 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.76-7.68 (m, 2H), 7.05-7.00 (m, 2H), 3.44-3.40 (m, 1H), 2.40 - 2.31 (m, 4H), 1.80-1.65 (m, 3H), 1.60-0.72 (m, 22H), 0.72 (s, 3H), 0.58 (s, 3H). LCMS Rt = 1.534 min in 2 min chromatography, 10-80AB, MS ESI calcd. for C₂₈H₄₀FO₂ [M+H]⁺ 427, found 427.

Example 40. Synthesis of compound 39.

[0305]



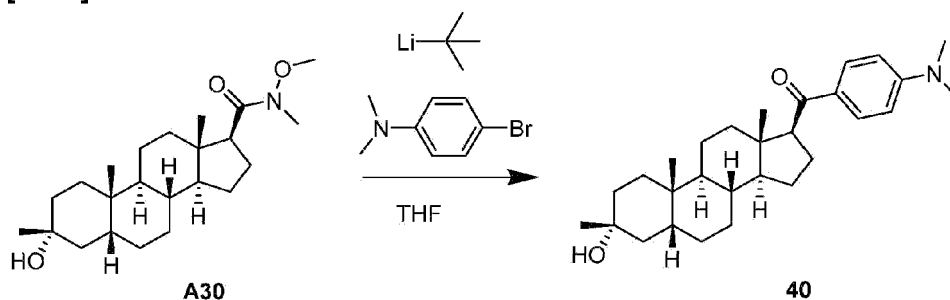


[0306] To a solution of **B30** (0.1 g, 0.264 mmol) in THF (2 mL) was added (3,4-dimethylphenyl)magnesium chloride (5.26 mL, 2.63 mmol, 0.5M in THF) under N₂. The reaction mixture was stirred at 15°C for 4 hours. LCMS indicated the reaction was finished and desired MS peak was found. To the reaction mixture was added saturated NH₄Cl solution (5 mL) and then extracted with EtOAc (2 mL x 3). The combined organic phase was concentrated and purified by prep-HPLC to give **39** (27.8 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.69 - 7.65 (m, 1H), 7.64 - 7.58 (m, 1H), 7.22 - 7.15 (m, 1H), 3.50 - 3.41 (m, 1H), 2.46 - 2.35 (m, 1H), 2.31 (s, 6H), 1.81 - 1.66 (m, 3H), 1.61 - 1.05 (m, 20H), 1.04 - 0.89 (m, 1H), 0.82 - 0.73 (m, 1H), 0.71 (s, 3H), 0.59 (s, 3H). LCMS Rt = 1.536 min in 2 min chromatography, 10-80AB, MS ESI calcd. for C₂₉H₄₃O₂ [M+H]⁺ 423, found 423.

Example 41. Synthesis of compound 40.

[0307]



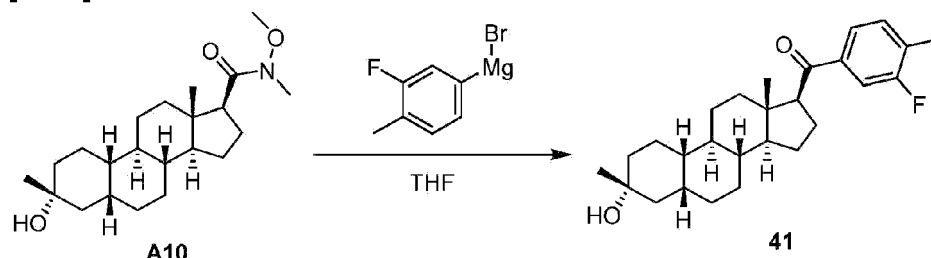
[0308] To a stirred solution of 4-bromo-N,N-dimethylaniline (262 mg, 1.31 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 1.92 mL, 2.50 mmol) dropwise at -78°C. After stirring at -78°C for 2 hrs, **A30** (100 mg, 0.264 mmol) was added. The mixture was stirred at -78°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with NH₄Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over (Na₂SO₄), filtered, and evaporated in vacuo to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 75-100% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **40** (11.2 mg) as a solid.

¹H NMR (CDCl₃, 400MHz): δ = 7.86 (d, J=9.0 Hz, 2H), 6.64 (d, J=9.0 Hz, 2H), 3.44 (t, J=8.6 Hz, 1H), 3.05 (s, 6H), 2.39-2.45 (m, 1H), 1.99 (d, J=12.0 Hz, 1H), 1.84 (d, J=13.6 Hz, 2H), 1.63-1.77 (m, 4H), 1.35-1.51 (m, 9H), 1.20-1.29 (m, 6H), 1.10-1.18 (m, 2H), 1.04 (dd, J=14.6 Hz, 1H), 0.91 (s, 3H), 0.59 (s, 3H). LCMS Rt = 2.511 min in 4.0 min chromatography, 30-30 AB,

MS ESI calcd. for $C_{29}H_{44}NO_2$ $[M + H]^+$ 438.33, found 438.1.

Example 42. Synthesis of compound 41.

[0309]

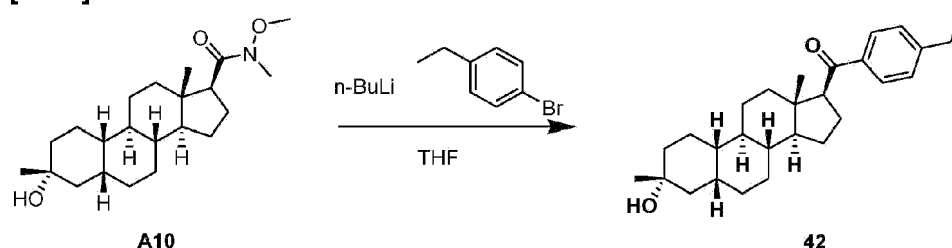


[0310] To a solution of **A10** (100 mg, 0.275 mmol) in THF (3 mL) was added (3-fluoro-4-methylphenyl)magnesium bromide (5.5 mL, 95%). The mixture was stirred at 20 °C for 3.5h. When TLC showed starting material was consumed and new spot was produced, to the mixture was added *sat. aq.* NH_4Cl (5 mL). The organic phase was extracted with DCM (5 mL x 2), washed with *sat. aq.* NaCl (8 mL x 2), concentrated in vacuum. The residue was purified by preparative. HPLC twice to give **41** (58 mg) as a solid.

1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.49 (m, 2H), 7.25-7.20 (m, 1H), 3.41 (t, J = 8.8 Hz, 1H), 2.47-2.36 (m, 1H), 2.32 (d, J = 1.5 Hz, 3H), 1.82-1.75 (m, 4H), 1.69-1.57 (m, 2H), 1.50-1.25 (m, 17H), 1.18-1.04 (m, 2H), 1.00-0.84 (m, 1H), 0.60 (s, 3H). LCMS Rt = 1.476 min in 2 min chromatography, 10-80AB, MS ESI calcd. for $C_{27}H_{37}F_2O$ $[M + H]^+$ 413.28, found 395 $[M - H_2O]^+$.

Example 43. Synthesis of compound 42.

[0311]



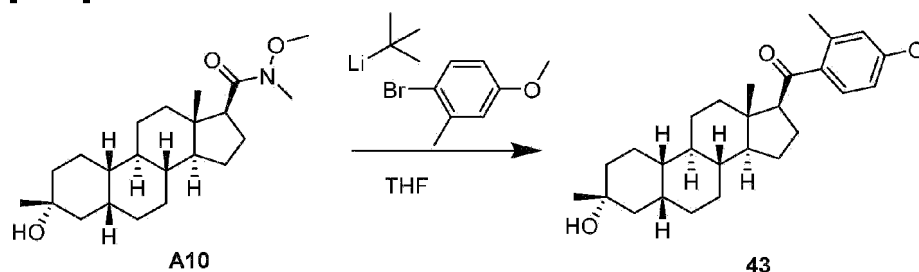
[0312] To a solution of 1-bromo-4-ethylbenzene (305 mg, 1.65 mmol) in THF (3 mL) was added butyllithium (0.66 mL, 0.825 mmol) dropwise at -68 °C. The mixture was stirred at -68 °C for 2h. **A10** (120 mg, 0.33 mmol) in 1 mL THF was added dropwise at -68 °C. The reaction was stirred at -68 °C for 2 hours. LCMS showed the reaction was complete. The reaction was quenched with NH_4Cl (20 mL), extracted with EtOAc (20 mL x 2). The combined organic layers

were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford crude product. The crude product was purified by prep-HPLC to give **42** (46.4 mg, 0.113 mmol) as a solid.

^1H NMR (400 MHz, CDCl_3) δ =7.82 (d, J =8.0 Hz, 2H), 7.25 (s, 1H), 3.49 (t, J =8.8 Hz, 1H), 2.70 (q, J =7.7 Hz, 2H), 2.48 - 2.38 (m, 1H), 1.87 - 1.69 (m, 5H), 1.69 - 1.55 (m, 2H), 1.54 - 1.41 (m, 4H), 1.41 - 1.34 (m, 5H), 1.34 - 1.21 (m, 11H), 1.20 - 1.01 (m, 2H), 1.00 - 0.84 (m, 1H), 0.61 (s, 3H). LCMS t_R = 1.299 min in 2 min chromatography, 30-90AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{40}\text{O}_2$ $[\text{M}]^+$ 408, found 408.

Example 44. Synthesis of compound 43.

[0313]

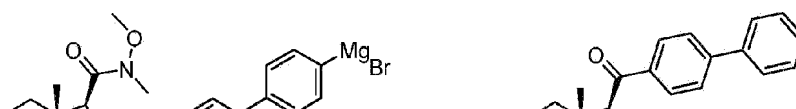


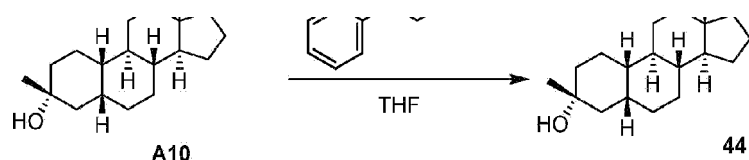
[0314] To a stirred solution of 1-bromo-4-methoxy-2-methylbenzene (275 mg, 1.37 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M, 2.00 mL, 2.61 mmol) dropwise at -78°C . After stirring at -78°C for 2 hrs, **A10** (100 mg, 0.275 mmol) was added. The mixture was stirred at -78°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over (Na_2SO_4), filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 70-100% B (A= 0.05% HCl -ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **42** (20 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz): δ = 7.54 (d, J =8.6 Hz, 1H), 6.68-6.77 (m, 2H), 3.83 (s, 3H), 3.34 (t, J =8.8 Hz, 1H), 2.47 (s, 3H), 2.34-2.42 (m, 1H), 1.69-1.85 (m, 5H), 1.57-1.68 (m, 2H), 1.22-1.50 (m, 14H), 0.97-1.22 (m, 4H), 0.86-0.93 (m, 1H), 0.62 (s, 3H). LCMS R_t = 2.600 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{41}\text{O}_3$ $[\text{M} + \text{H}]^+$ 425.3, found 425.2.

Example 45. Synthesis of compound 44.

[0315]



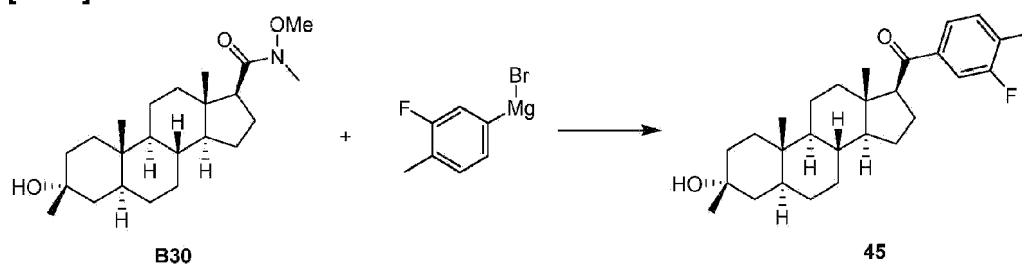


[0316] To a solution of **A10** (150 mg, 0.412 mmol) in THF (3 mL) was added [1,1'-biphenyl]-4-ylmagnesium bromide (8.22 mL, 0.5 M in THF). The mixture was stirred at 20 °C for 3.5h. When TLC showed starting material was consumed and new spot was produced, to the mixture was added *sat. aq.* NH₄Cl (5 mL). The organic phase was extracted with DCM (5 mL * 2), washed with *sat. aq.* NaCl (8 mL * 2), concentrated in vacuum. The residue was purified by *prep.* HPLC to give **44** (113 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.69-7.61 (m, 4H), 7.50-7.44 (m, 2H), 7.42-7.36 (m, 1H), 3.53 (t, *J* = 8.7 Hz, 1H), 2.52-2.37 (m, 1H), 1.79 (d, *J* = 10.3 Hz, 5H), 1.68-1.61 (m, 1H), 1.51-0.88 (m, 20H), 0.63 (s, 3H). **LCMS** Rt = 1.081 min in 1.5 min chromatography, 5-95AB, MS ESI calcd. for C₃₂H₄₁O₂ [M+H]⁺ 457.3, found 439[M-H₂O]⁺..

Example 46. Synthesis of compound 45.

[0317]

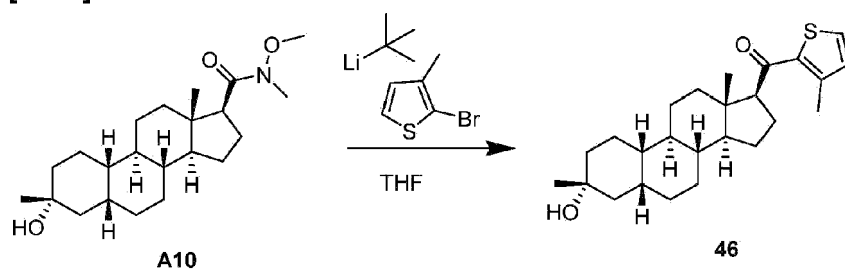


[0318] To a solution of **B30** (0.1 g, 0.264 mmol) in THF (2 mL) was added (3-fluoro-4-methylphenyl)magnesium bromide (5.26 mL, 2.63 mmol, 0.5M in THF) under N₂. The reaction mixture was stirred at 15°C for 16 hours. LCMS indicated the reaction was finished and desired MS peak was found. To the reaction mixture was added saturated NH₄Cl solution (5 mL) and then extracted with EtOAc (2 mL x 3). The combined organic phase was concentrated and purified by *prep*-HPLC to give **45** (22.7 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.64 - 7.47 (m, 2H), 7.25 - 7.17 (m, 1H), 3.47 - 3.36 (m, 1H), 3.10 - 2.91 (m, 2H), 2.32 (s, 4H), 1.87 - 1.06 (m, 21H), 1.04 - 0.90 (m, 1H), 0.71 (s, 4H), 0.58 (s, 3H). **LCMS** Rt = 1.541 min in 2 min chromatography, 10-80AB, MS ESI calcd. for C₂₈H₄₀FO₂ [M+H]⁺ 427, found 409 [M-H₂O]⁺.

Example 47. Synthesis of compound 46.

[0319]

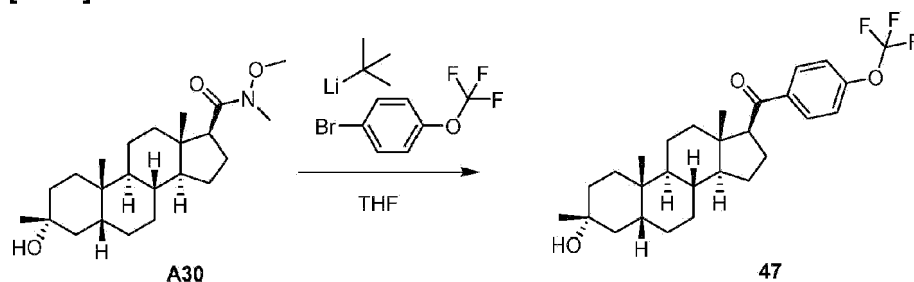


[0320] To a stirred solution of 2-bromo-3-methylthiophene (242 mg, 1.37 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 2.00 mL, 2.61 mmol) dropwise at -78°C . After stirring at -78°C for 2 hrs, **A10** (100 mg, 0.275 mmol) was added. The mixture was stirred at -78°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over (Na_2SO_4), filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 80-100% B (A= 0.05% HCl -ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **46** (10 mg) as a solid.

$^1\text{H NMR}$ (CDCl_3 , 400MHz): δ = 7.37 (d, J =5.0 Hz, 1H), 6.97 (d, J =5.0 Hz, 1H), 3.16 (t, J =8.8 Hz, 1H), 2.57 (s, 3H), 2.31-2.42 (m, 1H), 1.72-1.87 (m, 5H), 1.65 (d, J =13.6 Hz, 2H), 1.32-1.56 (m, 12H), 1.28 (s, 4H), 1.08-1.21 (m, 2H), 0.93-1.06 (m, 1H), 0.71 (s, 3H). **LCMS** R_t = 2.591 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{25}\text{H}_{37}\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 401.24, found 401.1.

Example 48. Synthesis of compound 47.

[0321]



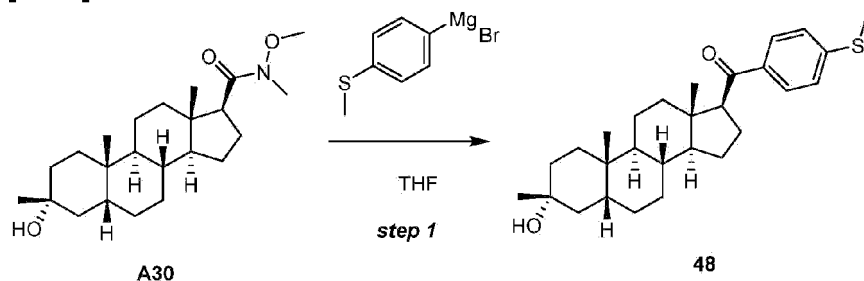
[0322] To a stirred solution of 1-bromo-4-(trifluoromethoxy)benzene (315 mg, 1.31 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 1.92 mL, 2.5 mmol) dropwise at -78°C . After stirring at -78°C for 2 hrs, **A30** (100 mg, 0.264 mmol) was added. The mixture was stirred at -78°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was

quenched with NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over (Na_2SO_4), filtered, and evaporated in vacuo to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 80-100% B (A= 0.05% HCl -ACN, B=acetonitrile), flow rate: 30 mL/min) for further purification to obtain **47** (19.3 mg) as a solid.

$^1\text{H NMR}$ (CDCl_3 , 400MHz): δ = 7.92 (d, J =8.0 Hz, 1H), 7.25 (d, J =7.0 Hz, 2H), 3.43 (br s, 1H), 2.31-2.47 (m, 1H), 1.62-2.01 (m, 6H), 1.32-1.53 (m, 11H), 1.19-1.30 (m, 6H), 0.97-1.17 (m, 3H), 0.90 (br. s., 3H), 0.57 (br. s., 3H). **LCMS** R_t = 2.907 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{38}\text{F}_3\text{O}_3$ $[\text{M} + \text{H}]^+$ 479.3, found 461.2 $[\text{M} - \text{H}_2\text{O}]^+$..

Example 49. Synthesis of compound 48.

[0323]

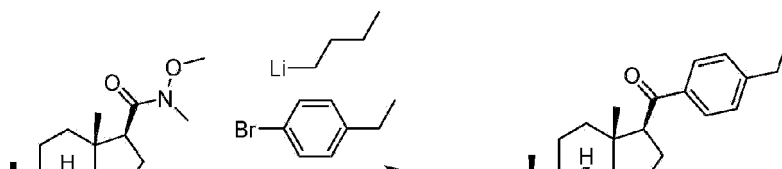


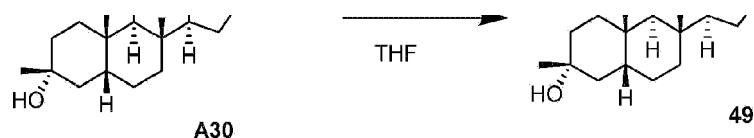
[0324] To a solution of **A30** (100 mg, 264 μmol) in anhydrous THF (2 mL) was added (4-(methylthio)phenyl)magnesium bromide (5.26 mL, 0.5 M, 2.63 mmol) at 25 $^\circ\text{C}$. The reaction mixture was stirred at 25 $^\circ\text{C}$ for 2 hours. LCMS showed the starting material was consumed completely. The reaction was quenched with saturated NH_4Cl aqueous (1 mL), concentrated under vacuum to give a residue, which was purified by Prep-HPLC (0.05% HCl -ACN) to afford **48** (65.4 mg) as a solid.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.81 (d, J =8.0 Hz, 2H), 7.24 (s, 1H), 3.44 (t, J =8.8 Hz, 1H), 2.52 (s, 3H), 2.48 - 2.37 (m, 1H), 2.04 - 1.92 (m, 1H), 1.91 - 1.81 (m, 1H), 1.79 - 1.64 (m, 3H), 1.54 - 1.19 (m, 17H), 1.18 - 0.97 (m, 3H), 0.91 (s, 3H), 0.58 (s, 3H). **LCMS** R_t = 1.441 min in 2 min chromatography, 10-80AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{41}\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$ 441.3, found 441.3 $[\text{M} + \text{H}]^+$.

Example 50. Synthesis of compound 49.

[0325]



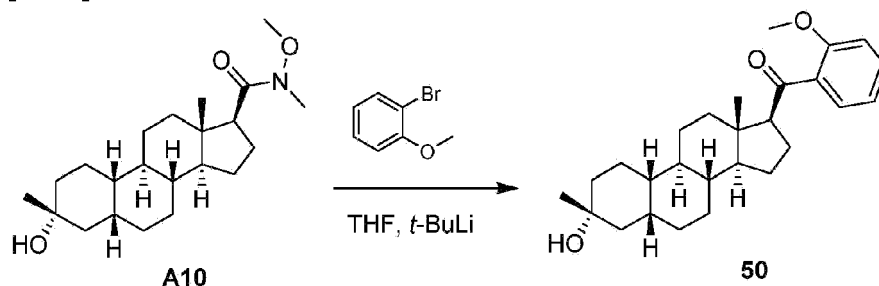


[0326] A solution of 1-bromo-4-ethylbenzene (366 mg, 1.98 mmol) in THF (3 mL) was added butyllithium (0.792 mL, 1.98 mmol) dropwise at -78°C . The mixture was stirred at -78°C for 2 h. **A30** in 1 mL THF was added dropwise at -78°C . The reaction was stirred at -78°C for 2 hours. LCMS showed the reaction was complete. Then, the reaction was quenched with NH_4Cl (20 mL). Extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford crude product. The crude product was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 85-100% B (A=0.05% HCl -ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **49** (69.9 mg) as a solid.

$^1\text{H NMR}$ (CDCl_3 , 400MHz): δ = 7.82 (d, $J=8.0$ Hz, 2H), 7.25 (br s, 1H), 3.48 (t, $J=8.8$ Hz, 1H), 2.70 (q, $J=7.6$ Hz, 2H), 2.37-2.48 (m, 1H), 1.93-2.03 (m, 1H), 1.81-1.91 (m, 1H), 1.64-1.79 (m, 3H), 1.31-1.55 (m, 11H), 1.18-1.30 (m, 8H), 0.92-1.18 (m, 4H), 0.91 (s, 3H), 0.59 (s, 3H). LCMS Rt = 3.492 min in 4.0 min chromatography, 10-80 AB, MS ESI calcd. for $\text{C}_{29}\text{H}_{43}\text{O}_2$ $[\text{M} + \text{H}]^+$ 423.32, found 405.1 $[\text{M} - \text{H}_2\text{O}]^+$.

Example 51. Synthesis of compound 50.

[0327]



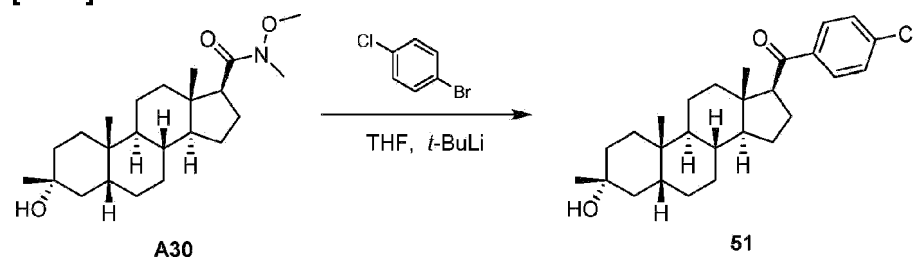
[0328] A solution of 1-bromo-2-methoxybenzene (514 mg, 2.75 mmol) in THF (3 mL) was added *t*-butyllithium (3.80 mL, 4.94 mmol) dropwise at -78°C . The mixture was stirred at -78°C for 2 h. **A10** (100 mg, 2.75 mmol) in THF (1 mL) was added dropwise at -78°C . The reaction was stirred at 15°C for 2 hours. TLC showed the reaction was complete. The reaction was quenched with Sat. NH_4Cl (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford crude product, which was purified by prep-HPLC to afford **50** (68 mg) as a solid.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.30 - 7.44 (m, 2 H) 6.88 - 7.00 (m, 2 H) 3.85 (s, 3 H) 3.54 (t,

$J=8.91$ Hz, 1 H) 2.27 - 2.42 (m, 1 H) 1.53 - 1.89 (m, 8 H) 0.96 - 1.52 (m, 20 H) 0.79 - 0.92 (m, 1 H) 0.61 (s, 3 H). **LCMS** $R_t = 1.593$ min in 2.0 min chromatography, 50-100 AB, MS ESI calcd. for $C_{27}H_{39}O_3$ $[M+H]^+$ 411, found 411

Example 52. Synthesis of compound 51.

[0329]

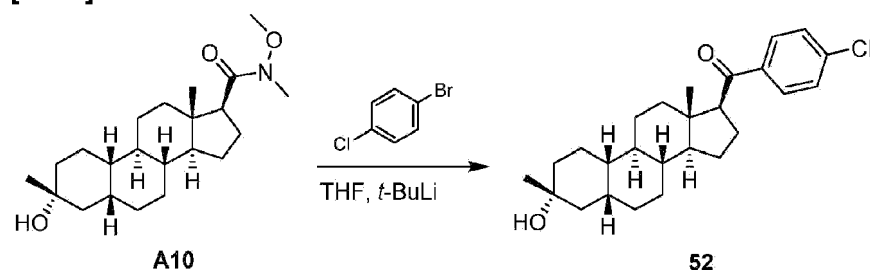


[0330] A solution of 1-bromo-4-chlorobenzene (503 mg, 2.63 mmol) in THF (3 mL) was added t-butyllithium (3.65 mL, 4.75 mmol) dropwise at -78°C . The mixture was stirred at -78°C for 2 h. **A30** (100 mg, 2.75 mmol) in THF (1 mL) was added dropwise at 15°C . The reaction was stirred at 15°C for 2 hours. TLC showed the reaction was complete. The reaction was quenched with Sat. NH_4Cl (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and evaporated to afford crude product, which was purified by prep-HPLC to afford **51** (38 mg) as a solid.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.82 (d, $J=8.53$ Hz, 2 H) 7.41 (d, $J=8.53$ Hz, 2 H) 3.43 (t, $J=8.78$ Hz, 1 H) 2.33 - 2.49 (m, 1 H) 1.91 - 2.05 (m, 1 H) 1.63 - 1.91 (m, 4 H) 1.28 - 1.60 (m, 15 H) 0.98 - 1.28 (m, 10 H) 0.91 (s, 3 H) 0.58 (s, 3 H). **LCMS** $R_t = 0.976$ min in 2.0 min chromatography, 50-100 AB, MS ESI calcd. for $C_{27}H_{38}\text{ClO}_2$ $[M]^+$ 430, found 429 $[M]^+$.

Example 53. Synthesis of compound 52.

[0331]



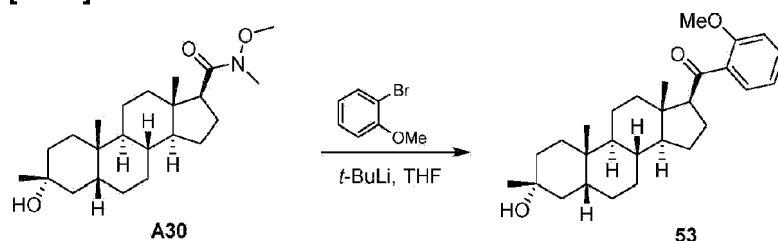
[0332] A solution of 1-bromo-4-chlorobenzene (526 mg, 2.75 mmol) in THF (3 mL) was added t-butyllithium (3.80 mL, 4.94 mmol) dropwise at -78°C . The mixture was stirred at -78°C for 2

hrs. **A10** (100 mg, 2.75 mmol) in THF (1 mL) was added dropwise at 15°C. The reaction was stirred at 15°C for 2 hours. TLC showed the reaction was complete. The reaction was quenched with Sat. NH_4Cl (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and evaporated to afford crude product, which was purified by prep-HPLC separation to afford **52** (60 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, J = 8.53 Hz, 2 H) 7.41 (d, J = 8.53 Hz, 2 H) 3.44 (t, J = 8.66 Hz, 1 H) 2.35-2.48 (m, 1 H) 1.71-1.87 (m, 5 H) 1.22-1.70 (m, 21 H) 1.02-1.21 (m, 2 H) 0.85-0.99 (m, 1 H) 0.60 (s, 3 H). LCMS Rt = 0.994 min in 2.0 min chromatography, 50-100 AB, MS ESI calcd. for $\text{C}_{26}\text{H}_{35}\text{ClO}_2$ $[\text{M}+\text{H}]^+$ 416.3, found 415 $[\text{M}]^+$.

Example 54. Synthesis of compound 53.

[0333]

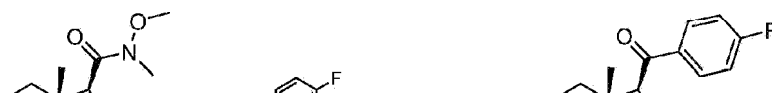


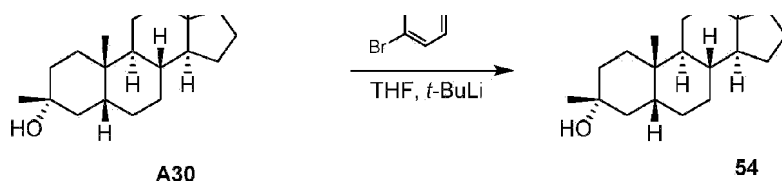
[0334] A solution of 1-bromo-2-methoxybenzene (491 mg, 2.63 mmol) in THF (3 mL) was added t-butyllithium (3.65 mL, 4.75 mmol) dropwise at -78°C. The mixture was stirred at -78°C for 2 hrs. **A30** (100 mg, 2.64mmol) in THF (1 mL) was added dropwise at -78°C. The reaction was stirred at 15°C for 2 hours. TLC showed the reaction was complete. The reaction was quenched with Sat. NH_4Cl (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and evaporated to afford the crude product, which was purified by prep-HPLC separation for further purification to afford **53** (38 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.30 - 7.41 (m, 2 H) 6.89 - 6.99 (m, 2 H) 3.86 (s, 3 H) 3.54 (t, J =9.03 Hz, 1 H) 2.27 - 2.44 (m, 1 H) 1.60 - 2.01 (m, 6 H) 0.93 - 1.57 (m, 22 H) 0.89 (s, 3 H) 0.59 (s, 3 H). LCMS Rt = 1.688 min in 3.0 min chromatography, 50-100 AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{41}\text{O}_3$ $[\text{M}+\text{H}]^+$ 425, found 425.

Example 55. Synthesis of compound 54.

[0335]



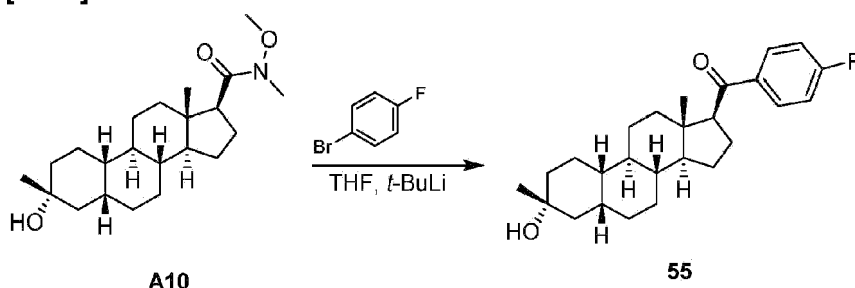


[0336] A solution of 1-bromo-4-fluorobenzene (460 mg, 2.63 mmol) in THF (3 mL) was added *t*-butyllithium (3.65 mL, 4.75 mmol) dropwise at -78°C . The mixture was stirred at -78°C for 2 hrs. **A30** (100 mg, 2.64 mmol) in THF (1 mL) was added dropwise at -78°C . The reaction was stirred at 15°C for 2 hours. TLC showed the reaction was complete. The reaction was quenched with Sat. NH_4Cl (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford crude product, which was purified by prep-HPLC to afford **54** (33 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.91 (dd, $J = 8.78, 5.52$ Hz, 2 H), 7.11 (t, $J = 8.53$ Hz, 2 H), 3.44 (t, $J = 8.78$ Hz, 1 H), 2.33-2.48 (m, 1 H), 1.62 - 2.05 (m, 5 H), 1.56 (s, 4 H), 0.98-1.53 (m, 20 H), 0.86-0.95 (m, 3 H), 0.58 (s, 3 H). LCMS Rt = 0.885 min in 2.0 min chromatography, 50-100 AB, MS ESI calcd. for $\text{C}_{27}\text{H}_{38}\text{FO}_2$ $[\text{M}+\text{H}]^+$ 413.3, found 395 $[\text{M}-\text{H}_2\text{O}]^+$.

Example 56. Synthesis of compound 55.

[0337]



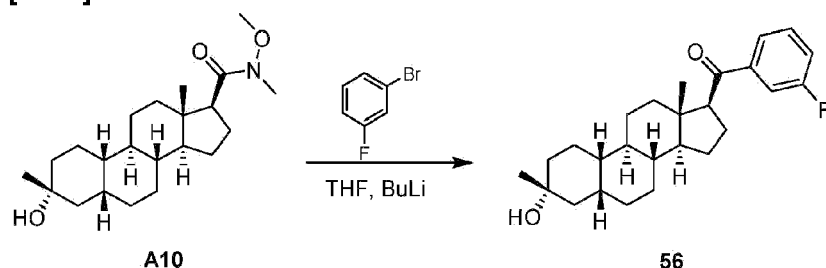
[0338] A solution of 1-bromo-4-fluorobenzene (359 mg, 2.75 mmol) in THF (3 mL) was added *t*-butyllithium (3.8 mL, 4.94 mmol) dropwise at -78°C . The mixture was stirred at -78°C for 2 h. **A10** (100 mg, 2.75 mmol) in THF (1 mL) was added dropwise at -78°C . The reaction was stirred at -78°C for 2 hours. TLC showed the reaction was completed. The reaction was quenched with Sat. NH_4Cl (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and evaporated to afford crude product, which was purified by prep-HPLC separation to afford **55** (101 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.91 (dd, $J = 8.78, 5.52$ Hz, 2 H), 7.11-7.11 (m, 1 H), 7.11-7.11 (m, 1 H), 7.10-7.11 (m, 1 H), 7.11 (t, $J = 8.66$ Hz, 2 H), 3.45 (t, $J = 8.66$ Hz, 1 H), 2.36-2.49 (m,

1 H), 1.70-1.89 (m, 5 H), 1.53-1.69 (m, 8 H), 1.03-1.52 (m, 19 H), 0.84-1.00 (m, 1 H), 0.60 (s, 3 H). **LCMS** Rt = 0.857 min in 2.0 min chromatography, 50-100 AB, MS ESI calcd. for $C_{26}H_{36}FO_2$ $[M+H]^+$ 399.3, found 381 $[M-H_2O]^+$.

