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(54) **C7, C12, and C16 substituted neuroactive steroids and their methods of use**

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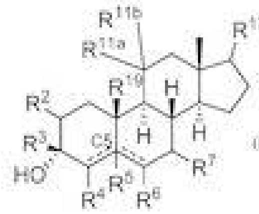
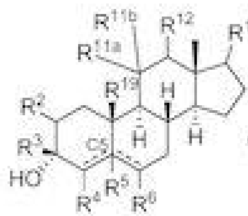
(71) Applicant(s):
Sage Therapeutics, Inc.

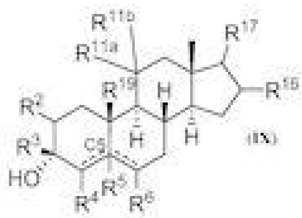
(74) Contact:
Spruson & Ferguson Pty Ltd

(72) Inventor(s):
SALITURO, Francesco, G.
MARTINEZ BOTELLA, Gabriel
HARRISON, Boyd, L.
ROBICHAUD, Albert, J.
BLANCO-PILLADO, Maria, Jesus
GRIFFIN, Andrew

(57) Abstract:


(I)


(V)


(IX)

Described herein are neuroactive steroids of Formula (I), Formula (V), or Formula (IX) or a pharmaceutically acceptable salt thereof; wherein each instance of R2, R3, R4, R5, R6, R7, R11a, R11b, R12, R16, R17, R19, and ----- are as defined herein. Such compounds are envisioned, in certain embodiments, to behave as GABA modulators. Also provided are pharmaceutical compositions comprising a compound described herein and methods of use and treatment, e.g., such as for inducing sedation and/or anesthesia.

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C7, C12, AND C16 SUBSTITUTED NEUROACTIVE STEROIDS AND THEIR METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a divisional application of New Zealand Patent Application No. 749714, filed 11 July 2017, and is related to International Patent Application No. PCT/US2017/041605, filed 11 July 2017, which claims priority to U.S.S.N. 62/360,887 filed 11 July 2016, U.S.S.N. 62/360,884 filed 11 July 2016, and U.S.S.N. 62/360,876 filed 11 July 2016. The entire contents of each of these applications are incorporated herein by reference in their entirety.

BACKGROUND

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.

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.

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 at least one distinct site for interaction with neuroactive steroids. See, *e.g.,* Lan, N. C. *et al., Neurochem. Res.* (1991) 16:347–356.

Neuroactive steroids can occur endogenously. The most potent endogenous neuroactive steroids are 3α–hydroxy-5-reduced pregnan-20-one and 3□□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)).

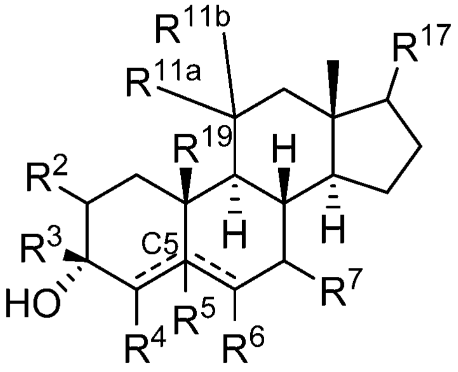
New and improved neuroactive steroids are needed that act as modulating agents for brain excitability, as well as agents for the prevention and treatment of CNS-related diseases. The compounds, compositions, and methods described herein are directed toward this end.

SUMMARY OF THE INVENTION

Compounds 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.

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 as described herein, *e.g.,* a compound of Formula (**I**), a compound of Formula (**V**), or a compound of Formula (**IX**). 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.

In an aspect, provided herein is a compound of Formula (**I**):

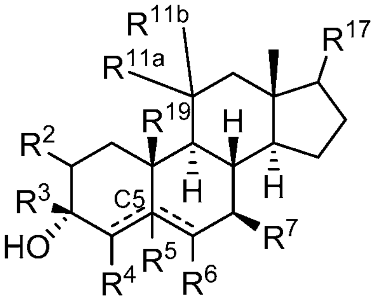


(**I**)

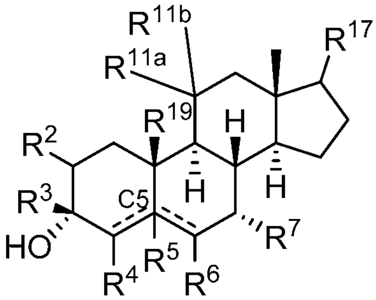
or a pharmaceutically acceptable salt thereof, wherein ⎓ represents a single or double bond as valency permits; each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-OR^{A1}$, $-SR^{A1}$, $-N(R^{A1})_2$,$-NHC(=O)R^{A1}$, $-NHC(=O)OR^{A1}$, $-S(=O)R^{A2}$, $-SO_2R^{A2}$, or $-S(=O)_2OR^{A1}$, wherein each instance of R^{A1} is independently hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{A1} groups are joined to form an heterocyclic or heteroaryl ring; and R^{A2} is alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or R^{11a} and R^{11b} together form oxo; R^3 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; R^5 is absent or hydrogen; and ⎓ represents a single or double bond, wherein when one of ⎓ at site is a double bond, the other ⎓ is a single bond; when both of ⎓ are single bonds, then R^5 is hydrogen; and when one of the ⎓ is a double bond, R^5 is absent; R^{17} is alkoxy, cyano, nitro, aryl, heteroaryl, or $-C(O)R^{B1}$, $-C(O)CH_2R^{B1}$, or $-C(O)CH_2CH_2R^{B1}$, wherein R^{B1} is hydrogen, $-OH$, alkoxy, aryl, or heteroaryl; R^{19} is hydrogen or alkyl; and R^7 is halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-OR^{A1}$, $-SR^{A1}$, $-N(R^{A1})_2$, $-NHC(=O)R^{A1}$, $-NHC(=O)OR^{A1}$, $-S(=O)R^{A2}$, $-SO_2R^{A2}$, or $-S(=O)_2OR^{A1}$.

In some embodiments, R^3 is alkyl.

In some embodiments, the compound of Formula **(I)** is a compound of Formula **(I-a)** or **(I-b)**:



(I-a)

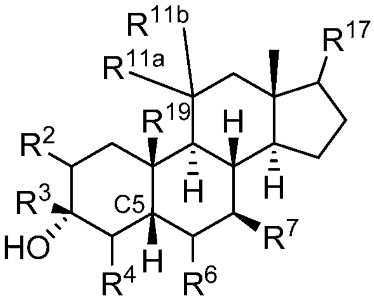


(I-b)

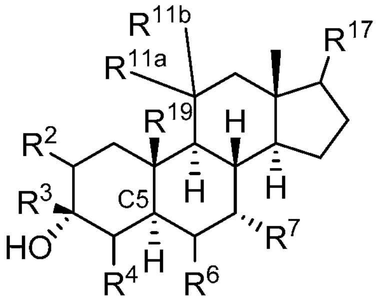
In some embodiments, each of R^2, R^4, and R^6, R^{11a}, and R^{11b} is independently hydrogen;

In some embodiments, R^2, R^4, R^6, R^{11a}, and R^{11b} are all hydrogen. In some embodiments, each of R^2, R^4, and R^6 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or $-OH$; In some embodiments, R^3 is C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl or $-CH_3$).

In some embodiments, the compound of Formula **(I)** is a compound of Formula **(II-a)** or **(II-b)**:

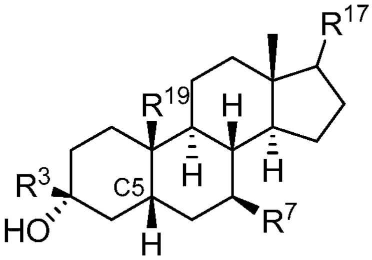
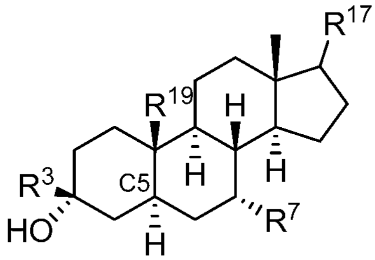


(II-a)

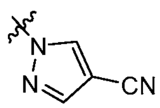
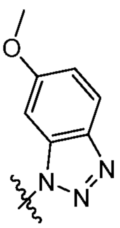
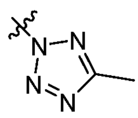
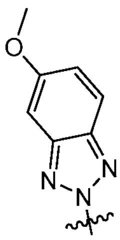
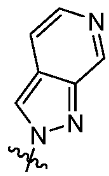
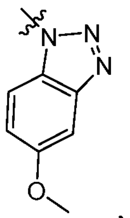
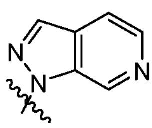
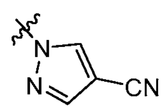
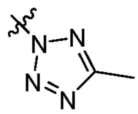
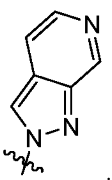


(II-b)

In some embodiments, the compound of Formula **(I)** is a compound of Formula **(II-c)** or **(II-d)**:

 **(II-c)**  **(II-d)**.

In some embodiments, R^{19} is $–CH_3$. In some embodiments, R^7 is alkyl (e.g., unsubstituted alkyl or $–CH_2OR^{A1}$) or $–OR^{A1}$. In some embodiments, R^7 is $–CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, or $-CH_2OCH_3$. In some embodiments, R^{17} is $–OCH_3$, -CN, or $-C(O)CH_3$. In some embodiments, R^{17} is $-C(O)CH_2R^{C1}$. In some embodiments, R^{17} is $-C(O)CH_2R^{B1}$. In some embodiments, R^{17} is alkoxy, cyano, or $-C(O)R^{B1}$. In some embodiments, R^{B1} is pyrazolyl (e.g., a cyano-substituted pyrazolyl). In some embodiments, R^{B1} is tetrazolyl (e.g., a methyl-substituted tetrazolyl). In some embodiments, R^{B1} is a bicyclic heteroaryl (e.g., a methoxy-substituted bicyclic heteroaryl.

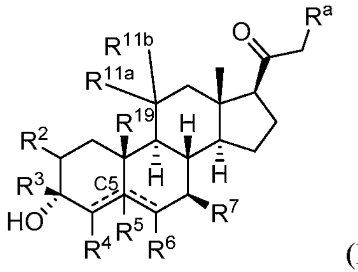
In some embodiments, R^{B1} is , , , , , , or . In some embodiments, R^{B1} is , , or .

In some embodiments, R^6 is halogen. In some embodiments, R^6 is fluorine.

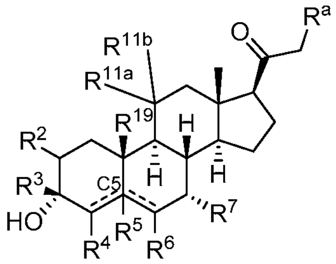
In some embodiments, each of R^{11a} and R^{11b} is independently hydrogen, C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl), C_1-C_6 alkoxy (*e.g.* C_1-C_6 alkoxyhalo), or –OH. In some embodiments,

R^{11a} and R^{11b} together form oxo. In some embodiments, R^{17} is C_1-C_6 alkoxy (*e.g.* $-OCH_3$), cyano, or nitro. In some embodiments, R^{19} is hydrogen or substituted or unsubtituted C_1-C_6 alkyl (*e.g.* $-CH_2OR^X$, wherein R^X is hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy).

In some embodiments, the compound of Formula **(I)** is a compound of Formula **(III-a)** or **(III-b)**:

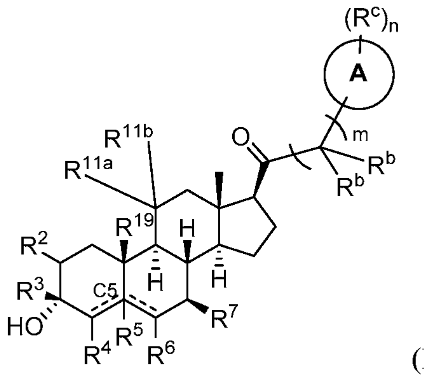


(III-a)

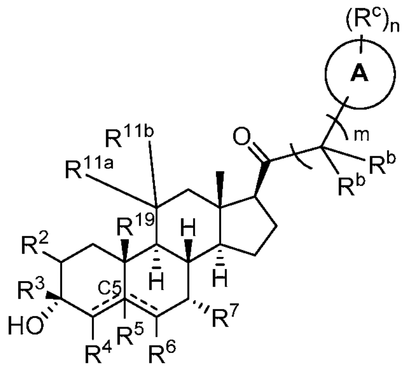


(III-b),

wherein R^a is hydrogen, halogen, C_1-C_6 alkyl (*e.g.* $-CH_3$), or $-OH$. In some embodiments, the compound of Formula **(I)** is a compound of Formula **(IV-a)** or **(IV-b)**:



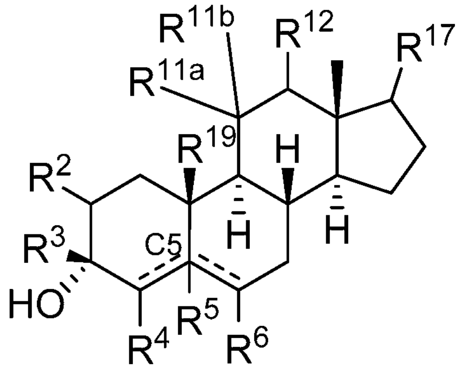
(IV-a)



(IV-b),

wherein: m is 0, 1, or 2; n is 0, 1, or 2; each R^b is independently hydrogen, halogen, or C_1-C_6 alkyl; and each R^c is independently halogen, C_1-C_6 alkyl (e.g. $-CH_3$ or C_1-C_6 haloalkyl), C_1-C_6 alkoxy, cyano, or $-OH$. In some embodiments, **A** is a 5-10-membered ring. In some embodiments, **A** is a fused bicyclic ring. In some embodiments, **A** is monocyclic heteroaryl or bicyclic heteroaryl.

In an aspect, provided is a compound of Formula **(V)**:

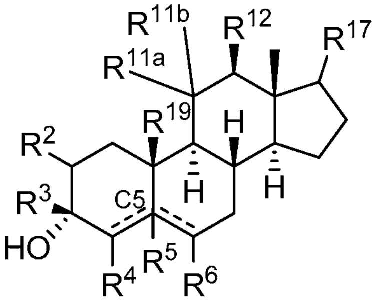


(V)

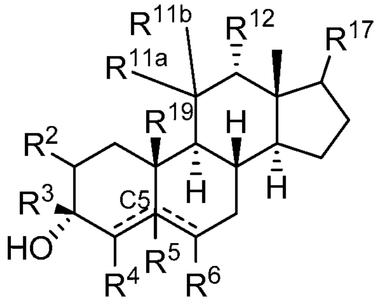
or a pharmaceutically acceptable salt thereof, wherein ===== represents a single or double bond as valency permits; each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-OR^{A1}$, $-SR^{A1}$, $-N(R^{A1})_2$,$-NHC(=O)R^{A1}$, $-NHC(=O)OR^{A1}$, $-S(=O)R^{A2}$, $-SO_2R^{A2}$, or $-S(=O)_2OR^{A1}$, wherein each instance of R^{A1} is independently hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{A1} groups are joined to form an heterocyclic or heteroaryl ring; and R^{A2} is alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or R^{11a} and R^{11b} together form oxo; R^3 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; R^5 is absent or hydrogen; and ===== represents a single or double bond, wherein when one of ===== at site is a double bond, the other ===== is a single bond; when both of ===== are single bonds, then R^5 is hydrogen; and when one of the ===== is a double bond, R^5 is absent; R^{17} is alkoxy, cyano, nitro, aryl, heteroaryl,$-C(O)R^{B1}$,$-C(O)CH_2R^{B1}$, or $-C(O)CH_2CH_2R^{B1}$, wherein R^{B1} is hydrogen,$-OH$, alkoxy, aryl, or heteroaryl; R^{19} is hydrogen or alkyl; and R^{12} is halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-OR^{A1}$, $-SR^{A1}$, $-N(R^{A1})_2$, $-NHC(=O)R^{A1}$, $-NHC(=O)OR^{A1}$, $-S(=O)R^{A2}$, $-SO_2R^{A2}$, or $-S(=O)_2OR^{A1}$.

In some embodiments, R^3 is alkyl.

In some embodiments, the compound of Formula **(V)** is a compound of Formula **(V-a)** or **(V-b)**:



(V-a)



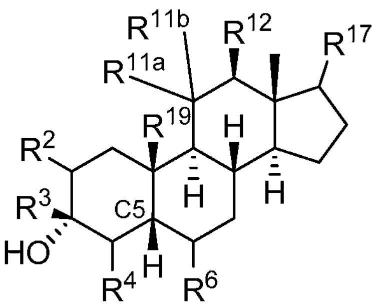
(V-b)

In some embodiments, each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen. In some embodiments, R^2, R^4, R^6, R^{11a}, and R^{11b} are all hydrogen.

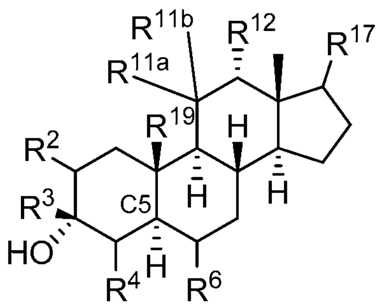
In some embodiments, each of R^2, R^4, and R^6 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or –OH.

In some embodiments, R^3 is C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl or $–CH_3$).

In some embodiments, the compound of Formula **(V)** is a compound of Formula **(VI-a)** or **(VI-b)**:

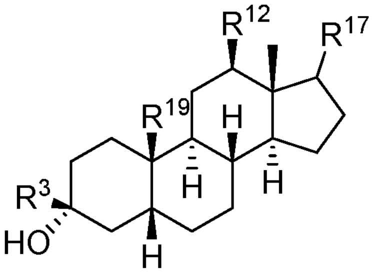
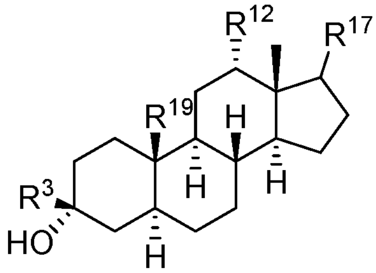


(VI-a)

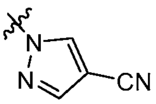
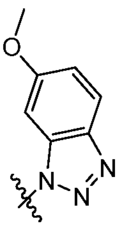
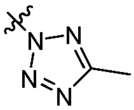
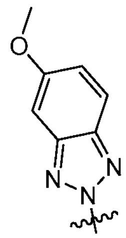
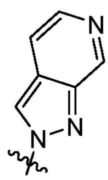
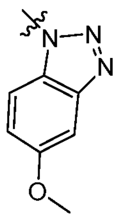
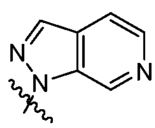
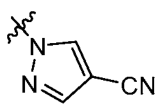
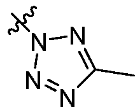
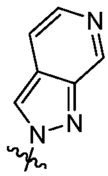


(VI-b).

In some embodiments, the compound of Formula **(V)** is a compound of Formula **(VI-c)** or **(VI-d)**:

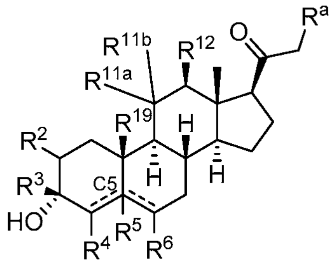

(VI-c)

(VI-d).

In some embodiments, R^{19} is $-CH_3$. In some embodiments, R^{12} is $-OR^{A1}$. In some embodiments, R^{12} is $-CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, or $-CH_2OCH_3$. In some embodiments, R^{17} is $-OCH_3$, -CN, or $-C(O)CH_3$. In some embodiments, R^{17} is $-C(O)CH_2R^{C1}$. In some embodiments, R^{17} is $-C(O)CH_2R^{B1}$. In some embodiments, R^{17} is alkoxy, cyano, or $-C(O)R^{B1}$.

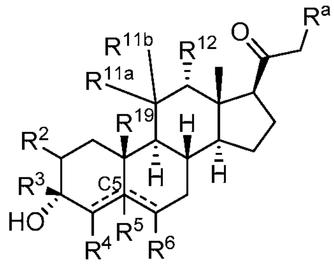
In some embodiments, R^{B1} is pyrazolyl (e.g., a cyano-substituted pyrazolyl). In some embodiments, R^{B1} is tetrazolyl (e.g., a methyl-substituted tetrazolyl). In some embodiments, R^{B1} is a bicyclic heteroaryl (e.g., a methoxy-substituted bicyclic heteroaryl. In some embodiments, R^{B1} is , , , , , , or . In some embodiments, R^{B1} is , , or .

In some embodiments, R^6 is halogen. In some embodiments, R^6 is fluorine.

In some embodiments, each of R^{11a} and R^{11b} is independently hydrogen, C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl), C_1-C_6 alkoxy (*e.g.* C_1-C_6 haloalkoxy), or –OH. In some embodiments, R^{11a} and R^{11b} together form oxo. In some embodiments, R^{17} is C_1-C_6 alkoxy (*e.g.* $-OCH_3$) or cyano. In some embodiments, R^{19} is hydrogen or substituted or unsubtituted C_1-C_6 alkyl (*e.g.* $-CH_2OR^X$, wherein R^X is hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy). In some embodiments, the compound of Formula **(V)** is a compound of Formula **(VII-a)** or **(VII-b)**:

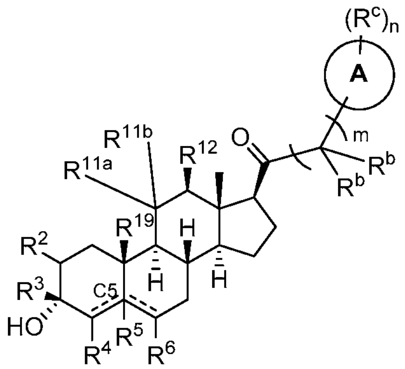


(VII-a)

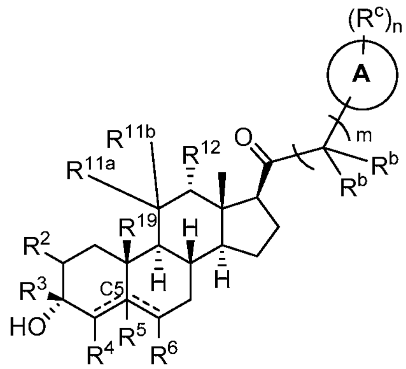


(VII-b),

wherein R^a is hydrogen, halogen, C_1-C_6 alkyl (*e.g.* $-CH_3$), or –OH. In some embodiments, the compound of Formula **(V)** is a compound of Formula **(VIII-a)** or **(VIII-b)**:



(VIII-a)

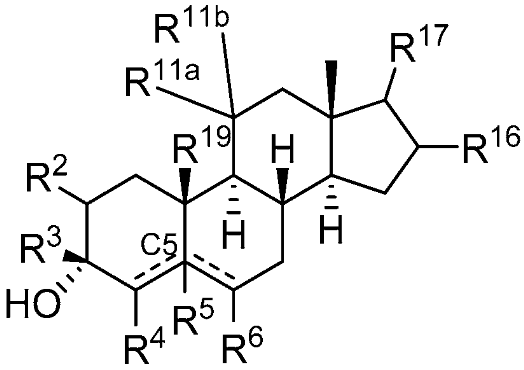


(VIII-b),

wherein m is 0, 1, or 2, n is 0, 1, or 2, and each R^b is independently hydrogen, halogen, or C_1.C_6 alkyl; and each R^c is independently halogen, C_1.C_6 alkyl (e.g. $-CH_3$ or C_1.C_6 haloalkyl), C_1.C_6 alkoxy, cyano, or –OH.

In some embodiments, **A** is a 5-10-membered ring. In some embodiments, **A** is a fused bicyclic ring. In some embodiments, **A** is monocyclic heteroaryl or bicyclic heteroaryl.

In an aspect, provided herein is a compound of Formula **(IX)**:

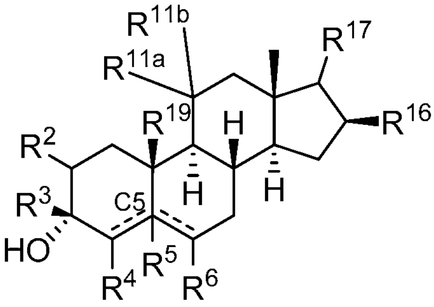
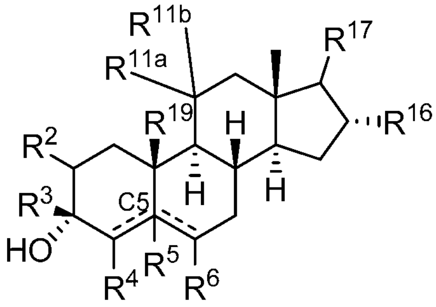


(IX),

or a pharmaceutically acceptable salt thereof, wherein $=\!=\!=$ represents a single or double bond as valency permits; each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, –OR^{A1}, –SR^{A1}, –$N(R^{A1})_2$,–$NHC(=O)R^{A1}$, –$NHC(=O)OR^{A1}$, –$S(=O)R^{A2}$, –SO_2R^{A2}, or –$S(=O)_2OR^{A1}$, wherein each instance of R^{A1} is independently hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{A1} groups are joined to form an heterocyclic or heteroaryl ring; and R^{A2} is alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or R^{11a} and R^{11b} together form oxo; R^3 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; R^5 is absent or hydrogen; and $=\!=\!=$ represents a single or double bond, wherein when one of $=\!=\!=$ at site is a double bond, the other $=\!=\!=$ is a single bond; when both of $=\!=\!=$ are single bonds, then R^5 is hydrogen; and when one of the $=\!=\!=$ is a double bond, R^5 is absent; R^{17} is alkoxy, cyano, nitro, aryl, heteroaryl, –$C(O)R^{B1}$, –$C(O)CH_2R^{B1}$, or –$C(O)CH_2CH_2R^{B1}$, wherein R^{B1} is hydrogen,–OH, –$N(R^{A1})_2$, alkoxy, aryl, or heteroaryl; R^{19} is hydrogen or alkyl; and R^{16} is halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, –OR^{A1}, –SR^{A1}, –$N(R^{A1})_2$, –$NHC(=O)R^{A1}$, –$NHC(=O)OR^{A1}$, –$S(=O)R^{A2}$, –SO_2R^{A2}, or –$S(=O)_2OR^{A1}$.

In some embodiments, R^3 is alkyl.

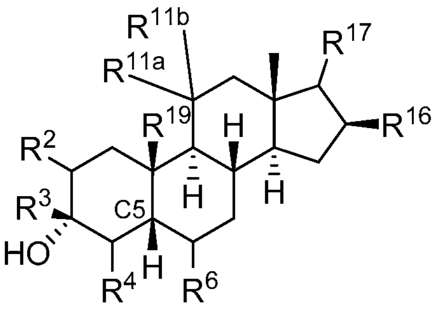
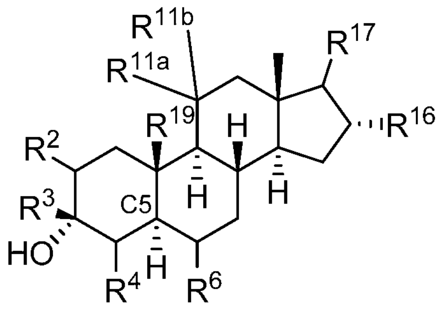
In some embodiments, the compound of Formula **(IX)** is a compound of Formula **(IX-a)** or **(IX-b)**:


(IX-a)

(IX-b).

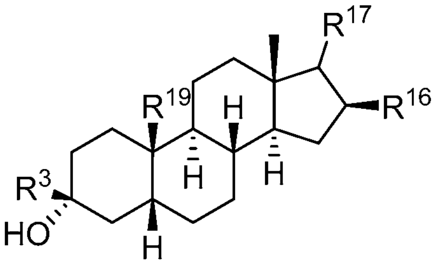
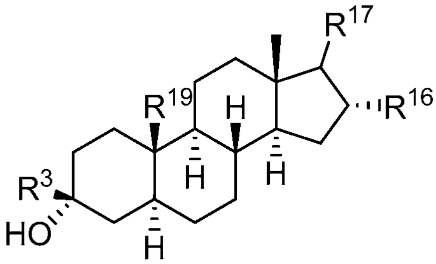
In some embodiments, each of R^2, R^4, and R^6, R^{11a}, and R^{11b} is independently hydrogen. In some embodiments, R^2, R^4, and R^6, R^{11a}, and R^{11b} are all hydrogen. In some embodiments, each of R^2, R^4, and R^6 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or –OH.

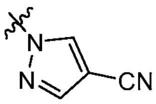
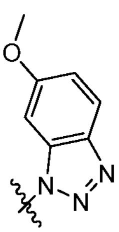
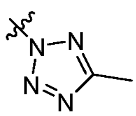
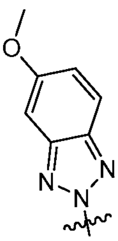
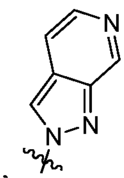
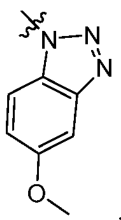
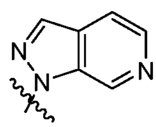
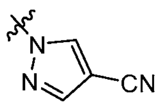
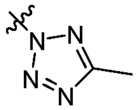
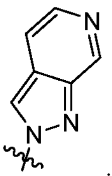
In some embodiments, R^3 is C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl or $–CH_3$).

In some embodiments, the compound of Formula **(IX)** is a compound of Formula **(X-a)** or **(X-b)**:


(X-a)

(X-b).

In some embodiments, the compound of Formula **(IX)** is a compound of Formula **(X-c)** or **(X-d)**:

 **(X-c)**  **(X-d)**.

In some embodiments, R^{19} is $–CH_3$. In some embodiments, R^{16} is alkyl or $–OR^{A1}$. In some embodiments, R^{16} is $–CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, or $-CH(CH_3)_2$. In some embodiments, R^{17} is $–OCH_3$, -CN, or $-C(O)CH_3$. In some embodiments, R^{17} is $-C(O)CH_2R^{C1}$. In some embodiments, R^{17} is $-C(O)CH_2R^{B1}$. In some embodiments, R^{17} is alkoxy, cyano, or $-C(O)R^{B1}$. In some embodiments, R^{B1} is pyrazolyl (e.g., a cyano-substituted pyrazolyl). In some embodiments, R^{B1} is tetrazolyl (e.g., a methyl-substituted tetrazolyl). In some embodiments, R^{B1} is a bicyclic heteroaryl (e.g., a methoxy-substituted bicyclic heteroaryl. In some embodiments, R^{B1} is , , , , , , or . In some embodiments, R^{B1} is , , or .

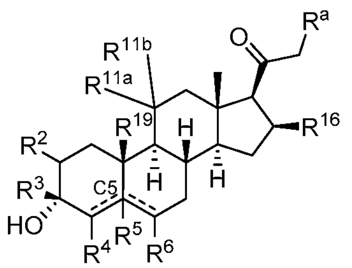
In some embodiments, R^6 is halogen. In some embodiments, R^6 is fluorine.

In some embodiments, each of R^{11a} and R^{11b} is independently hydrogen, C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl), C_1-C_6 alkoxy (*e.g.* C_1-C_6 haloalkoxy), or –OH. In some embodiments, R^{11a} and R^{11b} together form oxo.

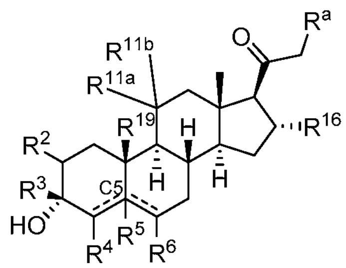
In some embodiments, R^{17} is C_1-C_6 alkoxy (*e.g.* $-OCH_3$), cyano, or nitro.

In some embodiments, R^{19} is hydrogen or substituted or unsubtituted C_1-C_6 alkyl (*e.g.* $-CH_2OR^X$, wherein R^X is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy).

In some embodiments, the compound of Formula **(IX)** is a compound of Formula **(X-a)** or **(X-b)**:



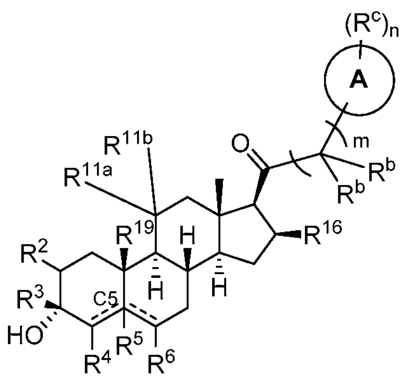
(X-a)



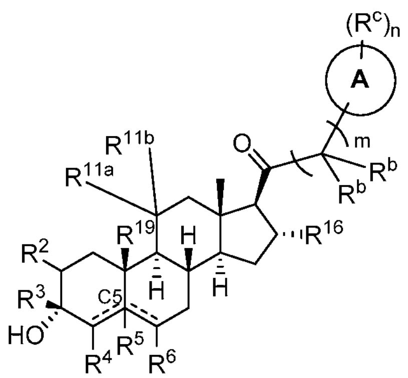
(X-b),

wherein R^a is hydrogen, halogen, C_1-C_6 alkyl (*e.g.* $-CH_3$), or –OH.

In some embodiments, the compound of Formula **(IX)** is a compound of Formula **(XI-a)** or **(XI-b)**:



(XI-a)



(XI-b),

wherein m is 0, 1, or 2, n is 0, 1, or 2, each R^b is independently hydrogen, halogen, or C_1-C_6 alkyl, and each R^c is independently halogen, C_1-C_6 alkyl (e.g. $-CH_3$ or C_1-C_6 haloalkyl), C_1-C_6 alkoxy, cyano, or –OH.

In some embodiments, **A** is a 5-10-membered ring. In some embodiments, **A** is a fused bicyclic ring. In some embodiments, **A** is monocyclic heteroaryl or bicyclic heteroaryl.

In an aspect, also provided herein are compounds described in **Table 1** or pharmaceutically acceptable salts thereof.

In an aspect, provided herein is a pharmaceutical composition comprising a compound described herein (e.g., a compound of the Formula **(I)**, Formula **(V)**, or Formula **(IX)**) and a pharmaceutically acceptable excipient.

In an aspect, provided herein is a method of inducing sedation and/or anesthesia in a subject, comprising administering to the subject an effective amount of a compound described herein (e.g., a compound of the Formula **(I)**, Formula **(V)**, or Formula **(IX)**), or a pharmaceutically acceptable salt thereof.

In an aspect, provided herein is a method of administering an effective amount of a compound, a pharmaceutically acceptable salt thereof, or pharmaceutical composition of a compound described herein (e.g., a compound of the Formula **(I)**, Formula **(V)**, or Formula **(IX)**), to a subject in need thereof, wherein the subject experiences sedation and/or anesthesia within two hours of administration. 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. In some embodiments, the compound is administered by intravenous administration. In some embodiments, the compound is administered chronically.

In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

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

In an aspect, provided herein is a method for treating seizure in a subject, comprising administering to the subject an effective amount of a compound described herein (e.g., a compound of the Formula **(I)**, Formula **(V)**, or Formula **(IX)**.

In an aspect, provided herein is a method for treating epilepsy or status epilepticus in a subject, the method comprising administering to the subject an effective amount of a compound described herein (e.g., a compound of the Formula **(I)**, Formula **(V)**, or Formula **(IX)**).

In an aspect, provided herein is a method for treating a neuroendocrine disorder or dysfunction in a subject, comprising administering to the subject an effective amount of a compound described herein (e.g., a compound of the Formula (**I**), Formula (**V**), or Formula (**IX**)).

In an aspect, provided herein is a method for treating a neurodegenerative disease or disorder in a subject, comprising administering to the subject an effective amount of a compound described herein (e.g., a compound of the Formula (**I**), Formula (**V**), or Formula (**IX**)).

In an aspect, provided herein is a method for treating a movement disorder or tremor in a subject, comprising administering to the subject an effective amount of a compound described herein (e.g., a compound of the Formula (**I**), Formula (**V**), or Formula (**IX**)).

In an aspect, provided herein is a method for treating a mood disorder or anxiety disorder in a subject, comprising administering to the subject an effective amount of a compound described herein (e.g., a compound of the Formula (**I**), Formula (**V**), or Formula (**IX**)).

In an aspect, provided herein 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 a compound described herein (e.g., a compound of the Formula (**I**), Formula (**V**), or Formula (**IX**)).

In an aspect, provided herein is a kit comprising a solid composition comprising a compound described herein (e.g., a compound of the Formula (**I**), Formula (**V**), or Formula (**IX**)) and a sterile diluent.

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 as described herein (e.g., a compound of the Formula (**I**), Formula (**V**), or Formula (**IX**)). 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.

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

Definitions

Chemical definitions

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.

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

The absolute configuration of an asymmetric center can be determined using methods known to one skilled in the art. In some embodiments, the absolute configuration of an asymmetric center in a compound can be elucidated from the X-ray single-crystal structure of the compound. In some embodiments, the abosolute configuration of an asymmetric center elucidated by the X-ray crystal structure of a compound can be used to infer the absolute configuration of a corresponding asymmetric center in another compound obtained from the same or similar synthetic methodologies. In some embodiments, absolute configuration of an asymmetric center can be determined using nuclear magnetic resonance (NMR) spectroscopy, *e.g.*, through nuclear Overhauser effect (NOE) experiments.