Example 57. Synthesis of compound 56.

[0339]

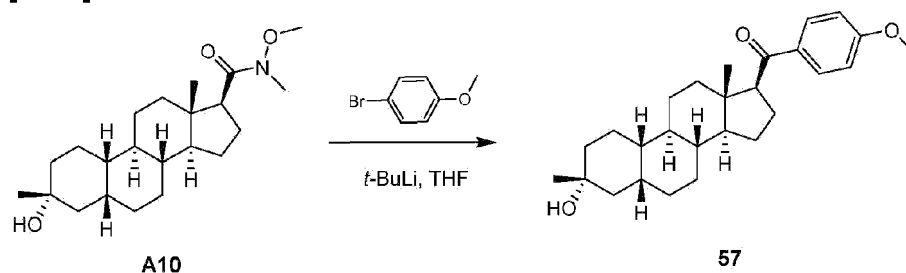


[0340] To a solution of 1-bromo-3-fluorobenzene (239 mg, 1.37 mmol) in THF (5 mL) was added n-butyllithium (1.90 mL, 2.47 mmol) dropwise at -68°C . The mixture was stirred at -68°C for 2 hrs. **A10** (100 mg, 275 μmol) in THF (3 mL) was added dropwise at -68°C . The reaction was stirred at 25°C for 2 hours. LCMS showed the reaction was complete. The reaction was quenched with NH_4Cl (20 mL), extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and evaporated to afford crude product, which was purified by prep-HPLC to give **56** (28.2 mg) as a solid.

^1H NMR (400 MHz, DMSO) δ 7.78 - 7.42 (m, 4H), 4.25 (s, 1H), 3.67 (t, $J = 8.4$ Hz, 1H), 2.28-2.15 (m, 1H), 1.79-1.63 (m, 5H), 1.62-1.48 (m, 2H), 1.47-1.34 (m, 4H), 1.32-1.17 (m, 7H), 1.16-0.96 (m, 8H), 0.84 (d, $J = 12.0$ Hz, 1H), 0.50 (s, 3H). **LCMS** Rt = 1.223 min in 2 min chromatography, 30-90AB, MS ESI calcd. for $C_{26}H_{36}FO_2$ $[M+H]^+$ 381, found 381 $[M-H_2O]^+$.

Example 58. Synthesis of compound 57.

[0341]



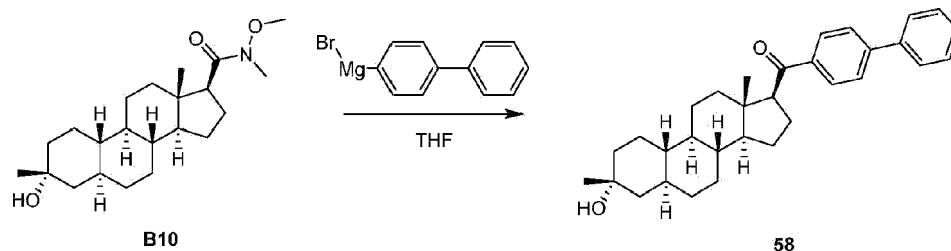
[0342] To a stirred solution of 1-bromo-4-methoxybenzene (256 mg, 1.37 mmol) in 3 mL of

THF was added tert-butyllithium (1.3 M; 2 mL, 2.61 mmol) dropwise at -78°C under N₂. After stirring at -78°C for 2 hrs, **A10** (100 mg, 0.275 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with NH₄Cl (30 mL), extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered and evaporated in vacuum. The crude product was purified by preparative HPLC (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 90-98% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) to obtain **57** (41.0 mg) as a solid.

¹H NMR (CDCl₃, 400MHz): δ 7.90 (d, J=8.6 Hz, 2H), 6.92 (d, J=9.0 Hz, 2H), 3.87 (s, 3H), 3.46 (t, J=8.6 Hz, 1H), 2.36-2.49 (m, 1H), 1.70-1.85 (m, 5H), 1.53-1.69 (m, 3H), 1.25-1.50 (m, 15H), 1.03-1.19 (m, 2H), 0.86-1.00 (m, 1H), 0.61 (s, 3H). LCMS Rt = 2.415 min in 4.0 min chromatography, 30-90 CD, MS ESI calcd. for C₂₇H₃₉O₃ [M + H]⁺ 411, found 411.

Example 59. Synthesis of compound 58.

[0343]

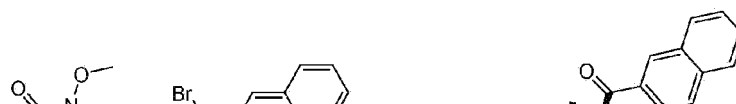


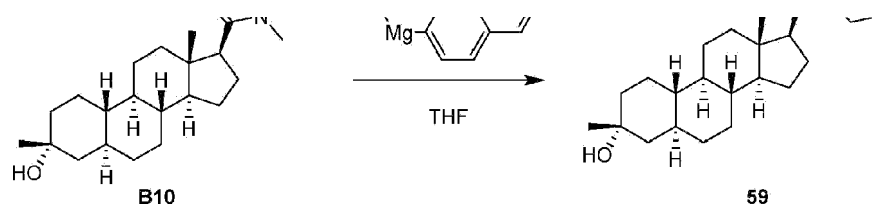
[0344] To a solution of **B10** (100 mg, 0.275 mmol) in THF (3 mL) was added naphthalen-2-ylmagnesium bromide (2.74 mL) at 25 °C for 2 hours. TLC showed the reaction was complete. Aqueous solution of NH₄Cl (5 mL) was added dropwise at 25 °C, and extracted with EtOAc (10 mL x2). The combined organic solution was washed with brine (5 mL), dried over Na₂SO₄. The organic layer was filtered and concentrated under reduced pressure to get the mixture, which was purified by HPLC to give **58** (18.5 mg, 40.5 μmol) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 8.03 - 7.93 (m, 2H), 7.72 - 7.61 (m, 4H), 7.53 - 7.45 (m, 2H), 7.44 - 7.37 (m, 1H), 3.60 - 3.51 (m, 1H), 2.54 - 2.42 (m, 1H), 1.85 - 1.62 (m, 7H), 1.37 (br. s., 7H), 1.24 - 0.93 (m, 10H), 0.66 (s, 5H). LCMS Rt = 1.392 min in 2 min chromatography, 30-90AB, MS ESI calcd for C₃₂H₄₁O₂ [M+H]⁺ 457, found 457.

Example 60. Synthesis of compound 59.

[0345]



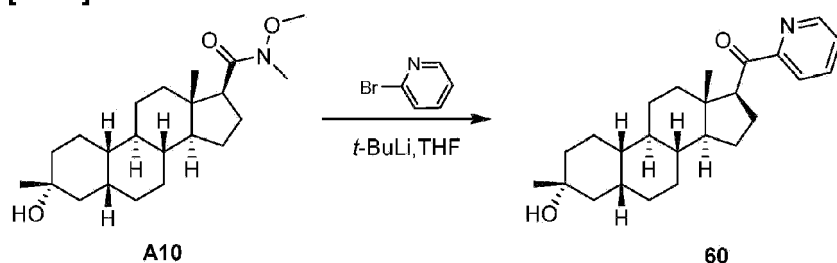


[0346] To a solution of **B10** (100 mg, 0.275 mmol) in THF (3 mL) was added naphthalen-2-ylmagnesium bromide (550 μ L) at 25 °C for 2 hours. TLC showed the reaction was complete. An aqueous solution of NH_4Cl (5 mL) was added dropwise into the reaction mixture at 25 °C, and extracted with EtOAc (10 mL x2). The combined organic solution was washed with brine (5 mL), dried over Na_2SO_4 . The organic layer was filtered and concentrated under reduced pressure to get the mixture, which was purified by HPLC to give **59** (7.8 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 8.41 (s, 1H), 8.03 - 7.97 (m, 2H), 7.93 - 7.87 (m, 2H), 7.64 - 7.54 (m, 2H), 3.74 - 3.66 (m, 1H), 2.59 - 2.46 (m, 1H), 1.88 - 1.76 (m, 2H), 1.76 - 1.60 (m, 5H), 1.56 - 1.53 (m, 1H), 1.40 (br. s., 6H), 1.21 (s, 10H), 0.81 - 0.70 (m, 1H), 0.67 (s, 4H). **LCMS** Rt = 1.346 min in 2 min chromatography, 30-90AB, MS ESI calcd. for $\text{C}_{30}\text{H}_{39}\text{O}_2$ $[\text{M}+\text{H}]^+$ 431, found 431.

Example 61. Synthesis of compound 60.

[0347]



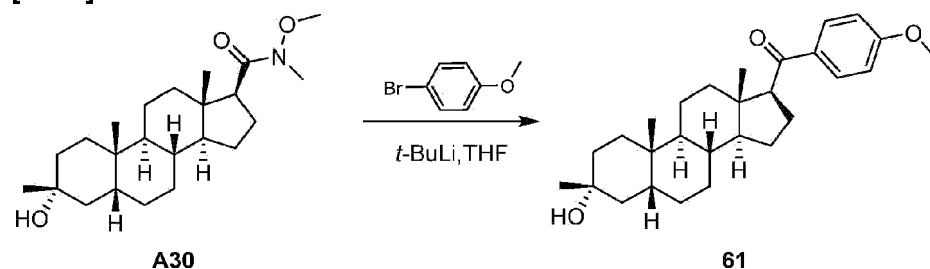
[0348] To a stirred solution of 2-bromopyridine (216 mg, 1.37 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 2 mL, 2.61 mmol) drop-wise at -78 °C under N_2 . After stirring at -78 °C for 2 hrs, **A10** (100 mg, 0.275 mmol) was added. The mixture was stirred at 25 °C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over (Na_2SO_4), filtered and evaporated in vacuum to give crude product. The crude product was purified by per-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 70-80% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) to obtain **60** (49.9 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz): δ 8.66 (d, J = 4.6 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.78-7.85 (m, 1H), 7.40-7.46 (m, 1H), 4.22 (t, J = 8.8 Hz, 1H), 2.24-2.41 (m, 1H), 1.74-1.87 (m, 5H), 1.23-

1.56 (m, 17H), 1.04-1.20 (m, 3H), 0.83-0.95 (m, 1H), 0.63 (s, 3H). LCMS Rt = 2.154 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for $C_{25}H_{36}NO_2$ $[M+H]^+$ 382, found 382.

Example 62. Synthesis of compound 61.

[0349]

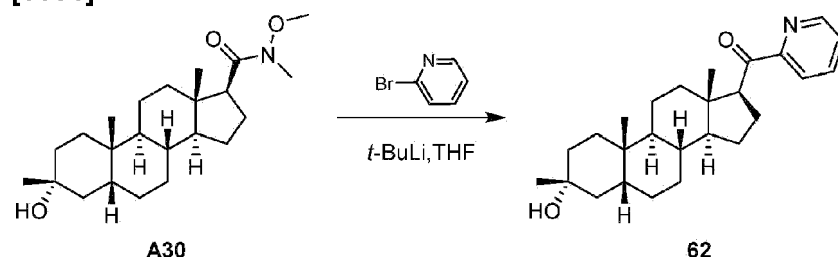


[0350] To a stirred solution of 1-bromo-4-methoxybenzene (245 mg, 1.31 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 1.92 mL, 2.50 mmol) drop-wise at -78°C under N_2 . After stirring at -78°C for 2 hrs, A30 (100 mg, 0.264 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 75-100% B (A = 0.05% HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to give 61 (13.3 mg) as a solid.

1H NMR ($CDCl_3$, 400MHz): δ 7.89 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.45 (t, J = 8.8 Hz, 1H), 2.37-2.47 (m, 1H), 1.97 (t, J = 13.2 Hz, 1H), 1.63-1.91 (m, 5H), 1.31-1.54 (m, 11H), 1.19-1.27 (m, 5H), 1.09-1.18 (m, 2H), 1.03 (td, J = 14.4, 3.3 Hz, 1H), 0.91 (s, 3H), 0.58 (s, 3H). LCMS Rt = 1.230 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $C_{28}H_{41}O_3$ $[M+H]^+$ 425.3, found 407 $[M-H_2O]^+$.

Example 63. Synthesis of compound 62.

[0351]

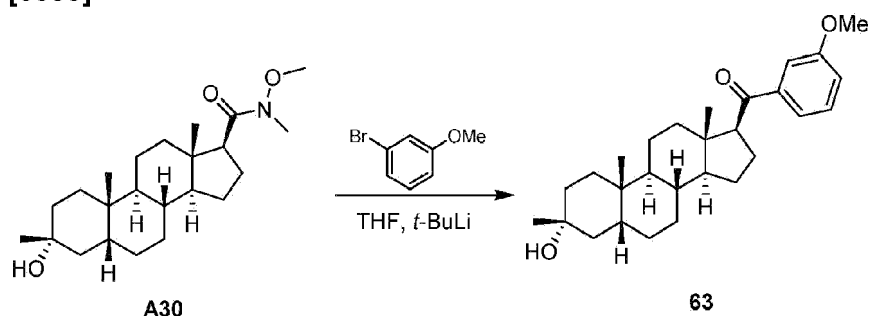


[0352] To a stirred solution of 2-bromopyridine (206 mg, 1.31 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 1.92 mL, 2.50 mmol) drop-wise at -78°C under N₂. After stirring at -78°C for 2 hrs, **A30** (100 mg, 0.264 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat NH₄Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over (Na₂SO₄), filtered, and evaporated in vacuum to give crude product. The crude product was purified by per-HPLC separation (column: Phenomenex Synergi C18 150*30mm*60, gradient: 84-84% B (A = 0.05%HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to give **62** (20.3 mg) as a solid.

¹H NMR (MeOD, 400MHz): δ 8.81 (d, *J* = 4.8 Hz, 1H), 8.33-8.39 (m, 1H), 8.26-8.32 (m, 1H), 7.87-7.94 (m, 1H), 4.03 (t, *J* = 8.8 Hz, 1H), 2.30-2.46 (m, 1H), 1.79-2.09 (m, 5H), 1.71 (d, *J* = 14.4 Hz, 1H), 1.34-1.60 (m, 10H), 1.21-1.31 (m, 7H), 1.03-1.20 (m, 2H), 0.96 (s, 3H), 0.65 (s, 3H). LCMS Rt = 2.257 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for C₂₆H₃₈NO₂ [M + H]⁺ 396, found 396.

Example 64. Synthesis of compound 63.

[0353]



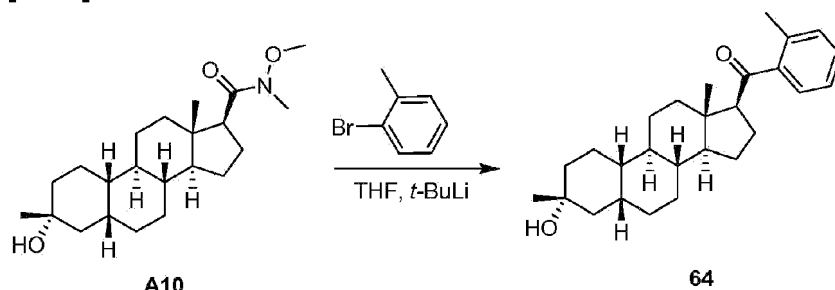
[0354] To a stirred solution of 1-bromo-3-methoxybenzene (245 mg, 1.31 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M, 1.92 mL, 2.50 mmol) dropwise at -78°C under N₂. After stirring at -78°C for 2 hrs, **A30** (100 mg, 0.264 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH₄Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2). The combined organic layer was washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuo to give crude product, which was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 75-100% B (A= 0.05%HCl-ACN, B=acetonitrile), flow rate: 30 mL/min) for further purification to afford **63** (19.4 mg) as a solid.

¹H NMR (CDCl₃, 400 MHz): δ 7.45 (d, *J* = 7.6 Hz, 1H), 7.40 (s, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.08 (dd, *J* = 8.0, 2.3 Hz, 1H), 3.86 (s, 3H), 3.45 (t, *J* = 8.8 Hz, 1H), 2.37-2.47 (m, 1H), 1.65-2.00 (m, 6H), 1.33-1.53 (m, 10H), 1.22-1.28 (m, 5H), 1.08-1.18 (m, 2H), 0.98-1.05 (m, 1H), 0.89-0.89 (m, 1H), 0.91 (s, 3H), 0.59 (s, 3H). LCMS Rt = 3.246 min in 4.0 min chromatography,

30-90 CD, MS ESI calcd. for $C_{28}H_{41}O_3$ $[M+H]^+$ 425.3, found 407.3 $[M-H_2O]^+$.

Example 65. Synthesis of compound 64.

[0355]

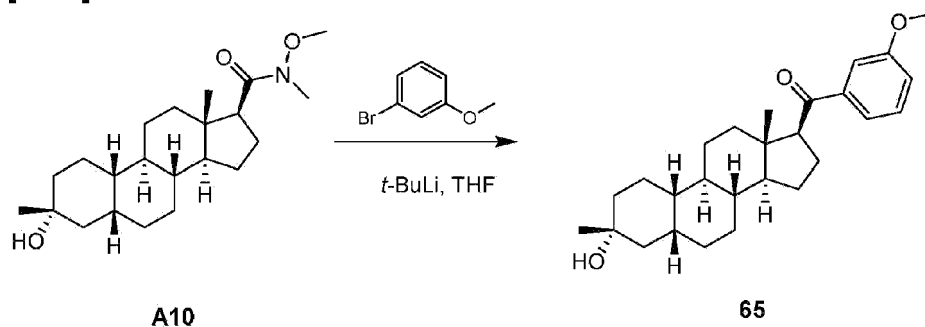


[0356] To a stirred solution of 1-bromo-2-methylbenzene (234 mg, 1.37 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 2 mL, 2.61 mmol) dropwise at -78°C under N_2 . After stirring at -78°C for 2 hrs, **A10** (100 mg, 0.275 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over (Na_2SO_4), filtered, and evaporated in vacuum to give crude product, which was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 70-95% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to give **64** (23.4 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz): δ 7.47 (d, $J = 7.4$ Hz, 1H), 7.30-7.34 (m, 1H), 7.22 (d, $J = 7.4$ Hz, 2H), 3.31 (t, $J = 8.8$ Hz, 1H), 2.31-2.46 (m, 4H), 1.69-1.83 (m, 5H), 1.19-1.51 (m, 16H), 0.97-1.19 (m, 4H), 0.82-0.90 (m, 1H), 0.66 (s, 3H). LCMS $R_t = 2.592$ min in 4.0 min chromatography, 30-90 CD, MS ESI calcd. for $C_{27}H_{39}O_2$ $[M+H]^+$ 395.3, found 377.29 $[M-H_2O]^+$.

Example 66. Synthesis of compound 65.

[0357]

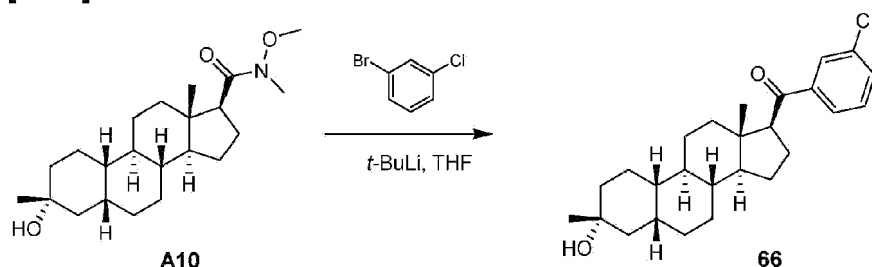


[0358] To a stirred solution of 1-bromo-3-methoxybenzene (256 mg, 1.37 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 2 mL, 2.61 mmol) dropwise at -78°C under N₂. After stirring at -78°C for 1 hrs, **A10** (100 mg, 0.275 mmol) was added. The mixture was stirred at 25°C for 20 min. LCMS showed the reaction was completed. The reaction mixture was quenched with NH₄Cl (30 mL), extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered and evaporated in vacuum. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 75-100% B (A= 0.05% HCl-ACN, B=acetonitrile), flow rate: 30 mL/min) to obtain **65** (63.3mg) as a solid.

¹H NMR (CDCl₃, 400MHz): 7.45 (d, *J* = 7.6 Hz, 1H), 7.40 (s, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.86 (s, 3H), 3.46 (t, *J* = 8.8 Hz, 1H), 2.38-2.46 (m, 1H), 1.70-1.87 (m, 5H), 1.58-1.68 (m, 2H), 1.11-1.52 (m, 17H), 1.03-1.10 (m, 1H), 0.84-0.99 (m, 1H), 0.61 (s, 3H). **LCMS** Rt = 3.153 min in 4.0 min chromatography, 10-80 CD, MS ESI calcd. for C₂₇H₃₈O₃ [M-H₂O+H]⁺ 393, found 393.

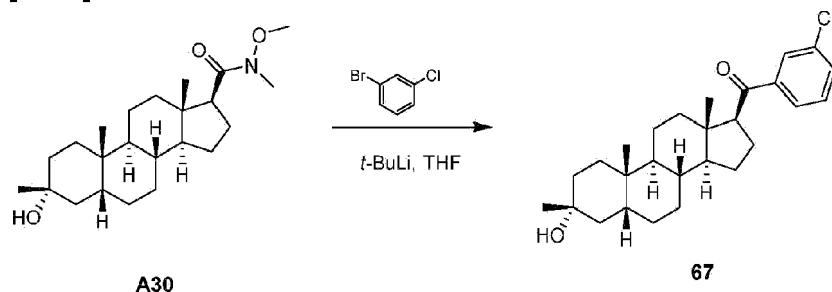
Example 67. Synthesis of compound 66.

[0359]



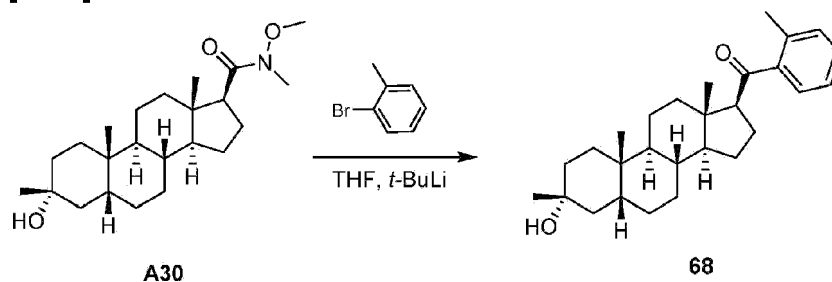
[0360] To a stirred solution of 1-bromo-3-chlorobenzene (262 mg, 1.37 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 2 mL, 2.61 mmol) dropwise at -78°C under N₂. After stirring at -78°C for 2 hrs, **A10** (100 mg, 0.275 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with NH₄Cl (30 mL), extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered and evaporated in vacuum. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 75-100% B (A = 0.05% HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to obtain **66** (67.6 mg) as a solid.

¹H NMR (CDCl₃, 400MHz): δ 7.84 (s, 1H), 7.73 (d, *J*=7.6 Hz, 1H), 7.50 (d, *J*=8.6 Hz, 1H), 7.34-7.43 (m, 1H), 3.43 (t, *J*=8.6 Hz, 1H), 2.36-2.45 (m, 1H), 1.70-1.86 (m, 5H), 1.57-1.67 (m, 2H), 1.41-1.54 (m, 3H), 1.21-1.41 (m, 13H), 1.04-1.17 (m, 2H), 0.88-0.99 (m, 1H), 0.60 (s, 3H). **LCMS** Rt = 2.722 min in 4.0 min chromatography, 30-90 CD, MS ESI calcd. for C₂₆H₃₆ClO₂ [M+H]⁺ 415.3, found 397.0 [M-H₂O]⁺.

Example 68. Synthesis of compound 67.**[0361]**

[0362] To a stirred solution of 1-bromo-3-chlorobenzene (250 mg, 1.31 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 1.92 mL, 2.50 mmol) dropwise at -78°C . After stirring at -78°C for 2 hrs, **A30** (100 mg, 0.264 mmol) was added. The mixture was stirred at -78°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with NH_4Cl (30 mL), extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered and evaporated in vacuum. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 80-100% B (A= 0.05% HCl-ACN, B=acetonitrile), flow rate: 30 mL/min) for to obtain **67** (22.3 mg) as a solid.

$^1\text{H NMR}$ (CDCl_3 , 400MHz): δ 7.84 (s, 1H), 7.73 (d, $J=7.6$ Hz, 1H), 7.50 (d, $J=8.0$ Hz, 1H), 7.33-7.43 (m, 1H), 3.41 (t, $J=8.6$ Hz, 1H), 2.34-2.45 (m, 1H), 1.96 (t, $J=13.2$ Hz, 1H), 1.59-1.87 (m, 5H), 1.20-1.53 (m, 17H), 1.09-1.16 (m, 1H), 0.98-1.07 (m, 1H), 0.90 (s, 3H), 0.58 (s, 3H). LCMS Rt =2.800 min in 4.0 min chromatography, 30-90 CD, MS ESI calcd. for $\text{C}_{27}\text{H}_{38}\text{ClO}_2$ $[\text{M}+\text{H}]^+$ 429.3, found 411.0 $[\text{M}-\text{H}_2\text{O}]^+$.

Example 69. Synthesis of compound 68.**[0363]**

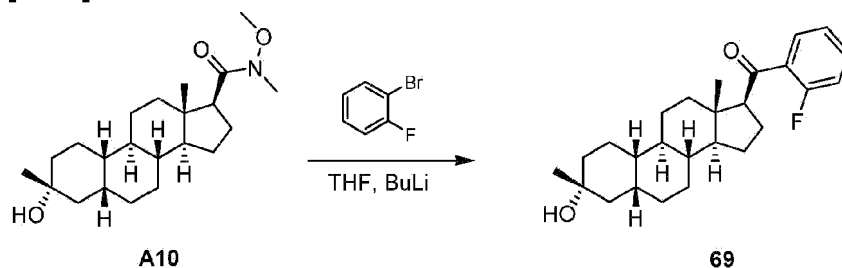
[0364] To a stirred solution of 1-bromo-2-methylbenzene (224 mg, 1.31 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 1.92 mL, 2.50 mmol) dropwise at -78°C under N_2 . After

stirring at -78°C for 2 hrs, **A30** (100 mg, 0.264 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuo to give crude product, which was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 70-95% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to obtain **68** (15.6 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz): δ 7.47 (d, $J=7.4$ Hz, 1H), 7.30-7.34 (m, 1H), 7.18-7.25 (m, 2H), 3.30 (t, $J=8.8$ Hz, 1H), 2.31-2.46 (m, 4H), 1.93 (t, $J=13.4$ Hz, 1H), 1.83 (dt, $J=9.2, 4.5$ Hz, 1H), 1.74 (d, $J=3.4$ Hz, 1H), 1.61-1.67 (m, 2H), 1.20-1.47 (m, 16H), 0.95-1.16 (m, 4H), 0.89 (s, 3H), 0.64 (s, 3H). LCMS Rt = 2.672 min in 4.0 min chromatography, 30-90 CD, MS ESI calcd. for $\text{C}_{28}\text{H}_{40}\text{O}_2$ $[\text{M}-\text{H}_2\text{O}+\text{H}]^+$ 391.1, found 391.3.

Example 70. Synthesis of compound 69.

[0365]

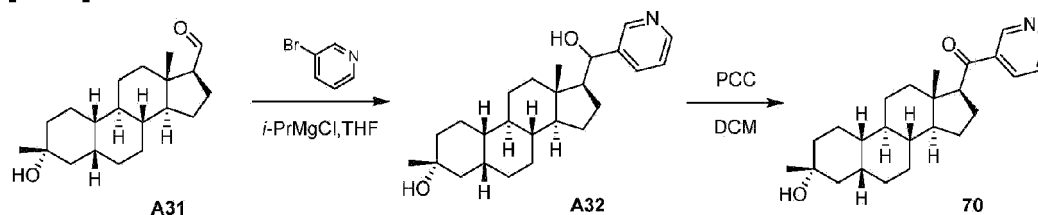


[0366] To a solution of 1-bromo-2-fluorobenzene (239 mg, 1.37 mmol) in THF (5 mL) was added n-butyllithium (1.90 mL, 2.47 mmol) dropwise at -68°C . The mixture was stirred at -68°C for 2 hrs. **A10** (100 mg, 275 μmol) in THF (3 mL) was added dropwise at -68°C . The reaction was stirred at 25°C for 2 hours. LCMS showed the reaction was complete. The reaction was quenched with Sat. NH_4Cl (20 mL), extracted with EtOAc (20 mL X 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and evaporated to afford crude product, which was purified by prep-HPLC to give **69** (21.6 mg) as a solid.

^1H NMR (400 MHz, DMSO) δ 7.68 - 7.54 (m, 2H), 7.34 - 7.28 (m, 2H), 4.21 (s, 1H), 3.40 (t, $J = 8.4$ Hz, 1H), 2.30-2.17 (m, 1H), 1.77-1.51 (m, 6H), 1.49-1.12 (m, 12H), 1.12-0.90 (m, 7H), 0.89-0.74 (m, 1H), 0.58-0.50 (m, 3H). LCMS Rt = 1.187 min in 2 min chromatography, 30-90AB, MS ESI calcd. for $\text{C}_{26}\text{H}_{36}\text{FO}_2$ $[\text{M}+\text{H}]^+$ 399.3, found 381 $[\text{M}-\text{H}_2\text{O}]^+$.

Example 71. Synthesis of compound 70.

[0367]



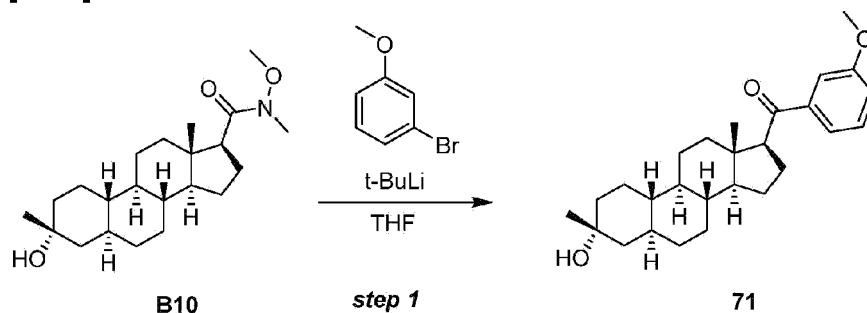
Step 1. To a solution of 3-bromopyridine (51.8 mg, 328 μmol) in 3 mL of THF was added isopropylmagnesium chloride (2 M, 164 μL , 328 μmol) drop-wise at 15°C under N_2 . After stirring at 15°C for 1 hour, **A31** (50 mg, 0.164 mmol) was added. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with saturated sat NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2). The combined organic layer washed with brine (30 mL), dried over Na_2SO_4 , filtered and evaporated in vacuum to give 60mg of crude product.

Step 2. To a solution of **A32** (60 mg, 156 μmol) in DCM (3 mL) was added PCC (50.3 mg, 234 μmol) at 15°C. The mixture was stirred at 15°C for 1 hr. LCMS showed the reaction was complete. The solution was filtered and the filter cake was washed with DCM (50 mL x 2). The combined filtrate was concentrated in vacuum. The residue was purified by silica gel column eluted with PE/EtOAc (10/1) to afford a crude product, which was then purified by prep-HPLC (column: Phenomenex Gemini 150*25mm*10 μm , gradient: 45-70% B (A = 0.05% HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to give **70** (1.6 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz) δ = 9.15-9.05 (m, 1H), 8.80-8.70 (m, 1H), 8.20-8.10 (m, 1H), 7.47-7.35 (m, 1H), 3.46 (t, $J=8.6$ Hz, 1H), 3.08 (br. s., 1H), 2.52-2.34 (m, 1H), 1.90-1.72 (m, 5H), 1.68-1.61 (m, 2H), 1.52-1.44 (m, 3H), 1.43-1.33 (m, 7H), 1.31-1.24 (m, 5H), 1.20-1.04 (m, 2H), 1.00-0.85 (m, 1H), 0.62 (s, 3H). **LCMS** Rt = 1.206 min in 2.0 min chromatography, 10-80 AB, MS ESI calcd. for $\text{C}_{25}\text{H}_{36}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 382, found 382.

Example 72. Synthesis of compound 71.

[0368]

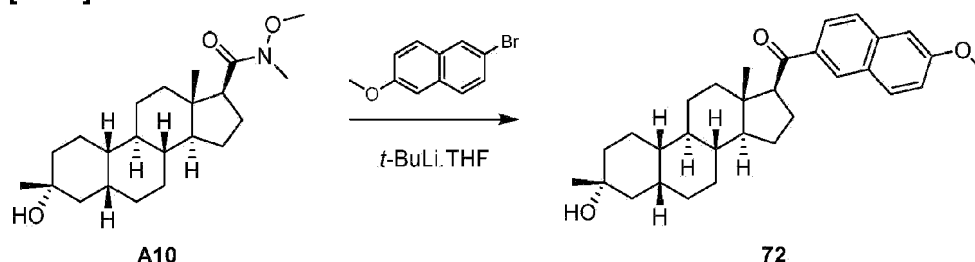


[0369] To a solution of 1-bromo-4-methylbenzene (203 mg, 1.09 mmol) in THF (0.3 mL) was added tert-butyllithium (1.68 mL, 1.3 M) at -60°C. The mixture was stirred at -60°C for 1 hr. A solution of **B10** (40 mg, 110 µmol) in THF (0.1 mL) was added into the mixture at -60°C. The reaction mixture was stirred at 25°C for 2 hrs. TLC showed the reaction was complete. Saturated NH₄Cl (1 mL) was added. The mixture was extracted with EtOAc (1.5 mL x 3). The combined organic layers were dried over Na₂SO₄. The mixture was filtered. The filtrate was concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4µm, gradient: 80-95% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) to give **71** (6.5 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.56-7.43 (m, 2H), 7.41-7.29 (m, 1H), 7.11-7.06 (m, 1H), 3.86 (s, 3H), 3.48-3.39 (m, 1H), 2.47-2.36 (m, 1H), 1.81-1.46 (m, 10H), 1.53-0.91 (m, 20H), 0.72-0.58 (m, 5H). LCMS t_R = 1.039 min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for C₂₇H₃₉O₃ [M+H]⁺ 411, found 411.

Example 73. Synthesis of compound 72.

[0370]

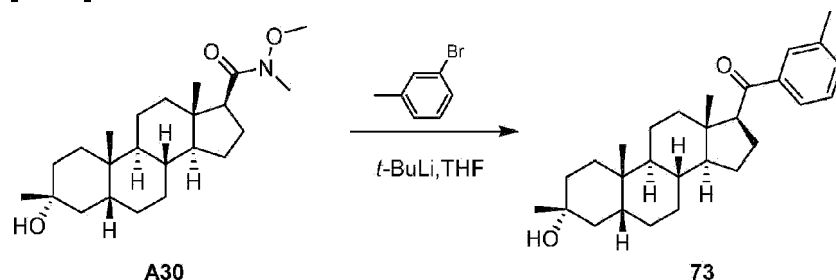


[0371] To a stirred solution of 2-bromo-6-methoxynaphthalene (258 mg, 1.09 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M, 1.6 mL, 2.09 mmol) drop-wise at -78°C under N₂. After stirring at -78°C for 1 hour, **A10** (80 mg, 0.220 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with saturated NH₄Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2). The combined organic layer washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give crude product, which was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4µm, gradient: 80-100% B (A = 0.05% HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to afford **72** (58.3 mg) as a solid.