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

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.

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.

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

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.

"Alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C_{1-20} alkyl"). In some embodiments, an alkyl group has 1 to 12 carbon atoms ("C_{1-12} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl", also referred to herein as "lower alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8) and the like. Unless otherwise specified, each instance of an alkyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents; *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkyl group is unsubstituted C_{1-10} alkyl (*e.g.,* $–CH_3$). In certain embodiments, the alkyl group is substituted C_{1-10} alkyl. Common alkyl abbreviations include Me ($–CH_3$), Et ($–CH_2CH_3$), iPr ($–CH(CH_3)_2$), nPr ($–CH_2CH_2CH_3$), n–Bu ($–CH_2CH_2CH_2CH_3$), or i–Bu ($–CH_2CH(CH_3)_2$).

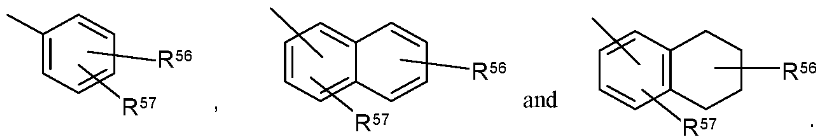
"Alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon double bonds, and no triple bonds ("C_{2-20} alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_{2-10} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkenyl group is unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-10} alkenyl.

"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 ("C_{2-20} alkynyl"). In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents; *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkynyl group is unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-10} alkynyl.

"Aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.*, anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. 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 C_{6-14} aryl. In certain embodiments, the aryl group is substituted C_{6-14} aryl.

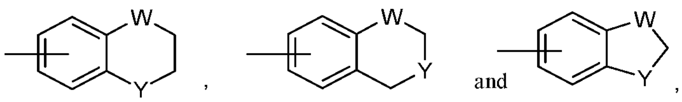
In certain embodiments, an aryl group substituted with one or more of groups selected from halo, C_1–C_8 alkyl, C_1–C_8 haloalkyl, cyano, hydroxy, C_1–C_8 alkoxy, and amino.

Examples of representative substituted aryls include the following



wherein one of R^{56} and R^{57} may be hydrogen and at least one of R^{56} and R^{57} is each independently selected from C_1–C_8 alkyl, C_1–C_8 haloalkyl, 4–10 membered heterocyclyl, alkanoyl, C_1–C_8 alkoxy, heteroaryloxy, alkylamino, arylamino, heteroarylamino, $NR^{58}COR^{59}$, $NR^{58}SOR^{59}$ $NR^{58}SO_2R^{59}$, COOalkyl, COOaryl, $CONR^{58}R^{59}$, $CONR^{58}OR^{59}$, $NR^{58}R^{59}$, $SO_2NR^{58}R^{59}$, S–alkyl, SOalkyl, SO_2alkyl, Saryl, SOaryl, SO_2aryl; or R^{56} and R^{57} may be joined to form a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group N, O, or S. R^{60} and R^{61} are independently hydrogen, C_1–C_8 alkyl, C_1–C_4 haloalkyl, C_3–C_{10} cycloalkyl, 4–10 membered heterocyclyl, C_6–C_{10} aryl, substituted C_6–C_{10} aryl, 5–10 membered heteroaryl, or substituted 5–10 membered heteroaryl.

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



wherein each W is selected from $C(R^{66})_2$, NR^{66}, O, and S; and each Y is selected from carbonyl, NR^{66}, O and S; and R^{66} is independently hydrogen, C_1–C_8 alkyl, C_3–C_{10} cycloalkyl, 4–10 membered heterocyclyl, C_6–C_{10} aryl, and 5–10 membered heteroaryl.

"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.

"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.

"Hydroxy" or "hydroxyl," independently or as part of another substituent, mean, unless otherwise stated, a –OH group.

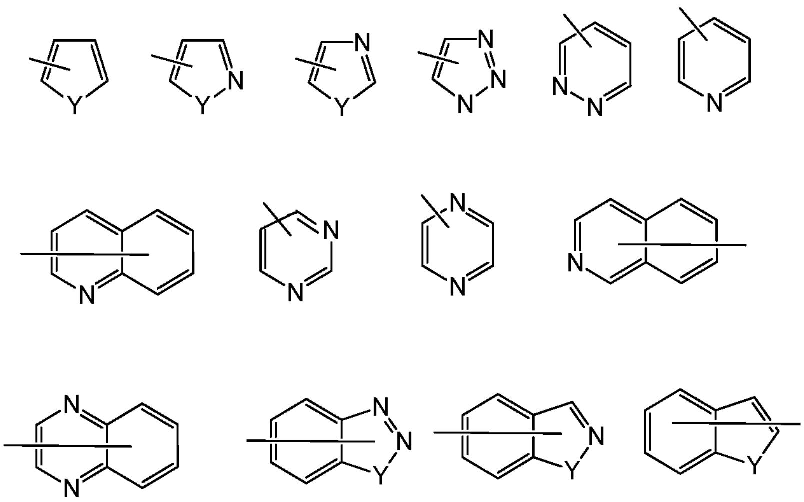
Hydroxyalkyl" or "hydroxylalkyl" can include alkyl structures that are substituted with one or more hydroxyl groups.

"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).

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.

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

Examples of representative heteroaryls include the following formulae:



wherein each Y is selected from carbonyl, N, NR^{65}, O, and S; and R^{65} is independently hydrogen, C_1–C_8 alkyl, C_3–C_{10} cycloalkyl, 4–10 membered heterocyclyl, C_6–C_{10} aryl, and 5–10 membered heteroaryl.

"Carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be saturated or can be partially unsaturated. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C_{3-10} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-10} carbocyclyl.

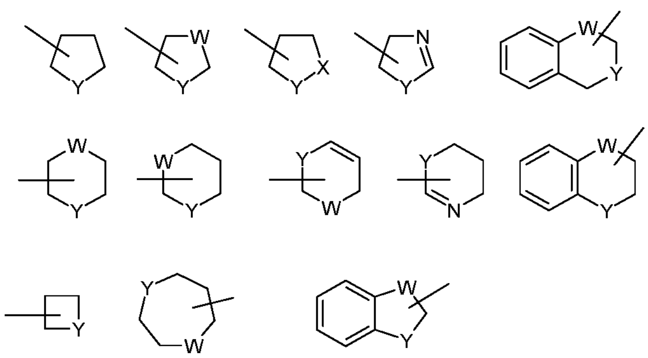
In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms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

"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.

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.

Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin–2–one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5–membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6–bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6–membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6–bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

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



wherein each W is selected from CR^{67}, $C(R^{67})_2$, NR^{67}, O, and S; and each Y is selected from NR^{67}, O, and S; and R^{67} is independently hydrogen, C_1–C_8 alkyl, C_3–C_{10} cycloalkyl, 4–10 membered heterocyclyl, C_6–C_{10} 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.

"Acyl" refers to a radical $-C(O)R^{20}$, where R^{20} is hydrogen, substituted or unsubstitued alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstitued 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.

"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 unsubstitued alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstitued 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.

"Acyloxy" refers to a radical $–OC(O)R^{27}$, where R^{27} is hydrogen, substituted or unsubstitued alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstitued 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.

"Alkoxy" refers to the group $–OR^{29}$ where R^{29} is substituted or unsubstituted alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstitued 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.

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 $–OCH_2CH_2NMe_2$.

"Amino" refers to the radical $–NH_2$.

"Substituted amino" refers to an amino group of the formula $–N(R^{38})_2$ wherein R^{38} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstitued heteroaryl, or an amino protecting group, wherein at least one of R^{38} is not a hydrogen. In certain embodiments,

each R^{38} is independently selected from hydrogen, C_1–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 C_1–C_8 alkyl, substituted with halo or hydroxy; C_3–C_8 alkenyl, substituted with halo or hydroxy; C_3–C_8 alkynyl, substituted with halo or hydroxy, or $–(CH_2)_t$(C_6–C_{10} aryl), $–(CH_2)_t$(5–10 membered heteroaryl), $–(CH_2)_t$(C_3–C_{10} cycloalkyl), or $–(CH_2)_t$(4–10 membered heterocyclyl), wherein t is an integer between 0 and 8, each of which is substituted by unsubstituted C_1–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; or both R^{38} groups are joined to form an alkylene group.

Exemplary "substituted amino" groups include, but are not limited to, $–NR^{39}$–C_1–C_8 alkyl, $–NR^{39}$–$(CH_2)_t$(C_6–C_{10} aryl), $–NR^{39}$–$(CH_2)_t$(5–10 membered heteroaryl), $–NR^{39}$–$(CH_2)_t$(C_3–C_{10} cycloalkyl), and $–NR^{39}$–$(CH_2)_t$(4–10 membered heterocyclyl), wherein t is an integer from 0 to 4, for instance 1 or 2, each R^{39} independently represents hydrogen or C_1–C_8 alkyl; and any alkyl groups present, may themselves be substituted by halo, substituted or unsubstituted amino, or hydroxy; and any aryl, heteroaryl, cycloalkyl, or heterocyclyl groups present, may themselves be substituted by unsubstituted C_1–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. 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.

"Azido" refers to the radical $-N_3$.

"Carbamoyl" or "amido" refers to the radical $-C(O)NH_2$.

"Substituted carbamoyl" or "substituted amido" refers to the radical $-C(O)N(R^{62})_2$ wherein each R^{62} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstitued heteroaryl, or an amino protecting group, wherein at least one of R^{62} is not a hydrogen. In certain embodiments, R^{62} is selected from H, C_1–C_8 alkyl, C_3–C_{10} cycloalkyl, 4–10 membered heterocyclyl, C_6–C_{10} aryl, and 5–10 membered heteroaryl; or 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, or 5–10 membered heteroaryl, each of which is 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; provided that at least one R^{62} is other than H.

"Carboxy" refers to the radical $-C(O)OH$.

"Cyano" refers to the radical –CN.

"Oxo" refers to =O.

"Nitro" refers to the radical $-NO_2$.

"Ethenyl" refers to substituted or unsubstituted –(C=C)–. "Ethylene" refers to substituted or unsubstituted –(C–C)–. "Ethynyl" refers to –(C≡C)–.

"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.

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.

Exemplary carbon atom substituents include, but are not limited to, halogen, –CN, –NO_2, –N_3, –SO_2H, –SO_3H, –OH, –OR^{aa}, –$ON(R^{bb})_2$, –$N(R^{bb})_2$, –$N(R^{bb})_3{}^+X^-$, –$N(OR^{cc})R^{bb}$, –SH, –SR^{aa}, –SSR^{cc}, –$C(=O)R^{aa}$, –CO_2H, –CHO, –$C(OR^{cc})_2$, –CO_2R^{aa}, –$OC(=O)R^{aa}$, –OCO_2R^{aa}, –$C(=O)N(R^{bb})_2$, –$OC(=O)N(R^{bb})_2$, –$NR^{bb}C(=O)R^{aa}$, –$NR^{bb}CO_2R^{aa}$, –$NR^{bb}C(=O)N(R^{bb})_2$, –$C(=NR^{bb})R^{aa}$, –$C(=NR^{bb})OR^{aa}$, –$OC(=NR^{bb})R^{aa}$, –$OC(=NR^{bb})OR^{aa}$, –$C(=NR^{bb})N(R^{bb})_2$, –$OC(=NR^{bb})N(R^{bb})_2$, –$NR^{bb}C(=NR^{bb})N(R^{bb})_2$, –$C(=O)NR^{bb}SO_2R^{aa}$, –$NR^{bb}SO_2R^{aa}$, –$SO_2N(R^{bb})_2$, –$SO_2R^{aa}$, –$SO_2OR^{aa}$, –$OSO_2R^{aa}$, –$S(=O)R^{aa}$, –$OS(=O)R^{aa}$, –$Si(R^{aa})_3$, –$OSi(R^{aa})_3$ –$C(=S)N(R^{bb})_2$, –$C(=O)SR^{aa}$, –$C(=S)SR^{aa}$, –$SC(=S)SR^{aa}$, –$SC(=O)SR^{aa}$, –$OC(=O)SR^{aa}$, –$SC(=O)OR^{aa}$, –$SC(=O)R^{aa}$, –$P(=O)_2R^{aa}$, –$OP(=O)_2R^{aa}$, –$P(=O)(R^{aa})_2$, –

$OP(=O)(R^{aa})_2$, $–OP(=O)(OR^{cc})_2$, $–P(=O)_2N(R^{bb})_2$, $–OP(=O)_2N(R^{bb})_2$, $–P(=O)(NR^{bb})_2$, $–OP(=O)(NR^{bb})_2$, $–NR^{bb}P(=O)(OR^{cc})_2$, $–NR^{bb}P(=O)(NR^{bb})_2$, $–P(R^{cc})_2$, $–P(R^{cc})_3$, $–OP(R^{cc})_2$, $–OP(R^{cc})_3$, $–B(R^{aa})_2$, $–B(OR^{cc})_2$, $–BR^{aa}(OR^{cc})$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

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

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

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

each instance of R^{dd} is, independently, selected from halogen, $–CN$, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, $–OH$, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3^{+}X^{–}$, $–N(OR^{ee})R^{ff}$, $–SH$, $–SR^{ee}$, $–SSR^{ee}$, $–C(=O)R^{ee}$, $–CO_2H$, $–CO_2R^{ee}$, $–OC(=O)R^{ee}$, $–OCO_2R^{ee}$, $–C(=O)N(R^{ff})_2$, $–OC(=O)N(R^{ff})_2$, $–NR^{ff}C(=O)R^{ee}$, $–NR^{ff}CO_2R^{ee}$, $–NR^{ff}C(=O)N(R^{ff})_2$, $–C(=NR^{ff})OR^{ee}$, $–OC(=NR^{ff})R^{ee}$, $–OC(=NR^{ff})OR^{ee}$, $–C(=NR^{ff})N(R^{ff})_2$, $–OC(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}C(=NR^{ff})N(R^{ff})_2$,$–NR^{ff}SO_2R^{ee}$, $–SO_2N(R^{ff})_2$, $–SO_2R^{ee}$, $–SO_2OR^{ee}$, $–OSO_2R^{ee}$, $–S(=O)R^{ee}$, $–Si(R^{ee})_3$, $–OSi(R^{ee})_3$, $–C(=S)N(R^{ff})_2$, $–C(=O)SR^{ee}$, $–C(=S)SR^{ee}$, $–SC(=S)SR^{ee}$, $–P(=O)_2R^{ee}$, $–P(=O)(R^{ee})_2$, $–OP(=O)(R^{ee})_2$, –

$OP(=O)(OR^{ee})_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

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

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

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1–6}$ alkyl, $–ON(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_3{}^+X^–$, $–NH(C_{1–6}$ alkyl$)_2{}^+X^–$, $–NH_2(C_{1–6}$ alkyl$)\,{}^+X^–$, $–NH_3{}^+X^–$, $–N(OC_{1–6}$ alkyl$)(C_{1–6}$ alkyl), $–N(OH)(C_{1–6}$ alkyl), –NH(OH), –SH, $–SC_{1–6}$ alkyl, $–SS(C_{1–6}$ alkyl), $–C(=O)(C_{1–6}$ alkyl), $–CO_2H$, $–CO_2(C_{1–6}$ alkyl), $–OC(=O)(C_{1–6}$ alkyl), $–OCO_2(C_{1–6}$ alkyl), $–C(=O)NH_2$, $–C(=O)N(C_{1–6}$ alkyl$)_2$, $–OC(=O)NH(C_{1–6}$ alkyl), $–NHC(=O)(C_{1–6}$ alkyl), $–N(C_{1–6}$ alkyl$)C(=O)(C_{1–6}$ alkyl), $–NHCO_2(C_{1–6}$ alkyl), $–NHC(=O)N(C_{1–6}$ alkyl$)_2$, $–NHC(=O)NH(C_{1–6}$ alkyl), $–NHC(=O)NH_2$, $–C(=NH)O(C_{1–6}$ alkyl),$–OC(=NH)(C_{1–6}$ alkyl), $–OC(=NH)OC_{1–6}$ alkyl, $–C(=NH)N(C_{1–6}$ alkyl$)_2$, $–C(=NH)NH(C_{1–6}$ alkyl), $–C(=NH)NH_2$, $–OC(=NH)N(C_{1–6}$ alkyl$)_2$, $–OC(NH)NH(C_{1–6}$ alkyl), $–OC(NH)NH_2$, $–NHC(NH)N(C_{1–6}$ alkyl$)_2$, $–NHC(=NH)NH_2$, $–NHSO_2(C_{1–6}$ alkyl), $–SO_2N(C_{1–6}$ alkyl$)_2$, $–SO_2NH(C_{1–6}$ alkyl), $–SO_2NH_2$,$–SO_2C_{1–6}$ alkyl, $–SO_2OC_{1–6}$ alkyl, $–OSO_2C_{1–6}$ alkyl, $–SOC_{1–6}$ alkyl, $–Si(C_{1–6}$ alkyl$)_3$, $–OSi(C_{1–6}$ alkyl$)_3$ $–C(=S)N(C_{1–6}$ alkyl$)_2$, $C(=S)NH(C_{1–6}$ alkyl), $C(=S)NH_2$, $–C(=O)S(C_{1–6}$ alkyl), $–C(=S)SC_{1–6}$ alkyl, $–SC(=S)SC_{1–6}$ alkyl, $–P(=O)_2(C_{1–6}$ alkyl), $–P(=O)(C_{1–6}$ alkyl$)_2$, $–OP(=O)(C_{1–6}$ alkyl$)_2$, $–OP(=O)(OC_{1–6}$ alkyl$)_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; wherein $X^–$ is a counterion.

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

Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substitutents include, but are not limited to, hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14–membered heteroaryl, or two R^{cc} groups 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.

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

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).

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

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

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

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

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.

“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.

“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.

"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.

"Stereoisomers": It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non–superimposable mirror images of each other are termed "enantiomers." When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R– and S–sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (–)–isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

"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.

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.

Disease, disorder, and condition are used interchangeably herein.

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").

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.

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.

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.

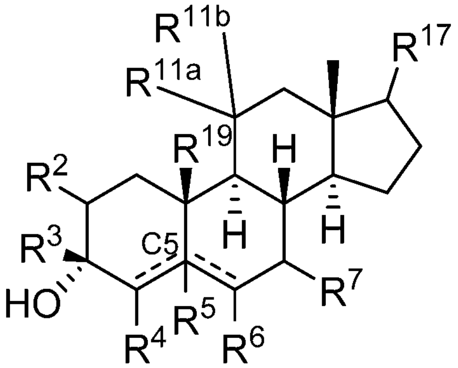
DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

Provided herein are compounds (e.g., a compound of Formula **(I)**, a compound of Formula **(V)**, or a compound of Formula **(IX)**), pharmaceutical compositions, and their methods of use to treat a disease or disorder as described herein.

Compounds

Compounds 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.

In an aspect, provided herein is a compound of Formula (**I**):

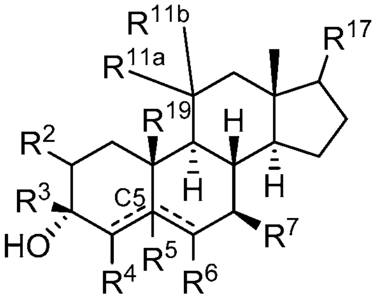


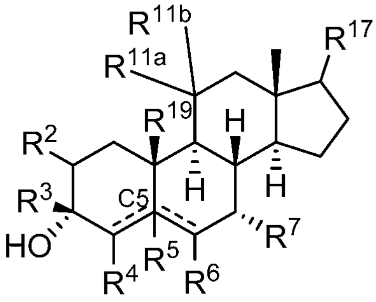
(**I**)

or a pharmaceutically acceptable salt thereof, wherein ---- represents a single or double bond as valency permits; each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-OR^{A1}$, $-SR^{A1}$, $-N(R^{A1})_2$,$-NHC(=O)R^{A1}$, $-NHC(=O)OR^{A1}$, $-S(=O)R^{A2}$, $-SO_2R^{A2}$, or $-S(=O)_2OR^{A1}$, wherein each instance of R^{A1} is independently hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{A1} groups are joined to form an heterocyclic or heteroaryl ring; and R^{A2} is alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or R^{11a} and R^{11b} together form oxo; R^3 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; R^5 is absent or hydrogen; and ------ represents a single or double bond, wherein when one of ------ at site is a double bond, the other ------ is a single bond; when both of ------ are single bonds, then R^5 is hydrogen; and when one of the ------ is a double bond, R^5 is absent; R^{17} is alkoxy, cyano, nitro, aryl, heteroaryl, or $-C(O)R^{B1}$, $-C(O)CH_2R^{B1}$, or $-C(O)CH_2CH_2R^{B1}$, wherein R^{B1} is hydrogen,–OH, alkoxy, aryl, or heteroaryl; R^{19} is hydrogen or alkyl; and R^7 is halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-OR^{A1}$, $-SR^{A1}$, $-N(R^{A1})_2$, $-NHC(=O)R^{A1}$, $-NHC(=O)OR^{A1}$, $-S(=O)R^{A2}$, $-SO_2R^{A2}$, or $-S(=O)_2OR^{A1}$.

In some embodiments, R^3 is alkyl.

In some embodiments, the compound of Formula (**I**) is a compound of Formula (**I-a**) or (**I-b**):

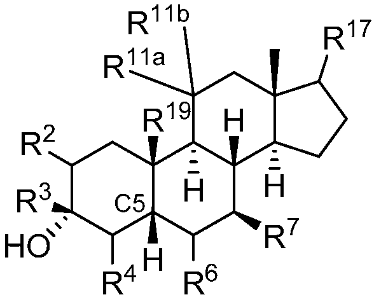

(I-a)

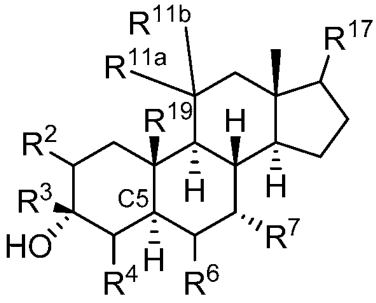

(I-b)

In some embodiments, each of R^2, R^4, and R^6, R^{11a}, and R^{11b} is independently hydrogen;

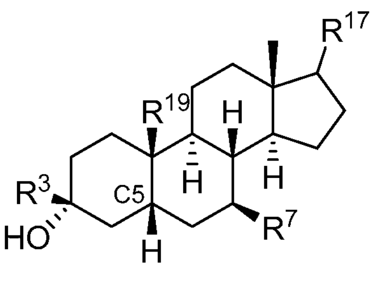
In some embodiments, R^2, R^4, R^6, R^{11a}, and R^{11b} are all hydrogen. In some embodiments, each of R^2, R^4, and R^6 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or –OH; In some embodiments, R^3 is C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl or $-CH_3$).

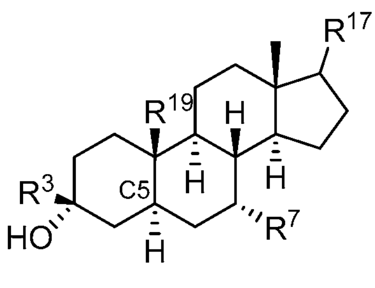
In some embodiments, the compound of Formula **(I)** is a compound of Formula **(II-a)** or **(II-b)**:


(II-a)


(II-b)

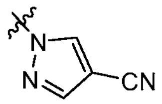
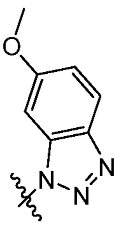
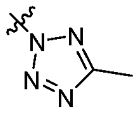
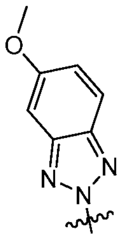
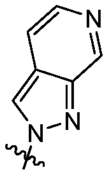
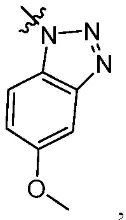
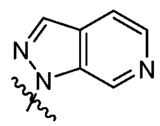
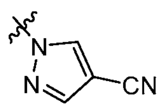
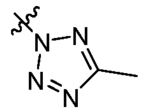
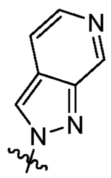
In some embodiments, the compound of Formula **(I)** is a compound of Formula **(II-c)** or **(II-d)**:


(II-c)


(II-d).

In some embodiments, R^{19} is $-CH_3$. In some embodiments, R^7 is alkyl (e.g., unsubstituted alkyl or $-CH_2OR^{A1}$) or $-OR^{A1}$. In some embodiments, R^7 is $-CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, or -

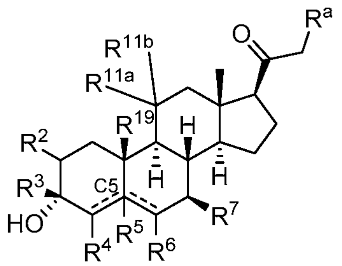
CH_2OCH_3. In some embodiments, R^{17} is $–OCH_3$, -CN, or $-C(O)CH_3$. In some embodiments, R^{17} is $-C(O)CH_2R^{C1}$. In some embodiments, R^{17} is $-C(O)CH_2R^{B1}$. In some embodiments, R^{17} is alkoxy, cyano, or $-C(O)R^{B1}$. In some embodiments, R^{B1} is pyrazolyl (e.g., a cyano-substituted pyrazolyl). In some embodiments, R^{B1} is tetrazolyl (e.g., a methyl-substituted tetrazolyl). In some embodiments, R^{B1} is a bicyclic heteroaryl (e.g., a methoxy-substituted bicyclic heteroaryl.

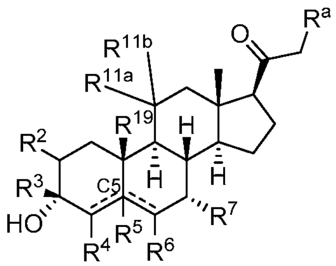
In some embodiments, R^{B1} is , , , , , , or . In some embodiments, R^{B1} is , , or .

In some embodiments, R^6 is halogen. In some embodiments, R^6 is fluorine.

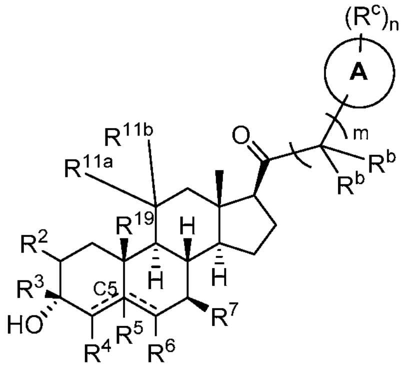
In some embodiments, each of R^{11a} and R^{11b} is independently hydrogen, C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl), C_1-C_6 alkoxy (*e.g.* C_1-C_6 alkoxyhalo), or –OH. In some embodiments, R^{11a} and R^{11b} together form oxo. In some embodiments, R^{17} is C_1-C_6 alkoxy (*e.g.* $–OCH_3$), cyano, or nitro. In some embodiments, R^{19} is hydrogen or substituted or unsubtituted C_1-C_6 alkyl (*e.g.* $–CH_2OR^X$, wherein R^X is hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy).

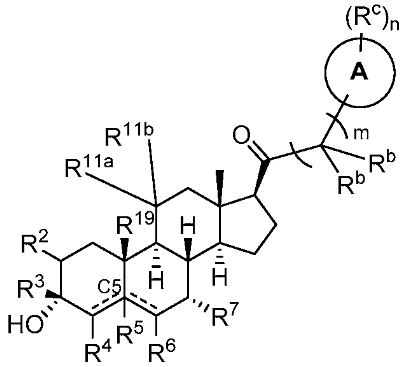
In some embodiments, the compound of Formula **(I)** is a compound of Formula **(III-a)** or **(III-b)**:


(III-a)


(III-b),

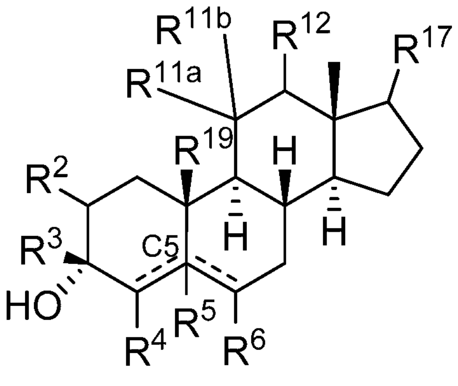
wherein R^a is hydrogen, halogen, C_1-C_6 alkyl (*e.g.* $-CH_3$), or –OH. In some embodiments, the compound of Formula **(I)** is a compound of Formula **(IV-a)** or **(IV-b)**:


(IV-a)


(IV-b),

wherein: m is 0, 1, or 2; n is 0, 1, or 2; each R^b is independently hydrogen, halogen, or C_1-C_6 alkyl; and each R^c is independently halogen, C_1-C_6 alkyl (e.g. $-CH_3$ or C_1-C_6 haloalkyl), C_1-C_6 alkoxy, cyano, or –OH. In some embodiments, **A** is a 5-10-membered ring. In some embodiments, **A** is a fused bicyclic ring. In some embodiments, **A** is monocyclic heteroaryl or bicyclic heteroaryl.

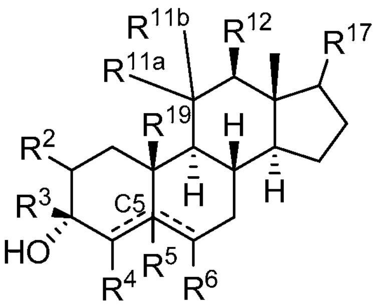
In an aspect, provided is a compound of Formula **(V)**:


(V)

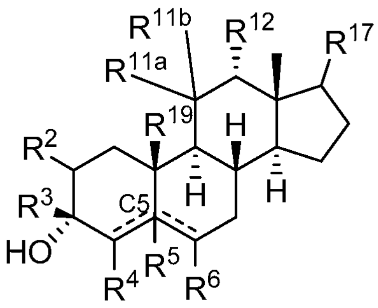
or a pharmaceutically acceptable salt thereof, wherein ═══ represents a single or double bond as valency permits; each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $–OR^{A1}$, $–SR^{A1}$, $–N(R^{A1})_2$,$–NHC(=O)R^{A1}$, $–NHC(=O)OR^{A1}$, $–S(=O)R^{A2}$, $–SO_2R^{A2}$, or $–S(=O)_2OR^{A1}$, wherein each instance of R^{A1} is independently hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{A1} groups are joined to form an heterocyclic or heteroaryl ring; and R^{A2} is alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or R^{11a} and R^{11b} together form oxo; R^3 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; R^5 is absent or hydrogen; and ------ represents a single or double bond, wherein when one of ------ at site is a double bond, the other ------ is a single bond; when both of ------ are single bonds, then R^5 is hydrogen; and when one of the ------ is a double bond, R^5 is absent; R^{17} is alkoxy, cyano, nitro, aryl, heteroaryl,$–C(O)R^{B1}$, $–C(O)CH_2R^{B1}$, or $–C(O)CH_2CH_2R^{B1}$, wherein R^{B1} is hydrogen,–OH, alkoxy, aryl, or heteroaryl; R^{19} is hydrogen or alkyl; and R^{12} is halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $–OR^{A1}$, $–SR^{A1}$, $–N(R^{A1})_2$, $–NHC(=O)R^{A1}$, $–NHC(=O)OR^{A1}$, $–S(=O)R^{A2}$, $–SO_2R^{A2}$, or $–S(=O)_2OR^{A1}$.

In some embodiments, R^3 is alkyl.

In some embodiments, the compound of Formula (**V**) is a compound of Formula (**V-a**) or (**V-b**):



(**V-a**)



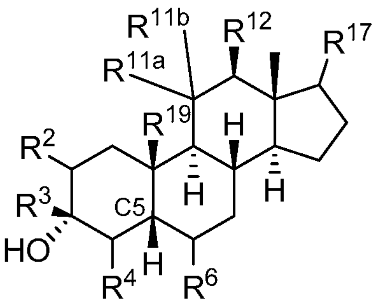
(**V-b**)

In some embodiments, each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen. In some embodiments, R^2, R^4, R^6, R^{11a}, and R^{11b} are all hydrogen.

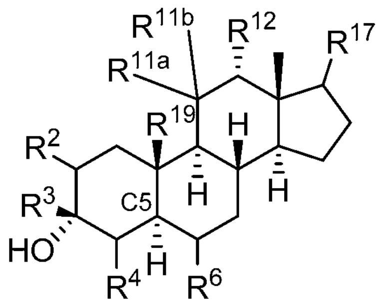
In some embodiments, each of R^2, R^4, and R^6 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or –OH.

In some embodiments, R^3 is C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl or $-CH_3$).

In some embodiments, the compound of Formula **(V)** is a compound of Formula **(VI-a)** or **(VI-b)**:

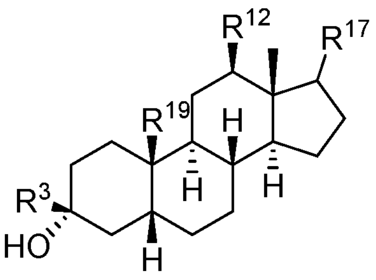


(VI-a)

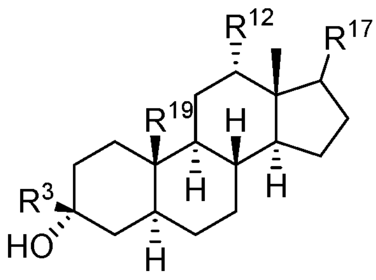


(VI-b).

In some embodiments, the compound of Formula **(V)** is a compound of Formula **(VI-c)** or **(VI-d)**:

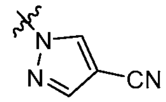
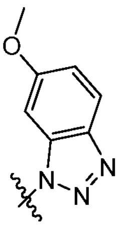
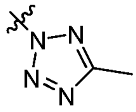
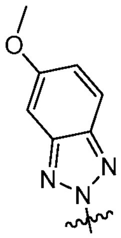
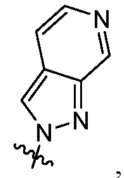
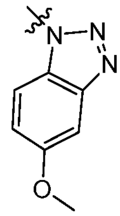
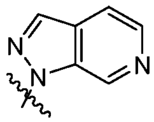
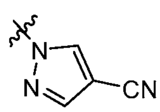
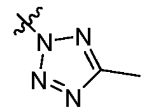
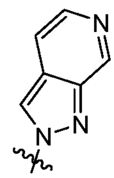


(VI-c)



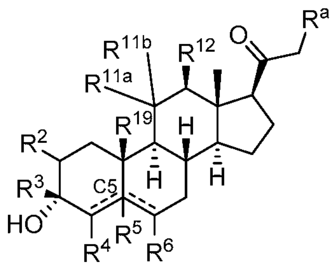
(VI-d).

In some embodiments, R^{19} is $-CH_3$. In some embodiments, R^{12} is $-OR^{A1}$. In some embodiments, R^{12} is $-CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, or $-CH_2OCH_3$. In some embodiments, R^{17} is $-OCH_3$, -CN, or $-C(O)CH_3$. In some embodiments, R^{17} is $-C(O)CH_2R^{C1}$. In some embodiments, R^{17} is $-C(O)CH_2R^{B1}$. In some embodiments, R^{17} is alkoxy, cyano, or $-C(O)R^{B1}$.

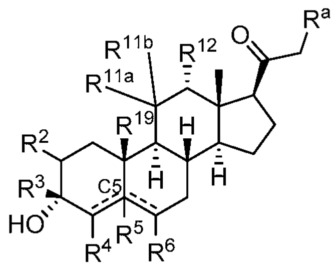
In some embodiments, R^{B1} is pyrazolyl (e.g., a cyano-substituted pyrazolyl). In some embodiments, R^{B1} is tetrazolyl (e.g., a methyl-substituted tetrazolyl). In some embodiments, R^{B1} is a bicyclic heteroaryl (e.g., a methoxy-substituted bicyclic heteroaryl. In some embodiments, R^{B1} is , , , , , , or . In some embodiments, R^{B1} is , , or .

In some embodiments, R^6 is halogen. In some embodiments, R^6 is fluorine.