¹H NMR (CDCl₃, 400MHz): δ 8.33 (s, 1H), 7.93-7.99 (m, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.20 (dd, J = 9.0, 2.5 Hz, 1H), 7.15 (d, J = 2.0 Hz, 1H), 3.95 (s, 3H), 3.64 (t, J = 8.6 Hz, 1H), 2.55-2.42 (m, 1H), 1.88-1.73 (m, 5H), 1.69-1.59 (m, 1H), 1.55-1.20 (m, 17H), 1.19-1.04 (m, 2H), 0.97-0.83 (m, 1H), 0.64 (s, 3H). LCMS Rt = 1.242 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C₃₁H₄₁O₃ [M +H]⁺ 461, found 461.

Example 74. Synthesis of compound 73.

[0372]

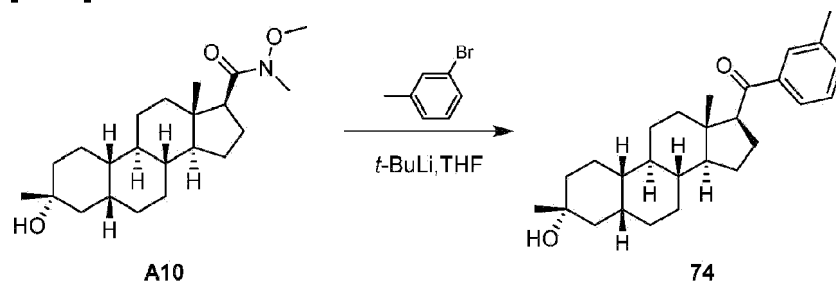


[0373] To a stirred solution of 1-bromo-3-methylbenzene (224 mg, 1.31 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 1.6 mL, 2.5 mmol) drop-wise at -78°C under N_2 . After stirring at -78°C for 2 hours, **A30** (100 mg, 0.264 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by prep-HPLC separation (column: Phenomenex Synergi C18 $150 \times 30 \text{ mm} \times 4 \mu\text{m}$, gradient: 80-100% B (A = 0.05% HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to afford **73** (12.2 mg) as a solid.

^1H NMR (CDCl_3 , 400 MHz): δ 7.62-7.70 (m, 2H), 7.28-7.36 (m, 2H), 3.47 (t, $J = 8.8$ Hz, 1H), 2.34-2.47 (m, 4H), 1.97 (t, $J = 13.2$ Hz, 1H), 1.59-1.92 (m, 5H), 1.28-1.51 (m, 10H), 1.20-1.27 (m, 5H), 0.96-1.18 (m, 4H), 0.90 (s, 3H), 0.59 (s, 3H). LCMS Rt = 1.261 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{41}\text{O}_2$ $[\text{M} + \text{H}]^+$ 409, found 409.

Example 75. Synthesis of compound 74.

[0374]



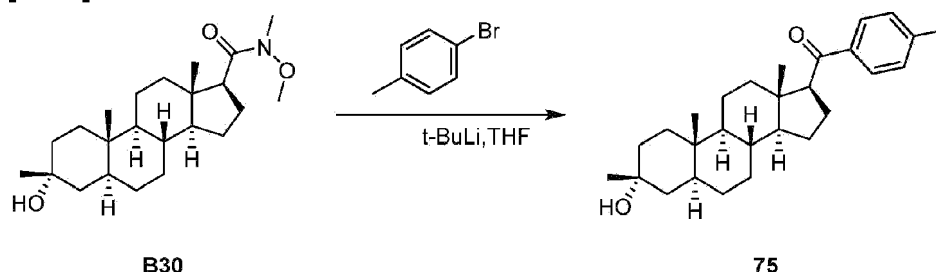
[0375] To a stirred solution of 1-bromo-3-methoxybenzene (186 mg, 1.09 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 1.6 mL, 2.09 mmol) drop-wise at -78°C under N_2 . After stirring at -78°C for 2 hrs, **A10** (80 mg, 0.22 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was

quenched with Sat NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 85-85% B (A = 0.05% HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to give **74** (18.8 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz): δ 7.60-7.74 (m, 2H), 7.29-7.39 (m, 2H), 3.48 (t, J = 8.6 Hz, 1H), 2.33-2.48 (m, 4H), 1.69-1.85 (m, 5H), 1.55-1.69 (m, 3H), 1.41-1.51 (m, 3H), 1.20-1.41 (m, 12H), 1.02-1.16 (m, 2H), 0.82-0.97 (m, 1H), 0.60 (s, 3H). LCMS Rt =1.232 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{27}\text{H}_{39}\text{O}_2$ $[\text{M}+\text{H}]^+$ 395.3, found 377 $[\text{M}-\text{H}_2\text{O}]^+$.

Example 76. Synthesis of compound 75.

[0376]



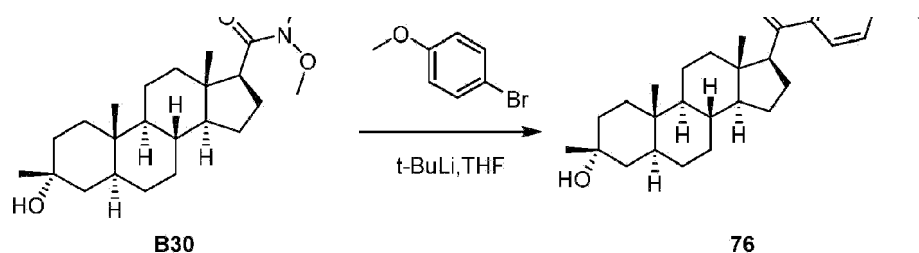
[0377] To a stirred solution of 1-bromo-4-methylbenzene (51.5 mg, 0.264 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M in hexane, 0.4 mL, 0.52 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, **B30** (50 mg, 0.132 mmol) was added. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*25*10um, gradient: 69-74% B (A = 0.1% TFA-ACN, B = acetonitrile), flow rate: 30 mL/min) for further purification to obtain **75** (21.9 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz) δ 7.79 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 3.47 (t, J = 8.6 Hz, 1H), 2.47 - 2.36 (m, 4H), 1.78 - 1.69 (m, 3H), 1.50 - 1.17 (m, 19H), 1.17 - 1.08 (m, 1H), 1.03 - 0.92 (m, 1H), 0.83 - 0.74 (m, 1H), 0.72 (s, 3H), 0.60 (s, 3H). LCMS Rt =1.277 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{41}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 409, found 409.

Example 77. Synthesis of compound 76.

[0378]



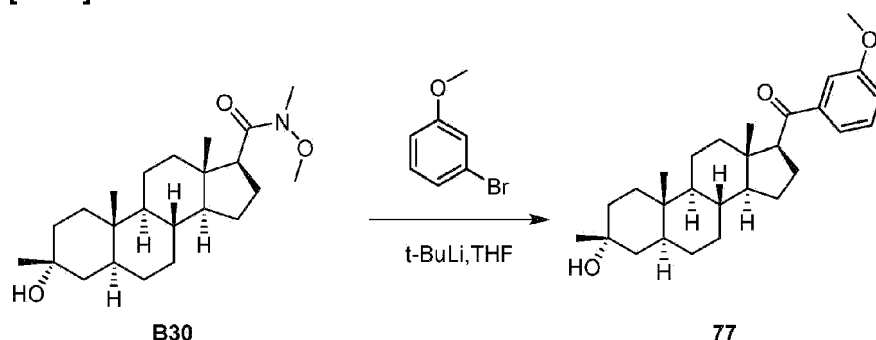


[0379] To a stirred solution of 1-bromo-4-methoxybenzene (49.3 mg, 0.264 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 406 μ L, 0.528 mmol) drop-wise at -65°C under N_2 . After stirring at -65°C for 2 hrs, **B30** (50 mg, 0.132 mmol) was added. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give the crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4 μ m, gradient: 90-95% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to obtain **76** (26.1 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz) δ 7.89 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.45 (t, J = 8.6 Hz, 1H), 2.45 - 2.36 (m, 1H), 1.78 - 1.68 (m, 3H), 1.53 - 1.12 (m, 20H), 1.03 - 0.92 (m, 1H), 0.82 - 0.75 (m, 1H), 0.71 (s, 3H), 0.59 (s, 3H). LCMS Rt = 1.302 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{41}\text{O}_3$ $[\text{M}+\text{H}]^+$ 425, found 425.

Example 78. Synthesis of compound 77.

[0380]



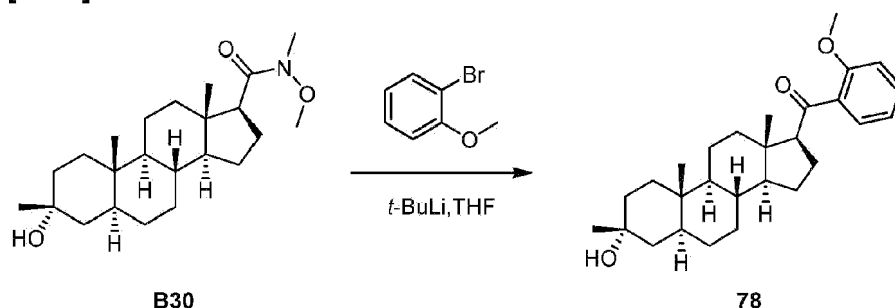
[0381] To a stirred solution of 1-bromo-3-methoxybenzene (49.3 mg, 0.264 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M, 406 μ L, 0.528 mmol) drop-wise at -65°C under N_2 . After stirring at -65°C for 2 hrs, **B30** (50 mg, 0.132 mmol) was added. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude

product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 90-95% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to obtain **77** (19.9 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 7.50 - 7.30 (m, 3H), 7.07 (dd, *J* = 2.0, 8.0 Hz, 1H), 3.85 (s, 3H), 3.45 (t, *J* = 8.8 Hz, 1H), 2.46 - 2.34 (m, 1H), 1.81 - 1.67 (m, 3H), 1.53 - 1.26 (m, 12H), 1.25 - 1.09 (m, 8H), 1.03 - 0.92 (m, 1H), 0.81 - 0.74 (m, 1H), 0.71 (s, 3H), 0.60 (s, 3H). LCMS Rt =1.315 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C₂₈H₄₁O₃ [M+H]⁺ 425, found 425.

Example 79. Synthesis of compound 78.

[0382]



[0383] To a stirred solution of 1-bromo-2-methoxybenzene (49.3 mg, 0.264 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M, 406 μL, 0.528 mmol) dropwise at -65°C under N₂. After stirring at -65°C for 2 hrs, **B30** (50 mg, 0.132 mmol) was added. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat.NH₄Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 95-95% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to obtain **78** (19.6 mg) as a solid.

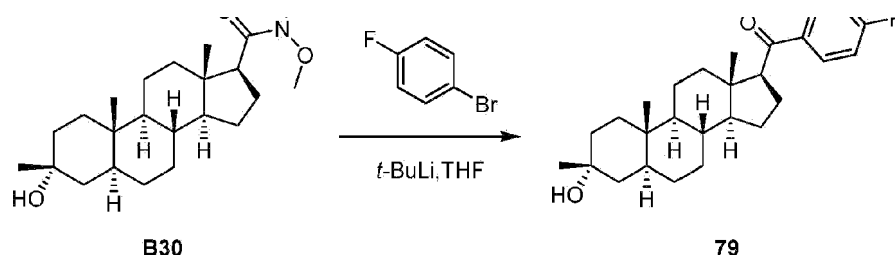
¹H NMR (CDCl₃, 400MHz) δ 7.43 - 7.28 (m, 2H), 7.02 - 6.82 (m, 2H), 3.84 (s, 3H), 3.55 - 3.45 (m, 1H), 2.43 - 2.25 (m, 1H), 1.79 - 1.63 (m, 5H), 1.48 - 1.33 (m, 6H), 1.25 - 1.16 (m, 10H), 1.12 - 1.04 (m, 2H), 1.00 - 0.85 (m, 1H), 0.77 - 0.70 (m, 1H), 0.69 (s, 3H), 0.60 (s, 3H). LCMS Rt =1.277 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C₂₈H₄₁O₃ [M+H]⁺ 425, found 425.

Example 80. Synthesis of compound 79.

[0384]

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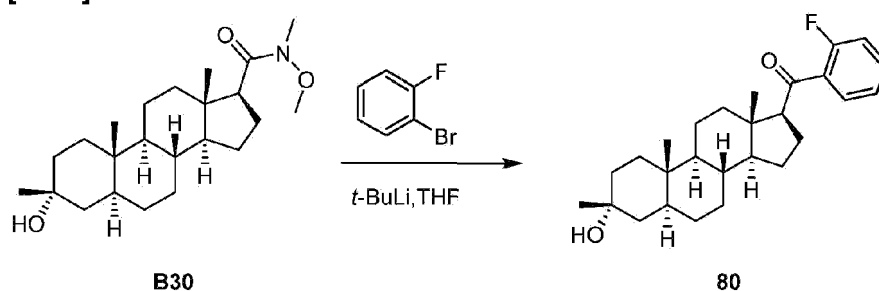


[0385] To a stirred solution of 1-bromo-4-fluorobenzene (46.1 mg, 0.264 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M, 406 μ L, 0.528 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, **B30** (50 mg, 0.132 mmol) was added. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*30mm*4 μ m, gradient: 85-95% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) to obtain **79** (22.1 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz) δ 7.91 (dd, J = 5.6, 8.5 Hz, 2H), 7.10 (t, J = 8.6 Hz, 2H), 3.44 (t, J = 8.6 Hz, 1H), 2.45 - 2.35 (m, 1H), 1.83 - 1.64 (m, 4H), 1.54 - 1.42 (m, 6H), 1.38 (d, J = 13.4 Hz, 2H), 1.32 - 1.14 (m, 11H), 1.02 - 0.92 (m, 1H), 0.83 - 0.74 (m, 1H), 0.71 (s, 3H), 0.59 (s, 3H). LCMS Rt = 1.240 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{27}\text{H}_{38}\text{FO}_2$ $[\text{M}+\text{H}]^+$ 413, found 413.

Example 81. Synthesis of compound 80.

[0386]



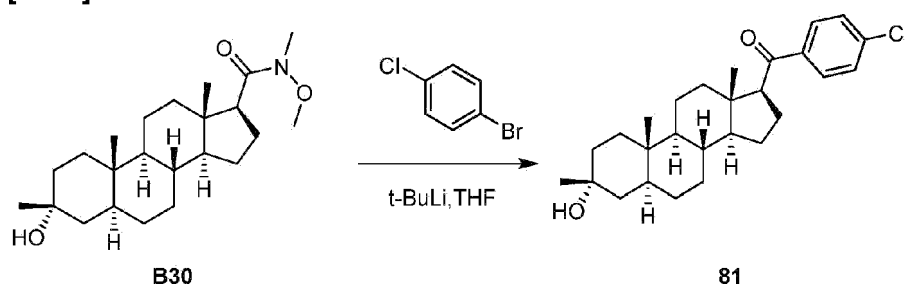
[0387] To a stirred solution of 1-bromo-2-fluorobenzene (46.1 mg, 0.264 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M in hexane, 406 μ L, 0.528 mmol) drop-wise at -65°C under N_2 . After stirring at -65°C for 2 hrs, **B30** (50 mg, 0.132 mmol) was added. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex

Synergi C18 150*30mm*4um, gradient: 84-84% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **80** (19.9 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 7.57 - 7.48 (m, 1H), 7.47 - 7.39 (m, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.12 - 7.05 (m, 1H), 3.39 (t, J = 8.6 Hz, 1H), 2.43 - 2.32 (m, 1H), 1.79 - 1.66 (m, 3H), 1.49 - 1.31 (m, 7H), 1.28 - 1.13 (m, 12H), 1.13 - 1.04 (m, 1H), 0.96 (dq, J = 5.4, 12.1 Hz, 1H), 0.79 - 0.73 (m, 1H), 0.70 (s, 3H), 0.60 (s, 3H). **LCMS** Rt = 1.217 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C₂₇H₃₉FO₂ [M+H]⁺ 413, found 395 [M-H₂O]⁺.

Example 82. Synthesis of compound 81.

[0388]

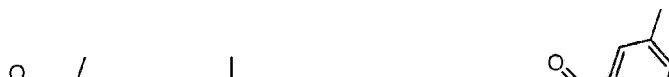


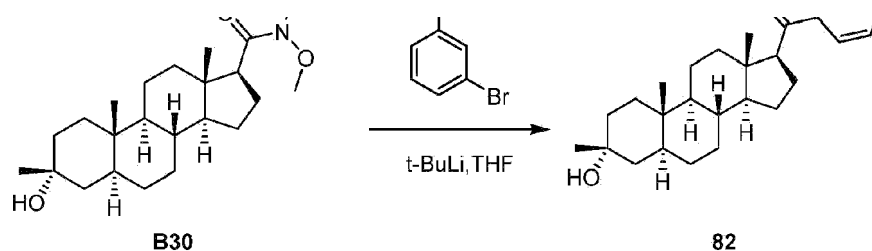
[0389] To a stirred solution of 1-bromo-4-chlorobenzene (50.5 mg, 0.264 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 406 μ L, 0.528 mmol) drop-wise at -65°C under N₂. After stirring at -65°C for 2 hrs, **B30** (50 mg, 0.132 mmol) was added. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat.NH₄Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column:Phenomenex Synergi C18 150*30mm*4um, gradient: 88-88% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **81** (11.8 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 7.85 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 3.45 (t, J = 8.6 Hz, 1H), 2.48 - 2.38 (m, 1H), 1.87 - 1.66 (m, 4H), 1.56 - 1.46 (m, 5H), 1.42 - 1.25 (m, 9H), 1.24 - 1.16 (m, 5H), 1.05 - 0.95 (m, 1H), 0.84 - 0.76 (m, 1H), 0.74 (s, 3H), 0.60 (s, 3H). **LCMS** Rt = 1.318 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C₂₇H₃₇ClO₂ [M+H]⁺ 429.3, found 411 [M-H₂O]⁺.

Example 83. Synthesis of compound 82.

[0390]



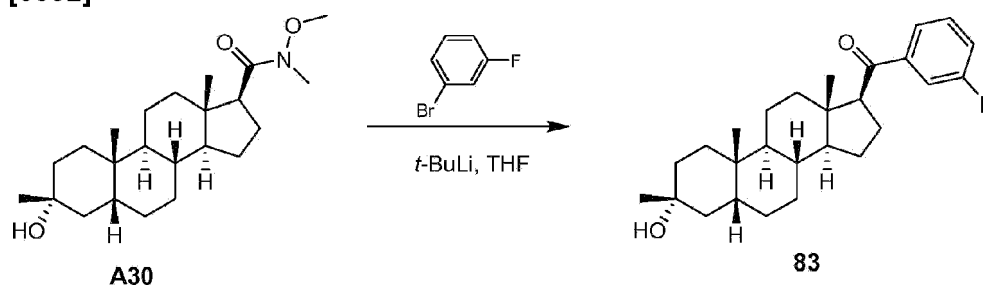


[0391] To a stirred solution of 1-bromo-3-methylbenzene (45.1 mg, 0.264 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 406 μ L, 0.528 mmol) drop-wise at -65°C under N_2 . After stirring at -65°C for 2 hrs, **B30** (50 mg, 0.132 mmol) was added. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column:Phenomenex Synergi C18 150*25*10um, gradient: 69-94% B (A= 0.1%TFA-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **82** (24.6 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz) δ 7.70-7.60 (m, 2H), 7.36 - 7.29 (m, 2H), 3.47 (t, J = 8.6 Hz, 1H), 2.48 - 2.33 (m, 4H), 1.80 - 1.67 (m, 3H), 1.52 - 1.41 (m, 6H), 1.41 - 1.22 (m, 9H), 1.19 (s, 4H), 1.16 - 1.07 (m, 1H), 1.03 - 0.92 (m, 1H), 0.82 - 0.74 (m, 1H), 0.71 (s, 3H), 0.60 (s, 3H). LCMS Rt = 1.273 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{41}\text{O}_2$ $[\text{M} + \text{H}]^+$ 409, found 409

Example 84. Synthesis of compound 83.

[0392]



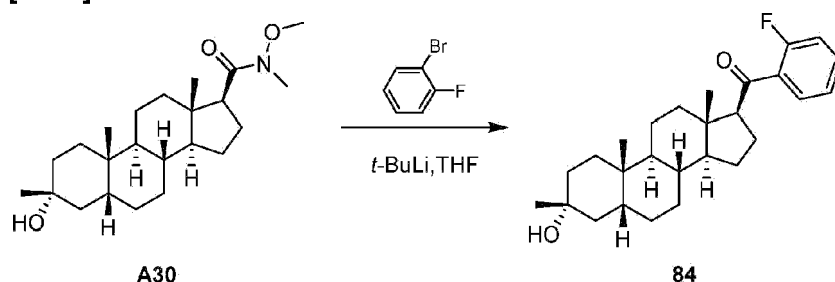
[0393] To a solution of 1-bromo-3-fluorobenzene (460 mg, 2.63 mmol) in THF (3 mL) was added *t*-butyllithium (4.75 mL, 4.75 mmol) dropwise at -78°C . After stirring at -78°C for 2 h a solution of **A30** (100 mg, 0.264 mmol) in THF (1 mL) was added dropwise at 15°C . The reaction was stirred at 15°C for 2 hours. TLC showed the reaction was completed. The reaction was quenched with sat. NH_4Cl (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and evaporated. The crude residue was purified by prep-HPLC separation (column: Phenomenex

Synergi C18 150*30mm*4um, gradient: 85-90% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) to obtain **83** (16.0 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, 1 H) 7.56 (dt, 1 H) 7.42 (td, 1 H) 7.19 - 7.25 (m, 1 H) 3.42 (t, 1 H) 2.36 - 2.47 (m, 1 H) 1.92 - 2.04 (m, 1 H) 1.62 - 1.91 (m, 4 H) 0.97 - 1.58 (m, 23 H) 0.86 - 0.93 (m, 3 H) 0.54 - 0.61 (m, 3 H). LCMS Rt = 0.893 min in 2.0 min chromatography, 10-80 AB, MS ESI calcd. for C₂₇H₃₈FO₂ 413 [M+H]⁺, found 395.2 [M-H₂O]⁺.

Example 85. Synthesis of compound 84.

[0394]

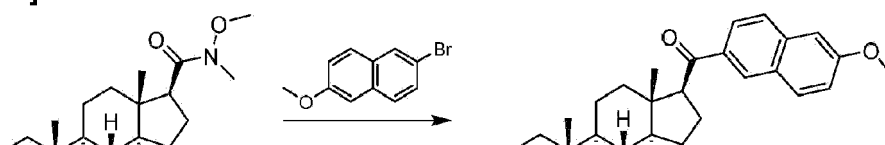


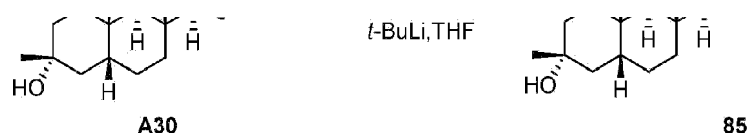
[0395] To a stirred solution of 1-bromo-2-fluorobenzene (229 mg, 1.31 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M, 1.92 mL, 2.50 mmol) drop-wise at -78°C under N₂. After stirring at -78°C for 1 hour, **A30** (100 mg, 0.264 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with saturated NH₄Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2). The combined organic layer washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give crude product, which was purified by prep-HPLC separation (column:Phenomenex Synergi C18 150*30mm*4um, gradient: 81-81% B (A = 0.05%HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to give **84** (18.7 mg) as a solid.

¹H NMR (CDCl₃, 400MHz): δ 7.53 (t, *J* = 6.8 Hz, 1H), 7.40-7.48 (m, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.12-7.05 (m, 1H), 3.40 (t, *J* = 8.8 Hz, 1H), 2.32-2.44 (m, 1H), 1.94 (t, *J* = 13.4 Hz, 1H), 1.88-1.61 (m, 5H), 1.52-1.27 (m, 10H), 1.26-1.18 (m, 6H), 1.16-0.96 (m, 3H), 0.89 (s, 3H), 0.59 (s, 3H). LCMS Rt =1.205 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C₂₇H₃₈FO₂ 413 [M+H]⁺, found 395.2 [M-H₂O]⁺.

Example 86. Synthesis of compound 85.

[0396]



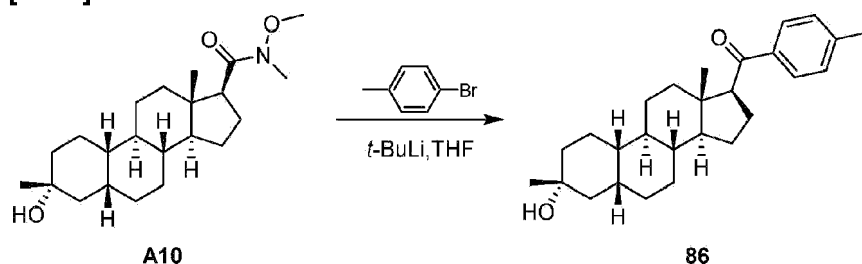


[0397] To a stirred solution of 2-bromo-6-methoxynaphthalene (310 mg, 1.31 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M, 1.92 mL, 2.50 mmol) drop-wise at -78°C under N_2 . After stirring at -78°C for 1 hour, **A30** (100 mg, 0.264 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with saturated NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2). The combined organic layer washed with brine (30 mL), dried over Na_2SO_4 , filtered and evaporated in vacuum to give crude product, which was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 85-90% B (A = 0.05% HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to afford **85** (29.3 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz): δ 8.33 (s, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.20 (dd, J = 8.8, 2.4 Hz, 1H), 7.15 (s, 1H), 3.95 (s, 3H), 3.64 (t, J = 8.8 Hz, 1H), 2.44-2.52 (m, 1H), 1.94-2.02 (m, 1H), 1.76-1.91 (m, 3H), 1.66 (d, J = 14.4 Hz, 1H), 1.29-1.54 (m, 12H), 1.21-1.28 (m, 5H), 0.97-1.19 (m, 3H), 0.90 (s, 3H), 0.62 (s, 3H). **LCMS** Rt = 1.267 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{32}\text{H}_{43}\text{O}_3$ $[\text{M}+\text{H}]^+$ 475.3, found 457 $[\text{M}-\text{H}_2\text{O}]^+$

Example 87. Synthesis of compound 86.

[0398]

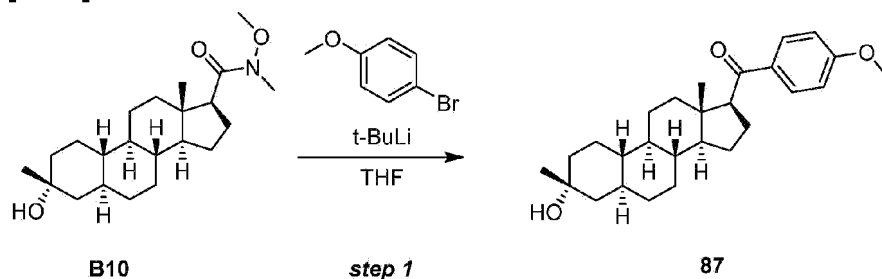


[0399] To a stirred solution of 1-bromo-4-methylbenzene (186 mg, 1.09 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 1.6 mL, 2.09 mmol) drop-wise at -78°C under N_2 . After stirring at -78°C for 2 hour, **A10** (80 mg, 0.22 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with saturated NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 80-100% B (A = 0.05% HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to obtain **86** (23.7 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz): δ 7.79 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 3.48 (t, J = 8.6 Hz, 1H), 2.37-2.48 (m, 4H), 1.72-1.84 (m, 5H), 1.59-1.67 (m, 2H), 1.25-1.49 (m, 15H), 1.06-1.17 (m, 2H), 0.82-0.99 (m, 2H), 0.60 (s, 3H). LCMS R_t = 1.233 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{27}\text{H}_{39}\text{O}_2$ $[\text{M}+\text{H}]^+$ 395.3, found 377 $[\text{M}-\text{H}_2\text{O}]^+$.

Example 88. Synthesis of compound 87.

[0400]

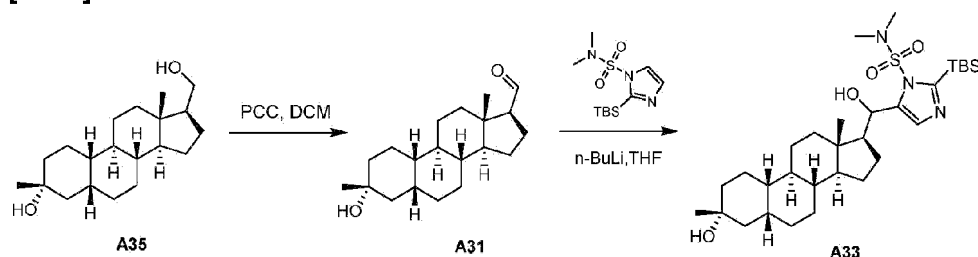


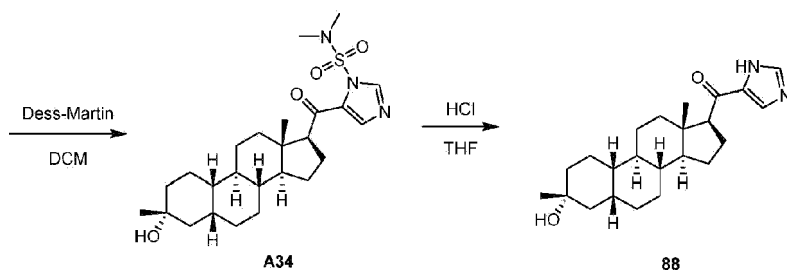
[0401] To a solution of 1-bromo-4-methylbenzene (203 mg, 1.09 mmol) in THF (0.3 mL) was added tert-butyllithium (1.68 mL, 1.3 M) at -60°C . The mixture was stirred at -60°C for 1 hr. A solution of **B10** (40 mg, 110 μmol) in THF (0.1 mL) was added into the mixture at -60°C . The reaction mixture was stirred at 25°C for 2 hrs. TLC showed the reaction was complete. Saturation NH_4Cl (1 mL) was added. The mixture was extracted with EtOAc (1.5 mL x 3). The combined organic layers were dried over Na_2SO_4 . The mixture was filtered. The filtrate was concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 95-100% B (A= 0.05% HCl -ACN, B= acetonitrile), flow rate: 25 mL/min) to give **87** (5 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 3.50-3.43 (m, 1H), 2.46-2.39 (m, 1H), 1.79-1.44 (m, 9H), 1.53-0.93 (m, 17H), 0.71-0.57 (m, 5H). LCMS t_R = 0.991 min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for $\text{C}_{27}\text{H}_{39}\text{O}_3$ $[\text{M}+\text{H}]^+$ 411, found 411.

Example 89. Synthesis of compound 88.

[0402]





Step 1. To a solution of **A35** (1 g, 3.26 mmol) in DCM (5 mL) was added PCC (1.05 g, 4.89 mmol) at 15°C. The mixture was stirred at 15°C for 1 hr. TLC showed the reaction was complete. The solution was filtered and the filter cake was washed with DCM (50 mL x 2). The combined filtrate was concentrated in vacuum. The residue was purified by silica gel column eluted with (PE/EtOAc = 10/1) to afford **A31** (300 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 9.85-9.70 (m, 1H), 2.34-2.26 (m, 1H), 2.16-2.06 (m, 1H), 2.01-1.95 (m, 1H), 1.89-1.60 (m, 8H), 1.49-1.18 (m, 16H), 1.13-1.00 (m, 3H), 0.69 (s, 3H).

Step 2. To a stirring solution of 2-(tert-butyldimethylsilyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide (189 mg, 656 μmol) in 2 mL of THF was added drop wise n-BuLi (2.5 M; 196 μL, 492 μmol) at -65°C. After stirring at -65°C for 40 min, a solution of **A31** (100 mg, 328 μmol) in 2 mL of THF was added drop wise at -65°C. After stirring at 15°C for 2 h, TLC showed the reaction was complete. The reaction mixture was poured into ice-cold water and extracted with EtOAc (20 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated in vacuum to afford **A33** (140 mg, crude) as a solid.

Step 3. To a stirring solution of **A33** (140 mg, 235 μmol) in 5 mL of DCM was added Dess-Martin (199 mg, 470 μmol) at 15°C. The mixture was stirring at 15°C for 2 hours. TLC showed the reaction was complete. The reaction mixture was poured into sat. Na₂S₂O₃ (20 mL) and extracted with EtOAc (20 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated in vacuum. The residue was purified by silica gel chromatography (PE/EA = 10/1~3/1) to afford **A34** (70 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 8.17 (s, 1H), 7.66 (s, 1H), 3.13-3.02 (m, 7H), 2.86 (s, 1H), 2.40-2.30 (m, 1H), 1.85-1.78 (m, 3H), 1.77-1.70 (m, 2H), 1.68-1.57 (m, 4H), 1.52-1.22 (m, 17H), 1.17-1.07 (m, 2H), 1.04-0.93 (m, 1H), 0.67 (s, 3H).

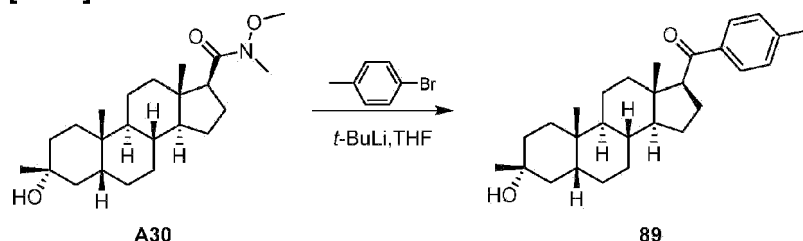
Step 4. To a solution of **A34** (30 mg, 62.8 μmol) in THF (3 mL) was added hydrogen chloride (1 M, 125 μL, 125 μmol) at 15°C. The mixture was stirred at 15°C for 1 hr. and then the reaction mixture was quenched with saturated sat. NaHCO₃ (30 mL). The mixture was extracted with EtOAc (20 mL x 2). The combined organic layer washed with brine (30 mL), dried over Na₂SO₄, filtered and evaporated in vacuum to give crude product which was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*25*10μm, gradient: 29-54% B (A = 0.225%FA-ACN, B = acetonitrile), flow rate: 30 mL/min) and then triturated with n-hexane (5 mL) to give **88** (8.8 mg) as a solid.

¹H NMR (CDCl₃, 400MHz): δ 7.77 (s, 1H), 7.68 (s, 1H), 3.25-3.05 (m, 1H), 2.39-2.31 (m, 1H), 1.87-1.80 (m, 3H), 1.78-1.60 (m, 8H), 1.51-1.30 (m, 10H), 1.27 (s, 3H), 1.17-1.06 (m, 2H),

1.04-0.96 (m, 1H), 0.65 (s, 3H). **LCMS** Rt = 1.000 min in 2.0 min chromatography, 10-80 AB, MS ESI calcd. for $C_{23}H_{35}N_2O_2$ $[M + H]^+$ 371, found 371.

Example 90. Synthesis of compound 89.

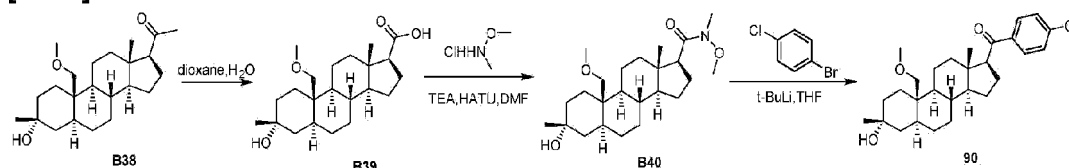
[0403]



[0404] To a stirred solution of 1-bromo-4-methylbenzene (224 mg, 1.31 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M, 1.92 mL, 2.5 mmol) drop-wise at -78°C under N_2 . After stirring at -78°C for 1 hour, **A30** (100 mg, 0.264 mmol) was added. The mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with saturated NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product, which was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um, gradient: 85-85% B (A = 0.05% HCl-ACN, B = acetonitrile), flow rate: 30 mL/min) to give **89** (18.1 mg) as a solid. 1H NMR ($CDCl_3$, 400MHz): δ 7.79 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 3.47 (t, J = 8.8 Hz, 1H), 2.38-2.48 (m, 4H), 1.97 (t, J = 13.2 Hz, 1H), 1.62-1.90 (m, 5H), 1.32-1.51 (m, 10H), 1.20-1.30 (m, 6H), 1.08-1.18 (m, 2H), 1.04 (dd, J = 14.1, 3.6 Hz, 1H), 0.91 (s, 3H), 0.58 (s, 3H). **LCMS** Rt = 1.267 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $C_{28}H_{41}O_2$ $[M + H]^+$ 409, found 409.

Example 91. Synthesis of compound 90.

[0405]



Step 1. To a solution of **B38** (10 g, 27.5 mmol) in dioxane/ H_2O (374 mL/110 mL) at 0°C was added sodium hypobromide [prepared from NaOH (145 g), bromine (47.7 mL), dioxane (798 mL) and H_2O (1230 mL)]. The resulting mixture was stirred at 25°C for 24 hours and was

cooled to 0°C. Saturated aqueous sodium sulfite solution (1000 mL) and aqueous HCl solution (1 M, 500 mL) were sequentially added. The mixture was extracted with ethyl acetate (1000mL X 2). The organic phase was washed with water (1000mL X 3), brine (1000mL), dried over anhydrous Na₂SO₄, filtered and evaporated to afford **B39** (8 g) as a solid.

¹H NMR (DMSO-d₆, 400MHz) δ = 11.90 (br. s., 1H), 3.89 (s, 1H), 3.67 - 3.61 (m, 1H), 3.43 (d, J = 10.0 Hz, 1H), 3.31 (br. s., 1H), 3.20 (s, 3H), 2.25 (t, J = 9.0 Hz, 1H), 2.00 - 1.77 (m, 3H), 1.72 - 1.28 (m, 11H), 1.22 - 0.99 (m, 11H), 0.95 - 0.81 (m, 1H), 0.76 - 0.67 (m, 1H), 0.63 (s, 3H).

Step 2. To a solution of **B39** (7.8 g, 21.3 mmol) in DMF (100 mL) was added HATU (9.69 g, 25.5mmol), TEA (14.6 mL, 106 mmol) and N,O-dimethylhydroxylamine hydrochloride (7.26 g, 74.5 mmol) at 15°C. The mixture was stirred at 15°C for 2 hrs. TLC (PE/EA=1/1) showed the reaction was complete. The mixture was poured into water (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica (petroleum ether/ ethyl acetate = 10:1) to afford **B40** (8 g) as a solid .

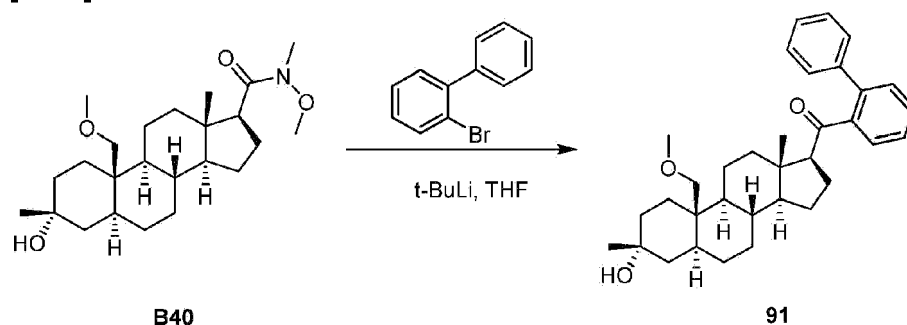
¹H NMR (CDCl₃, 400MHz) δ = 3.64 (s, 3H), 3.49 - 3.44 (m, 1H), 3.39 - 3.35 (m, 1H), 3.28 (s, 3H), 3.19 (s, 3H), 2.78 (br. s., 1H), 2.25 - 2.11 (m, 1H), 2.02 (td, J = 3.4, 13.2 Hz, 1H), 1.84 - 1.62 (m, 5H), 1.59 - 1.41 (m, 6H), 1.34 - 1.04 (m, 11H), 0.96 (dd, J = 4.8, 12.0 Hz, 1H), 0.85 - 0.72 (m, 4H). **LCMS** Rt = 3.497 min in 7.0 min chromatography, 10-80 AB, MS ESI calcd. for C₂₄H₄₂NO₄ [M + H]⁺ 408, found 408

Step 3. To a stirred solution of 1-bromo-4-chlorobenzene (75 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 uL, 0.764 mmol) dropwise at -65°C under N₂. After stirring at -65°C for 2 hrs, **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat.NH₄Cl (30 mL).The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column:Phenomenex Synergi Max-RP 250*50mm*10 um, gradient: 88-93% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) to obtain **90** (19.7 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 7.82 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 3.47 - 3.39 (m, 2H), 3.37 - 3.30 (m, 1H), 3.23 (s, 3H), 2.48 - 2.35 (m, 1H), 2.00 - 1.93 (m, 1H), 1.81 - 1.69 (m, 3H), 1.65 - 1.59 (m, 2H), 1.56 - 1.44 (m, 5H), 1.39 - 1.28 (m, 5H), 1.27 - 1.14 (m, 7H), 1.13 - 0.97 (m, 2H), 0.86 - 0.77 (m, 1H), 0.61 (s, 3H). **LCMS** Rt = 3.085 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for C₂₈H₄₀ClO₃ [M+H]⁺ 460.3, found 441 [M-H₂O]⁺.

Example 92. Synthesis of compound 91.

[0406]

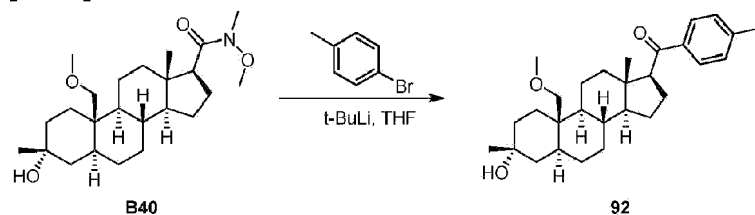


[0407] To a stirring solution of 2-bromo-1,1'-biphenyl (91.3 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 μ L, 0.764 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 92-98% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to obtain **91** (17.8 mg) as a solid.

$^1\text{H NMR}$ (CDCl_3 , 400MHz) δ 7.51 - 7.30 (m, 9H), 3.38 - 3.34 (m, 1H), 3.30 - 3.25 (m, 1H), 3.22 (s, 3H), 2.31 - 2.25 (m, 1H), 2.23 - 2.14 (m, 1H), 1.93 - 1.86 (m, 1H), 1.51 - 1.32 (m, 8H), 1.31 - 1.16 (m, 6H), 1.15 - 0.69 (m, 8H), 0.64 - 0.54 (m, 5H). **LCMS** Rt = 3.112 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{34}\text{H}_{45}\text{O}_3$ $[\text{M} + \text{H}]^+$ 501, found 501.

Example 93. Synthesis of compound 92.

[0408]



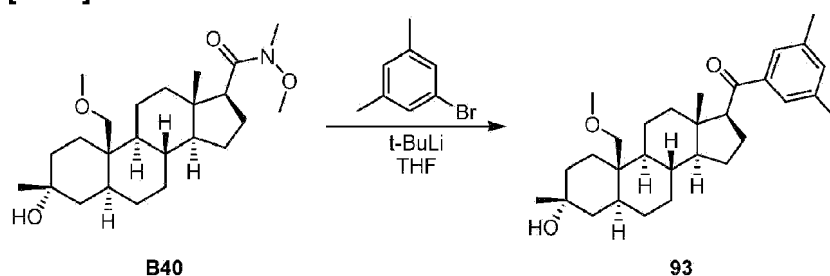
[0409] To a stirring solution of 1-bromo-4-methylbenzene (67 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 μ L, 0.764 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC

separation (column: Boston Green ODS 150*30 5u, gradient: 82-98% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to obtain **92** (24.9 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 7.78 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 3.50 - 3.39 (m, 2H), 3.37 - 3.31 (m, 1H), 3.23 (s, 3H), 2.48 - 2.37 (m, 4H), 2.00 - 1.93 (m, 1H), 1.79 - 1.69 (m, 3H), 1.62 - 1.54 (m, 3H), 1.50 - 1.44 (m, 3H), 1.42 - 1.25 (m, 6H), 1.25 - 1.15 (m, 5H), 1.15 - 0.92 (m, 3H), 0.86 - 0.76 (m, 1H), 0.61 (s, 3H). **LCMS** Rt = 2.954 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for C₂₉H₄₃O₃ [M + H]⁺ 439, found 421 [M-H₂O]⁺.

Example 94. Synthesis of compound 93.

[0410]



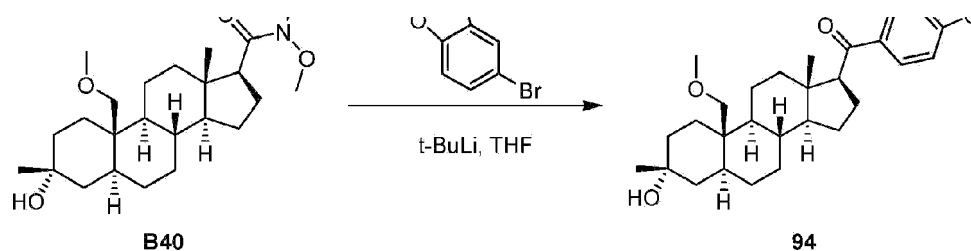
[0411] To a stirring solution of 1-bromo-3,5-dimethylbenzene (72.5 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 μ L, 0.764 mmol) dropwise at -65°C under N₂. After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with sat. NH₄Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi Max-RP 250*50mm*10 μ m, gradient: 88-93% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **93** (47.4 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 7.45 (s, 2H), 7.16 (s, 1H), 3.49 - 3.40 (m, 2H), 3.37 - 3.32 (m, 1H), 3.23 (s, 3H), 2.45 - 2.33 (m, 7H), 2.00 - 1.95 (m, 1H), 1.80 - 1.70 (m, 3H), 1.56 - 1.44 (m, 6H), 1.43 - 1.25 (m, 6H), 1.24 - 1.17 (m, 5H), 1.16 - 0.95 (m, 3H), 0.87 - 0.75 (m, 1H), 0.62 (s, 3H). **LCMS** Rt = 3.124 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for C₃₀H₄₅O₃ [M + H]⁺ 453, found 453.

Example 95. Synthesis of compound 94.

[0412]



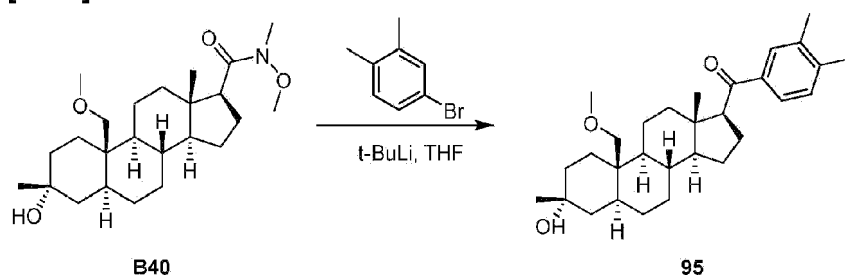


[0413] To a stirring solution of 5-bromobenzo[d][1,3]dioxole (78.7 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 μ L, 0.764 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi Max-RP 250*50mm*10 μ m, gradient: 88-93% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) to obtain **94** (28.2 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz) δ 7.49 (dd, 1H), 7.39 (d, 1H), 6.83 (d, 1H), 6.03 (s, 2H), 3.45 - 3.33 (m, 3H), 3.24 (s, 3H), 2.45 - 2.36 (m, 1H), 2.01 - 1.95 (m, 1H), 1.77 - 1.68 (m, 3H), 1.60 - 1.50 (m, 2H), 1.53 - 1.42 (m, 5H), 1.42 - 1.18 (m, 10H), 1.15 - 0.96 (m, 3H), 0.86 - 0.77 (m, 1H), 0.61 (s, 3H). LCMS Rt = 3.401 min in 4.0 min chromatography, 10-10 AB, MS ESI calcd. for $\text{C}_{29}\text{H}_{41}\text{O}_5$ $[\text{M}+\text{H}]^+$ 469.3, found 451 $[\text{M}-\text{H}_2\text{O}]^+$.

Example 94. Synthesis of compound 95.

[0414]



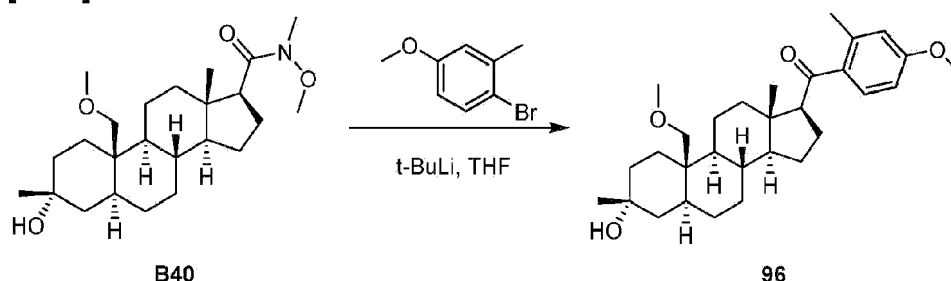
[0415] To a stirring solution of 4-bromo-1,2-dimethylbenzene (72.5 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 μ L, 0.764 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC

separation (column:Phenomenex Synergi Max-RP 250*50mm*10 um, gradient: 88-93% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **95** (12 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 7.65 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 3.49 - 3.39 (m, 2H), 3.37 - 3.31 (m, 1H), 3.23 (s, 3H), 2.47 - 2.36 (m, 1H), 2.30 (s, 6H), 2.00 - 1.95 (m, 1H), 1.78 - 1.68 (m, 3H), 1.54 - 1.44 (m, 6H), 1.42 - 1.17 (m, 11H), 1.16 - 0.92 (m, 3H), 0.86 - 0.75 (m, 1H), 0.61 (s, 3H). **LCMS** Rt =3.079 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for C₃₀H₄₅O₃ [M +H]⁺ 453, found 453

Example 97. Synthesis of compound 96.

[0416]



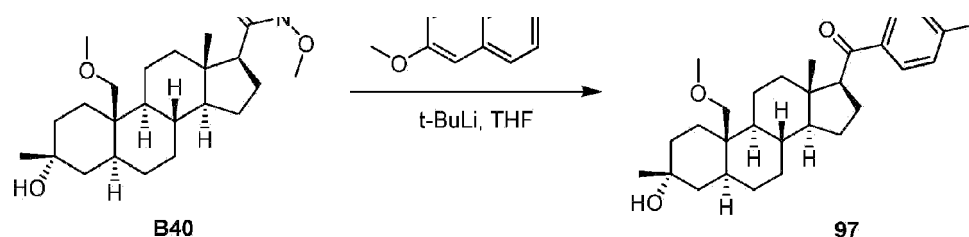
[0417] To a stirring solution of 1-bromo-4-methoxy-2-methylbenzene (78.8 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 uL, 0.764 mmol) dropwise at -65°C under N₂. After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with sat.NH₄Cl (30 mL).The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column:Boston Green ODS 150*30 5u, gradient: 92-98% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to obtain **96** (14.3 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 7.53 (d, *J* = 8.6 Hz, 1H), 6.76 - 6.68 (m, 2H), 3.83 (s, 3H), 3.44 - 3.40 (m, 1H), 3.36 - 3.29 (m, 2H), 3.23 (s, 3H), 2.47 (s, 3H), 2.44 - 2.34 (m, 1H), 1.99 - 1.90 (m, 1H), 1.77 - 1.67 (m, 3H), 1.51 - 1.41 (m, 6H), 1.39 - 1.12 (m, 11H), 1.11 - 0.94 (m, 3H), 0.81 - 0.72 (m, 1H), 0.64 (s, 3H). **LCMS** Rt =2.925 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for C₃₀H₄₅O₄ [M +H]⁺ 469, found 469.

Example 98. Synthesis of compound 97.

[0418]



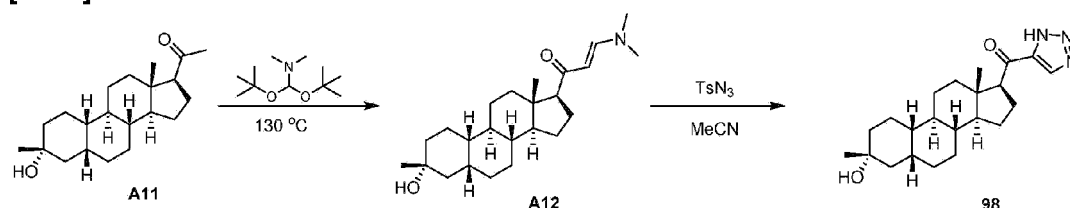


[0419] To a stirring solution of 2-bromo-6-methoxynaphthalene (92.9 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 μ L, 0.764 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi Max-RP 250*50mm*10 μ m, gradient: 84-84% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **97** (36.5 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz) δ 8.33 (s, 1H), 7.96 (dd, J = 1.4, 8.7 Hz, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.20 (dd, J = 2.4, 8.9 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 3.95 (s, 3H), 3.63 (t, J = 8.8 Hz, 1H), 3.46 - 3.40 (m, 1H), 3.36 - 3.30 (m, 1H), 3.22 (s, 3H), 2.55 - 2.42 (m, 1H), 2.00-1.90 (m, 1H), 1.82 - 1.71 (m, 3H), 1.53 - 1.44 (m, 6H), 1.43 - 1.31 (m, 6H), 1.25 - 1.20 (m, 5H), 1.17 - 0.99 (m, 3H), 0.87 - 0.80 (m, 1H), 0.66 (s, 3H). LCMS Rt = 1.278 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{33}\text{H}_{45}\text{O}_4$ $[\text{M}+\text{H}]^+$ 505.3, found 487 $[\text{M}-\text{H}_2\text{O}]^+$.

Example 99. Synthesis of compound 98.

[0420]



Step 1. To a solution of **A11** (1.0 g, 3.13 mmol) in 1,1-di-tert-butoxy-N,N-dimethylmethanamine (10 mL) was refluxed at 130°C for 18 hours. The mixture was concentrated to give 8.4 g of crude product **A12** which was used for next step directly.

LCMS Rt = 1.754 min in 3.0 min chromatography, 10-80 AB, MS ESI calcd. for $\text{C}_{24}\text{H}_{40}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 374, found 374.

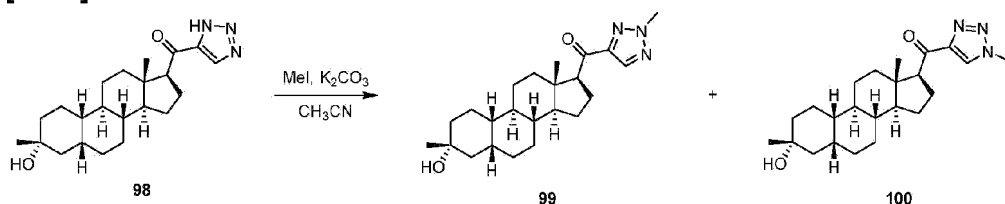
Step 2. To a solution of crude **A12** (1.16 g, 3.10 mmol, 8.4 g crude) in CH_3CN (20 mL) was

added 4-methylbenzenesulfonyl azide (3.05 g, 15.5 mmol). The mixture was stirred at 15 °C for 25 hours. LCMS showed the starting material was consumed, and the desired compound was determined by LCMS. The solution was quenched with Sat. $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL). The mixture was extracted with EA (50 mL X 2). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated in vacuum to give the crude product (3.6 g). The crude product was purified by silica gel chromatography (PE: EA=1: 1) to give product as solid (450 mg, crude), which was purified by prep-HPLC (column: Phenomenex Synergi C18 150*25*10um, gradient: 38-63% B (A= water (0.1%TFA), B= acetonitrile), flow rate: 30 mL/min) to afford 110mg of **98**.

^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 3.63 (t, J = 8.5 Hz, 1H), 2.43-2.29 (m, 1H), 1.95-0.90 (m, 29H), 0.66 (s, 3H). **LCMS** Rt = 1.860 min in 3.0 min chromatography, 10-80 AB, MS ESI calcd. for $\text{C}_{22}\text{H}_{34}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 372, found 372.

Example 100. Synthesis of compounds **99** and **100**.

[0421]



[0422] To a solution of **98** (88 mg, 236 μmol) in CH_3CN (1 mL) was added K_2CO_3 (97.7 mg, 708 μmol) and MeI (0.650, 4.58 mmol). The reaction mixture was stirred at 15 °C for another 15 hrs. The starting material was consumed completely which was determined by LCMS. The reaction was quenched with aqueous sodium hypochlorite (5%, 20 mL). The mixture was extracted with EA (50 mL X 3). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuum to give the crude product. The crude product was purified by silica gel chromatography (PE: EA=1: 1) to give the crude **99** (25 mg) and **100** (13 mg). **99** was purified by prep-HPLC (column: Boston Green ODS 150*30 5u, gradient: 68-98% B (A= water (0.05% HCl), B= acetonitrile), flow rate: 25 mL/min) to give purified **99** (5 mg), the structure of **99** was randomly assigned. **100** was purified by prep-HPLC (column: Boston Green ODS 150*30 5u, gradient: 65-95% B (A= water (0.05% HCl), B= acetonitrile), flow rate: 25 mL/min) to give **100** (4.2 mg).

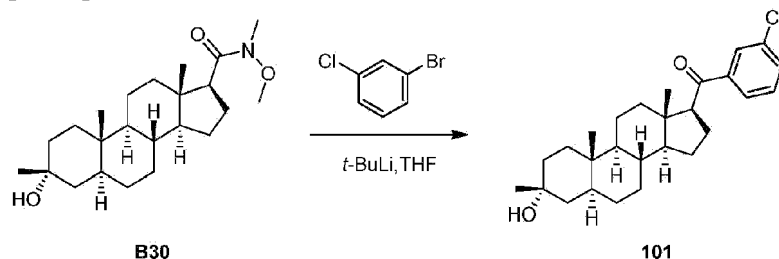
99: **^1H NMR** (400 MHz, CDCl_3) δ 7.99 (s, 1H), 4.24 (s, 3H), 3.53 (t, J = 8.5 Hz, 1H), 2.42 - 2.25 (m, 1H), 2.09 - 0.84 (m, 32H), 0.65 (s, 3H). **LCMS** Rt = 1.228 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{23}\text{H}_{36}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 386, found 368 $[\text{M}-\text{H}_2\text{O}]^+$.

100: **^1H NMR** (400 MHz, CDCl_3) δ 8.01 (s, 1H), 4.14 (s, 3H), 3.83 (t, J = 8.9 Hz, 1H), 2.38 -

2.25 (m, 1H), 1.88 - 0.81 (m, 35H), 0.65 (s, 3H). LCMS Rt = 1.085 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $C_{23}H_{36}N_3O_2$ $[M+H]^+$ 386, found 386.

Example 101. Synthesis of compound 101.

[0423]

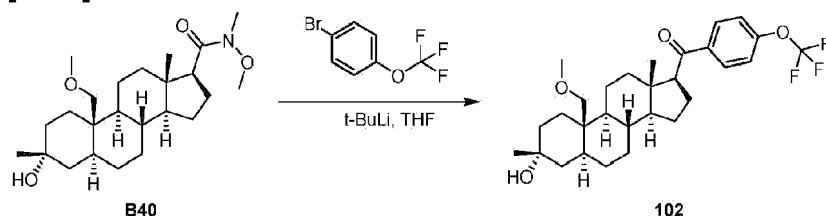


[0424] To a stirred solution of 1-bromo-3-chlorobenzene (50.5 mg, 0.264 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M, 406 μ L, 0.528 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, **B30** (50 mg, 0.132 mmol) was added. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 150*25*10 μ m, gradient: 72-97% B (A= 0.225%FA-ACN, B= acetonitrile), flow rate: 30 mL/min) to obtain 30mg of impure material. Additional HPLC separation (column: Phenomenex Synergi C18 250*21.2mm*4 μ m, gradient: 95-95% B (A=0.05%HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) gave **101** as (8.2 mg) a white solid.

^1H NMR (CDCl_3 , 400MHz) δ 7.84 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.41 - 7.35 (m, 1H), 3.41 (t, J = 8.8 Hz, 1H), 2.43 - 2.35 (m, 1H), 1.84 - 1.65 (m, 4H), 1.53 - 1.44 (m, 5H), 1.38 - 1.22 (m, 9H), 1.21 - 1.11 (m, 5H), 1.03 - 0.92 (m, 1H), 0.82 - 0.75 (m, 1H), 0.71 (s, 3H), 0.59 (s, 3H). LCMS Rt = 1.326 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{27}\text{H}_{38}\text{ClO}_2$ $[M+H]^+$ 429.2, found 411 $[M-\text{H}_2\text{O}]^+$.

Example 102. Synthesis of compound 102.

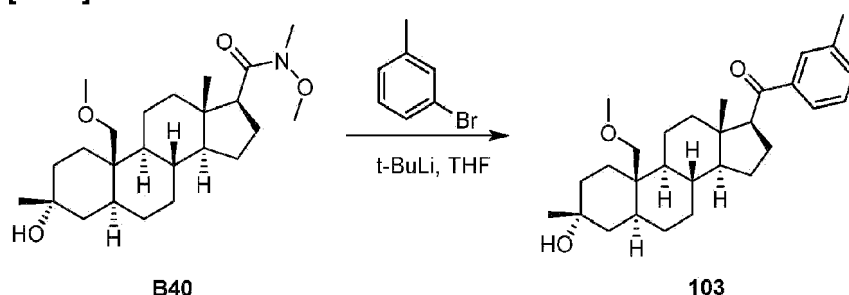
[0425]



[0426] To a stirring solution of 1-bromo-4-(trifluoromethoxy)benzene (94.4 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 μ L, 0.764 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 90-100% B (A= 0.05% HCl -ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **102** (45.8 mg) as a solid. ^1H NMR (CDCl_3 , 400MHz) δ 7.92 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 3.47 - 3.40 (m, 2H), 3.36 - 3.32 (m, 1H), 3.23 (s, 3H), 2.47 - 2.35 (m, 1H), 2.00 - 1.94 (m, 1H), 1.79 - 1.70 (m, 3H), 1.53 - 1.43 (m, 6H), 1.41 - 1.27 (m, 6H), 1.26 - 1.18 (m, 5H), 1.16 - 0.96 (m, 3H), 0.86 - 0.78 (m, 1H), 0.62 (s, 3H). LCMS R_t = 3.164 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{29}\text{H}_{40}\text{F}_3\text{O}_4$ $[\text{M} + \text{H}]^+$ 509.3, found 491 $[\text{M} - \text{H}_2\text{O}]^+$.

Example 103. Synthesis of compound 103.

[0427]



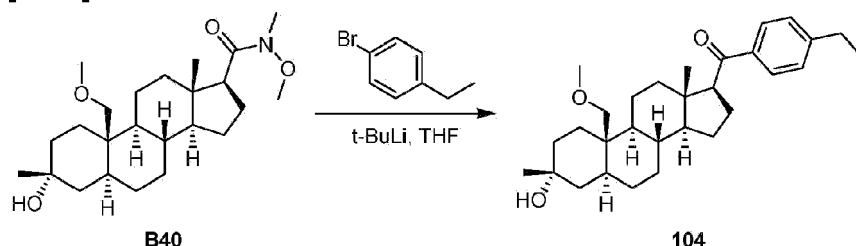
[0428] To a stirring solution of 1-bromo-3-methylbenzene (67 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 μ L, 0.764 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 82-98% B (A= 0.05% HCl -ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to obtain **103** (40.3 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz) δ 7.69 - 7.62 (m, 2H), 7.36 - 7.28 (m, 2H), 3.50 - 3.40 (m, 2H), 3.37 - 3.31 (m, 1H), 3.23 (s, 3H), 2.48 - 2.37 (m, 4H), 2.00 - 1.93 (m, 1H), 1.80 - 1.70 (m, 3H), 1.65 - 1.50 (m, 4H), 1.48 - 1.44 (m, 2H), 1.38 - 1.25 (m, 6H), 1.25-1.18 (m, 5H), 1.16 - 0.93 (m, 3H), 0.86 - 0.78 (m, 1H), 0.62 (s, 3H). LCMS R_t = 2.960 min in 4.0 min chromatography, 30-90 AB,

MS ESI calcd. for $C_{29}H_{43}O_3$ $[M + H]^+$ 439.3, found 421 $[M - H_2O]^+$.

Example 104. Synthesis of compound 104.

[0429]

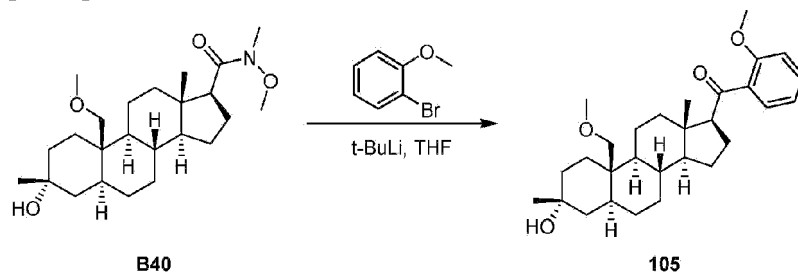


[0430] To a stirring solution of 1-bromo-4-ethylbenzene (72.5 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 μ L, 0.764 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi Max-RP 250*50mm*10 μ m, gradient: 88-93% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **104** (22.6 mg) as a solid.

1H NMR ($CDCl_3$, 400MHz) δ 7.80 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 3.49 - 3.40 (m, 2H), 3.36 - 3.31 (m, 1H), 3.23 (s, 3H), 2.69 (q, J = 7.6 Hz, 2H), 2.49 - 2.36 (m, 1H), 2.01 - 1.93 (m, 1H), 1.77 - 1.68 (m, 3H), 1.54 - 1.44 (m, 6H), 1.41 - 1.34 (m, 2H), 1.33 - 1.16 (m, 12H), 1.16 - 0.95 (m, 3H), 0.86 - 0.77 (m, 1H), 0.62 (s, 3H). LCMS R_t = 3.113 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for $C_{30}H_{45}O_3$ $[M + H]^+$ 453, found 453

Example 105. Synthesis of compound 105.

[0431]

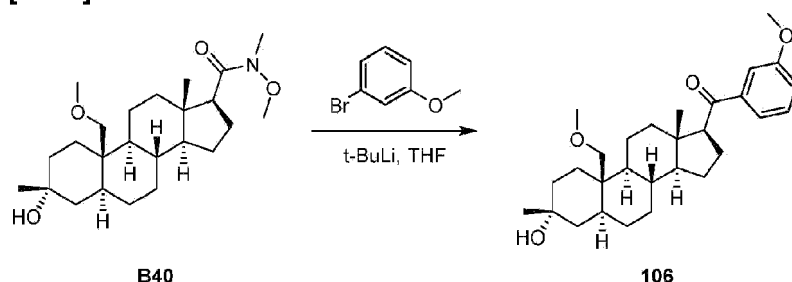


[0432] To a stirring solution of 1-bromo-2-methoxybenzene (228 mg, 1.22mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 1.69 mL, 2.2 mmol) dropwise at -65°C under N₂. After stirring at -65°C for 2 hrs, a solution of **B40** (100 mg, 0.245 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with sat.NH₄Cl (30 mL).The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column:Phenomenex Synergi Max-RP 250*50mm*10 um, gradient: 83-88% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 30 mL/min)to obtain **105** (11.4 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 7.40 - 7.34 (m, 1H), 7.31 (dd, *J* = 1.6, 7.7 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.51 (t, *J* = 9.0 Hz, 1H), 3.44 - 3.38 (m, 1H), 3.35 - 3.29 (m, 1H), 3.23 (s, 3H), 2.41 - 2.30 (m, 1H), 2.00 - 1.90 (m, 1H), 1.78 - 1.67 (m, 4H), 1.53-1.40 (m, 7H), 1.33 - 1.26 (m, 2H), 1.25 - 1.20 (m, 5H), 1.18 - 0.87 (m, 5H), 0.80 - 0.70 (m, 1H), 0.63 (s, 3H). LCMS Rt =2.730 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for C₂₉H₄₃O₄ [M +H]⁺ 455, found 455.

Example 106. Synthesis of compound 106.

[0433]



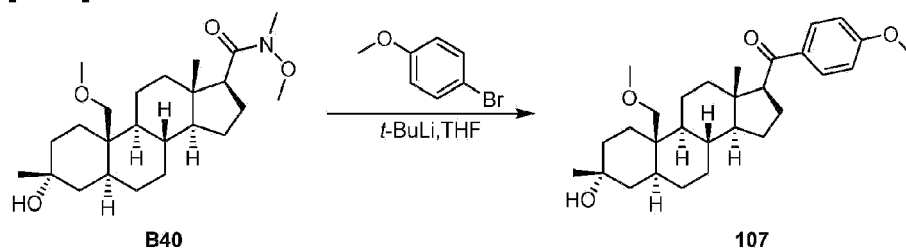
[0434] To a stirring solution of 1-bromo-3-methoxybenzene (183 mg, 0.980 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 1.35 mL, 1.76 mmol) dropwise at -65°C under N₂. After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with sat.NH₄Cl (30 mL).The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi Max-RP 250*50mm*10 um, gradient: 85-95% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **106** (15.4 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 7.45 (d, *J* = 7.8 Hz, 1H), 7.39 (s, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* = 2.0, 8.3 Hz, 1H), 3.85 (s, 3H), 3.48 - 3.39 (m, 2H), 3.36 - 3.31 (m, 1H), 3.23 (s, 3H), 2.47 - 2.35 (m, 1H), 1.97 (d, *J* = 13.2 Hz, 1H), 1.81 - 1.69 (m, 3H), 1.52 - 1.17 (m, 17H), 1.16 -

0.92 (m, 3H), 0.85 - 0.75 (m, 1H), 0.62 (s, 3H). **LCMS** Rt =2.821 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $C_{29}H_{43}O_4$ $[M + H]^+$ 455, found 455.

Example 107. Synthesis of compound 107.

[0435]

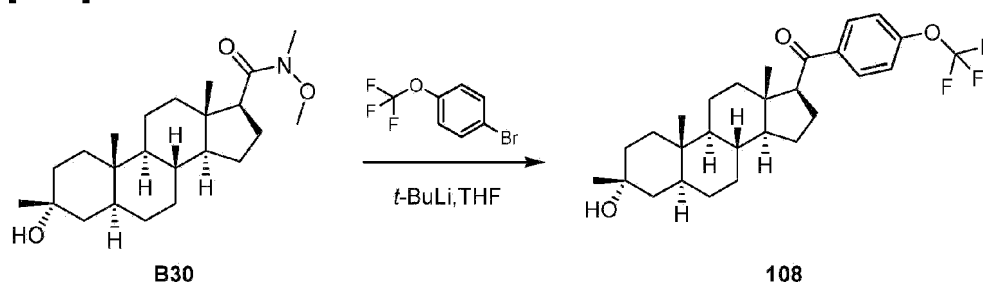


[0436] To a stirred solution of 1-bromo-4-methoxybenzene (91.6 mg, 0.490 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 753 μ L, 0.98 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, **B40** (100 mg, 0.245 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi C18 250*21.2mm*4 μ m, gradient: 75-95% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) to obtain **107** (25.6 mg) as a solid.

1H NMR ($CDCl_3$, 400MHz) δ 7.89 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 3.49 - 3.39 (m, 2H), 3.37 - 3.30 (m, 1H), 3.23 (s, 3H), 2.49 - 2.35 (m, 1H), 2.01 - 1.93 (m, 1H), 1.78-1.68 (m, 3H), 1.54 - 1.39 (m, 7H), 1.38 - 1.17 (m, 10H), 1.16 - 0.92 (m, 3H), 0.85 - 0.75 (m, 1H), 0.61 (s, 3H). **LCMS** Rt =2.790 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for $C_{29}H_{43}O_4$ $[M + H]^+$ 455, found 455

Example 108. Synthesis of compound 108.