In some embodiments, each of R^{11a} and R^{11b} is independently hydrogen, C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl), C_1-C_6 alkoxy (*e.g.* C_1-C_6 haloalkoxy), or –OH. In some embodiments, R^{11a} and R^{11b} together form oxo. In some embodiments, R^{17} is C_1-C_6 alkoxy (*e.g.* $–OCH_3$) or cyano. In some embodiments, R^{19} is hydrogen or substituted or unsubtituted C_1-C_6 alkyl (*e.g.* $–CH_2OR^X$, wherein R^X is hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy). In some embodiments, the compound of Formula **(V)** is a compound of Formula **(VII-a)** or **(VII-b)**:

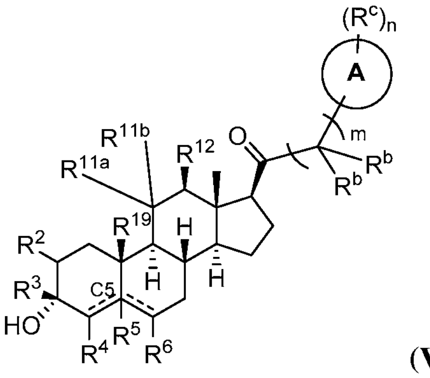


(VII-a)

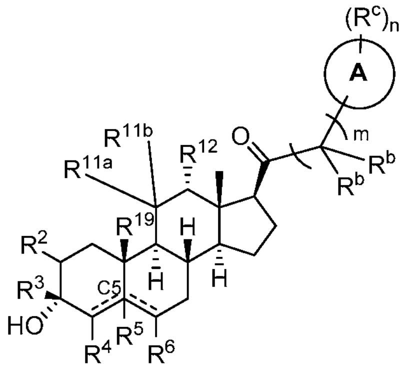


(VII-b),

wherein R^a is hydrogen, halogen, C_1-C_6 alkyl (*e.g.* $–CH_3$), or –OH. In some embodiments, the compound of Formula **(V)** is a compound of Formula **(VIII-a)** or **(VIII-b)**:



(VIII-a)

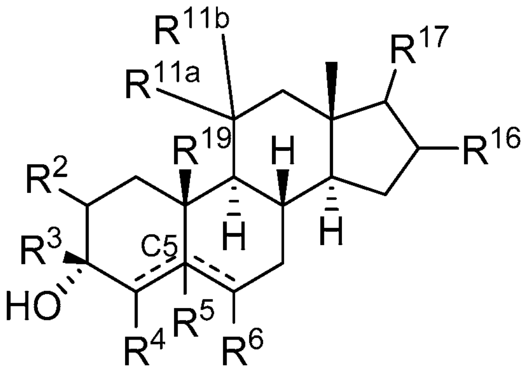


(VIII-b),

wherein m is 0, 1, or 2, n is 0, 1, or 2, and each R^b is independently hydrogen, halogen, or C_1-C_6 alkyl; and each R^c is independently halogen, C_1-C_6 alkyl (e.g. $-CH_3$ or C_1-C_6 haloalkyl), C_1-C_6 alkoxy, cyano, or –OH.

In some embodiments, **A** is a 5-10-membered ring. In some embodiments, **A** is a fused bicyclic ring. In some embodiments, **A** is monocyclic heteroaryl or bicyclic heteroaryl.

In an aspect, provided herein is a compound of Formula **(IX)**:

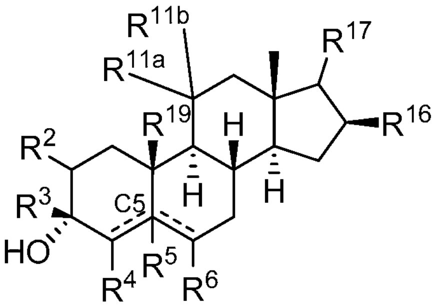


(IX),

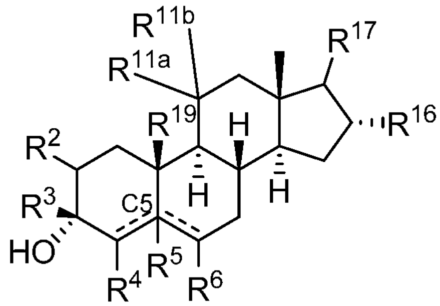
or a pharmaceutically acceptable salt thereof, wherein ═══ represents a single or double bond as valency permits; each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-OR^{A1}$, $-SR^{A1}$, $-N(R^{A1})_2$,$-NHC(=O)R^{A1}$, $-NHC(=O)OR^{A1}$, $-S(=O)R^{A2}$, $-SO_2R^{A2}$, or $-S(=O)_2OR^{A1}$, wherein each instance of R^{A1} is independently hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{A1} groups are joined to form an heterocyclic or heteroaryl ring; and R^{A2} is alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or R^{11a} and R^{11b} together form oxo; R^3 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; R^5 is absent or hydrogen; and ⎓ represents a single or double bond, wherein when one of ⎓ at site is a double bond, the other ⎓ is a single bond; when both of ⎓ are single bonds, then R^5 is hydrogen; and when one of the ⎓ is a double bond, R^5 is absent; R^{17} is alkoxy, cyano, nitro, aryl, heteroaryl, –C(O)R^{B1}, –C(O)CH_2R^{B1}, or –C(O)$CH_2CH_2R^{B1}$, wherein R^{B1} is hydrogen,–OH, –N(R^{A1})$_2$, alkoxy, aryl, or heteroaryl; R^{19} is hydrogen or alkyl; and R^{16} is halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, –OR^{A1}, –SR^{A1}, –N(R^{A1})$_2$, –NHC(=O)R^{A1}, –NHC(=O)OR^{A1}, –S(=O)R^{A2}, –SO_2R^{A2}, or –S(=O)$_2$OR^{A1}.

In some embodiments, R^3 is alkyl.

In some embodiments, the compound of Formula (**IX**) is a compound of Formula (**IX-a**) or (**IX-b**):



(**IX-a**)

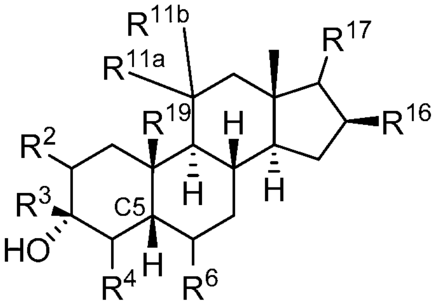
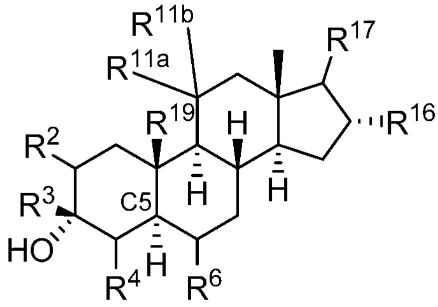


(**IX-b**).

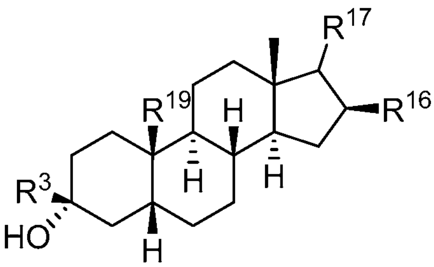
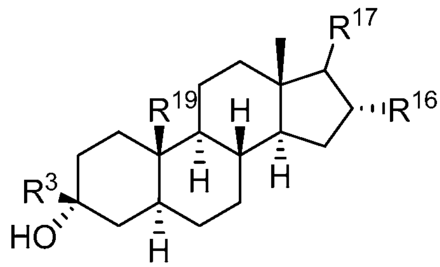
In some embodiments, each of R^2, R^4, and R^6, R^{11a}, and R^{11b} is independently hydrogen. In some embodiments, R^2, R^4, and R^6, R^{11a}, and R^{11b} are all hydrogen. In some embodiments, each of R^2, R^4, and R^6 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or –OH.

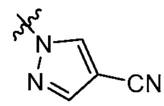
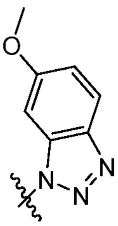
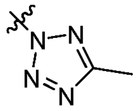
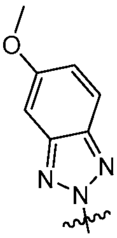
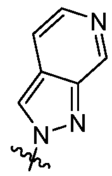
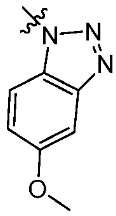
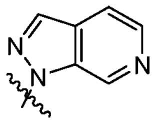
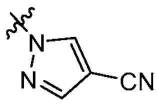
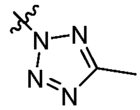
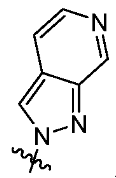
In some embodiments, R^3 is C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl or –CH_3).

In some embodiments, the compound of Formula (**IX**) is a compound of Formula (**X-a**) or (**X-b**):


(X-a)

(X-b).

In some embodiments, the compound of Formula (**IX**) is a compound of Formula (**X-c**) or (**X-d**):


(X-c)

(X-d).

In some embodiments, R^{19} is $–CH_3$. In some embodiments, R^{16} is alkyl. In some embodiments, R^{16} is $–CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, or $-CH(CH_3)_2$. In some embodiments, R^{17} is $–OCH_3$, -CN, or $-C(O)CH_3$. In some embodiments, R^{17} is $-C(O)CH_2R^{C1}$. In some embodiments, R^{17} is $-C(O)CH_2R^{B1}$. In some embodiments, R^{17} is alkoxy, cyano, or $-C(O)R^{B1}$. In some embodiments, R^{B1} is pyrazolyl (e.g., a cyano-substituted pyrazolyl). In some embodiments, R^{B1} is tetrazolyl (e.g., a methyl-substituted tetrazolyl). In some embodiments, R^{B1} is a bicyclic heteroaryl (e.g., a methoxy-substituted bicyclic heteroaryl. In some embodiments, R^{B1} is , , , , , , or . In some embodiments, R^{B1} is , , or .

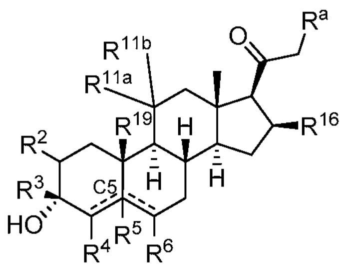
In some embodiments, R^6 is halogen. In some embodiments, R^6 is fluorine.

In some embodiments, each of R^{11a} and R^{11b} is independently hydrogen, C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl), C_1-C_6 alkoxy (*e.g.* C_1-C_6 haloalkoxy), or –OH. In some embodiments, R^{11a} and R^{11b} together form oxo.

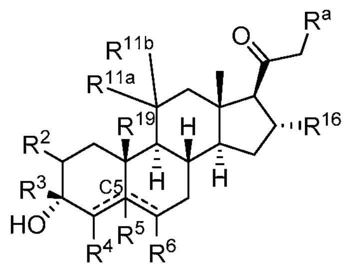
In some embodiments, R^{17} is C_1-C_6 alkoxy (*e.g.* $–OCH_3$), cyano, or nitro.

In some embodiments, R^{19} is hydrogen or substituted or unsubtituted C_1-C_6 alkyl (*e.g.* $–CH_2OR^X$, wherein R^X is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy).

In some embodiments, the compound of Formula **(IX)** is a compound of Formula **(X-a)** or **(X-b)**:



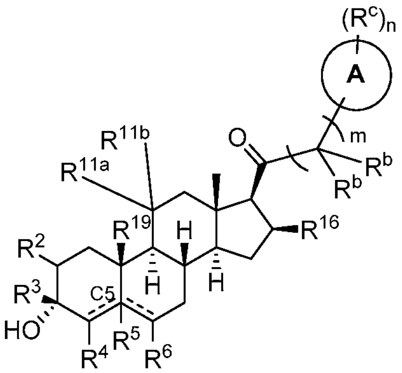
(X-a)



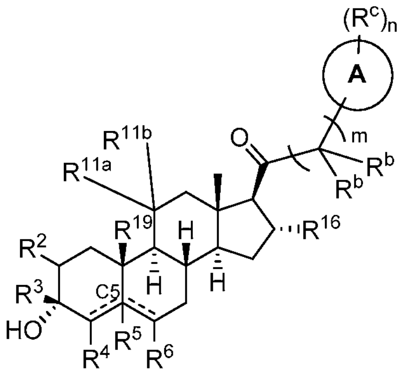
(X-b),

wherein R^a is hydrogen, halogen, C_1-C_6 alkyl (*e.g.* $–CH_3$), or –OH.

In some embodiments, the compound of Formula **(IX)** is a compound of Formula **(XI-a)** or **(XI-b)**:



(XI-a)



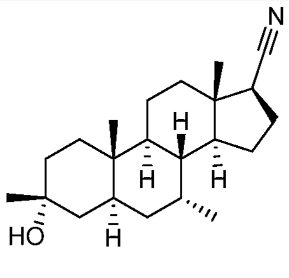
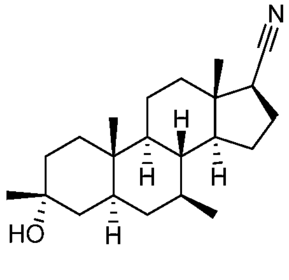
(XI-b),

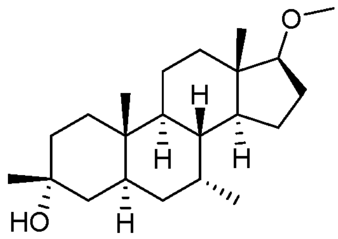
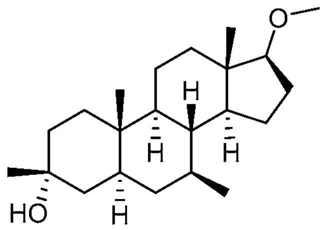
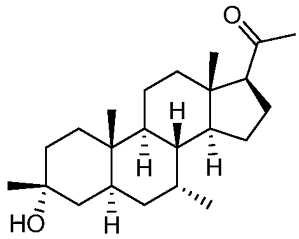
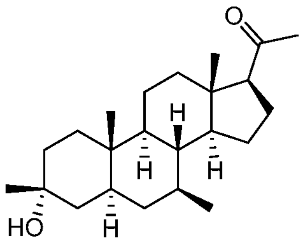
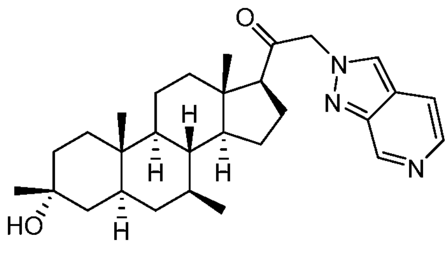
wherein m is 0, 1, or 2, n is 0, 1, or 2, each R^b is independently hydrogen, halogen, or C_1-C_6 alkyl, and each R^c is independently halogen, C_1-C_6 alkyl (e.g. $-CH_3$ or C_1-C_6 haloalkyl), C_1-C_6 alkoxy, cyano, or –OH.

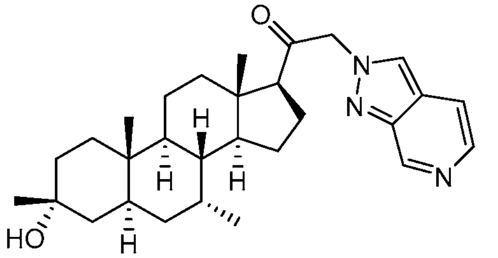
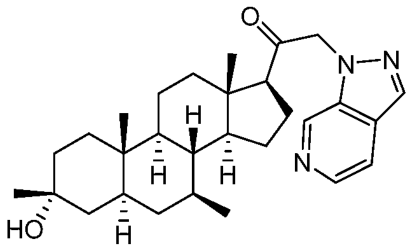
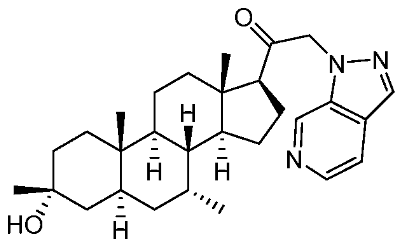
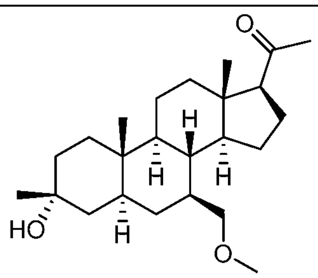
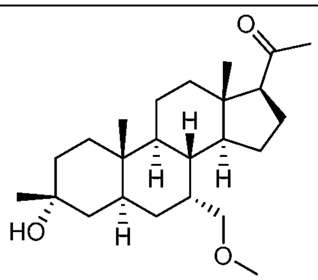
In some embodiments, **A** is a 5-10-membered ring. In some embodiments, **A** is a fused bicyclic ring. In some embodiments, **A** is monocyclic heteroaryl or bicyclic heteroaryl.

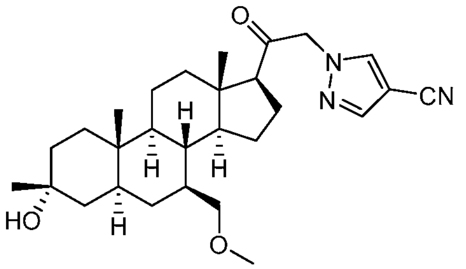
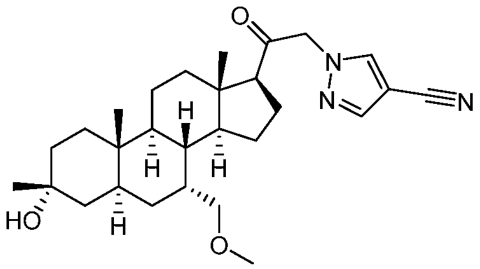
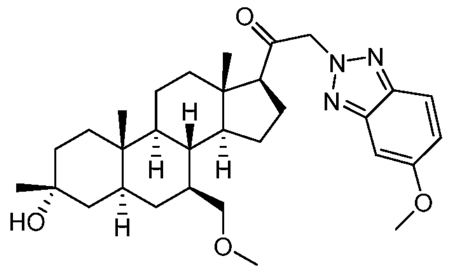
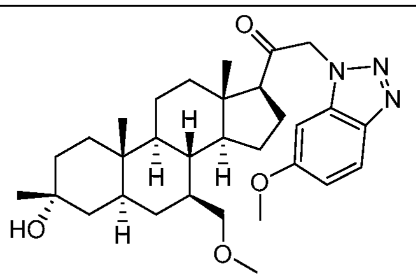
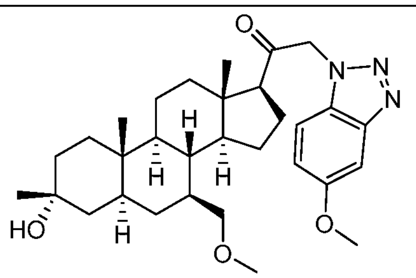
Also provided herein are compounds described in **Table 1** below or pharmaceutically acceptable salts thereof.