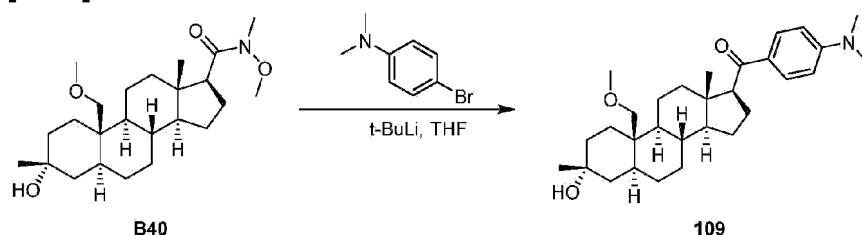
[0437]



[0438] To a stirred solution of 1-bromo-4-(trifluoromethoxy)benzene (127 mg, 0.528 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 807 μ L, 1.05 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, a solution of **B30** (50 mg, 0.132 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product, which was purified by prep-HPLC separation (column:Phenomenex Synergi C18 150*30mm*4 μ m, gradient: 90-95% B (A= 0.05% HCl -ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to obtain **108** (49.1 mg) as a solid. ^1H NMR (CDCl_3 , 400MHz) δ 7.93 (d, J = 8.8 Hz, 2H), 7.26 - 7.23 (m, 2H), 3.44 (t, J = 8.8 Hz, 1H), 2.47 - 2.34 (m, 1H), 1.80 - 1.67 (m, 3H), 1.55 - 1.41 (m, 6H), 1.40 - 1.22 (m, 9H), 1.20 - 1.13 (m, 5H), 1.04 - 0.91 (m, 1H), 0.83 - 0.74 (m, 1H), 0.71 (s, 3H), 0.59 (s, 3H). LCMS Rt =1.342 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{38}\text{F}_3\text{O}_3$ $[\text{M} + \text{H}]^+$ 479.3, found 461 $[\text{M}-\text{H}_2\text{O}]^+$.

Example 109. Synthesis of compound 109.

[0439]



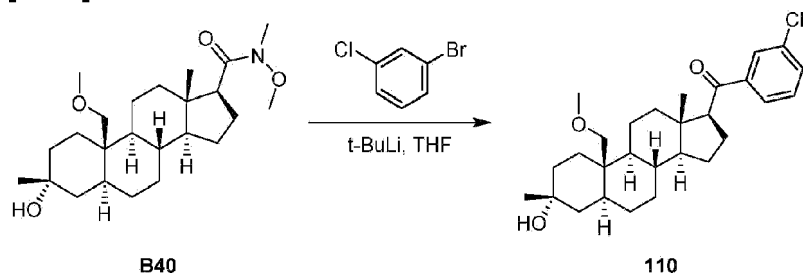
[0440] To a stirring solution of 4-bromo-N,N-dimethylaniline (78.4 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M;587 μ L, 0.764 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with sat. NH_4Cl (30 mL).The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column:Phenomenex Synergi Max-RP 250*50mm*10 μ m, gradient: 83-88% B (A= 0.05% HCl -ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **109** (26.3 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz) δ 7.87 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.0 Hz, 2H), 3.46 - 3.40 (m, 2H), 3.38 - 3.32 (m, 1H), 3.23 (s, 3H), 3.06 (s, 6H), 2.49 - 2.37 (m, 1H), 2.00 - 1.95 (m, 1H), 1.77 - 1.68 (m, 3H), 1.54 - 1.44 (m, 7H), 1.42 - 1.27 (m, 5H), 1.27 - 1.16 (m, 5H), 1.15 - 0.93 (m, 3H), 0.86 - 0.78 (m, 1H), 0.62 (s, 3H). LCMS Rt =2.113 min in 3.0 min chromatography,

30-90 AB, MS ESI calcd. for $C_{30}H_{46}NO_3$ $[M + H]^+$ 468, found 468

Example 110. Synthesis of compound 110.

[0441]

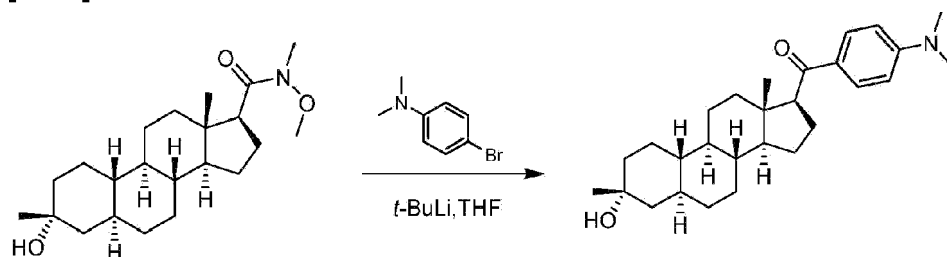


[0442] To a stirring solution of 1-bromo-3-chlorobenzene (75 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 μ L, 0.764 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi Max-RP 250*50mm*10 μ m, gradient: 88-93% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **110** (10.3 mg) as a solid.

1H NMR ($CDCl_3$, 400MHz) δ 7.83 (t, J = 1.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.52 - 7.47 (m, 1H), 7.41 - 7.34 (m, 1H), 3.45 - 3.39 (m, 2H), 3.36 - 3.31 (m, 1H), 3.23 (s, 3H), 2.46 - 2.35 (m, 1H), 2.00 - 1.92 (m, 1H), 1.80 - 1.68 (m, 4H), 1.52 - 1.42 (m, 5H), 1.38 - 1.25 (m, 6H), 1.25 - 1.21 (m, 5H), 1.15 - 0.98 (m, 3H), 0.85 - 0.75 (m, 1H), 0.61 (s, 3H). LCMS R_t = 3.113 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for $C_{28}H_{40}ClO_3$ $[M + H]^+$ 459.3, found 441 $[M - H_2O]^+$.

Example 111. Synthesis of compound 111.

[0443]



B10

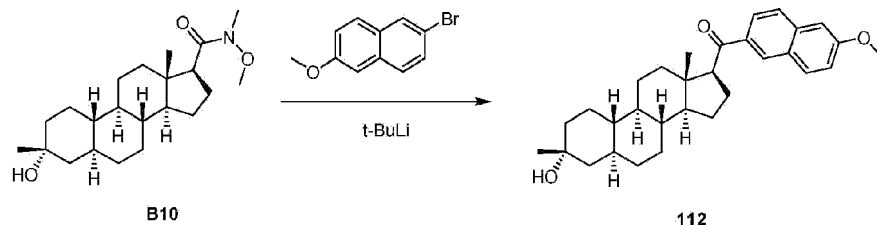
111

[0444] To a stirred solution of 4-bromo-N,N-dimethylaniline (110 mg, 0.550 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 838 μ L, 1.09 mmol) dropwise at -65°C under N_2 . After stirring at -65°C for 2 hrs, a solution of **B10** (100 mg, 0.275 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat. NH_4Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na_2SO_4 , filtered, and evaporated in vacuum to give crude product, which was purified by HPLC separation (column:Phenomenex Synergi C18 150*25*10 μ m, gradient: 59-84% B (A= 0.1%TFA-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **111** (20 mg) as a solid.

^1H NMR (CDCl_3 , 400MHz) δ 7.87 (d, J = 9.0 Hz, 2H), 6.66 (d, J = 8.8 Hz, 2H), 3.45 (t, J = 8.8 Hz, 1H), 3.05 (s, 6H), 2.45 - 2.38 (m, 1H), 1.71 - 1.48 (m, 9H), 1.45 - 1.24 (m, 6H), 1.20 (s, 3H), 1.15 - 0.93 (m, 6H), 0.78 - 0.64 (m, 2H), 0.61 (s, 3H). LCMS R_t = 1.189 min in 2.0 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{42}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 424, found 424.

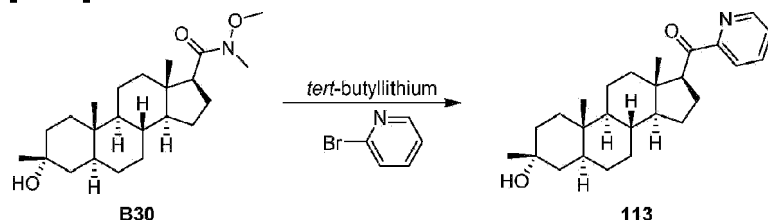
Example 112. Synthesis of compound 112.

[0445]



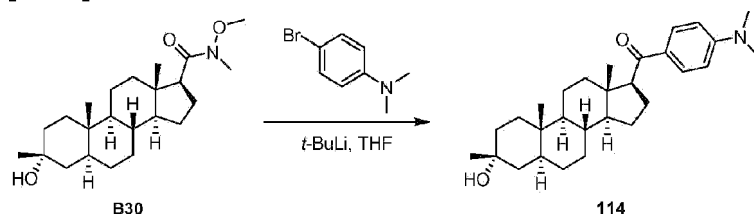
[0446] To a solution of 2-bromo-6-methoxynaphthalene (488 mg, 2.06 mmol) in THF (3 mL) was added tert-butyllithium (2.85 mL, 1.3 M in) at -70°C . The mixture was stirred at -70°C for 1 h. A solution of **B10** (150 mg, 0.4126 mmol) in THF (1 mL) was added at -70°C . The mixture was stirred at 25°C for 1 hrs. The mixture was quenched with Sat. NH_4Cl (10 mL), extracted with EtOAc (10 mL x 3), washed with brine (30 mL x 3), dried over Na_2SO_4 , filtered, concentrated in vacuum to give a crude product, which was purified with prep. HPLC (Column: Phenomenex Synergi C18 150*30mm*4 μ m; Condition: water (0.05% HCl)-ACN; Gradient 90%-95%B; Gradient Time(min):10; FlowRate(ml/min): 25) to give **112** (64.2 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 8.35-8.31 (m, 1H), 7.98-7.94 (m, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.22-7.17 (m, 1H), 7.16-7.14 (m, 1H), 3.95 (s, 3H), 3.64 (t, J = 8.7 Hz, 1H), 2.57-2.39 (m, 1H), 1.84-1.59 (m, 7H), 1.45-1.24 (m, 7H), 1.20-0.93 (m, 10H), 0.82-0.57 (m, 5H). LCMS t_R = 1.096 min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for $\text{C}_{31}\text{H}_{41}\text{O}_3$ $[\text{M} + \text{H}]^+$ 461, found 461.

Example 113. Synthesis of compound 113.**[0447]**

[0448] To a solution of 2-bromopyridine (165 mg, 1.05 mmol) in THF (5 mL) was added *tert*-butyllithium (1.45 mL) at -68°C . The mixture was stirred at -68°C for 1 hrs. **B30** (80 mg, 211 μmol) in THF (5 mL) was added dropwise at -68°C . The reaction was stirred at 25°C for 1 hrs. LCMS showed the reaction was completed. The reaction was quenched with NH_4Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give crude product, which was purified by HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 91-100% condition: (water(0.05% HCl)-ACN), flow rate: 25 mL/min) to give **113** (15 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 8.67-8.66 (m, 1H), 7.95-7.93 (m, 1H), 7.82-7.81 (m, 1H), 7.44-7.41 (m, 1H), 4.21-4.17 (m, 1H), 2.36-2.31 (m, 1H), 1.78-1.69 (m, 3H), 1.47-1.18 (m, 22H), 1.12-0.92 (m, 1H), 0.78-0.75 (m, 1H), 0.71 (s, 3H), 0.62 (s, 3H). LCMS Rt = 1.299 min in 2 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{26}\text{H}_{38}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 396, found 396.

Example 114. Synthesis of compound 114.**[0449]**

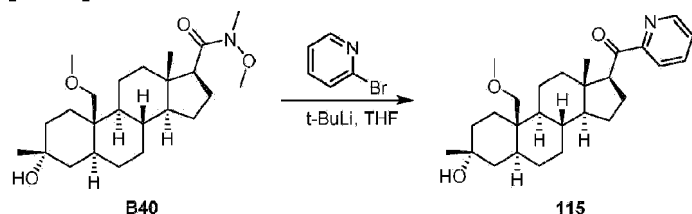
[0450] To a solution of 4-bromo-N,N-dimethylaniline (210 mg, 1.05 mmol) in THF (5 mL) was added *tert*-butyllithium (1.45 mL) at -68°C . The mixture was stirred at -68°C for 1 hrs. A solution of **B30** (80 mg, 211 μmol) in THF (5 mL) was added dropwise at -68°C . The reaction was stirred at 25°C for 1 hrs. LCMS showed the reaction was completed. The reaction was quenched with NH_4Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers

were washed with brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude product, which was purified by HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 92-98% condition: (water(0.05%HCl)-ACN), flow rate: 25 mL/min) to give **114** (57.2 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 9.0 Hz, 2H), 6.65 (d, *J* = 9.0 Hz, 2H), 3.44 (t, *J* = 8.8 Hz, 1H), 3.05 (s, 6H), 2.48 - 2.36 (m, 1H), 1.79 - 1.66 (m, 4H), 1.51 - 1.09 (m, 19H), 1.07 - 0.69 (m, 5H), 0.60 (s, 3H). LCMS Rt = 1.032 min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for C₂₉H₄₄NO₂ [M+H]⁺ 438, found 438.

Example 115. Synthesis of compound 115.

[0451]



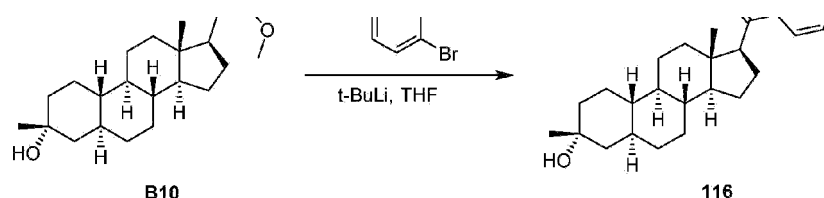
[0452] To a stirring solution of 2-bromopyridine (61.9 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 uL, 0.764 mmol) dropwise at -65°C under N₂. After stirring at -65°C for 2 hrs, a solution of **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. and then the reaction mixture was quenched with sat.NH₄Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi Max-RP 250*50mm*10 um, gradient: 83-88% B (A= 0.05%HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) for further purification to obtain **115** (36.3 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 8.67 (d, *J* = 4.6 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.2 Hz, 1H), 7.47 - 7.41 (m, 1H), 4.19 (t, *J* = 9.0 Hz, 1H), 3.46 - 3.41 (m, 1H), 3.36 - 3.31 (m, 1H), 3.23 (s, 3H), 2.40 - 2.27 (m, 1H), 2.00 - 1.92 (m, 1H), 1.85 - 1.68 (m, 4H), 1.54 - 1.44 (m, 5H), 1.44 - 1.26 (m, 6H), 1.25 - 1.13 (m, 5H), 1.12 - 0.96 (m, 3H), 0.85 - 0.75 (m, 1H), 0.64 (s, 3H). LCMS Rt = 3.208 min in 4.0 min chromatography, 10-80 AB, MS ESI calcd. for C₂₇H₄₀NO₃ [M+H]⁺ 426, found 426

Example 116. Synthesis of compound 116.

[0453]



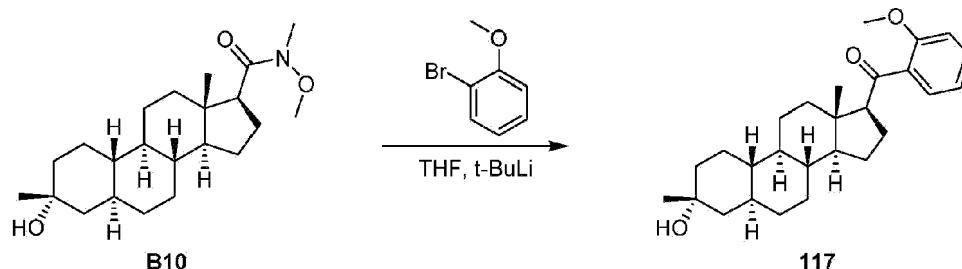


[0454] To a solution of 1-bromo-4-ethylbenzene (381 mg, 2.06 mmol) in THF (3 mL) was added tert-butyllithium (2.85 mL, 1.3 M in THF) at -70°C . The mixture was stirred at -70°C for 1 h. A solution of **B10** (150 mg, 0.4126 mmol) in THF (1 mL) was added at -70°C and the mixture was stirred at 25°C for 1 hr. The mixture was quenched with Sat. NH_4Cl (10 mL), extracted with EtOAc (10 mL x 3), washed with brine (30 mL x 3), dried over Na_2SO_4 , filtered, concentrated in vacuum to give a crude product which was purified with prep. HPLC (Column: Phenomenex Synergi C18 150*30mm*4um; Condition: water (0.05% HCl)-ACN; Gradient 90%-95%B; Gradient Time(min):10; FlowRate (ml/min): 25) to give **116** (84.4 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 3.48 (t, J = 8.7 Hz, 1H), 2.70 (q, J = 7.7 Hz, 2H), 2.50-2.26 (m, 1H), 1.77-1.59 (m, 6H), 1.55-1.50 (m, 1H), 1.45-0.85 (m, 20H), 0.77-0.57 (m, 5H). LCMS t_{R} = 1.090 min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for $\text{C}_{28}\text{H}_{41}\text{O}_2$ $[\text{M}+\text{H}]^+$ 409, found 409.

Example 117. Synthesis of compound 117.

[0455]



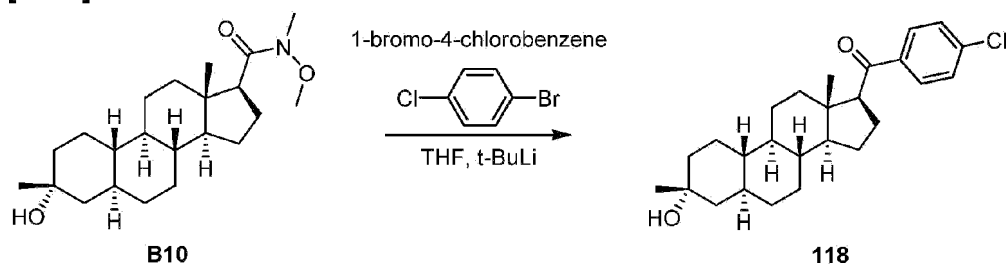
[0456] To a solution of 1-bromo-2-methoxybenzene (256 mg, 1.37 mmol) in THF (5 mL) was added tert-butyllithium (1.90 mL, 2.47 mmol) at -68°C . The mixture was stirred at -68°C for 1 hour. **B10** (100 mg, 275 μmol) in THF (5 mL) was added dropwise at -68°C . The reaction was stirred at 25°C for 2 hours. The reaction was quenched with NH_4Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give crude product which was purified by HPLC separation (Phenomenex Synergi C18 150*30mm*4um, gradient: 90-98% condition: (water(0.05% HCl)-ACN), flow rate: 25 mL/min) to give **117** (27.7 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.42 - 7.36 (m, 1H), 7.32 (dd, J = 1.8, 7.5 Hz, 1H), 7.01 - 6.89 (m,

2H), 3.85 (s, 3H), 3.56 - 3.49 (m, 1H), 2.40 - 2.29 (m, 1H), 1.83 - 1.74 (m, 1H), 1.69 - 1.49 (m, 7H), 1.36 - 1.21 (m, 5H), 1.19 (s, 3H), 1.16 - 0.83 (m, 7H), 0.70 - 0.56 (m, 5H). LCMS Rt = 1.283 min in 2 min chromatography, 30-90 AB, MS ESI calcd. for $C_{27}H_{39}O_3$ $[M+H]^+$ 411, found 411.

Example 118. Synthesis of compound 118.

[0457]

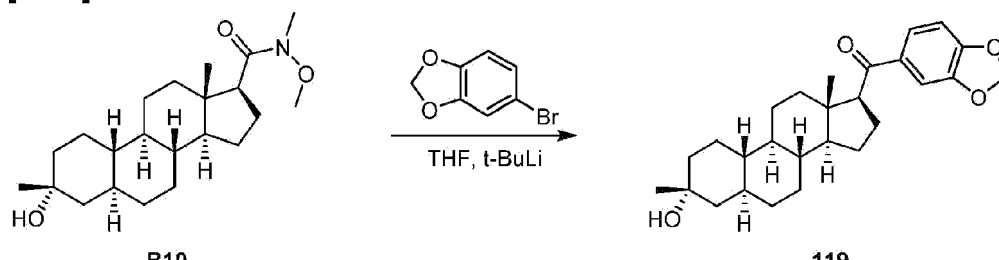


[0458] To a solution of 1-bromo-4-chlorobenzene (275 mg, 1.37 mmol) in THF (5 mL) was added tert-butyllithium (1.90 mL, 2.47 mmol) at -68°C . The mixture was stirred at -68°C for 1 hour. **B10** (100 mg, 275 μmol) in THF (5 mL) was added dropwise at -68°C . The reaction was stirred at 25°C for 2 hours. The reaction was quenched with NH_4Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give crude product which was purified by HPLC separation (Phenomenex Synergi C18 150*30mm*4 μm , gradient: 90-98% condition: (water(0.05% HCl)-ACN), flow rate: 25 mL/min) to give **118** (27.4 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H), 3.44 (t, $J = 8.7$ Hz, 1H), 2.47 - 2.36 (m, 1H), 1.82 - 1.65 (m, 5H), 1.64 - 1.61 (m, 1H), 1.55 - 1.56 (m, 1H), 1.55-1.50 (m, 1H), 1.35 - 1.32 (m, 6H), 1.22 - 0.85 (m, 10H), 0.78 - 0.57 (m, 5H). LCMS Rt = 1.411 min in 2 min chromatography, 30-90 AB, MS ESI calcd. for $C_{26}H_{36}\text{ClO}_2$ $[M+H]^+$ 415, found 415.

Example 119. Synthesis of compound 119.

[0459]

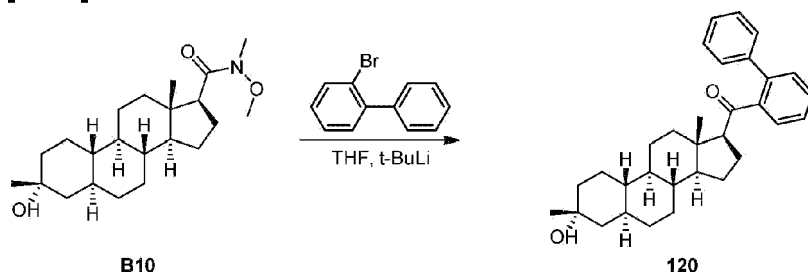


[0460] To a solution of 6-bromobenzo[d][1,3]dioxole (275 mg, 1.37 mmol) in THF (5 mL) was added tert-butyllithium (1.90 mL, 2.47 mmol) at -68°C. The mixture was stirred at -68°C for 1 hrs. **B10** (100 mg, 275 µmol) in THF (5 mL) was added dropwise at -68°C. The reaction was stirred at 25°C for 2 hours. The reaction was quenched with NH₄Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude product which was purified by HPLC separation (Phenomenex Synergi C18 150*30mm*4µm, gradient: 90-98% condition: (water(0.05%HCl)-ACN), flow rate: 25 mL/min) to give **119** (41.2 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.50 (dd, *J* = 1.6, 8.2 Hz, 1H), 7.40 (d, *J* = 1.5 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.04 (s, 2H), 3.40 (t, *J* = 8.5 Hz, 1H), 2.46 - 2.35 (m, 1H), 1.79 - 1.61 (m, 6H), 1.52-1.54 (m, 1H), 1.44-1.48 (m, 1H), 1.40 - 1.24 (m, 5H), 1.22 - 1.16 (m, 4H), 1.16 - 0.92 (m, 6H), 0.60 (m, 5H). LCMS Rt = 1.293 min in 2 min chromatography, 30-90 AB, MS ESI calcd. for C₂₇H₃₇O₄ [M+H]⁺ 425, found 425.

Example 120. Synthesis of compound 120.

[0461]



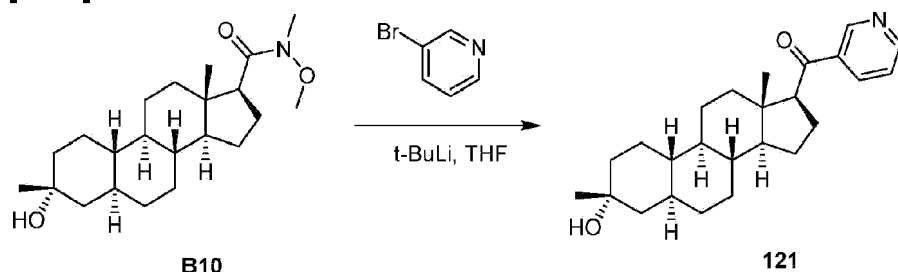
[0462] To a solution of 2-bromo-1,1'-biphenyl (319 mg, 1.37 mmol) in THF (5 mL) was added tert-butyllithium (1.90 mL, 2.47 mmol) at -68°C. The mixture was stirred at -68°C for 1 hour. **B10** (100 mg, 275 µmol) in THF (5 mL) was added dropwise at -68°C. The reaction was stirred at 25°C for 2 hours. The reaction was quenched with NH₄Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude product which was purified by HPLC separation (Phenomenex Synergi C18 150*30mm*4µm, gradient: 90-98% condition: (water(0.05%HCl)-ACN), flow rate: 25 mL/min) to give **120** (30.7 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.53 - 7.30 (m, 9H), 2.36 - 2.27 (m, 1H), 2.23 - 2.10 (m, 1H), 1.54 - 1.39 (m, 6H), 1.34 - 1.19 (m, 3H), 1.17 (s, 3H), 1.15 - 0.63 (m, 13H), 0.62 - 0.44 (m, 5H). LCMS Rt = 1.099 min in 2 min chromatography, 5-95 AB, MS ESI calcd. for C₃₂H₄₁O₂

[M+H]⁺ 457, found 457.

Example 121. Synthesis of compound 121.

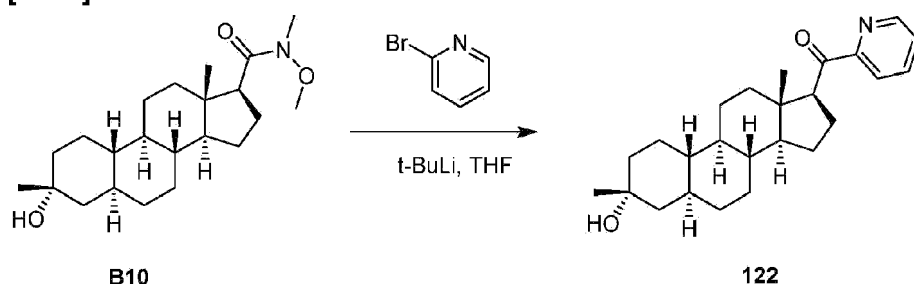
[0463]



[0464] To a solution of 3-bromopyridine (325 mg, 2.06 mmol) in THF (3 mL) was added tert-butyllithium (2.85 mL, 1.3 M in THF) at -70°C. The mixture was stirred at -70°C for 1 h. A solution of **B10** (150 mg, 0.4126 mmol) in THF (1 mL) was added at -70°C. The mixture was stirred at 25°C for 1 hrs. The mixture was quenched with Sat. NH₄Cl (10 mL), extracted with EtOAc (10 mL x 3), washed with brine (30 mL x 3), dried over Na₂SO₄, filtered, concentrated in vacuum to give a crude product, which was purified with prep. HPLC (Column: Boston Green ODS 150*30 5u; Condition: water (0.05% HCl)-CAN; Gradient: 60%-90% B; Gradient Time(min):10; 100%B Hold Time(min): 4; FlowRate(ml/min): 25) to give **121** (68 mg) as a solid. ¹H NMR (400 MHz, CD₃OD) δ 9.08 (s, 1H), 8.78 (d, *J* = 3.5 Hz, 1H), 8.44 (d, *J* = 8.3 Hz, 1H), 7.68 (dd, *J* = 5.0, 8.0 Hz, 1H), 3.66 (t, *J* = 8.5 Hz, 1H), 2.48-2.36 (m, 1H), 1.87-1.61 (m, 7H), 1.55-1.44 (m, 3H), 1.37-0.98 (m, 13H), 0.83-0.59 (m, 5H). LCMS t_R = 0.881 min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for C₂₅H₃₆NO₂ [M+H]⁺ 382, found 382.

Example 122. Synthesis of compound 122.

[0465]



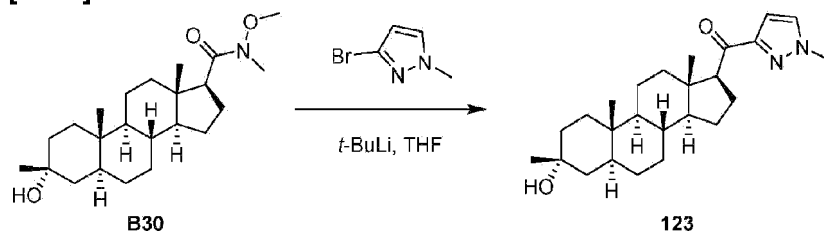
[0466] To a solution of 2-bromopyridine (325 mg, 2.06 mmol) in THF (3 mL) was added tert-butyllithium (2.85 mL, 1.3 M in THF) at -70°C. The mixture was stirred at -70°C for 1 h. A

solution of **B10** (150 mg, 0.4126 mmol) in THF (1 mL) was added at -70°C. The mixture was stirred at 25°C for 1 hrs. The mixture was quenched with Sat. NH_4Cl (10 mL), extracted with EtOAc (10 mL x 3), washed with brine (30 mL x 3), dried over Na_2SO_4 , filtered, concentrated in vacuum to give a crude product, which was purified with prep. HPLC (Column: Phenomenex Synergi C18 150*30mm*4um; Condition: water (0.05% HCl)-ACN; Gradient 90%-95%B; Gradient Time(min):10; FlowRate(ml/min): 25) to give **122** (17.7 mg,) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 8.68-8.64 (m, 1H), 7.96-7.92 (m, 1H), 7.84-7.77 (m, 1H), 7.45-7.40 (m, 1H), 4.20 (t, $J = 9.0$ Hz, 1H), 2.39-2.24 (m, 1H), 1.85-1.60 (m, 7H), 1.52-1.25 (m, 6H), 1.21-0.85 (m, 11H), 0.78-0.56 (m, 5H). LCMS $t_R = 0.998$ min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for $\text{C}_{25}\text{H}_{35}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 382, found 382.

Example 123. Synthesis of compound 123.

[0467]



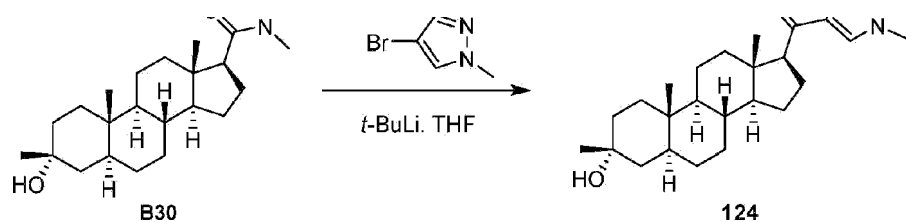
[0468] To a solution of 3-bromo-1-methyl-1H-pyrazole (169 mg, 1.05 mmol) in THF (5 mL) was added tert-butyllithium (1.45 mL) at -68°C. The mixture was stirred at -68°C for 1 hrs. **B30** (80 mg, 211 μmol) in THF (5 mL) was added dropwise at -68°C. The reaction was stirred at 25°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with NH_4Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give crude product, which was purified by HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 92-98% condition: (water(0.05% HCl)-ACN), flow rate: 25 mL/min) to give **123** (6.4 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.35 - 7.34 (m, 1H), 6.75 - 6.74 (m, 1H), 3.96 (s, 3H), 3.62 (t, $J = 8.7$ Hz, 1H), 2.38 - 2.26 (m, 1H), 1.83 - 1.67 (m, 3H), 1.56 - 1.09 (m, 19H), 1.07 - 0.91 (m, 1H), 0.89 - 0.69 (m, 4H), 0.65 (s, 3H). LCMS $R_t = 0.956$ min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for $\text{C}_{25}\text{H}_{39}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 399, found 399.

Example 124. Synthesis of compound 124.

[0469]



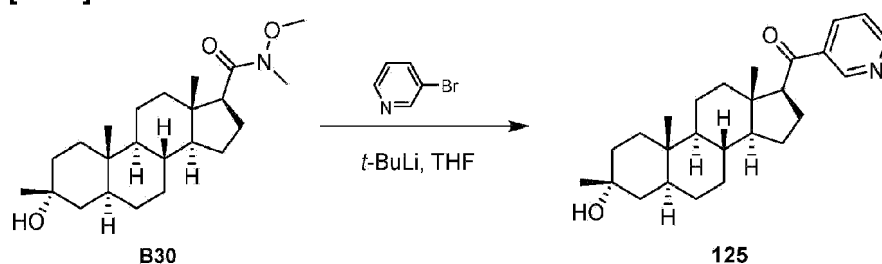


[0470] To a solution of 4-bromo-1-methyl-1H-pyrazole (169 mg, 1.05 mmol) in THF (5 mL) was added tert-butyllithium (1.45 mL) at -68°C. The mixture was stirred at -68°C for 1 hr. B30 (80 mg, 211 μ mol) in THF (5 mL) was added dropwise at -68°C. The reaction mixture was stirred at 25°C for 1 hour. LCMS showed the reaction was completed. The reaction was quenched with NH_4Cl (10 mL), extracted with EtOAc (10 mL X 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give crude product, which was purified by HPLC separation (column: Boston Green ODS 150*30 5 μ , gradient: 92-98% condition: (water(0.05% HCl)-ACN), flow rate: 25 mL/min) to give 124 (23 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.87 (s, 1H), 7.83 (s, 1H), 3.93 (s, 3H), 3.04 - 2.97 (m, 1H), 2.42-2.29 (m, 1H), 1.78 - 1.62 (m, 5H), 1.55 - 1.11 (m, 21H), 1.06 - 0.91 (m, 1H), 0.85 - 0.69 (m, 4H), 0.62 (s, 3H). LCMS Rt = 1.124 min in 2 min chromatography, 30-90 AB, MS ESI calcd. for $\text{C}_{25}\text{H}_{39}\text{N}_2\text{O}_2[\text{M}+\text{H}]^+$ 399, found 399.

Example 125. Synthesis of compound 125.

[0471]

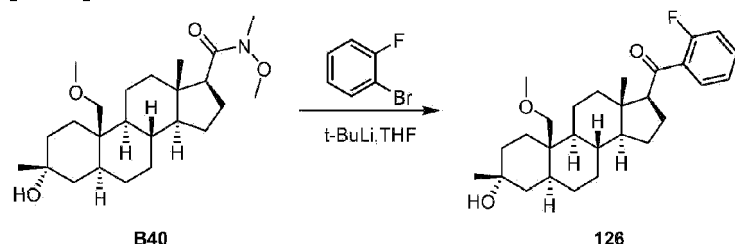


[0472] To a solution of 3-bromopyridine (206 mg, 1.31 mmol) in THF (5 mL) was added tert-butyllithium (1.82 mL) at -68°C. The mixture was stirred at -68°C for 1 hour. B30 (100 mg, 264 μ mol) in THF (5 mL) was added dropwise at -68°C. The reaction was stirred at 25°C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was quenched with NH_4Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give crude product, which was purified by HPLC separation (column: Boston Green ODS 150*30 5 μ , gradient: 92-98% condition: (water(0.05% HCl)-ACN), flow rate: 25 mL/min) to give 125 (7.4 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 9.25-9.15 (m, 1H), 8.85-8.70 (m, 1H), 8.25-2.15 (m, 1H), 7.55-7.40 (m, 1H), 3.50 - 3.40 (m, 1H), 2.51 - 2.36 (m, 1H), 1.93 - 1.62 (m, 11H), 1.56 - 1.08 (m, 26H), 1.07 - 0.65 (m, 7H), 0.60 (s, 3H). **LCMS** Rt = 0.903 min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for C₂₆H₃₈NO₂ [M+H]⁺ 396, found 396.

Example 126. Synthesis of compound 126.

[0473]

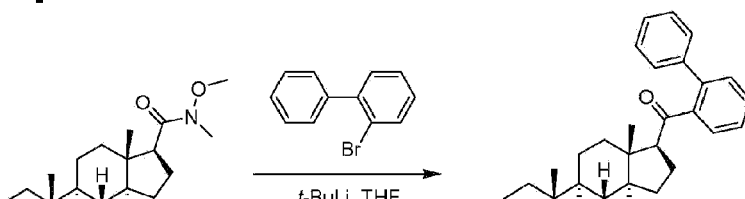


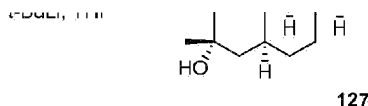
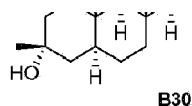
[0474] To a stirred solution of 1-bromo-2-fluorobenzene (68.5 mg, 0.392 mmol) in 3 mL of THF was added tert-butyllithium (1.3 M; 587 uL, 0.764 mmol) dropwise at -65°C under N₂. After stirring at -65°C for 2 hrs, **B40** (80 mg, 0.196 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at 15°C for 1 hour. LCMS showed the reaction was complete. The reaction mixture was quenched with Sat.NH₄Cl (30 mL). The mixture was extracted with EtOAc (20 mL x 2), washed with brine (30 mL), dried over Na₂SO₄, filtered, and evaporated in vacuum to give crude product. The crude product was purified by HPLC separation (column: Phenomenex Synergi Max-RP 250*50mm*10 um, gradient: 85-90% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 30 mL/min) to obtain **126** (19.4 mg) as a solid.

¹H NMR (CDCl₃, 400MHz) δ 7.51 (dt, *J* = 1.8, 7.6 Hz, 1H), 7.48 - 7.39 (m, 1H), 7.22 - 7.14 (m, 1H), 7.08 (dd, *J* = 8.3, 10.8 Hz, 1H), 3.43 - 3.36 (m, 2H), 3.34 - 3.29 (m, 1H), 3.23 (s, 3H), 2.45-2.32 (m, 1H), 1.94 (td, *J* = 3.5, 13.1 Hz, 1H), 1.83 - 1.66 (m, 4H), 1.51 - 1.41 (m, 6H), 1.34 - 1.16 (m, 10H), 1.15 - 0.90 (m, 3H), 0.82 - 0.71 (m, 1H), 0.62 (s, 3H). **LCMS** Rt = 2.809 min in 4.0 min chromatography, 30-90 AB, MS ESI calcd. for C₂₈H₄₀FO₃ [M + H]⁺ 443.3, found 425 [M-H₂O]⁺.

Example 127. Synthesis of compound 127.

[0475]



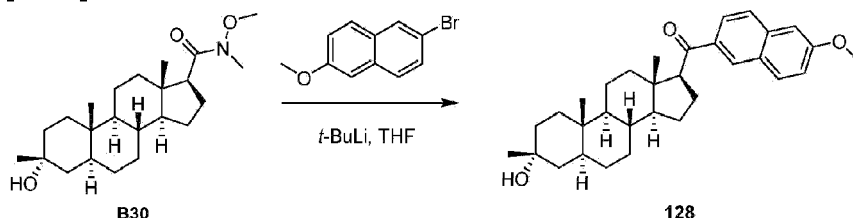


[0476] To a solution of 2-bromo-1,1'-biphenyl (244 mg, 1.05 mmol) in THF (5 mL) was added tert-butyllithium (1.45 mL) at -68°C. The mixture was stirred at -68°C for 1 hrs. A solution of **B30** (80 mg, 211 µmol) in THF (5 mL) was added dropwise at -68°C. The reaction was stirred at 25°C for 1 hour. LCMS showed the reaction was completed. The reaction was quenched with NH₄Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude product, which was purified by HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 91-100% condition: (water(0.05% HCl)-ACN), flow rate: 25 mL/min) to give **127** (27.3 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.53 - 7.30 (m, 9H), 2.33 - 2.26 (m, 1H), 2.22 - 2.09 (m, 1H), 1.50 - 0.62 (m, 27H), 0.56 (m, 4H). LCMS Rt = 1.473 min in 2 min chromatography, 30-90 AB, MS ESI calcd. for C₃₃H₄₃O₂[M+H]⁺ 471, found 471.

Example 128. Synthesis of compound 128.

[0477]



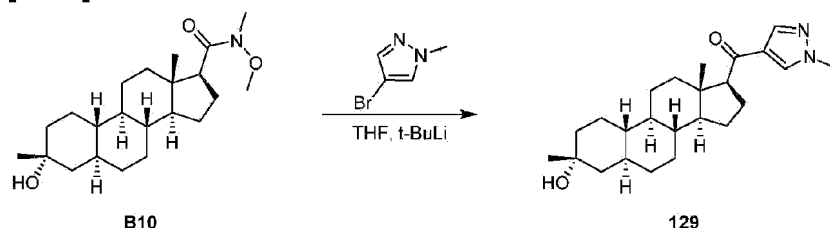
[0478] To a solution of 2-bromo-6-methoxynaphthalene (248 mg, 1.05 mmol) in THF (5 mL) was added tert-butyllithium (1.45 mL) at -68°C. The mixture was stirred at -68°C for 1 hrs. A solution of **B30** (80 mg, 211 µmol) in THF (5 mL) was added dropwise at -68°C. The reaction was stirred at 25°C for 1 hour. LCMS showed the reaction was completed. The reaction was quenched with NH₄Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude product, which was purified by HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 92-98% condition: (water(0.05% HCl)-ACN), flow rate: 25 mL/min) to give **128** (42.9 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 7.97 (dd, *J* = 1.5, 8.5 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.23 - 7.14 (m, 2H), 3.95 (s, 3H), 3.64 (t, *J* = 8.7 Hz, 1H), 2.53-2.43 (m, 1H), 1.85 - 1.69 (m, 3H), 1.50 - 1.17 (m, 19H), 1.16 - 0.93 (m, 2H), 0.85 - 0.76 (m, 1H), 0.71 (s, 3H), 0.63 (s, 3H). LCMS Rt = 1.100 min in 1.5 min chromatography, 5-95 AB, MS

ESI calcd. for $C_{32}H_{43}O_3$ $[M+H]^+$ 475, found 475.

Example 129. Synthesis of compound 129.

[0479]

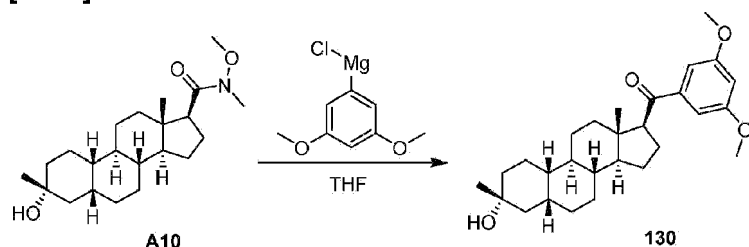


[0480] To a solution of (220 mg, 1.37 mmol) in THF (5 mL) was added tert-butyllithium (1.90 mL, 2.47 mmol) at -68°C . The mixture was stirred at -68°C for 1 hour. **B10** (100 mg, 275 μmol) in THF (5 mL) was added dropwise at -68°C . The reaction was stirred at 25°C for 2 hours. The reaction was quenched with NH_4Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give crude product which was purified by HPLC separation (Phenomenex Synergi C18 150*30mm*4 μm , gradient: 90-98% condition: (water(0.05% HCl)-ACN), flow rate: 25 mL/min) to give **129** (25.9 mg) as a solid.

^1H NMR (400 MHz, CDCl_3) δ 7.87 (s, 1H), 7.83 (s, 1H), 3.93 (s, 3H), 3.02 (t, $J=8.9$ Hz, 1H), 2.42 - 2.32 (m, 1H), 1.81 - 1.62 (m, 8H), 1.61 - 1.55 (m, 2H), 1.43 - 1.24 (m, 5H), 1.20 (s, 3H), 1.18-0.95 (m, 6H), 0.80 - 0.60 (m, 5H). LCMS Rt = 1.058 min in 2 min chromatography, 30-90 AB, MS ESI calcd. for $C_{24}H_{37}N_2O_2$ $[M+H]^+$ 385, found 385.

Example 130. Synthesis of compound 130.

[0481]



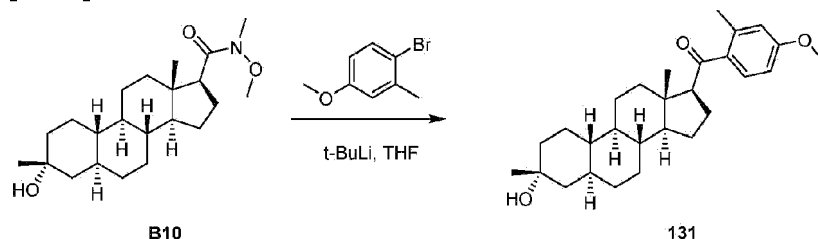
[0482] To a solution of **A10** (100 mg, 0.275 mmol) in THF (3 mL) was added (3,5-dimethoxyphenyl)magnesium chloride (2.75 mL, 1 M in THF). The mixture was stirred at 20°C for 3.5h and then to the mixture was added sat. aq. NH_4Cl (5 mL). The organic phase was

extracted with DCM (5 mL * 2), washed with sat. aq. NaCl (8 mL * 2), concentrated in vacuum. The residue was purified by prep. HPLC to give 130 (19 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.01 (d, *J* = 2.5 Hz, 2H), 6.62 (t, *J* = 2.3 Hz, 1H), 3.83 (s, 6H), 3.42 (t, *J* = 8.7 Hz, 1H), 2.49-2.33 (m, 1H), 1.86-1.58 (m, 7H), 1.52-1.27 (m, 13H), 1.26 (s, 3H), 1.20-0.85 (m, 3H), 0.61 (s, 3H). **LCMS** Rt = 1.427 min in 2 min chromatography, 10-80AB, MS ESI calcd. for C₂₈H₄₁O₄[M+H]⁺ 441.3, found 423 [M-H₂O]⁺.

Example 131. Synthesis of compound 131.

[0483]

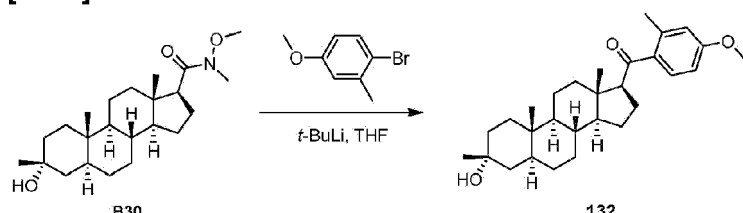


[0484] To a solution of 1-bromo-4-methoxy-2-methylbenzene (414 mg, 2.06 mmol) in THF (3 mL) was added tert-butyllithium (2.85 mL, 1.3 M in THF) at -70°C. The mixture was stirred at -70°C for 1 h. A solution of **B10** (150 mg, 0.4126 mmol) in THF (1 mL) was added at -70°C. The mixture was stirred at 25°C for 1 hrs. TLC showed starting material was consumed and new spots were produced. The mixture was quenched with Sat. NH₄Cl (10 mL), extracted with EtOAc (10 mL x 3), washed with brine (30 mL x 3), dried over Na₂SO₄, filtered, concentrated in vacuum to give a crude product which was purified with prep. HPLC (Column: Phenomenex Synergi C18 150*30mm*4um; Condition: water (0.05% HCl)-ACN; Gradient 90%-95%B; Gradient Time(min):10; FlowRate(ml/min): 25) to give 131 (26 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 8.5 Hz, 1H), 6.75-6.68 (m, 2H), 3.83 (s, 3H), 3.34 (t, *J* = 8.7 Hz, 1H), 2.50-2.33 (m, 4H), 1.80-1.45 (m, 8H), 1.36-1.22 (m, 5H), 1.20-0.89 (m, 11H), 0.72-0.54 (m, 5H). **LCMS** t_R = 1.058 min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for C₂₈H₄₁O₃ [M+H]⁺ 425, found 425.

Example 132. Synthesis of compound 132.

[0485]

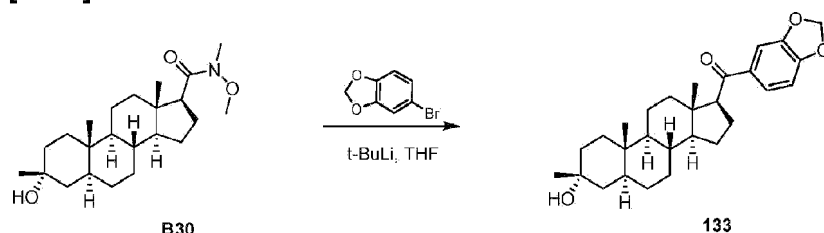


[0486] To a solution of 1-bromo-4-methoxy-2-methylbenzene (211 mg, 1.05 mmol) in THF (5 mL) was added tert-butyllithium (1.45 mL) at -68°C. The mixture was stirred at -68°C for 1 hrs. A solution of **B30** (80 mg, 211 µmol) in THF (5 mL) was added dropwise at -68°C. The reaction was stirred at 25°C for 1 hour. LCMS showed the reaction was completed. The reaction was quenched with NH₄Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude product, which was purified by HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 91-100% condition: (water(0.05% HCl)-ACN), flow rate: 25 mL/min) to give **132** (29.3 mg) as a solid.

¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, *J* = 8.3 Hz, 1H), 6.77 - 6.68 (m, 2H), 3.83 (s, 3H), 3.33 (t, *J* = 8.5 Hz, 1H), 2.47 (s, 3H), 2.43 - 2.32 (m, 1H), 1.78 - 1.65 (m, 4H), 1.52 - 1.31 (m, 9H), 1.30-1.06 (m, 14H), 1.04 - 0.87 (m, 1H), 0.79 - 0.67 (m, 4H), 0.61 (s, 3H). LCMS Rt = 1.066 min in 2 min chromatography, 5-95 AB, MS ESI calcd. for C₂₉H₄₃O₃ [M+H]⁺ 439, found 439.

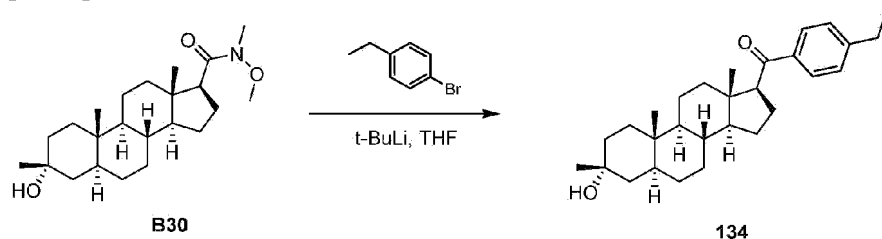
Example 133. Synthesis of compound 133.

[0487]



[0488] To a solution of 6-bromobenzo[d][1,3]dioxole (158 mg, 789 µmol) in THF (5 mL) was added tert-butyllithium (1.09 mL) at -68°C. After stirring at -68°C for 1 hr, a solution of **B30** (60 mg, 158 µmol) in THF (5 mL) was added dropwise at -68°C. The reaction was stirred at 25°C for 2 hours. TLC showed the reaction was completed. The reaction was quenched with Sat.NH₄Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product, which was purified by HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 80-95% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) and lyophilized to give **133** (14.9 mg) as a solid.

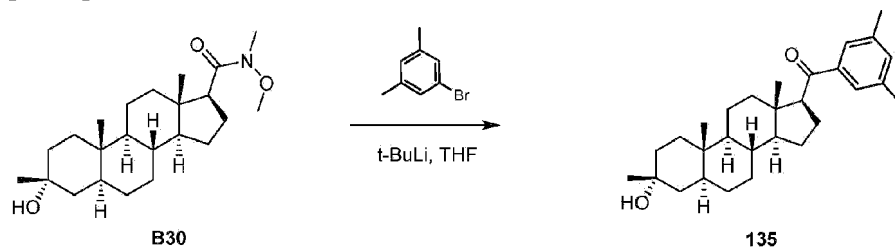
¹H NMR (400 MHz, CDCl₃) δ 7.55 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.40 (d, *J* = 1.3 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.13 (d, *J* = 1.0 Hz, 2H), 3.87 (s, 1H), 3.58 (t, *J* = 8.3 Hz, 1H), 2.29 - 2.17 (m, 1H), 1.74 - 1.58 (m, 3H), 1.55 - 1.39 (m, 3H), 1.36 - 1.00 (m, 17H), 0.98 - 0.84 (m, 1H), 0.78 - 0.61 (m, 4H), 0.47 (s, 3H). LCMS Rt = 1.033 min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for C₂₈H₄₀O₄ [M+H]⁺ 439, found 439.

Example 134. Synthesis of compound 134.**[0489]**

[0490] To a solution of 1-bromo-4-ethylbenzene (146 mg, 789 μmol) in THF (5 mL) was added tert-butyllithium (1.09 mL) at -68°C . After stirring at -68°C for 1 hr, a solution of **B30** (60 mg, 158 μmol) in THF (5 mL) was added dropwise at -68°C . The reaction was stirred at 25°C for 2 hours. TLC showed the reaction was completed. The reaction was quenched with Sat. NH_4Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to a crude product, which was purified by HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 95-100% B (A= 0.05% HCl-ACN, B= acetonitrile), flow rate: 25 mL/min) and lyophilized to give **134** (23.3 mg) as a solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.83 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 3.86 (s, 1H), 3.63 (t, $J = 8.5$ Hz, 1H), 2.67 (q, $J = 7.5$ Hz, 2H), 2.32 - 2.20 (m, 1H), 1.76 - 1.60 (m, 3H), 1.52 - 1.31 (m, 7H), 1.27 - 1.10 (m, 11H), 1.08 - 0.88 (m, 5H), 0.76 - 0.60 (m, 4H), 0.48 (s, 3H).

LCMS Rt = 1.115 min in 1.5 min chromatography, 5-95 AB, MS ESI calcd. for $\text{C}_{29}\text{H}_{44}\text{O}_2$ $[\text{M}+\text{H}]^+$ 423, found 423.

Example 135. Synthesis of compound 135.**[0491]**

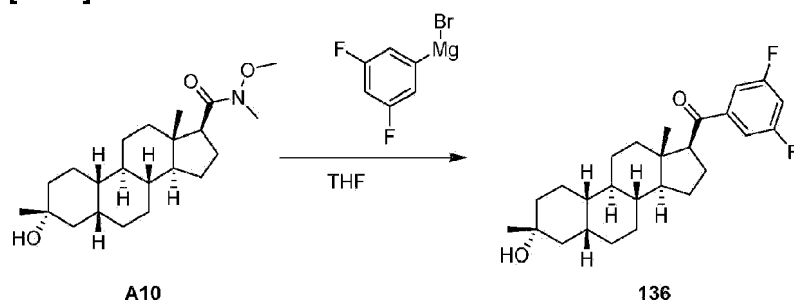
[0492] To a solution of 1-bromo-3,5-dimethylbenzene (146 mg, 789 μmol) in THF (5 mL) was added tert-butyllithium (1.09 mL) at -68°C . After stirring at -68°C for 1 hr, **B30** (60 mg, 158 μmol) in THF (5 mL) was added dropwise at -68°C . The reaction was stirred at 25°C for 2

hours. The reaction was quenched with Sat NH_4Cl (10 mL), extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a product, which was purified by prep-HPLC (column: Boston Green ODS 150*30 5u, gradient: 95-100% condition: (0.05% HCl -ACN), flow rate: 25 mL/min) and lyophilized to give **135** (27.6 mg) as a solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.48 (s, 2H), 7.23 (s, 1H), 3.86 (s, 1H), 3.61 (t, J = 8.4 Hz, 1H), 2.33 (s, 6H), 2.30 - 2.18 (m, 1H), 1.75 - 1.60 (m, 3H), 1.55 - 0.80 (m, 21H), 0.77 - 0.61 (m, 4H), 0.48 (s, 3H). LCMS Rt = 1.113 min in 1.5 min chromatography, 5-95 AB, ESI calcd. for $\text{C}_{29}\text{H}_{43}\text{O}_2$ $[\text{M}+\text{H}]^+$ 423, found 423.

Example 136. Synthesis of compound 136.

[0493]



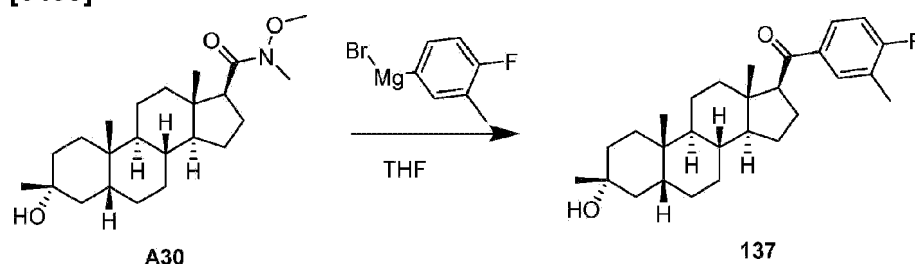
[0494] To a stirred solution of **A10** (110 mg, 302 μmol) in 3 mL of THF was added (4-(trifluoromethoxy)phenyl)magnesium bromide (0.5 M, 6.02 mL, 3.01 mmol) dropwise at 25°C. After stirring at 25°C for 12 hrs, LCMS showed the reaction was complete. The reaction mixture was poured into ice-cold water and extracted with EtOAc (50 mLx2), washed with brine (30 mLx2), dried (Na_2SO_4), filtered, and evaporated in vacuo to give crude product, which was purified by prep-HPLC separation (column: Boston Green ODS 150*30 5u, gradient: 90-100% B (A= 0.05% HCl -ACN, B= acetonitrile), flow rate: 25 mL/min) for further purification to obtain (3,5-difluorophenyl)((3R,5R,8R,9R,10S,13S,14S,17S)-3-hydroxy-3,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)methanone (67 mg, 53%) as a solid.

^1H NMR (CDCl_3 , 400MHz): δ 7.38 (d, J =6.0 Hz, 2H), 6.99 (t, J =8.6 Hz, 1H), 3.36 (t, J =8.6 Hz, 1H), 2.36-2.42 (m, 1H), 1.73-1.85 (m, 5H), 1.63 (d, J =13.6 Hz, 2H), 1.26-1.50 (m, 15H), 1.04-1.15 (m, 2H), 0.85-1.02 (m, 2H), 0.61 (s, 3H)

LCMS Rt = 3.219 min in 4.0 min chromatography, 10-80 AB, purity 100%, MS ESI calcd. for $\text{C}_{26}\text{H}_{35}\text{F}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 417.3, found 399.0 $[\text{M}-\text{H}_2\text{O}]^+$.

Example 137. Synthesis of compound 137.

[0495]



[0496] To a stirred solution of **A30** (110 mg, 291 μmol) in 3 mL of THF was added (4-fluoro-3-methylphenyl)magnesiumbromide (0.5 M, 5.8 mL, 2.9 mmol) dropwise at 25°C. After stirring at 25°C for 12 hrs, LCMS showed the reaction was complete. The reaction mixture was poured into ice-cold water and extracted with EtOAc (50 mLx2), washed with brine (30 mLx2), dried (Na_2SO_4), filtered, and evaporated in vacuo to give crude product. The reaction mixture was purified by HPLC separation (column: Phenomenex Synergi C18 150*25*10 μm , gradient: 80-100% B (A= 0.05% HCl -ACN,B=acetonitrile), flow rate: 25 mL/min) for further purification to obtain (4-fluoro-3-methylphenyl)((3R,5R,8R,9S,10S,13S,14S,17S)-3-hydroxy-3,10,13-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)methanone (52.1 mg, 40.2%) as a solid.

^1H NMR (CDCl_3 , 400MHz): δ = 7.76 (d, J =7.6 Hz, 1H), 7.71 (br. s., 1H), 7.04 (t, J =9.0 Hz, 1H), 3.44 (t, J =8.8 Hz, 1H), 2.36-2.43 (m, 1H), 2.33 (s, 3H), 1.92-2.05 (m, 2H), 1.81-1.88 (m, 1H), 1.67-1.78 (m, 3H), 1.32-1.51 (m, 10H), 1.26 (s, 3H), 1.23 (br. s., 2H), 1.09-1.18 (m, 2H), 0.98-1.08 (m, 2H), 0.91 (s, 3H), 0.58 (s, 3H)

LCMS Rt = 3.430 min in 4.0 min chromatography, 10-80 AB, purity 95.9%, MS ESI calcd. for $\text{C}_{28}\text{H}_{40}\text{FO}_2$ $[\text{M}+\text{H}]^+$ 426.6, found 409.0 $[\text{M}-\text{H}_2\text{O}]^+$.

Assay Methods

[0497] Compounds provided herein can be evaluated using various assays; examples of which are described below.

Steroid Inhibition of TBPS Binding

[0498] TBPS binding assays using rat brain cortical membranes in the presence of 5 μM 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).

[0499] 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 µL) of the membrane suspensions are incubated with 3 nM [³⁵S]-TBPS and 5 µL aliquots of test drug dissolved in dimethyl sulfoxide (DMSO) (final 0.5%) in the presence of 5 µM GABA. The incubation is brought to a final volume of 1.0 mL with buffer. Nonspecific binding is determined in the presence of 2 µM 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 (IC₅₀) 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 ± 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.

[0500] 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 discussed procedures.

[0501] For **Table 1**, "A" indicates an IC₅₀ < 20 nM, "B" indicates an IC₅₀ of 20 nM to 50 nM, "C" indicates an IC₅₀ > 50 nM to 100 nM, and "D" indicates IC₅₀ > 100 nM.

Table 1.

| Compound | ³⁵ S-TBPS Radioligand Displacement (IC ₅₀) |
|----------|--|
| 1 | A |

| | |
|---|---|
| 2 | D |
| 3 | D |
| 4 | B |
| 5 | B |

| | |
|----|---|
| 6 | D |
| 7 | C |
| 8 | D |
| 9 | B |
| 10 | A |

| | |
|----|---|
| 14 | C |
| 39 | C |
| 38 | C |
| 37 | C |
| 36 | C |

| | |
|-----|---|
| 11 | B |
| 12 | B |
| 130 | B |
| 24 | A |
| 23 | C |
| 28 | B |
| 27 | B |
| 26 | B |
| 48 | B |
| 15 | B |
| 18 | C |
| 21 | D |
| 17 | C |
| 20 | C |
| 25 | B |
| 19 | C |
| 16 | A |
| 13 | D |
| 22 | C |

| | |
|----|---|
| 45 | D |
| 35 | A |
| 41 | B |
| 44 | C |
| 49 | A |
| 29 | D |
| 34 | A |
| 47 | B |
| 33 | D |
| 32 | B |
| 31 | C |
| 30 | D |
| 43 | B |
| 46 | D |
| 40 | B |
| 42 | A |
| 59 | C |
| 58 | C |
| 56 | B |

| | |
|----|---|
| 55 | B |
| 54 | C |
| 53 | D |
| 52 | B |
| 51 | C |
| 50 | D |
| 64 | D |
| 68 | D |
| 63 | C |
| 60 | D |
| 62 | D |
| 61 | D |

| | |
|-----|---|
| 75 | D |
| 82 | D |
| 81 | D |
| 80 | D |
| 79 | D |
| 78 | D |
| 77 | D |
| 76 | D |
| 101 | D |
| 133 | D |
| 134 | D |
| 135 | D |

| | |
|----|---|
| 74 | B |
| 73 | C |
| 86 | B |
| 89 | C |
| 72 | B |
| 85 | D |
| 84 | D |
| 83 | B |
| 88 | D |
| 70 | C |
| 71 | D |
| 87 | D |

| | |
|-----|---|
| 98 | D |
| 108 | D |
| 111 | D |
| 99 | D |
| 100 | D |
| 107 | C |
| 106 | D |
| 105 | D |
| 110 | C |
| 102 | C |
| 104 | D |
| 109 | D |

| | |
|-----|---|
| 92 | D |
| 103 | D |
| 97 | D |
| 91 | D |
| 96 | D |
| 95 | D |
| 94 | C |
| 93 | C |
| 115 | D |
| 114 | D |

| | |
|-----|---|
| 128 | D |
| 127 | D |
| 132 | D |
| 113 | D |
| 125 | B |
| 124 | C |
| 123 | D |
| 136 | B |
| 137 | B |

Patch clamp electrophysiology of recombinant $\alpha_1\beta_2\gamma_2$ and $\alpha_4\beta_3\delta$ GABA_A receptors

[0502] Cellular electrophysiology is used to measure the pharmacological properties of our GABA_A receptor modulators in heterologous cell systems. Each compound is tested for its ability to affect GABA mediated currents at a submaximal agonist dose (GABA EC₂₀ = 2μM). LTK cells are stably transfected with the $\alpha_1\beta_2\gamma_2$ subunits of the GABA receptor and CHO cells are transiently transfected with the $\alpha_4\beta_3\delta$ subunits via the Lipofecatamine method. Cells were passaged at a confluence of about 50-80% and then seeded onto 35mm sterile culture dishes

containing 2 ml culture complete medium without antibiotics or antimycotics. Confluent clusters of cells are electrically coupled (Pritchett et al., Science, 1988, 242, 1306-1308.). Because responses in distant cells are not adequately voltage clamped and because of uncertainties about the extent of coupling (Verdoorn et al., Neuron 1990, 4, 919-928), cells were cultivated at a density that enables the recording of single cells (without visible connections to other cells).

[0503] Whole cell currents were measured with HEKA EPC-10 amplifiers using PatchMaster software or by using the high throughput QPatch platform (Sophion). Bath solution for all experiments contained (in mM): NaCl 137 mM, KCl 4 mM, CaCl₂ 1.8 mM, MgCl₂ 1 mM, HEPES 10 mM, D-Glucose 10 mM, pH (NaOH) 7.4. In some cases 0.005% cremophor was also added. Intracellular (pipette) solution contained: KCl 130 mM, MgCl₂ 1 mM, Mg-ATP 5mM, HEPES 10 mM, EGTA 5mM, pH 7.2. During experiments, cells and solutions were maintained at room temperature (19°C - 30°C). For manual patch clamp recordings, cell culture dishes were placed on the dish holder of the microscope and continuously perfused (1 ml/min) with bath solution. After formation of a Gigaohm seal between the patch electrodes and the cell (pipette resistance range: 2.5 MΩ - 6.0 MΩ; seal resistance range: >1 GΩ) the cell membrane across the pipette tip was ruptured to assure electrical access to the cell interior (whole-cell patch-configuration). For experiments using the QPatch system, cells were transferred as suspension to the QPatch system in the bath solution and automated whole cell recordings were performed.

[0504] Cells were voltage clamped at a holding potential of -80 mV. For the analysis of test articles, GABA receptors were stimulated by 2 μM GABA after sequential pre-incubation of increasing concentrations of the test article. Pre-incubation duration was 30 s and the duration of the GABA stimulus was 2s. Test articles were dissolved in DMSO to form stock solutions (10mM). Test articles were diluted to 0.01, 0.1, 1, and 10 μM in bath solution. All concentrations of test articles were tested on each cell. The relative percentage potentiation was defined as the peak amplitude in response to GABA EC₂₀ in the presence of the test article divided by the peak amplitude in response to GABA EC₂₀ alone, multiplied by 100.

Table 2. Electrophysiological evaluation of the exemplary compounds at GABA_A-R.

| Name | GABA (α1β2γ2) Qpatch in Ltk, |
|------|------------------------------|
| | % efficacy at 10 μM |
| 1 | C |
| 8 | B |

For **Table 2.** GABA_A receptors α1β2γ2 and α4β3δ %efficacy: "A" 10-100, "B" >100-500, "C" >500; D indicates the data is not available or has not been determined.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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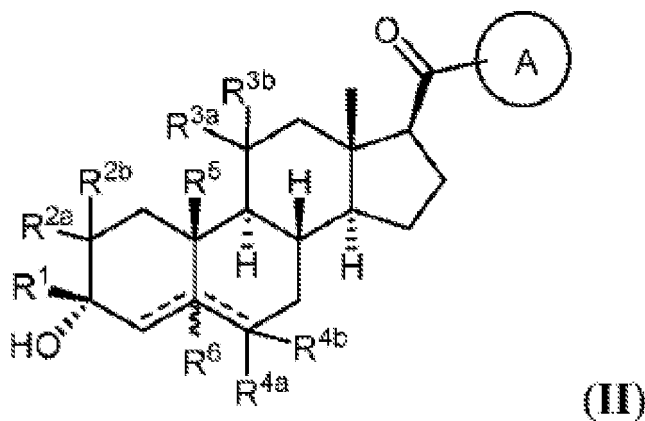
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PATENTKRAV

1. En forbindelse med formelen (II):



5

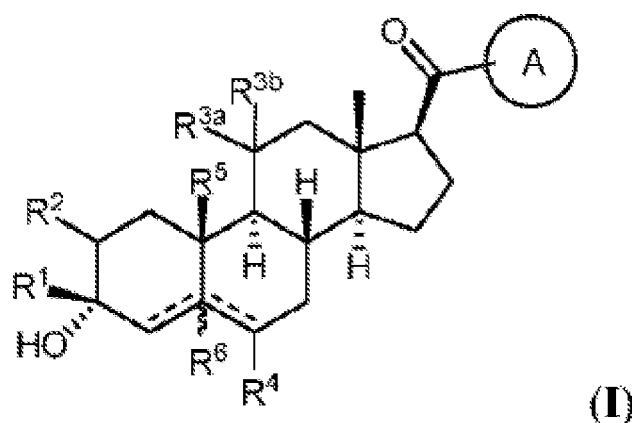
eller et farmaceutisk acceptabelt salt deraf;

hvor:

- 10 ring A er substitueret eller usubstitueret aryl eller heteroaryl;
 R¹ er hydrogen eller substitueret eller usubstitueret C₁₋₆alkyl, substitueret eller usubstitueret C₂₋₆alkenyl, substitueret eller usubstitueret C₂₋₆alkynyl eller substitueret eller usubstitueret C₃₋₆carbocyclyl;
 hver af R^{2a} og R^{2b} er uafhængigt udvalgt blandt hydrogen, halogen, substitueret eller usubstitueret C₁₋₆alkyl, substitueret eller usubstitueret C₂₋₆alkenyl,
 15 substitueret eller usubstitueret C₂₋₆alkynyl, substitueret eller usubstitueret C₃₋₆carbocyclyl, substitueret eller usubstitueret aryl, substitueret eller usubstitueret heteroaryl, -N(R^A)(R^B) eller -OR^{A2},
 hvor hver af R^A og R^B uafhængigt er hydrogen, substitueret eller usubstitueret C₁₋₆alkyl, substitueret eller usubstitueret C₂₋₆alkenyl, substitueret eller usubstitueret C₂₋₆alkynyl, substitueret eller usubstitueret C₃₋₆carbocyclyl,
 20 substitueret eller usubstitueret heterocyclyl, substitueret eller usubstitueret aryl eller substitueret eller usubstitueret heteroaryl eller R^A og R^B sammen med nitrogenatomet, hvortil de er bundet, danner en ring (f.eks. heteroaryl, heterocyclyl) eller R^{2a} og R^{2b} sammen med det carbonatom, hvortil de er
- 25

- bundet danner en ring; R^{A2} er hydrogen eller substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl, substitueret eller usubstitueret C_{3-6} carbocyclyl, substitueret eller usubstitueret aryl eller substitueret eller usubstitueret heteroaryl;
- 5 R^{3a} er hydrogen, $-N(R^A)(R^B)$ eller $-OR^{A3}$, hvor R^{A3} er hydrogen, substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl eller substitueret eller usubstitueret C_{3-6} carbocyclyl, substitueret eller usubstitueret aryl, substitueret eller usubstitueret heteroaryl, og
- 10 R^{3b} er hydrogen eller $-N(R^A)C(O)R^{A3}$; eller R^{3a} og R^{3b} er forbundet til dannelse af en oxo ($=O$) gruppe; hver af R^{4a} og R^{4b} er uafhængigt udvalgt blandt hydrogen eller halogen; R^5 er hydrogen, usubstitueret C_{1-6} alkyl eller $-CH_2OR^{A5}$, hvor R^{A5} er hydrogen, substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret
- 15 C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl eller substitueret eller usubstitueret C_{3-6} carbocyclyl, substitueret eller usubstitueret aryl, substitueret eller usubstitueret heteroaryl; R^6 er fraværende eller hydrogen; og
- repræsenterer en enkelt- eller dobbeltbinding, hvor
- 20 når den ene af ----- er en dobbeltbinding, den anden ----- er en enkeltbinding; og
- når en af ----- er en dobbeltbinding, er R^6 fraværende.