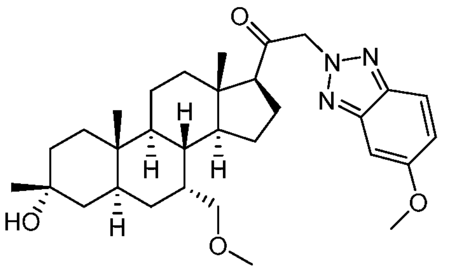
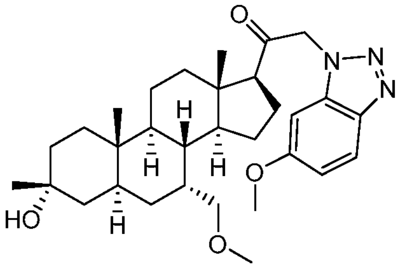
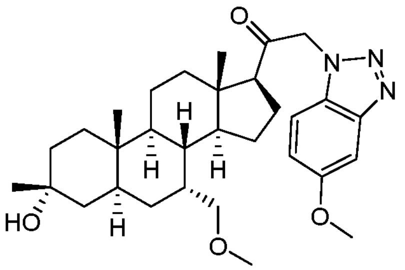
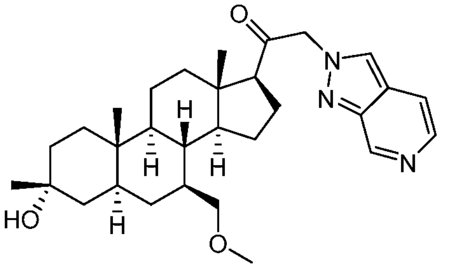
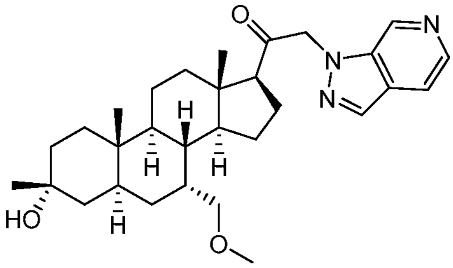
Table 1. Exemplary Compounds of the Invention

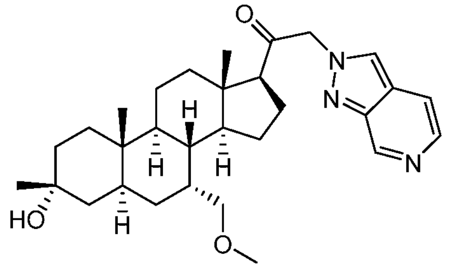
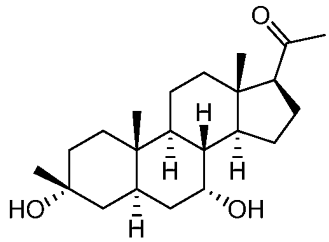
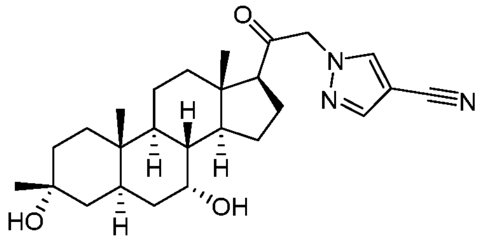
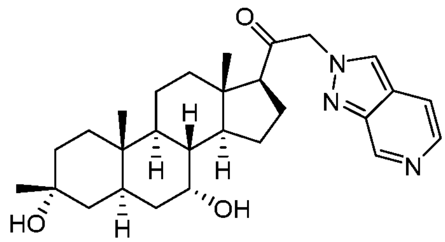
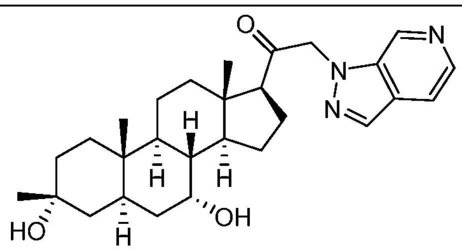
Compound structure	Compound number
	1
	2

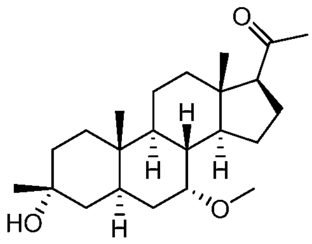
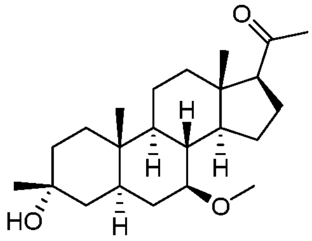
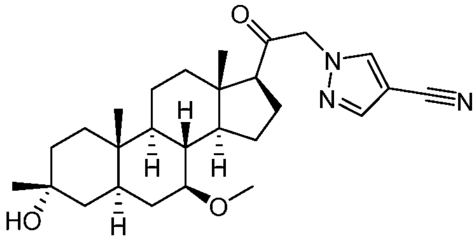
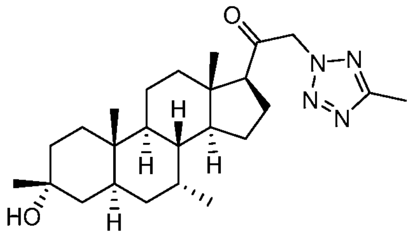
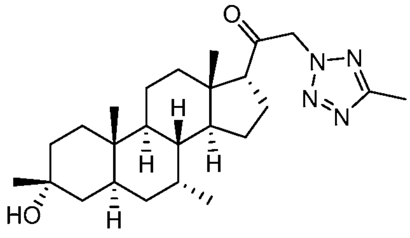
O H H H HO H	**3**
O H H H HO H	**4**
O H H H HO H	**5**
O H H H HO H	**6**
O N N N H H H HO H	**7**

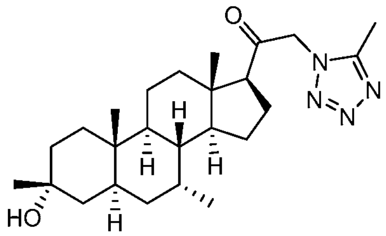
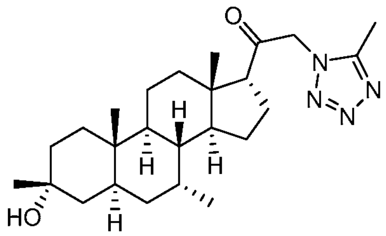
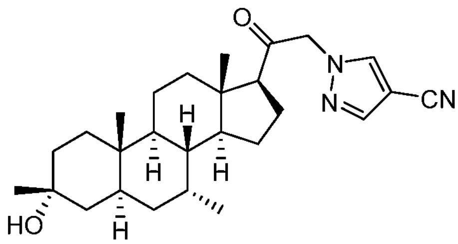
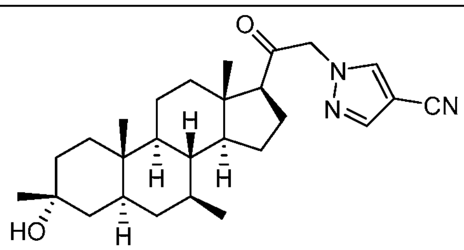
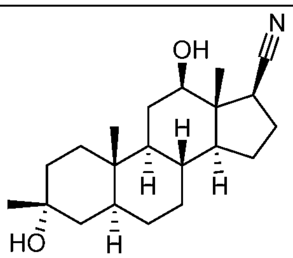
	**8**
	**9**
	**10**
	**11**
	**12**

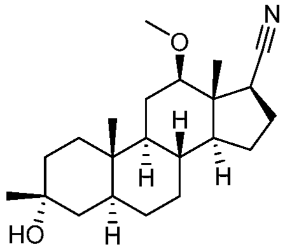
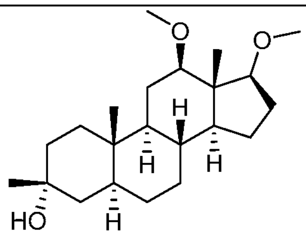
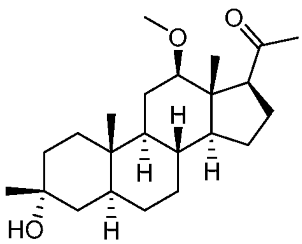
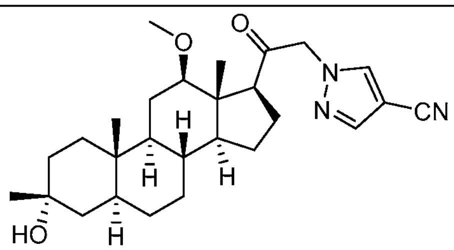
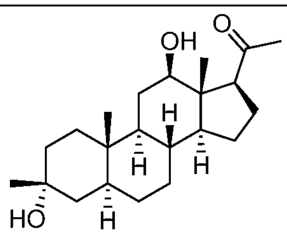
	**13**
	**14**
	**15**
	**16**
	**17**

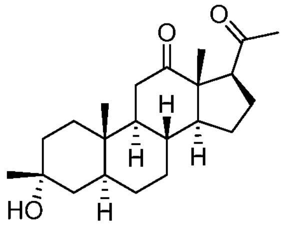
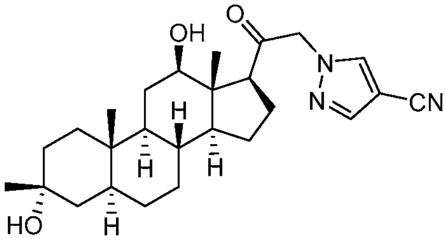
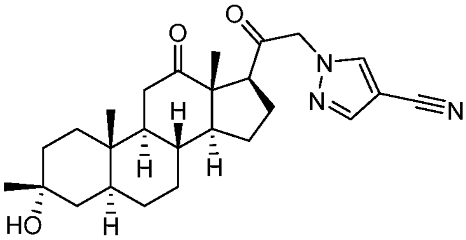
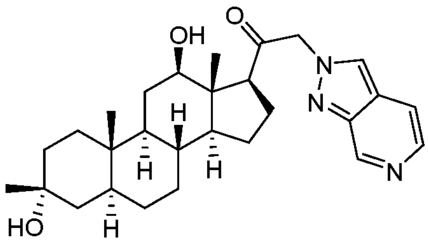
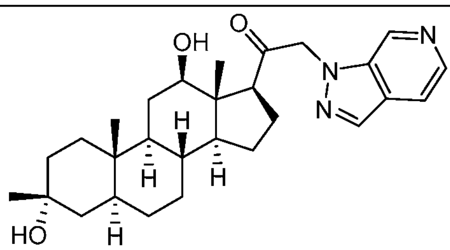
	**18**
	**19**
	**20**
	**21**
	**23**

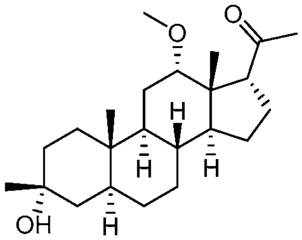
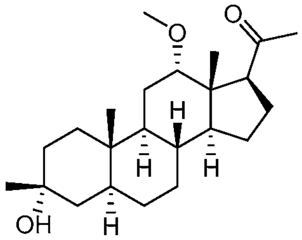
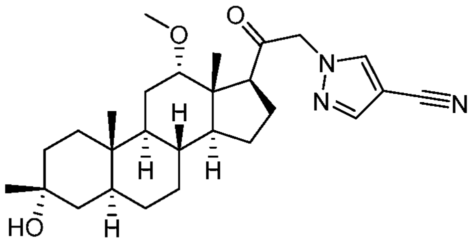
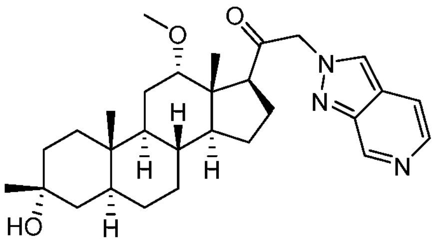
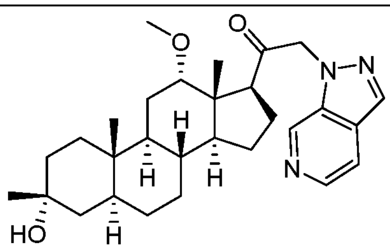
	**24**
	**25**
	**26**
	**27**
	**28**

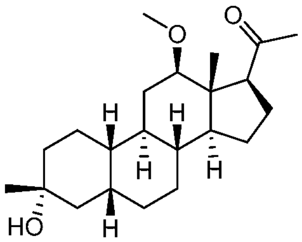
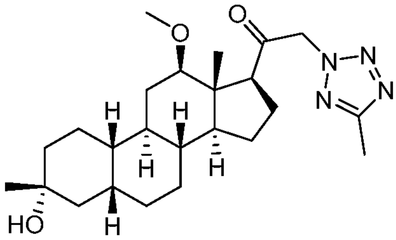
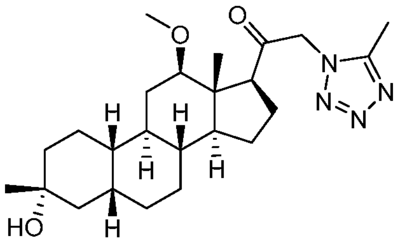
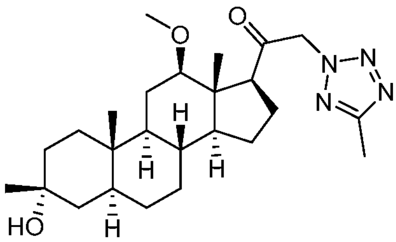
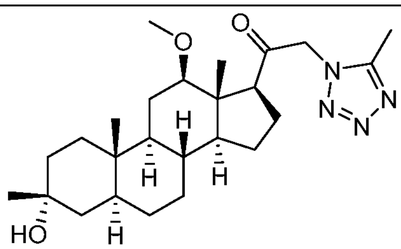
	**29**
	**30**
	**31**
	**34**
	**35**

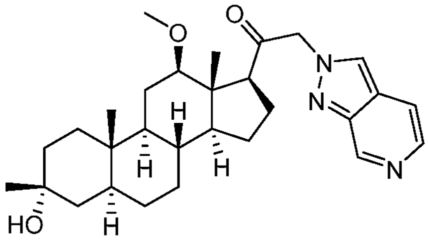
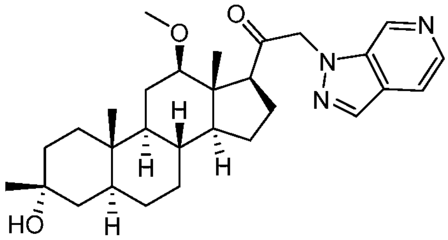
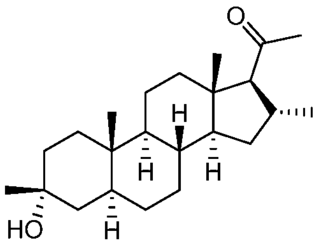
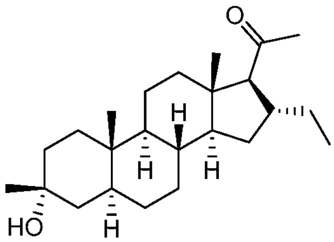
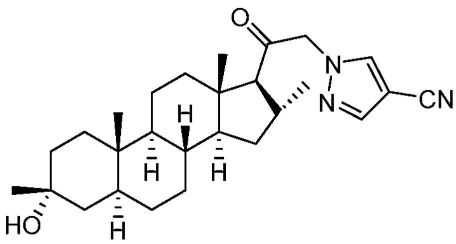
	**36**
	**37**
	**38**
	**39**
	**40**

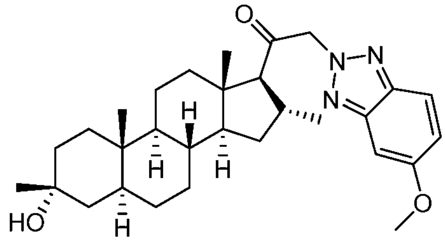
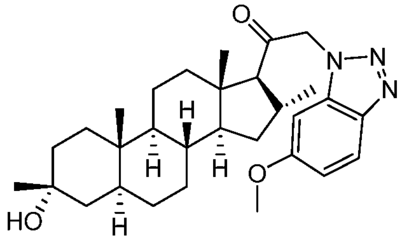
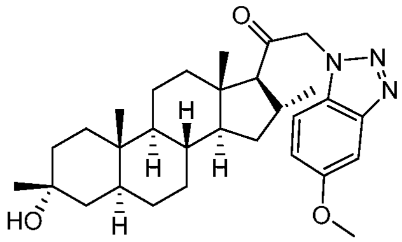
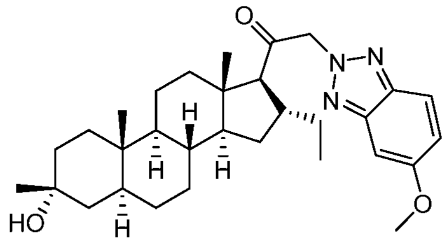
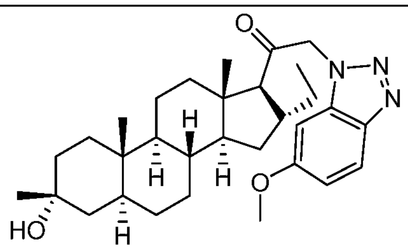
	**41**
	**42**
	**43**
	**44**
	**45**

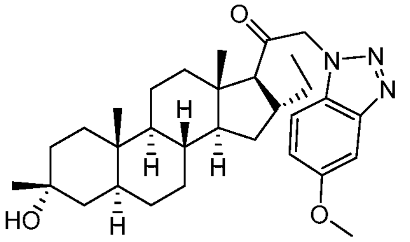
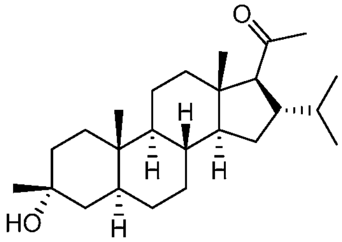
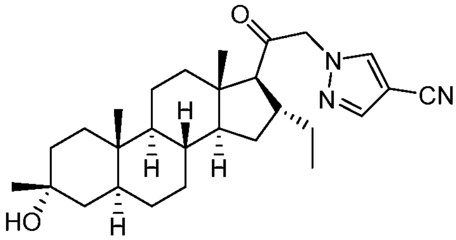
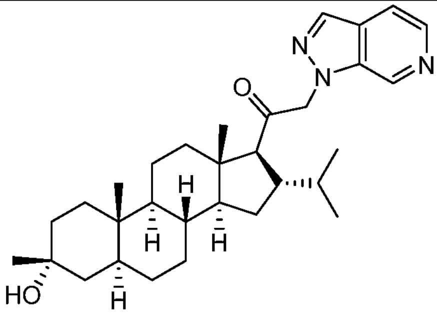
	**46**
	**47**
	**48**
	**49**
	**50**

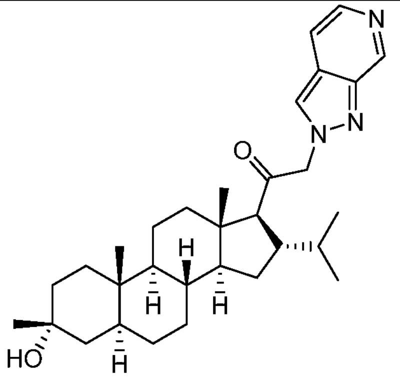
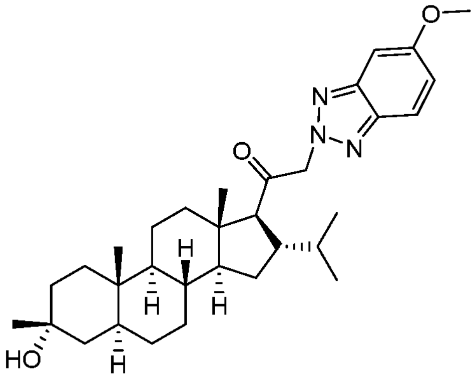
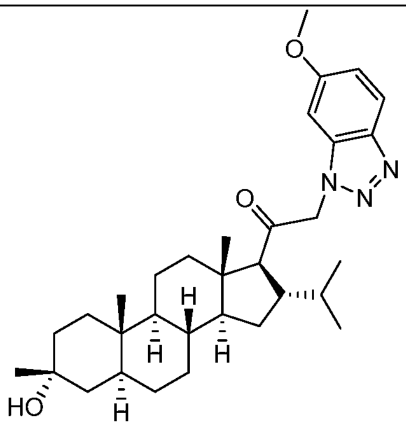
	**51**
	**52**
	**53**
	**54**
	**55**