2. Forbindelse ifølge krav 1, hvor forbindelsen har formlen (I):



eller et farmaceutisk acceptabelt salt deraf;

hvor:

5

ring A er substitueret eller usubstitueret aryl eller heteroaryl;

R¹ er hydrogen eller substitueret eller usubstitueret C₁₋₆alkyl, substitueret eller usubstitueret C₂₋₆alkenyl, substitueret eller usubstitueret C₂₋₆alkynyl eller substitueret eller usubstitueret C₃₋₆carbocyclyl;

10

R² er hydrogen, halogen, hydrogen eller substitueret eller usubstitueret C₁₋₆alkyl, substitueret eller usubstitueret C₂₋₆alkenyl, substitueret eller usubstitueret C₂₋₆alkynyl eller substitueret eller usubstitueret C₃₋₆carbocyclyl, -N(R^A)(R^B) eller -OR^{A2},

15

hvor hver af R^A og R^B uafhængigt er hydrogen, substitueret eller usubstitueret C₁₋₆alkyl, substitueret eller usubstitueret C₂₋₆alkenyl, substitueret eller usubstitueret C₂₋₆alkynyl eller substitueret eller usubstitueret C₃₋₆carbocyclyl eller substitueret eller usubstitueret heterocyclyl eller R^A og R^B sammen med nitrogenatomet, hvortil de er bundet, danner en ring (f.eks. heteroaryl, heterocyclyl); R^{A2} er hydrogen eller substitueret eller usubstitueret C₁₋₆alkyl, substitueret eller usubstitueret C₂₋₆alkenyl, substitueret eller usubstitueret C₂₋₆alkynyl eller substitueret eller usubstitueret C₃₋₆carbocyclyl;

20

R^{3a} er hydrogen, -N(R^A)(R^B) eller -OR^{A3}, hvor R^{A3} er hydrogen, substitueret eller usubstitueret C₁₋₆alkyl, substitueret eller usubstitueret C₂₋₆alkenyl, substitueret eller usubstitueret C₂₋₆alkynyl eller substitueret eller usubstitueret C₃₋₆carbocyclyl, og R^{3b} er hydrogen eller -N(R^A)C(O)R^{A3}; eller

25

R^{3a} og R^{3b} er forbundet til dannelsen af en oxo (=O) gruppe;

R^4 er hydrogen eller halogen;

R^5 er hydrogen, usubstitueret C_{1-6} alkyl eller $-CH_2OR^{A5}$, hvor $RA5$ er hydrogen, substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl eller substitueret eller usubstitueret C_{3-6} carbocyclyl;

R^6 er fraværende eller hydrogen; og

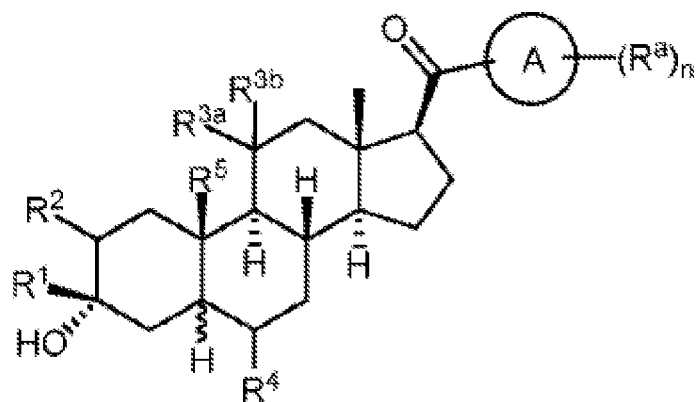
----- repræsenterer en enkelt- eller dobbeltbinding, hvor

når den ene af ----- er en dobbeltbinding, den anden ----- er en enkeltbinding; og

når en af ----- er en dobbeltbinding, er R^6 fraværende.

3. Forbindelse ifølge krav 2, hvor forbindelsen med formlen (I) er;

i) en forbindelse med formlen (I-a):



(I-a)

hvor:

n er 0, 1, 2, 3, 4, 5 eller 6; og

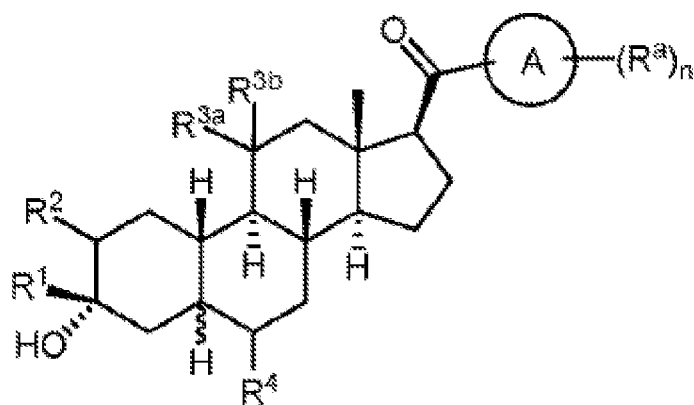
hver R^a uafhængigt er halogen, cyano, C_{1-6} alkyl, $-N(R^A)(R^B)$, $-N(R^A)C(O)R^{AA}$, $-N(R^A)C(O)OR^{AA}$, $-SR^{AA}$ eller $-OR^{AA}$, hvor R^{AA} er hydrogen, substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl eller substitueret eller

5

usubstitueret C_{3-6} carbocyclyl; substitueret eller usubstitueret aryl eller substitueret eller usubstitueret heteroaryl; eller
to R^a -grupper sammen med de atomer, hvortil de er forbundet, danner en ring;

5

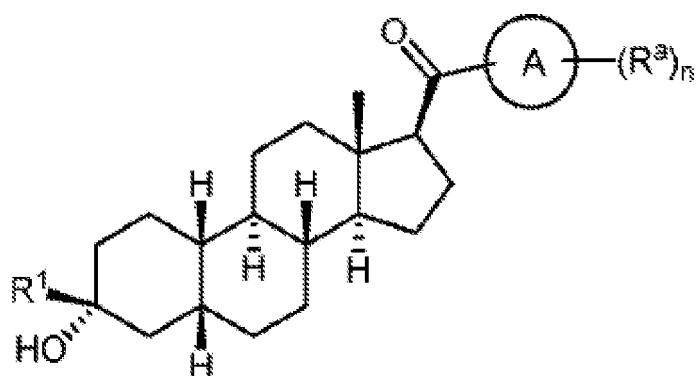
ii) en forbindelse med formlen **(I-b)**:



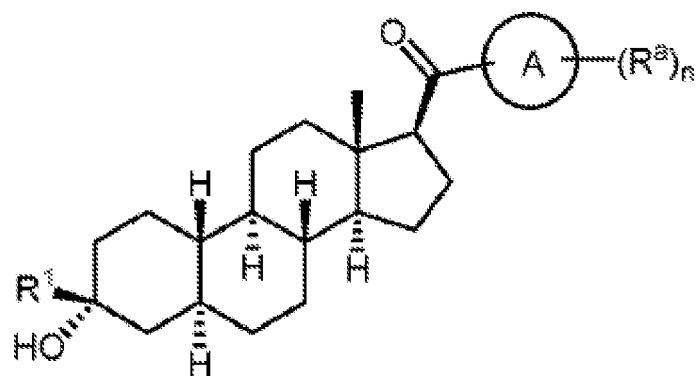
(I-b);

10 iii) en forbindelse med formlen **(I-b-i)** eller **(I-b-ii)**:

6

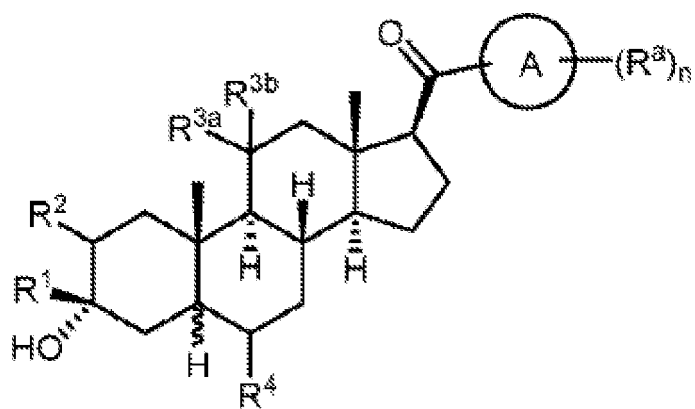


(I-b-i),



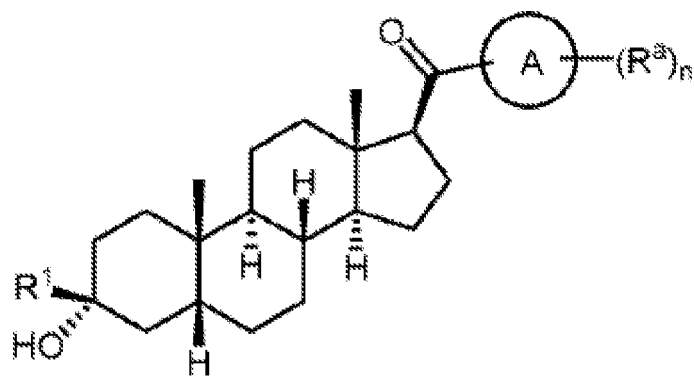
(I-b-ii);

iv) en forbindelse med formelen (I-c):

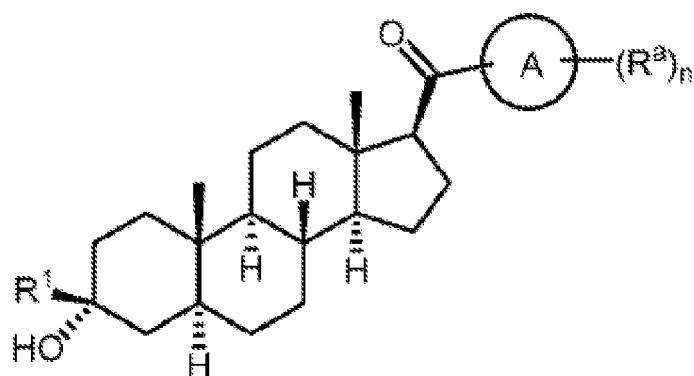


(I-c);

v) en forbindelse med formelen **(I-c-i)** eller **(I-c-ii)**:



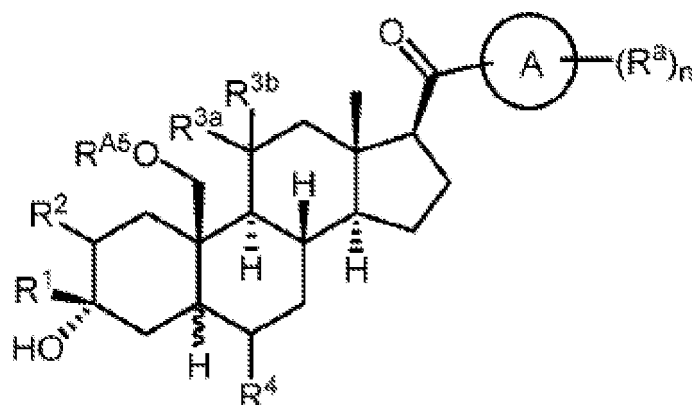
(I-c-i),



(I-c-ii);

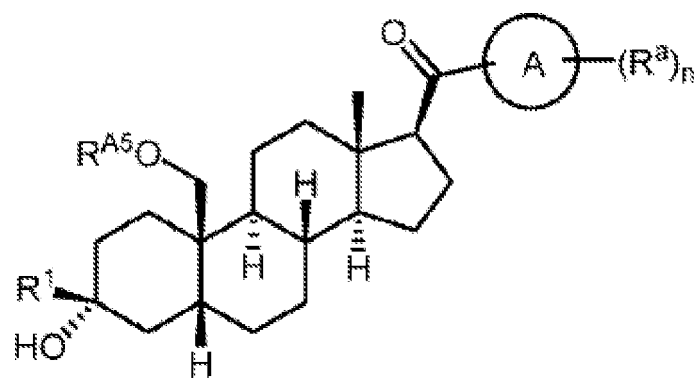
vi) er en forbindelse med formelen **(I-d)**:

8

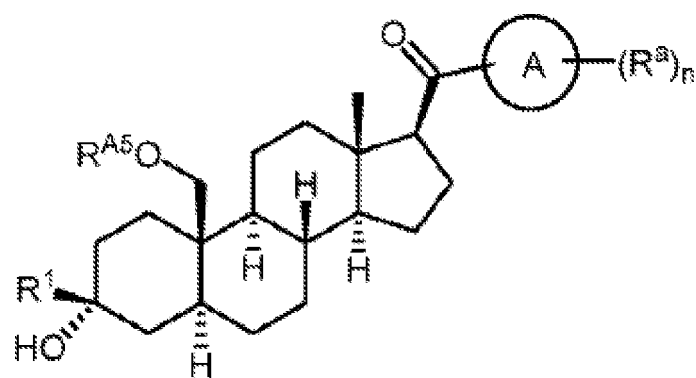


(I-d); or

vii) en forbindelse med formlen (I-d-i) eller (I-d-ii):



(I-d-i),



(I-d-ii).

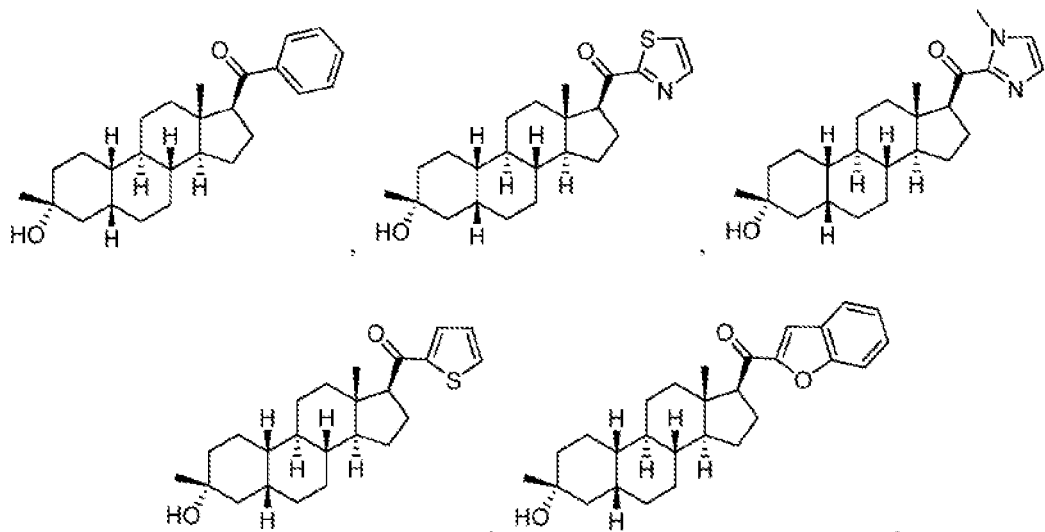
4. Forbindelse ifølge krav 2, hvor A er en 5-10-leddet ring, for eksempel phenyl, naphthyl, furan, thiophen, thiazol, pyrrol, imidazol, pyrazol, triazol eller en sammen-smeltet bicyklisk ring, for eksempel benzofuran, benzoimidazol, indol, benzothiazol eller benzothiophen, og hvor A eventuelt er forbundet via et carbonatom.

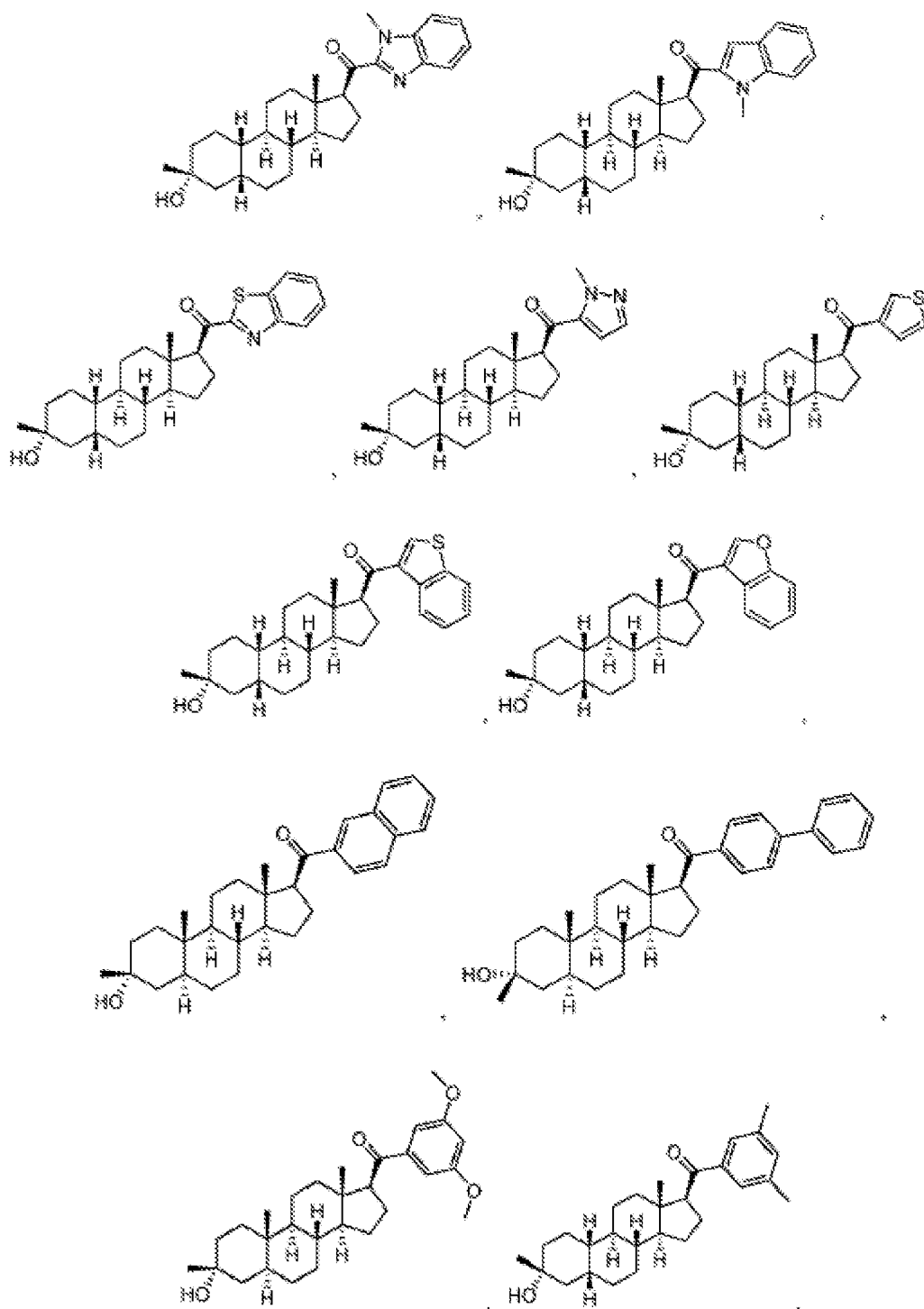
5. Forbindelse ifølge krav 2, hvor R^1 er hydrogen eller substitueret eller usubstitueret C_{1-6} alkyl, for eksempel $-CH_3$.

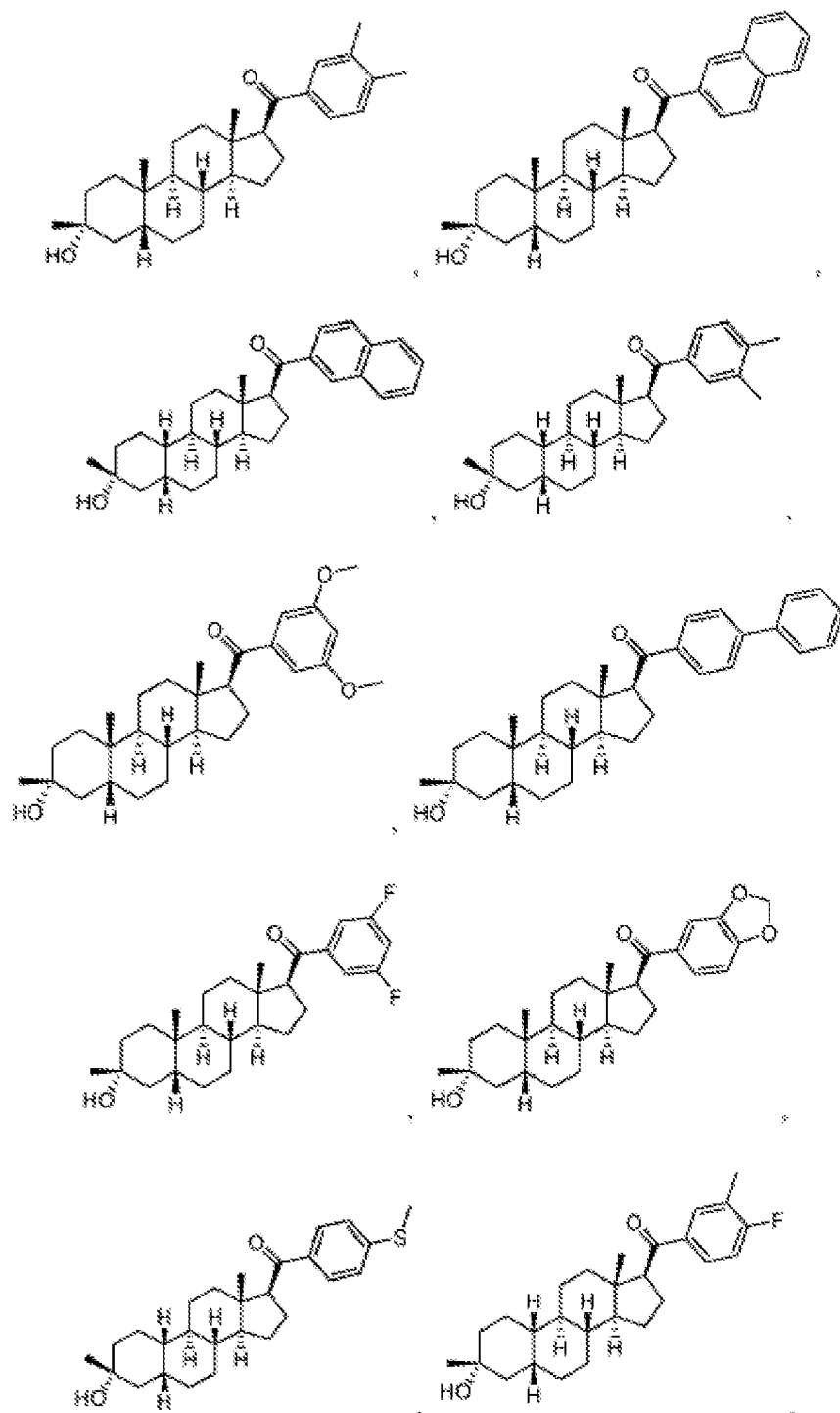
10 6. Forbindelse ifølge krav 3, hvor n er 0, 1 eller 2, og hver R^a uafhængigt er halogen, C_{1-6} alkyl (f.eks. $-CH_3$) eller $-OR^{AA}$, hvor R^{AA} er hydrogen eller substitueret eller usubstitueret C_{1-6} alkyl.

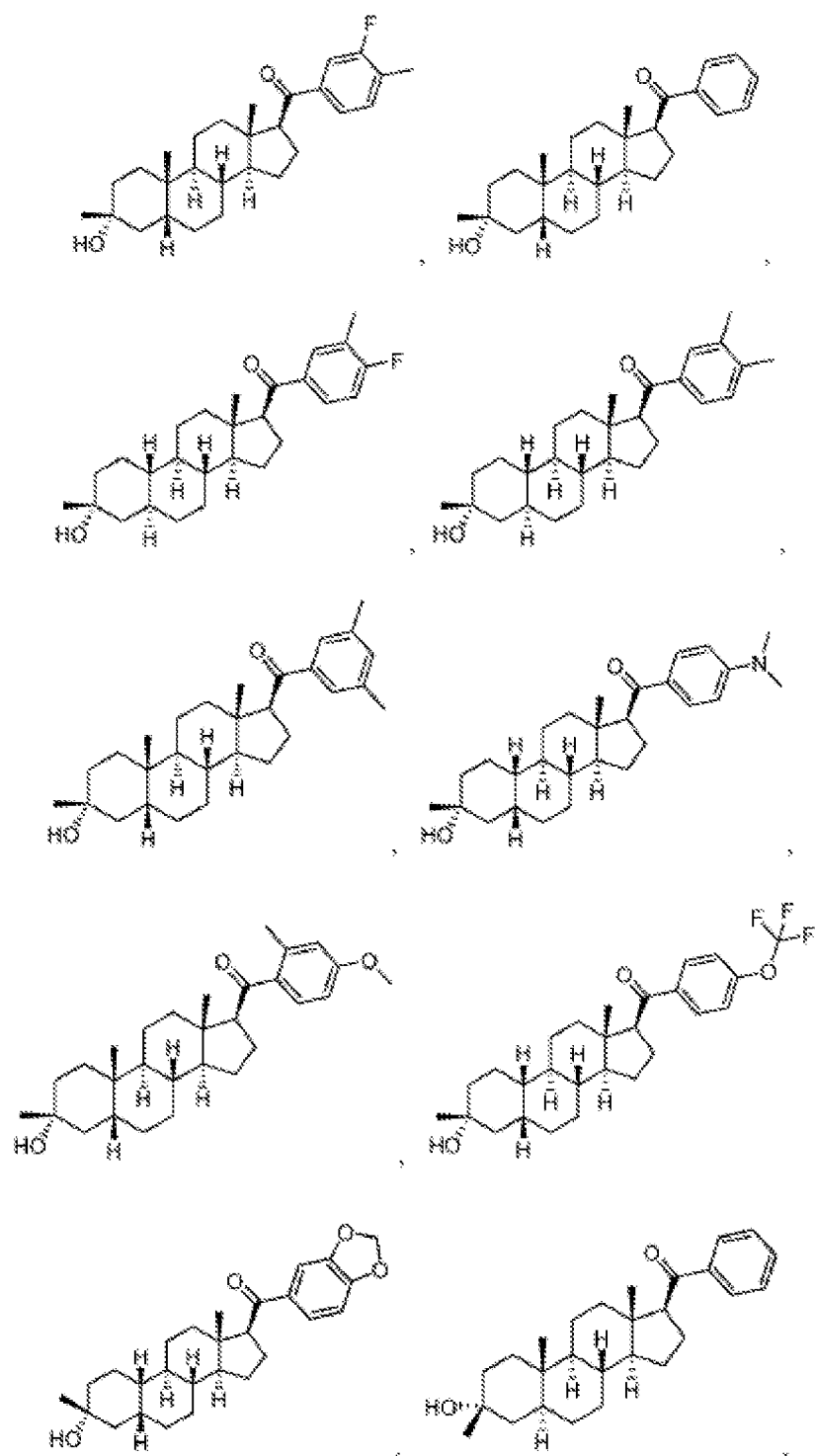
7. Forbindelse ifølge krav 1, hvor forbindelsen er:

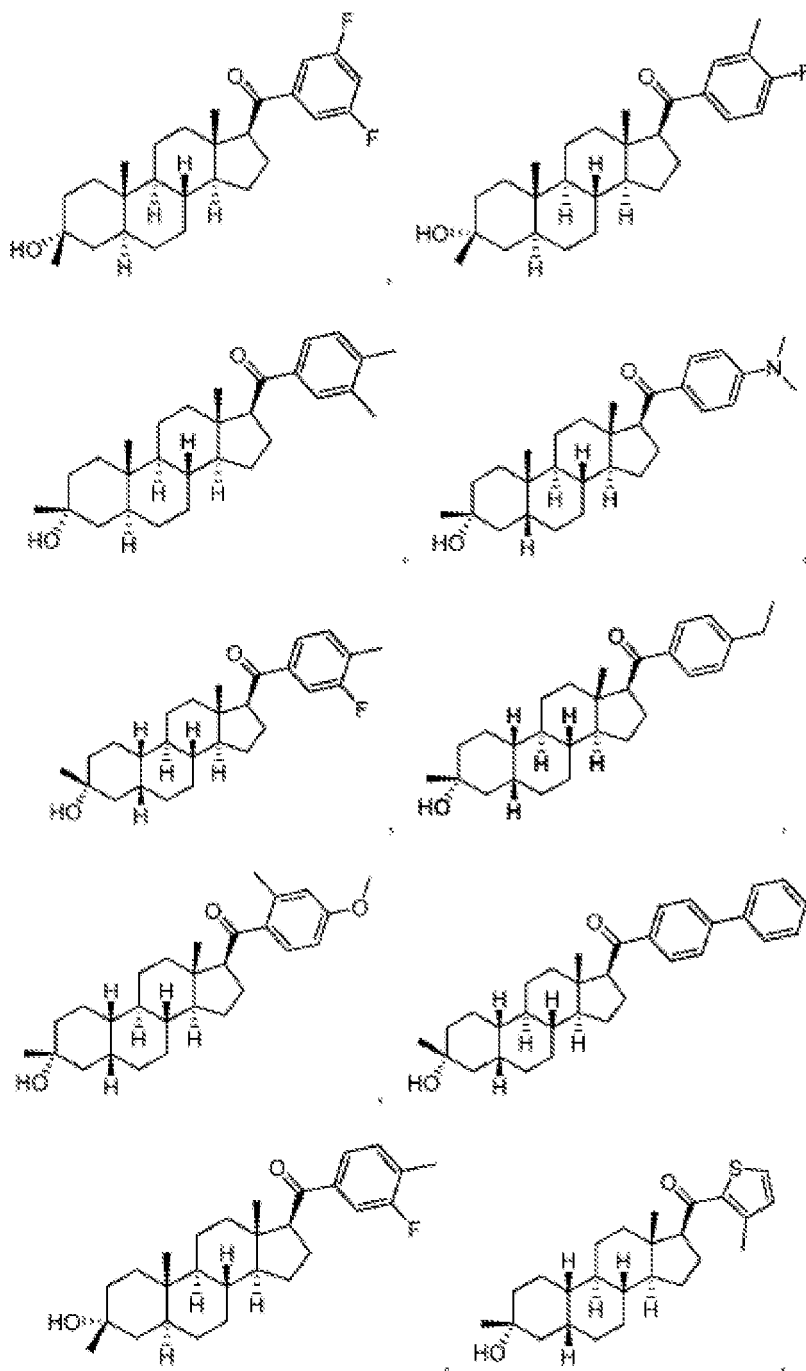
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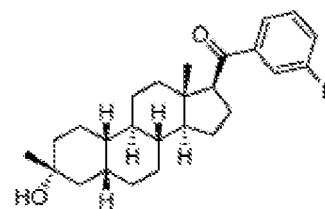
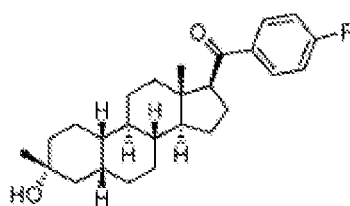
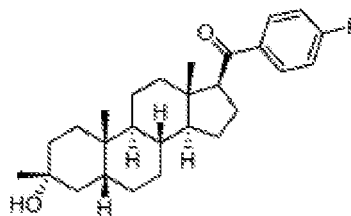
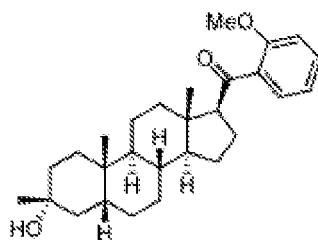
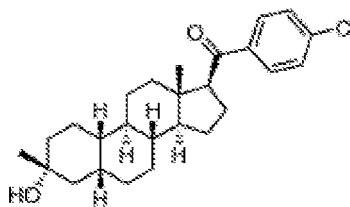
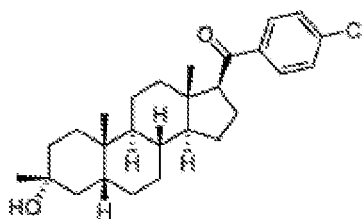
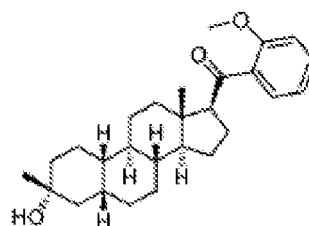
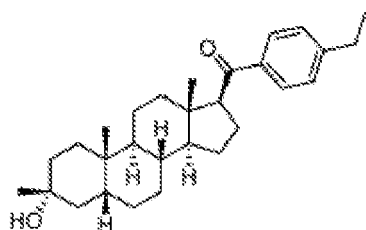
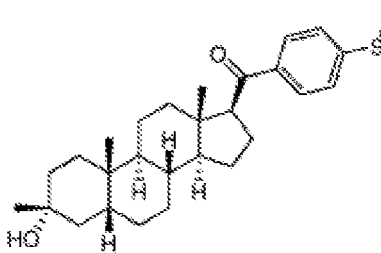
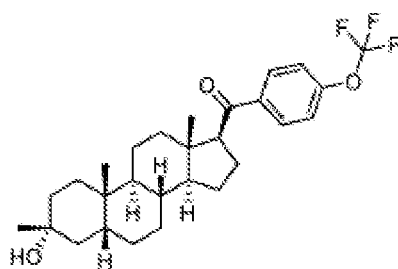


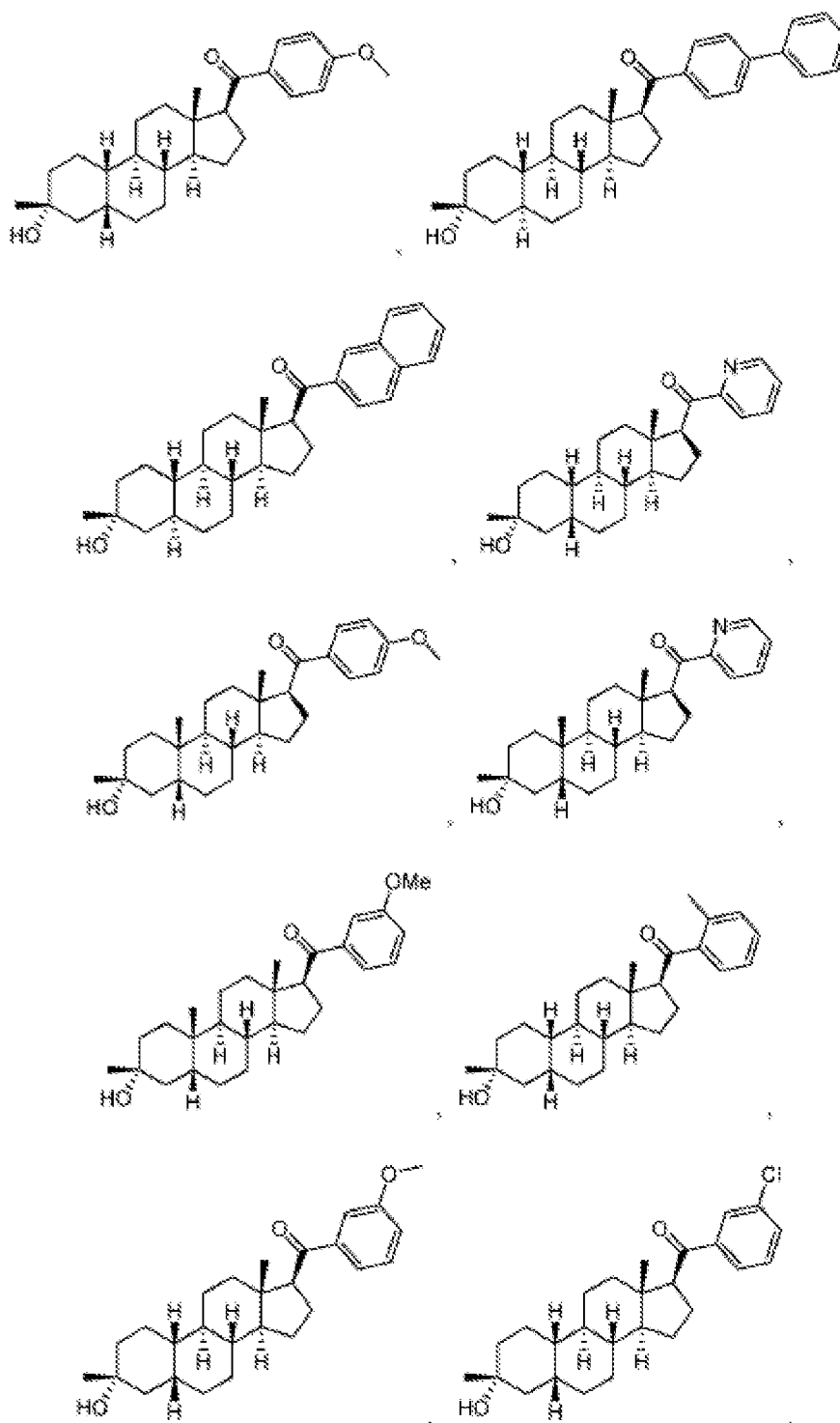


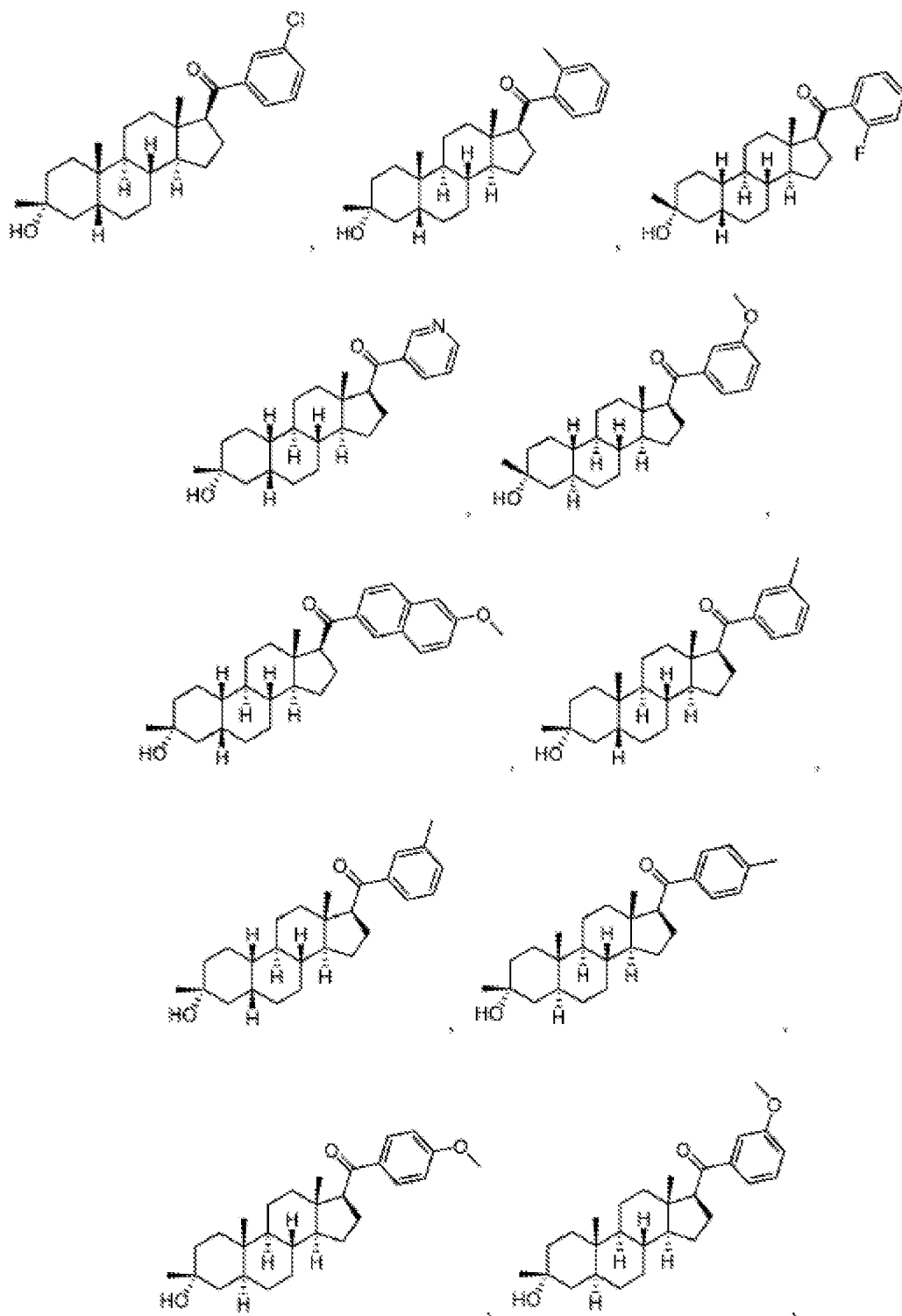


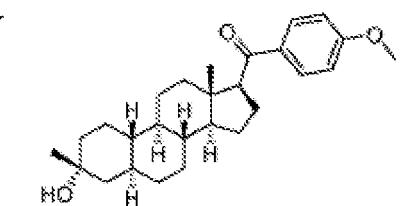
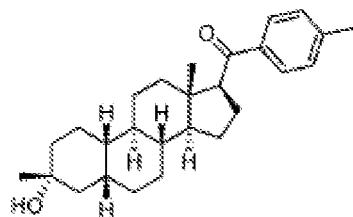
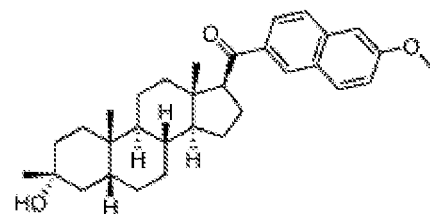
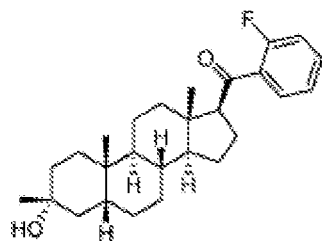
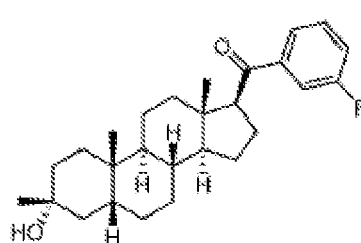
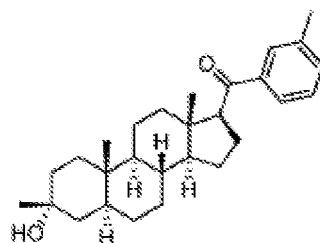
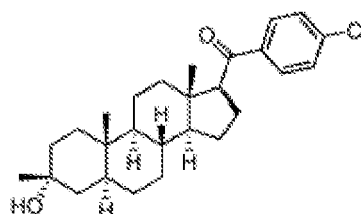
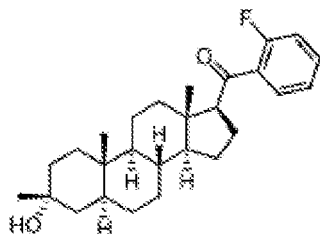
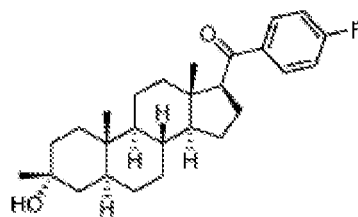
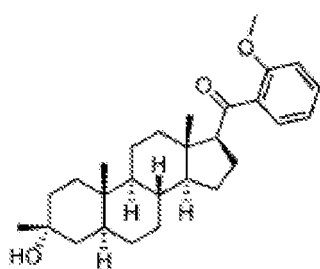


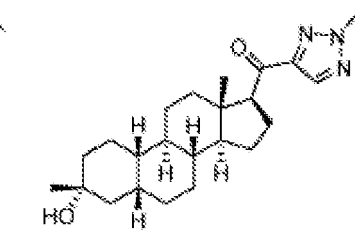
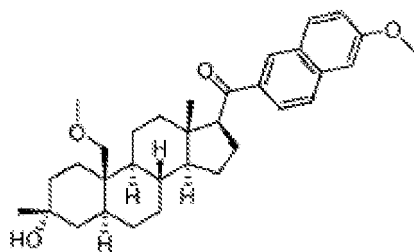
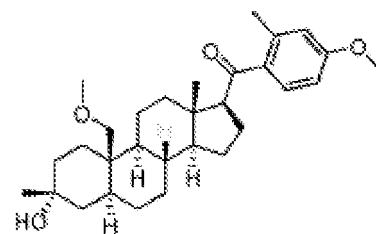
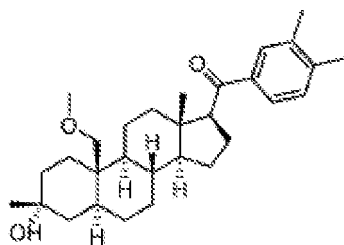
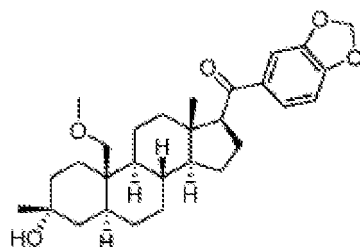
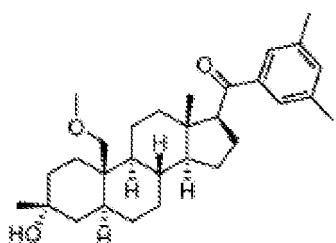
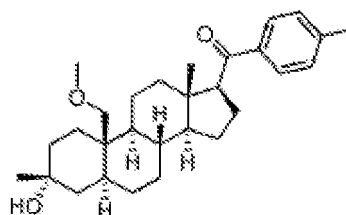
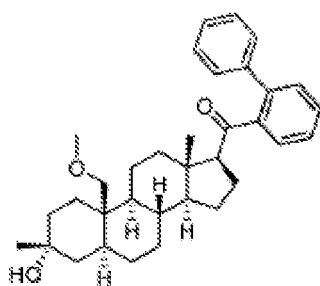
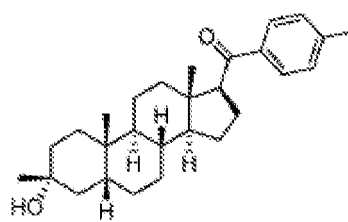
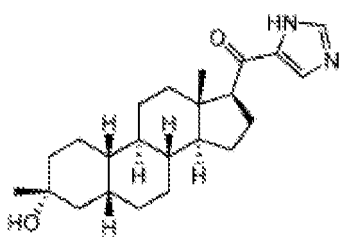


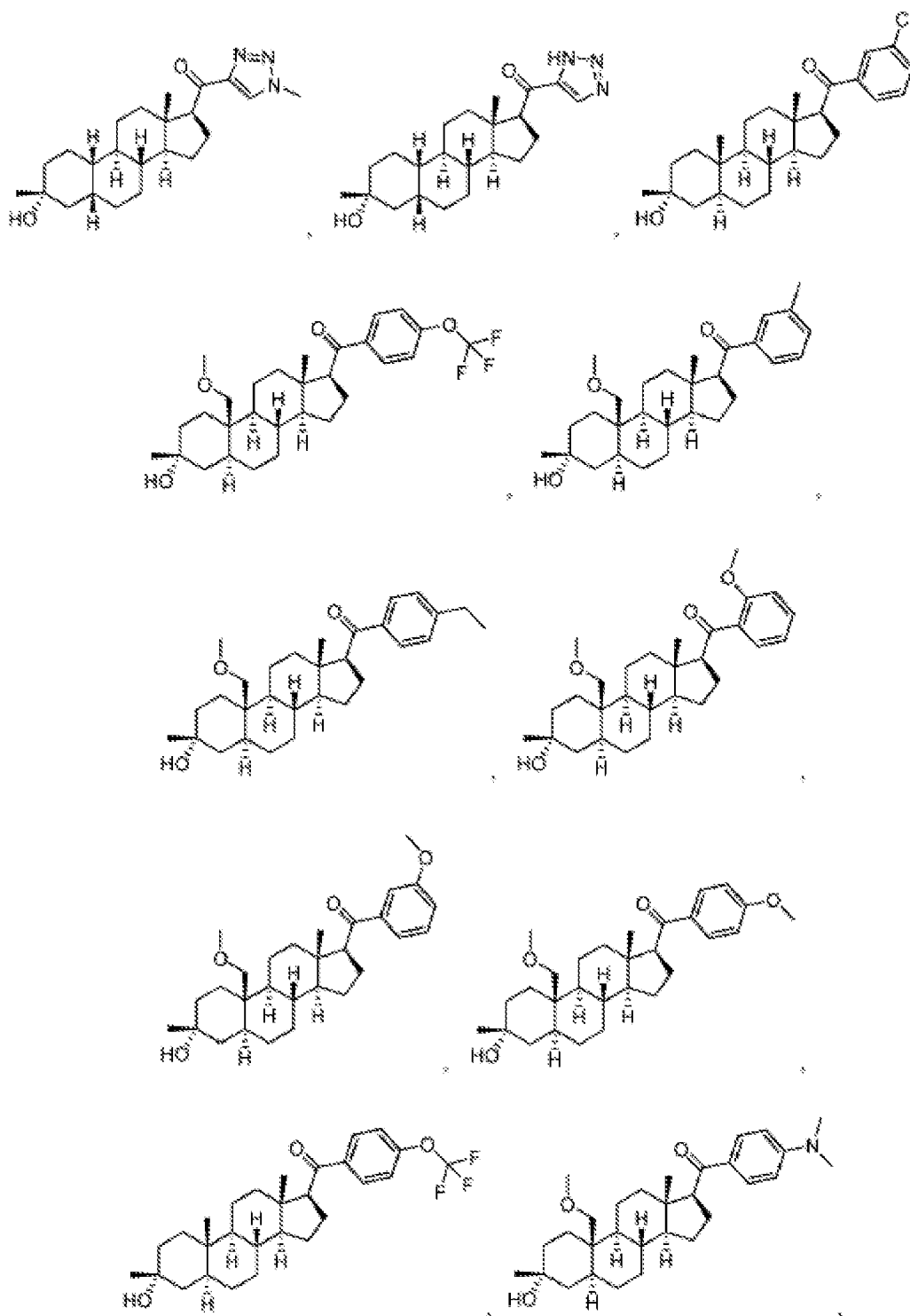


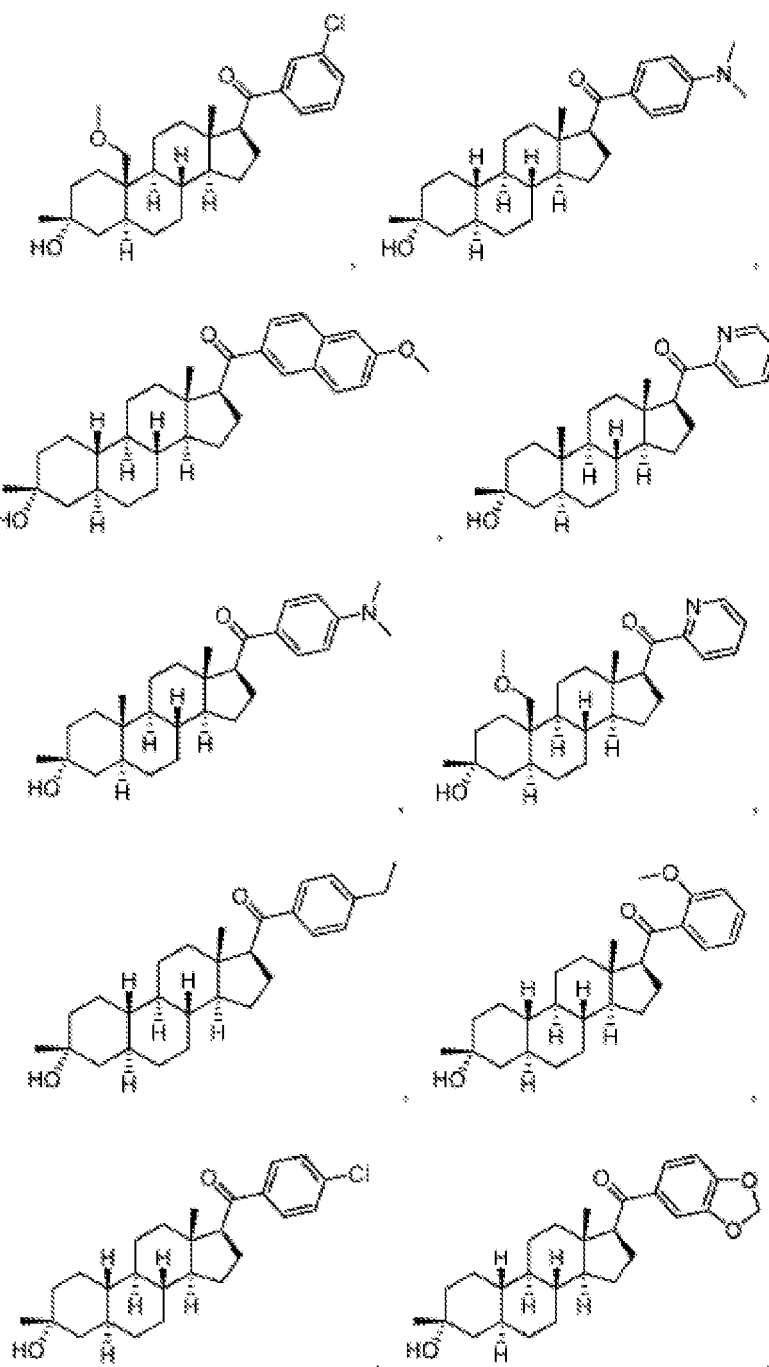


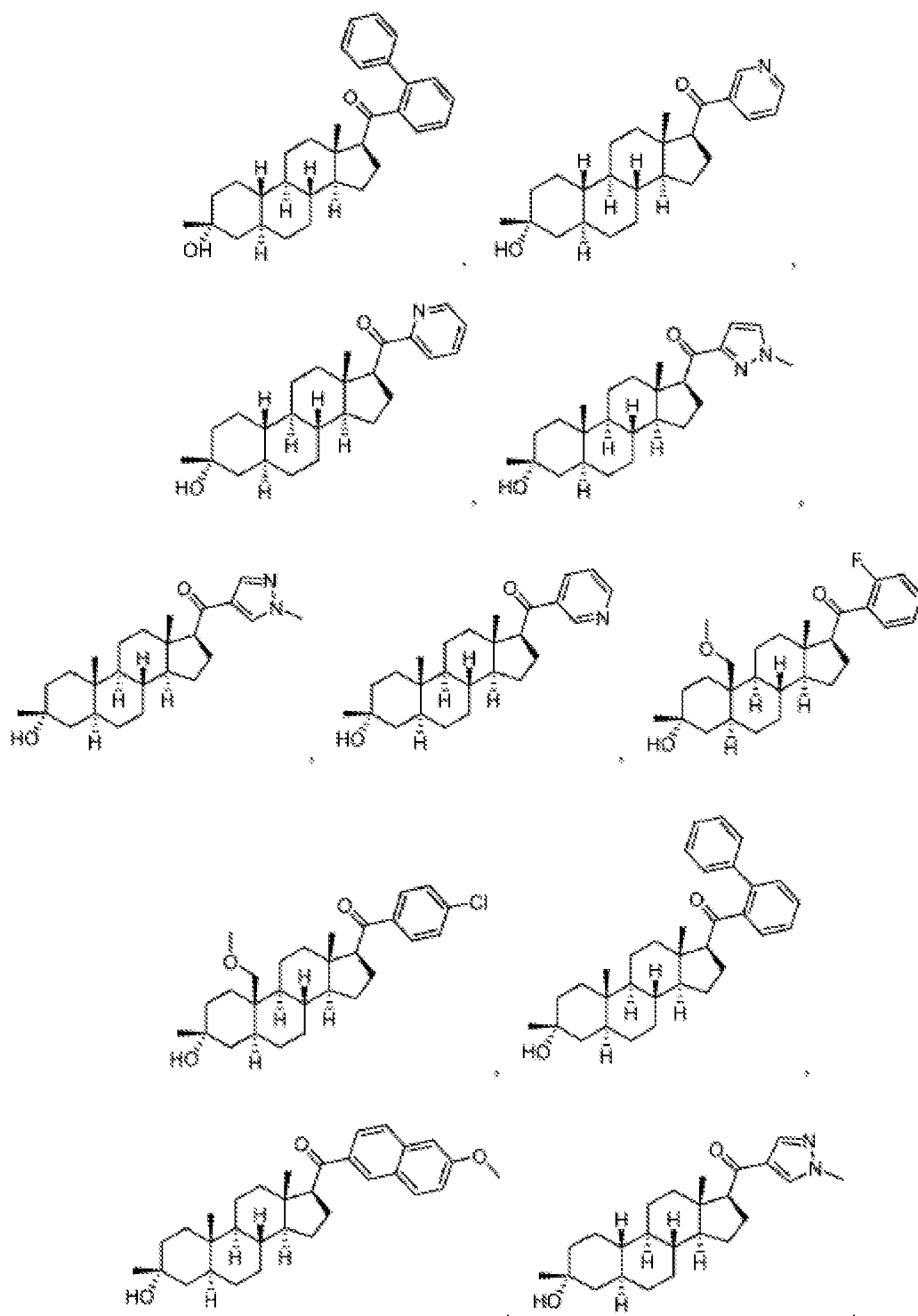


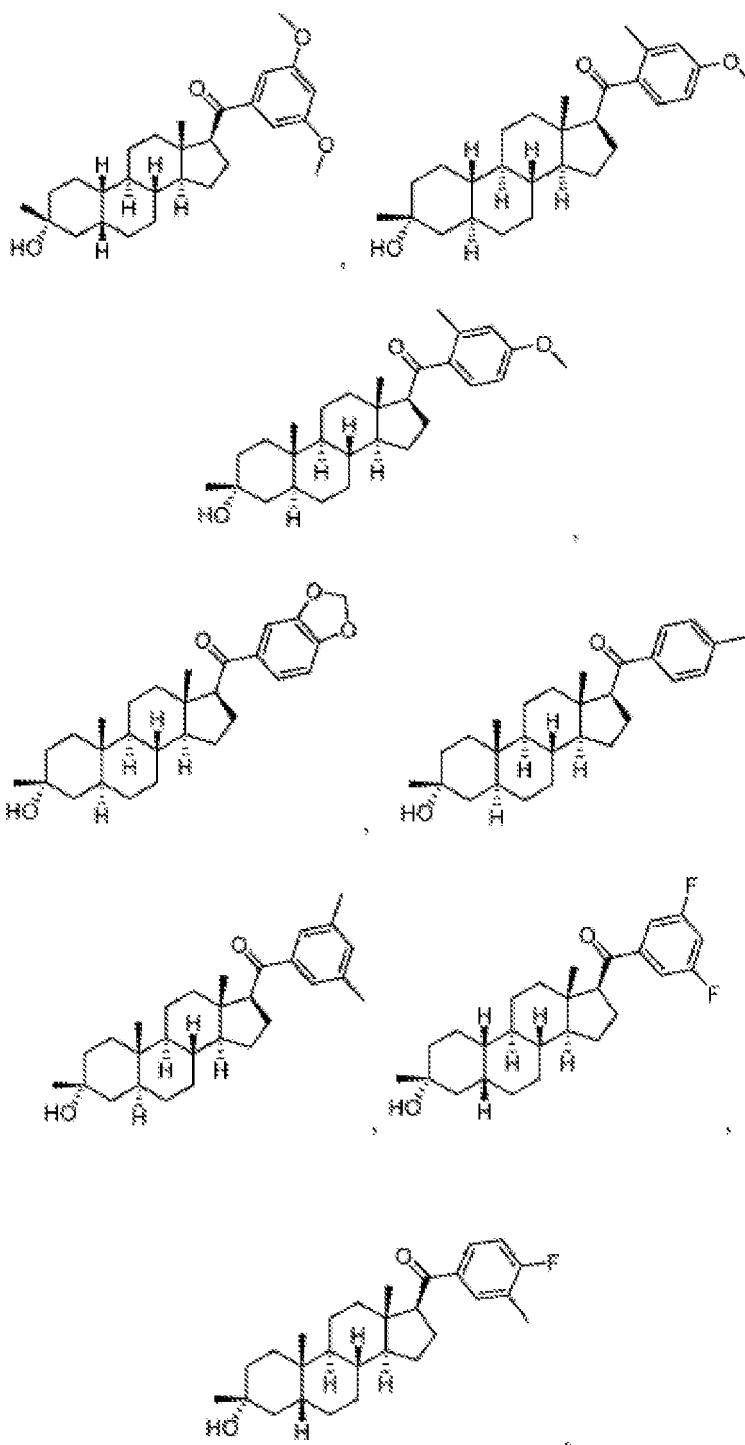










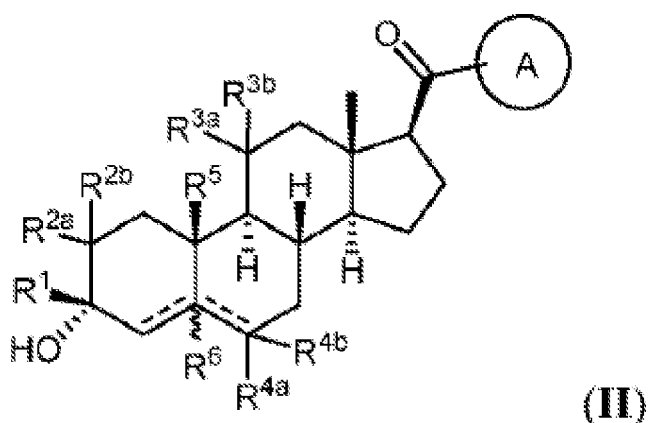


eller et farmaceutisk acceptabelt salt deraf.

- 5 8. Farmaceutisk sammensætning omfattende en forbindelse ifølge et hvilket som helst af de foregående krav, eller et farmaceutisk acceptabelt salt deraf og en farmaceutisk acceptabel excipiens.

9. Forbindelse med formelen (II), et farmaceutisk acceptabelt salt deraf eller farmaceutisk sammensætning af forbindelsen med formelen (II) til anvendelse i en fremgangsmåde til behandling af forstyrrelser relateret til GABA-funktion hos et individ med behov dertil:

5



hvor:

10

ring A er substitueret eller usubstitueret aryl eller heteroaryl;

R^1 er hydrogen eller substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl eller substitueret eller usubstitueret C_{3-6} carbocyclyl;

15

hver af R^{2a} og R^{2b} er uafhængigt udvalgt blandt hydrogen, halogen, substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl, substitueret eller usubstitueret C_{3-6} carbocyclyl, substitueret eller usubstitueret aryl, substitueret eller usubstitueret heteroaryl, $-N(R^A)(R^B)$ eller $-OR^{A2}$,

20

hvor hver af R^A og R^B uafhængigt er hydrogen, substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl, substitueret eller usubstitueret C_{3-6} carbocyclyl, substitueret eller usubstitueret heterocyclyl, substitueret eller usubstitueret aryl eller substitueret eller usubstitueret heteroaryl eller R^A og R^B sammen med nitrogenatomet, hvortil de er bundet, danner en ring (f.eks. heteroaryl,

25

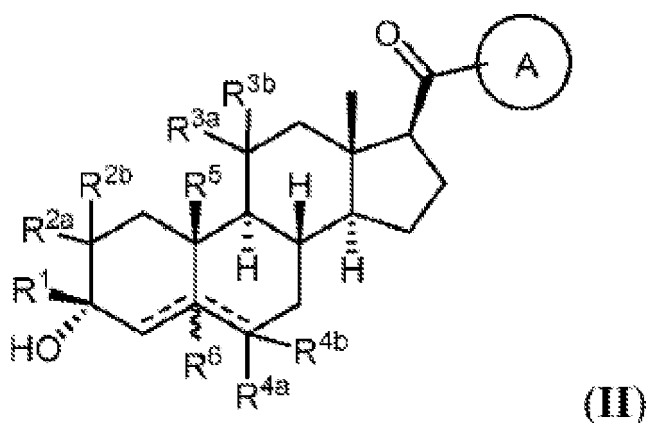
- heterocyclyl) eller R^{2a} og R^{2b} sammen med det carbonatom, hvortil de er bundet danner en ring; R^{A2} er hydrogen eller substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl, substitueret eller usubstitueret C_{3-6} carbocyclyl, substitueret eller usubstitueret aryl eller substitueret eller usubstitueret heteroaryl; R^{3a} er hydrogen, $-N(R^A)(R^B)$ eller $-OR^{A3}$, hvor R^{A3} er hydrogen, substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl eller substitueret eller usubstitueret C_{3-6} carbocyclyl, substitueret eller usubstitueret aryl, substitueret eller usubstitueret heteroaryl, og R^{3b} er hydrogen eller $-N(R^A)C(O)R^{A3}$; eller R^{3a} og R^{3b} er forbundet til dannelse af en oxo ($=O$) gruppe; hver af R^{4a} og R^{4b} er uafhængigt udvalgt blandt hydrogen eller halogen; R^5 er hydrogen, usubstitueret C_{1-6a} alkyl eller $-CH_2OR^{A5}$, hvor R^{A5} er hydrogen, substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl eller substitueret eller usubstitueret C_{3-6} carbocyclyl, substitueret eller usubstitueret aryl, substitueret eller usubstitueret heteroaryl; R^6 er fraværende eller hydrogen; og
- repræsenterer en enkelt- eller dobbeltbinding, hvor når den ene af ----- er en dobbeltbinding, den anden ----- er en enkeltbinding; og når en af ----- er en dobbeltbinding, er R^6 fraværende.
10. Forbindelse med formlen (II) som defineret i krav 1 eller et farmaceutisk acceptabelt salt deraf til anvendelse i en fremgangsmåde til behandling af en CNS-relateret forstyrrelse hos et individ med behov dertil.
11. Forbindelse til anvendelse ifølge krav 10, hvor den CNS-relaterede forstyrrelse er en søvnforstyrrelse, en humørforstyrrelse, en skizofrenispektrumforstyrrelse, en konvulsiv forstyrrelse, en hukommelsesforstyrrelse og/eller kognition, en bevægelsesforstyrrelse, en personlighedsforstyrrelse, autismspektrumforstyrrelse, smerter, traumatisk hjerneskade, en vaskulær sygdom, en stofmisbrugsforstyrrelse og/eller abstinens-

symptom, tinnitus, tremor f.eks. essentiel tremor eller depression f.eks. postpartum depression.

12. Forbindelse til anvendelse ifølge krav 10, hvor forbindelsen administreres oralt,
5 parenteralt, intravenøst eller intramuskulært.

13. Forbindelse til anvendelse ifølge krav 10, hvor individet er et individ med Rett syndrom, Fragile X-syndrom eller Angelmans syndrom.

10 14. Sæt omfattende en fast sammensætning omfattende en forbindelse med formelen (II):



15 eller et farmaceutisk acceptabelt salt deraf;

hvor:

ring A er substitueret eller usubstitueret aryl eller heteroaryl;

20 R¹ er hydrogen eller substitueret eller usubstitueret C₁₋₆alkyl, substitueret eller usubstitueret C₂₋₆alkenyl, substitueret eller usubstitueret C₂₋₆alkynyl eller substitueret eller usubstitueret C₃₋₆carbocyclyl;

25 hver af R^{2a} og R^{2b} er uafhængigt udvalgt blandt hydrogen, halogen, substitueret eller usubstitueret C₁₋₆alkyl, substitueret eller usubstitueret C₂₋₆alkenyl, substitueret eller usubstitueret C₂₋₆alkynyl, substitueret eller usubstitueret C₃₋₆carbocyclyl, substitueret eller usubstitueret aryl, substitueret eller usubstitue-

- ret heteroaryl, $-N(R^A)(R^B)$ eller $-OR^{A2}$,
 hvor hver af R^A og R^B uafhængigt er hydrogen, substitueret eller usubstitue-
 ret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller
 usubstitueret C_{2-6} alkynyl, substitueret eller usubstitueret C_{3-6} carbocyclyl,
 5 substitueret eller usubstitueret heterocyclyl, substitueret eller usubstitueret
 aryl eller substitueret eller usubstitueret heteroaryl eller R^A og R^B sammen
 med nitrogenatomet, hvortil de er bundet, danner en ring (f.eks. heteroaryl,
 heterocyclyl) eller R^{2a} og R^{2b} sammen med det carbonatom, hvortil de er
 bundet danner en ring; R^{A2} er hydrogen eller substitueret eller usubstitueret
 10 C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, substitueret eller usub-
 stitueret C_{2-6} alkynyl, substitueret eller usubstitueret C_{3-6} carbocyclyl, substitu-
 eret eller usubstitueret aryl eller substitueret eller usubstitueret heteroaryl;
 R^{3a} er hydrogen, $-N(R^A)(R^B)$ eller $-OR^{A3}$, hvor R^{A3} er hydrogen, substitueret
 eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret C_{2-6} alkenyl, sub-
 15 stitueret eller usubstitueret C_{2-6} alkynyl eller substitueret eller usubstitueret
 C_{3-6} carbocyclyl, substitueret eller usubstitueret aryl, substitueret eller usubsti-
 tueret heteroaryl, og
 R^{3b} er hydrogen eller $-N(R^A)C(O)R^{A3}$; eller
 R^{3a} og R^{3b} er forbundet til dannelse af en oxo ($=O$) gruppe;
 20 hver af R^{4a} og R^{4b} er uafhængigt udvalgt blandt hydrogen eller halogen;
 R^5 er hydrogen, usubstitueret C_{1-6a} alkyl eller $-CH_2OR^{A5}$, hvor R^{A5} er hydro-
 gen, substitueret eller usubstitueret C_{1-6} alkyl, substitueret eller usubstitueret
 C_{2-6} alkenyl, substitueret eller usubstitueret C_{2-6} alkynyl eller substitueret eller
 usubstitueret C_{3-6} carbocyclyl, substitueret eller usubstitueret aryl, substitueret
 25 eller usubstitueret heteroaryl;
 R^6 er fraværende eller hydrogen; og
 ----- repræsenterer en enkelt- eller dobbeltbinding, hvor
 når den ene af ----- er en dobbeltbinding, den anden ----- er en enkelt-
 binding; og
 30 når en af ----- er en dobbeltbinding, er R^6 fraværende.