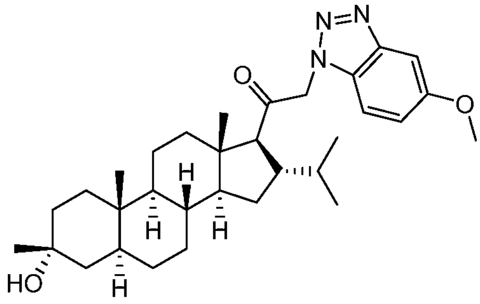
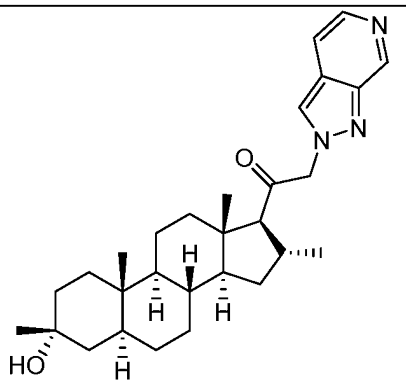
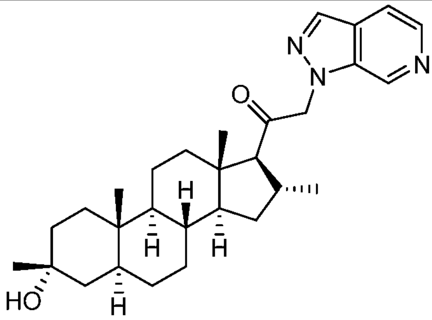
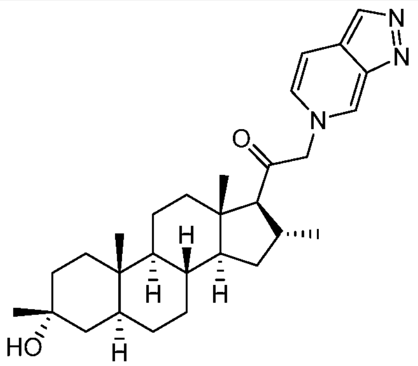
O O H H H H HO H	**56**
O O N N N N H H H H HO H	**58**
O O N N N N H H H H HO H	**59**
O O N N N N H H H HO H	**60**
O O N N N N H H H HO H	**61**

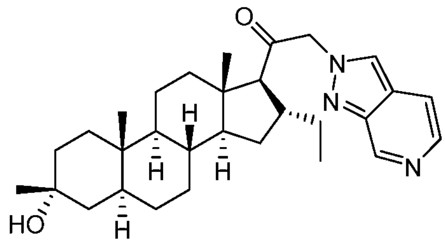
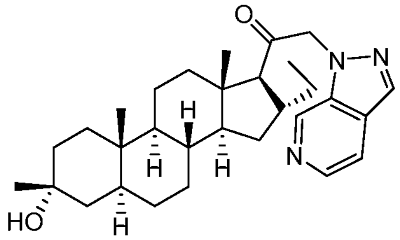
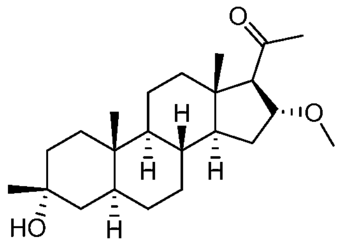
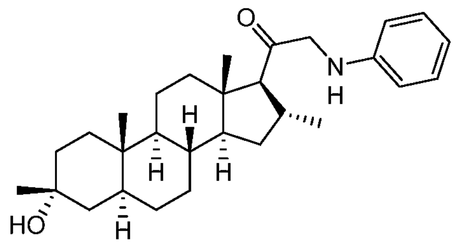
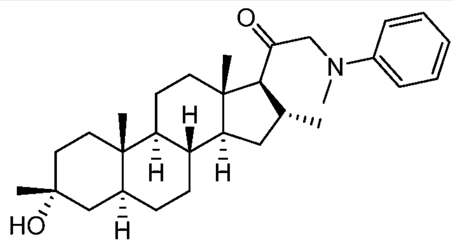
	**62**
	**63**
	**64**
	**65**
	**66**

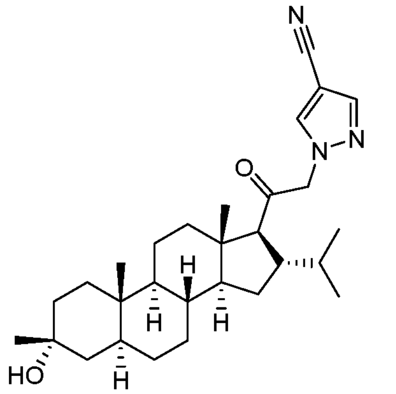
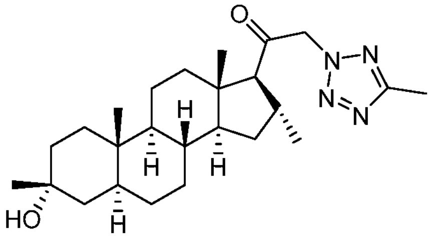
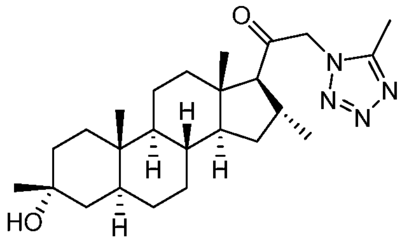
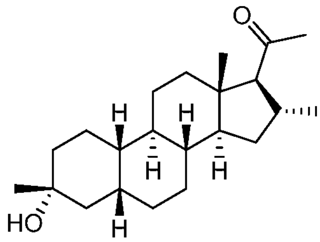
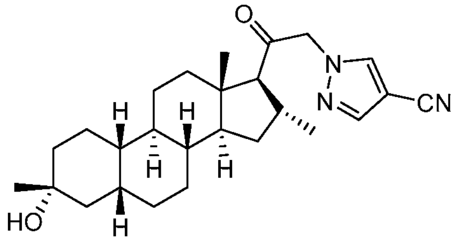
	**67**
	**68**
	**69**
	**70**
	**71**

O N N N H H H HO H O	**72**
O H H H HO H	**73**
O N N CN H H H HO H	**74**
N N N O H H H HO H	**75**

N N N O H H H HO H	**76**
O N N N O H H H HO H	**77**
O N N N O H H H HO H	**78**

	**79**
	**80**
	**81**
	**82**

	**83**
	**84**
	**85**
	**86**
	**87**

	**88**
	**89**
	**90**
	**91**
	**92**

Alternative Embodiments

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

Pharmaceutical Compositions

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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

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*.

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.

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.

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).

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.

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 □□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–□–cyclodextrin. In a more particular embodiment, the composition comprises hexapropyl–□–cyclodextrin (10–50% in water).

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.

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.

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.

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.

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

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

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 such as depression, a schizophrenia spectrum disorder, a convulsive disorder, epileptogenesis, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, or tinnitus) in a subject in need (*e.g.*, a subject with Rett syndrome, Fragile X syndrome, or Angelman syndrome). Exemplary CNS conditions related to GABA-modulation include, but are not limited to, sleep disorders [*e.g.*, insomnia], mood disorders [*e.g.*, depression, 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.

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.

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

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

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.

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.

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.

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

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.

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

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

Neuroendocrine Disorders and Dysfunction

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

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

Neurodegenerative Diseases and Disorders

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

Mood disorders

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

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

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

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

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

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

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

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

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

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

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

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

Depressive Personality Disorder (DPD) refers to a personality disorder with depressive features.

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

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

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

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

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

Post-surgical depression refers to feelings of depression that follow a surgical procedure (e.g., as a result of having to confront one's mortality). For example, individuals may feel sadness or empty mood persistently, a loss of pleasure or interest in hobbies and activities normally enjoyed, or a persistent felling of worthlessness or hopelessness.

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

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

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

In some embodiments, the method provides therapeutic effect (e.g., as measured by reduction in Hamilton Depression Score (HAM-D)) within 4, 3, 2, 1 days; 96, 84, 72, 60, 48, 24, 20, 16, 12, 10, 8 hours or less. In some embodiments, the therapeutic effect is a decrease from baseline in HAM-D score at the end of a treatment period (e.g., 12, 24, 48 hours after administration; 24, 48, 72, 96 hours or more). In some embodiments, the decrease from baseline in HAM-D score is from severe (e.g., HAM-D score of 24 or greater) to symptom-free (e.g., HAM-D score of 7 or lower). In some embodiments, the baseline score is about 10 to 52 (e.g., more than 10, 15, or 20; 10 to 52, 12 to 52, 15 to 52, 17 to 52, 20 to 52, 22 to 52). In some embodiments, the baseline score is at least 10, 15, or 20. In some embodiments, the HAM-D score at the end of the treatment period is about 0 to 10 (e.g., less than 10; 0 to 10, 0 to 6, 0 to 4, 0 to 3, 0 to 2, 1.8). In some embodiments, the HAM-D score at the end of the treatment period is less than 10, 7, 5, or 3. In some embodiments, the decrease in HAM-D score is from a baseline score of about 20 to 30 (e.g., 22 to 28, 23 to 27, 24 to 27, 25 to 27, 26 to 27) to a HAM-D score at the end of the treatment period is about 0 to 10 (e.g., less than 10; 0 to 10, 0 to 6, 0 to 4, 0 to 3, 0 to 2, 1.8). In some embodiments, the decrease in the baseline HAM-D score to HAM-D score at the end of the treatment period is at least 1, 2, 3, 4, 5, 7, 10, 25, 40, 50, or 100 fold). In some embodiments, the percentage decrease in the baseline HAM-D score to HAM-D score at the end of the treatment period is at least 50% (e.g., 60%, 70%, 80%, 90%). In some embodiments, the therapeutic effect is a decrease from baseline in HAM-D score at the end of a treatment period (e.g., 12, 24, 48 hours after administration; 24, 48, 72, 96 hours or more) at least 10, 15, or 20 points. In some embodiments, the therapeutic effect is a decrease from baseline in HAM-D score at the end of a treatment period (e.g., 12, 24, 48 hours after administration; 24, 48, 72, 96 hours or more) at least 5, 7, or 10 points more relative to the therapeutic effect provided by a placebo treatment.

In some embodiments, the method provides therapeutic effect (e.g., as measured by reduction in Montgomery-Asberg Depression Rating Scale (MADRS)) within 4, 3, 2, 1 days; 96, 84, 72, 60, 48, 24, 20, 16, 12, 10, 8 hours or less. The Montgomery–Åsberg Depression Rating Scale (MADRS) is a ten-item diagnostic questionnaire (regarding apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts) which psychiatrists use to measure the severity of depressive episodes in patients with mood disorders. 0-6 indicates normal/symptom absent; 7-19 indicates mild depression; 20-34 indicates moderate depression;

and >34 indicates severe depression. In some embodiments, the therapeutic effect is a decrease from baseline in MADRS score at the end of a treatment period (e.g., 12, 24, 48 hours after administration; 24, 48, 60, 72, 96 hours or more). In some embodiments, the decrease from baseline in MADRS score is from severe (e.g., MADRS score of 30 or greater) to symptom-free (e.g., MADRS score of 20 or lower). For example, the mean change from baseline in MADRS total score from treatment with a compound described herein is about -15, -20, -25, -30, while the mean change from baseline in MADRS total score from treatment with placebo is about -15, -10, -5.

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

In some embodiments, the method provides therapeutic effect (e.g., as measured by reduction in Clinical Global Impression-Improvement Scale (CGI)) within 4, 3, 2, 1 days; 24, 20, 16, 12, 10, 8 hours or less. In some embodiments, the therapeutic effect is a CGI score of 2 or less.

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

Anxiety Disorders

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

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.

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).

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.

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.

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

Women's Health Disorders

Provided herein are methods for treating conditions or disorders related to women's health. Conditions or disorders related to women's health include, but are not limited to, Gynecological health and disorders (e.g., premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD)), pregnancy issues (e.g., miscarriage, abortion), infertility and related disorders (e.g., polycystic ovary syndrome (PCOS)), other disorders and conditions, and issues related to women's overall health and wellness (e.g., menopause).

Gynecological health and disorders affecting women includemenstruation and menstrual irregularities; urinary tract health, including urinary incontinence and pelvic floor disorders; and such disorders as bacterial vaginosis,vaginitis, uterine fibroids, andvulvodynia.

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

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

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

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

Abortion referse to the deliberate termination of a pregnancy, which can be performed during the first 28 weeks of pregnancy.

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

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

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

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

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

Epilepsy

The compound of **Formula (I)**, the compound of Formula (**V**), or the compound of Formula (**IX**), or pharmaceutically acceptable salt, or a pharmaceutically acceptable composition thereof, can be used in a method described herein, for example in the treatment of a disorder described herein such as epilepsy, status epilepticus, or seizure, for example as described in WO2013/112605 and WO/2014/031792, the contents of which are incorporated herein in their entirety.

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

Epileptogenesis

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

Status epilepticus (SE)

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.

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.

The compound of **Formula (I)**, a compound of Formula (**V**), or a compound of Formula (**IX**) or pharmaceutically acceptable salt, or a pharmaceutically acceptable composition thereof, can also be administered as a prophylactic to a subject having a CNS disorder *e.g.,* a traumatic brain injury, status epilepticus, *e.g.,* convulsive status epilepticus, *e.g.,* early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus; non-convulsive status epilepticus, *e.g.,* generalized status epilepticus, complex partial status epilepticus; generalized periodic epileptiform discharges; and periodic lateralized epileptiform discharges; prior to the onset of a seizure.

Seizure

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.

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.

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.

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.

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."

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.

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

Tonic seizures are characterized by stiffening of the muscles.

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

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

Movement Disorders

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

Tremor

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

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

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

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

Essential tremor or benign essential tremor is the most common type of tremor. Essential tremor may be mild and nonprogressive in some, and may be slowly progressive, starting on one side of the body but affect both sides within 3 years. The hands are most often affected, but the head, voice, tongue, legs, and trunk may also be involved. Tremor frequency may decrease as the person ages, but severity may increase. Heightened emotion, stress, fever, physical exhaustion, or low blood sugar may trigger tremors and/or increase their severity. Symptoms generally evolve over time and can be both visible and persistent following onset.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Anesthesia / Sedation

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.

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

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

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.

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.

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.

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.

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.

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.

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.

Examples

In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic examples described in this application are offered to illustrate the invention provided herein and are not to be construed in any way as limiting its scope.

Materials and Methods

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.

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.

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 oxysterols that have been listed herein. The compounds provided herein may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis. Exemplary chiral columns available for use in the separation/purification of the enantiomers/diastereomers provided herein include, but are not limited to, CHIRALPAK® AD-10, CHIRALCEL® OB, CHIRALCEL® OB-H, CHIRALCEL® OD, CHIRALCEL® OD-H, CHIRALCEL® OF, CHIRALCEL® OG, CHIRALCEL® OJ and CHIRALCEL® OK.

Exemplary general method for preparative HPLC: Column: Durashell. Mobile phase: A: water, B: acetonitrile. %B at 0 min: 41%, %B at 8 min: 71%, flow rate: 35 mL/min, detection wavelength: 220 nm.

Exemplary general method for analytical HPLC: Mobile phase: A: water (10 mM NH_4HCO_3), 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 □m at 45 C.

Exemplary general method for SFC: Column: CHIRALPAK® AD (250 mm * 30 mm, 5 µm), A= supercritical CO_2, B= MeOH (0.1%NH_3-H_2O), A:B = 70:30, flow rate: 60 mL/min, column temperature: 38°C, nozzle pressure: 100 bar, detection wavelength = 220 nm.

Exemplary LCMS conditions include:

30-90AB_2MIN_E

Column	Xtimate C18 2.1*30mm,3um	
Mobile Phase	A:water(4L)+TFA(1.5mL)	
	B:acetonitrile(4L)+TFA(0.75mL)	
	TIME(min)	B%
	0	30
	0.9	90
	1.5	90
	1.51	30
	2	30
Flow Rate	1.2mL/min	
wavelength	UV 220nm	
Oven Temp	50 °C	
MS ionization	ESI	
Detector	PDA,ELSD	

10-80AB_2MIN_E

Column	Xtimate C18 2.1*30mm,3um	
Mobile Phase	A:water(4L)+TFA(1.5mL)	
	B:acetonitrile(4L)+TFA(0.75mL)	
	TIME(min)	B%
	0	10
	0.9	80
	1.5	80
	1.51	10
	2	10
Flow Rate	1.2mL/min	
wavelength	UV 220nm	
Oven Temp	50 °C	
MS ionization	ESI	
Detector	PDA,ELSD	

30-90CD_3MIN_E

Column	Xbrige Shield RP-18,5um,2.1*50mm	
Mobile Phase	A:water(1L)+NH3H2O(0.5mL)	
	B:acetonitrile	
	TIME(min)	B%
	0	30
	2	90

	2.48	90
	2.49	30
	3	30
Flow Rate	1.0mL/min	
wavelength	UV 220nm	
Oven Temp	30 ^{o}C	
MS ionization	ESI	
Detector	PDA,ELSD	

Steroid Inhibition of TBPS Binding

[^{35}S]-t-Butylbicyclophosphorothionate (TBPS) binding assays using rat brain cortical membranes in the presence of 5 mM GABA has been described (Gee et al, *J. Pharmacol. Exp. Ther.* 1987, **241**, 346-353; Hawkinson et al, *Mol. Pharmacol.* 1994, **46**, 977-985; Lewin, A.H et al., *Mol. Pharmacol.* 1989, ***35,*** *189-194*).

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 ^{o}C. The resultant supernatants are centrifuged at 10,000 x *g* for 20 min at 4 ^{o}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 ^{o}C. This washing procedure is repeated twice and the pellets are resuspended in 10 volumes of buffer. Aliquots (100 mL) of the membrane suspensions are incubated with 3 nM [^{35}S]-TBPS and 5 mL aliquots of test drug dissolved in dimethyl sulfoxide (DMSO) (final 0.5%) in the presence of 5 mM GABA. The incubation is brought to a final volume of 1.0 mL with buffer. Nonspecific binding is determined in the presence of 2 mM unlabeled TBPS and ranged from 15 to 25 %. Following a 90 min incubation at room temp, the assays are terminated by filtration through glass fiber filters (Schleicher and Schuell No. 32) using a cell harvester (Brandel) and rinsed three times with ice-cold buffer. Filter bound radioactivity is measured by liquid scintillation spectrometry. Non-linear curve fitting of the overall data for each drug averaged for each concentration is done using Prism (GraphPad). The data are fit to a partial instead of a full inhibition model if the sum of squares is significantly lower by F-test. Similarly, the data are fit to a two component instead of a one component inhibition model if the sum of squares is significantly lower by F-test. The concentration of test compound producing 50% inhibition

(IC_{50}) of specific binding and the maximal extent of inhibition (I_{max}) are determined for the individual experiments with the same model used for the overall data and then the means $\pm$ SEM.s of the individual experiments are calculated. Picrotoxin serves as the positive control for these studies as it has been demonstrated to robustly inhibit TBPS binding.

Various compounds are or can be screened to determine their potential as modulators of [^{35}S]-TBPS binding *in vitro*. These assays are or can be performed in accordance with the above discussed procedures. The results of the TBPS binding assays are shown in **Table 2**.

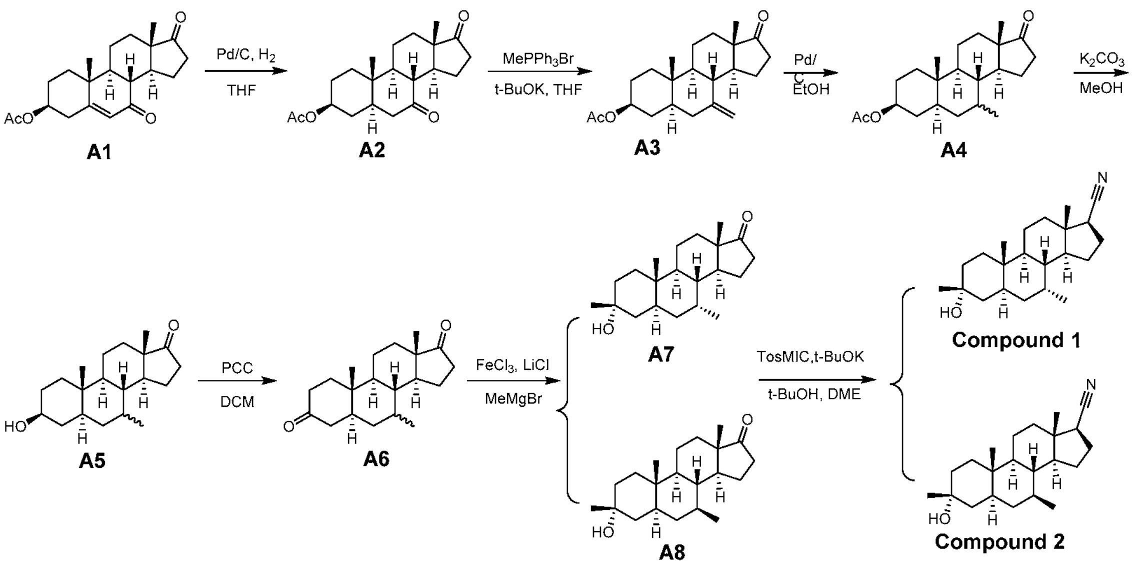
Abbreviations

PCC: pyridinium chlorochromate; t-BuOK: potassium tert-butoxide; 9-BBN: 9-borabicyclo[3.3.1]nonane; Pd(*t*-$Bu_3P)_2$: bis(tri-tert-butylphosphine)palladium(0); AcCl: acetyl chloride; *i*-PrMgCl: Isopropylmagnesium chloride; TBSCl: tert-Butyl(chloro)dimethylsilane; (*i*-PrO)$_4$Ti: titanium tetraisopropoxide; BHT: 2,6-di-t-butyl-4-methylphenoxide; Me: methyl; *i*-Pr: iso-propyl; *t*-Bu: tert-butyl; Ph: phenyl; Et: ethyl; Bz: benzoyl; BzCl: benzoyl chloride; CsF: cesium fluoride; DCC: dicyclohexylcarbodiimide; DCM: dichloromethane; DMAP: 4-dimethylaminopyridine; DMP: Dess-Martin periodinane; EtMgBr: ethylmagnesium bromide; EtOAc: ethyl acetate; TEA: triethylamine; AlaOH: alanine; Boc: t-butoxycarbonyl. Py: pyridine; TBAF: tetra-n-butylammonium fluoride; THF: tetrahydrofuran; TBS: t-butyldimethylsilyl; TMS: trimethylsilyl; $TMSCF_3$: (Trifluoromethyl)trimethylsilane; Ts: p-toluenesulfonyl; Bu: butyl; Ti(OiPr)$_4$: tetraisopropoxytitanium; LAH: Lithium Aluminium Hydride; LDA: lithium diisopropylamide; $LiOH.H_2O$: lithium hydroxide hydrates; MAD: methyl aluminum bis(2,6-di-t-butyl-4-methylphenoxide); MeCN: acetonitrile; NBS: N-bromosuccinimide; Na_2SO_4: sodium sulfate; $Na_2S_2O_3$: sodium thiosulfate; PE: petroleum ether; MeCN: acetonitrile; MeOH: methanol**;** Boc: t-butoxycarbonyl; MTBE: methyl tert-butyl ether; EDCI: *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride; HATU: 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate.

Abbreviations

PCC: pyridinium chlorochromate; t-BuOK: potassium tert-butoxide; 9-BBN: 9-borabicyclo[3.3.1]nonane; Pd(*t*-$Bu_3P)_2$: bis(tri-tert-butylphosphine)palladium(0); AcCl: acetyl chloride; *i*-PrMgCl: Isopropylmagnesium chloride; TBSCl: tert-Butyl(chloro)dimethylsilane; (*i*-$PrO)_4Ti$: titanium tetraisopropoxide; BHT: 2,6-di-t-butyl-4-methylphenoxide; Me: methyl; *i*-Pr: iso-propyl; *t*-Bu: tert-butyl; Ph: phenyl; Et: ethyl; Bz: benzoyl; BzCl: benzoyl chloride; CsF: cesium fluoride; DCC: dicyclohexylcarbodiimide; DCM: dichloromethane; DMAP: 4-dimethylaminopyridine; DMP: Dess-Martin periodinane; EtMgBr: ethylmagnesium bromide; EtOAc: ethyl acetate; TEA: triethylamine; AlaOH: alanine; Boc: t-butoxycarbonyl. Py: pyridine; TBAF: tetra-n-butylammonium fluoride; THF: tetrahydrofuran; TBS: t-butyldimethylsilyl; TMS: trimethylsilyl; $TMSCF_3$: (Trifluoromethyl)trimethylsilane; Ts: p-toluenesulfonyl; Bu: butyl; $Ti(OiPr)_4$: tetraisopropoxytitanium; LAH: Lithium Aluminium Hydride; LDA: lithium diisopropylamide; $LiOH.H_2O$: lithium hydroxide hydrates; MAD: methyl aluminum bis(2,6-di-t-butyl-4-methylphenoxide); MeCN: acetonitrile; NBS: N-bromosuccinimide; Na_2SO_4: sodium sulfate; $Na_2S_2O_3$: sodium thiosulfate; PE: petroleum ether; MeCN: acetonitrile; MeOH: methanol**;** Boc: t-butoxycarbonyl; MTBE: methyl tert-butyl ether; EDCI: *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride; HATU: 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate.

Example 1. Syntheses of Compounds 1 and 2



Step 1. To a solution of **A1** (100 g, 290 mmol) in THF (500 mL) was added Pd-C (wet, 10%, 10 g) under N_2. The suspension was degassed under vacuum and purged with H_2 for three times. The mixture was stirred under H_2 (15 psi) at 25 C for 48 hours to give a black suspension. The reaction mixture was filtered through a pad of Celite and washed with THF (500 mL). The filtrate was concentrated and to give **A2** (98 g, 97%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 4.73-4.62 (m, 1H), 2.65-2.54 (m, 1H), 2.51-2.32 (m, 3H), 2.20-2.06 (m, 2H), 2.04 (s, 3H), 1.95-1.86 (m, 1H), 1.84-1.67 (m, 5H), 1.67-1.42 (m, 5H), 1.25-1.02 (m, 6H), 0.91-0.81 (m, 3H).

Step 2. To a solution of $MePPh_3Br$ (20.6 g, 57.7 mmol, 1.0 eq) in THF (200 mL) was added t-BuOK (6.47 g, 57.7 mmol, 1.0 eq) at 0°C. After addition, the reaction mixture was heated to 20°C and stirred for 1 hour. Then the mixture was added to a solution **A2** (20 g, 57.7 mmol, 1.0 eq) in THF (200 mL) and the reaction mixture was stirred at 20°C for 2 h. The mixture was treated with NH_4Cl (100 mL, 10%) and extracted with EtOAc (2 x 100 mL). The organic phase was separated and concentrated in vacuum to afford product a crude residue. The residue was triturated from $MeOH/H_2O$ (400ml, 1/1) at 20°C to give a crude residue. The crude residue was dissolved in DCM (200 mL), washed with saturated brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **A3** (19 g, 96%) as a solid.

^{1}**H NMR** (400MHz, $CDCl_3$) δ 4.75 (s, 1H), 4.64 (s, 1H), 2.51-2.44 (m, 1H), 2.35-2.32 (m, 1H), 2.23-2.11 (m, 2H), 2.04 (s, 3H), 1.99-1.93 (m, 1H), 1.86-1.63 (m, 7H), 1.54-1.19 (m, 7H), 1.08-1.01 (m, 1H), 0.99 (s, 3H), 0.90 (s, 3H), 0.89-0.81 (m, 1H).

Step 3. To a solution of **A3** (19 g, 55.1 mmol) in ethanol (100 mL) was added Pd-C (dry, 10%, 2 g) under N_2. The suspension was degassed under vacuum and purged with H_2 for three times. The mixture was stirred for 20 hrs at 15°C under H_2. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give **A4** (18 g, 95%) as a solid.

^{1}**H NMR** (400MHz, $CDCl_3$) δ 4.72-4.67 (m, 1H), 2.46-2.40 (m, 1H), 2.13-2.03 (m, 4H), 1.94-1.91 (m, 1H), 1.80-1.22 (m, 15H), 1.15-1.01 (m, 4H), 0.94-0.75 (m, 8H).

Step 4. To a solution of **A4** (18 g, 51.9 mmol) in MeOH (200 mL) was added K_2CO_3 (28.6 g, 207 mmol) in one portion at 15°C under N_2. The mixture was stirred at 15°C for 2 h and quenched with water (100 mL). The aqueous phase was extracted with DCM (3 x 100 mL). The combined organic phase was washed with saturated brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford **A5** (15.2 g, 96%) as colourless oil.

^{1}**H NMR** (400MHz, $CDCl_3$) δ 3.62-3.60 (m, 1H), 2.62-2.40 (m, 1H), 2.11-2.04 (m, 2H), 1.96-1.90 (m, 1H), 1.80-1.02 (m, 20H), 0.90-0.80 (m, 6H), 0.76-0.70 (m, 1H).

Step 5. To a solution of **A5** (8 g, 26.2 mmol) in DCM (100 mL) was added silica gel (11.2 g) and PCC (11.2 g, 52.6 mmol) at 25°C. The reaction mixture was stirred at 25°C for 1 h. The resulting mixture was filtered and the filtrate was concentrated in vacuum. To a solution of the crude product in DCM (20 mL) was added silica gel (20 g) and PE (100 mL). After stirring at 25°C for 30 mins, the mixture was and filtered and the filtrate was concentrated in vacuum to give **A6** (7 g) as a solid.

^{1}**H NMR** (400MHz, $CDCl_3$) δ 2.42-2.06 (m, 8H), 1.80-1.77 (m, 4H), 1.45-1.22 (m, 8H), 1.05-0.84 (m, 10H).

Step 6. A suspension of LiCl (2.05 g, 48.5 mmol, anhydrous) in THF (200 mL, anhydrous) was stirred at 10°C for 30 mins under N_2. $FeCl_3$ (4.11 g, 25.4 mmol, anhydrous) was added at 10°C. After cooling to -30°C, MeMgBr (30.8 mL, 3M in diethyl ether) was added drop-wise at -30°C. After stirring at -30°C for 10 mins, **A6** (7 g, 23.1 mmol) was added at -30°C. The mixture was stirred at -15°C for 2 hours and quenched with citric acid (200 mL, 10% aq.). The mixture was extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with saturated brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a crude product, which was purified by a silica gel column (PE/EtOAc = 0~10/1) to give **A7** (1 g, 14%, Rf = 0.45 in PE/EtOAc) and **A8** (0.8 g, 11%, Rf = 0.40 in PE/EtOAc) and a mixture (4 g) as solid.

A7:

^{1}H NMR (400MHz, $CDCl_3$) δ 2.48-2.41 (m, 1H), 2.13-2.08 (m, 1H), 1.97-1.90 (m, 1H), 1.84-1.67 (m, 4H), 1.55-1.47 (m, 5H), 1.41-1.25 (m, 5H), 1.23-1.01 (m, 8H), 0.97-0.94 (m, 3H), 0.86 (s, 3H), 0.79 (s, 3H).

The stereochemistry at C7 of **A7** was confirmed by NOE.

A8:

^{1}H NMR (400MHz, $CDCl_3$) δ 2.48-2.38 (m, 1H), 2.12-2.07 (m, 1H), 1.79-1.73 (m, 2H), 1.56-1.49 (m, 4H), 1.46-1.38 (m, 2H), 1.32-1.19 (m, 12H), 1.03-0.97 (m, 4H), 0.87 (s, 3H), 0.86-0.76 (m, 2H), 0.73 (s, 3H).

The stereochemistry at C7 of **A8** was confirmed by NOE.

Step 7a (Compound 1). Into a over-dried bottom was added t-BuOH (2 mL) and t-BuOK (703 mg, 6.27 mmol). After evaporating and filling with N_2, a solution of **A7** (200 mg, 0.627 mmol) in DME (1 mL) was added. After 30 min, a solution of TosMic (243 mg, 1.25 mmol) in DME (1 mL) was added. The mixture became yellow. The resulting mixture was stirred at 25°C for 16 h and quenched with water. The mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluting with (petroleum ether/ethyl acetate = 10/1) to give **Compound 1** (50 mg, 24%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ2.30-2.24 (m, 1H), 2.16-2.06 (m, 1H), 1.97-1.87 (m, 2H), 1.83-1.71 (m, 3H), 1.67-1.58 (m, 1H), 1.54-1.42 (m, 5H), 1.39-1.24 (m, 4H), 1.20-1.01 (m, 9H), 0.93-0.88 (m, 6H), 0.77 (s, 3H).

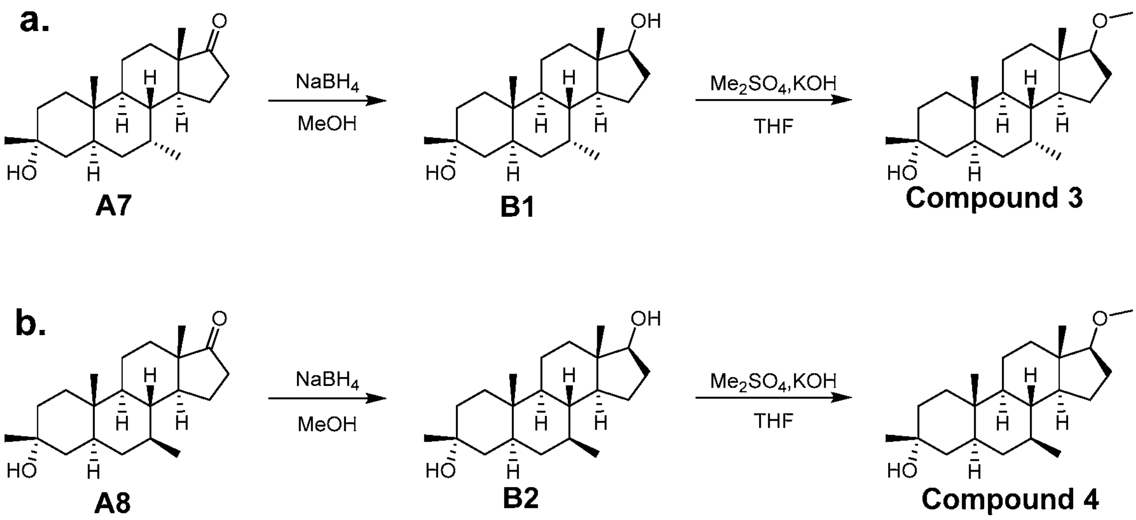
LCMS Rt = 1.918 min in 3.0 min chromatography, 10-80 AB_3MIN_E.M, purity 100%, MS ESI calcd. for $C_{22}H_{34}N$ $[M+H-H_2O]^+$ 312, found 312.

Step 7b (Compound 2). In an oven-dried round bottom flask was added t-BuOH (2 mL) and t-BuOK (703 mg, 6.27 mmol). The reaction vessel was evaporated and filled with N_2. **A8** (200 mg, 0.627 mmol) in DME (1 mL) was added into the suspension. After 30 min, TosMIC (243 mg, 1.25 mmol) in DME (1 mL) was added. The mixture became yellow. The resulting mixture was stirred at 25°C for 16 h. Water was added and the mixture was stirred. Then it was extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine.The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluting with (petroleum ether:ethyl acetate= 4:1) to give **Compound 2** (13 mg, 6%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 2.26-2.17 (m, 1H), 2.14-2.00 (m, 1H), 1.99-1.85 (m, 3H), 1.73-1.67 (m, 1H), 1.56-1.44 (m, 5H), 1.30-1.24 (m, 4H), 1.20 (s, 3H), 1.17-1.09 (m, 4H), 1.04-0.88 (m, 8H), 0.85-0.76 (m, 2H), 0.72 (s, 3H).

LCMS Rt = 1.939 min in 3.0 min chromatography, 10-80 AB_3MIN_E.M, purity 100%, MS ESI calcd. for $C_{22}H_{34}NO$ $[M+H-H_2O]^+$ 312, found 312.

Example 2. Syntheses of Compounds 3 and 4.



Step 1a (B1). To a solution of **A7** (200 mg, 0.627 mmol) in MeOH (5 mL) was added $NaBH_4$ (47.2 mg, 1.25 mmol) at 25°C. After stirring at 25°C for 30 mins, the reaction was quenched by

adding water (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum to give **B1** (180 mg, crude) as a solid, which was directly used for next step without further purification.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.67-3.62 (m, 1H), 2.11-2.02 (m, 1H), 1.82-1.75 (m, 3H), 1.63-1.37 (m, 11H), 1.34-1.20 (m, 8H),1.14-1.01(m, 4H), 0.90 (d, *J* = 4.0 Hz, 2H), 0.78 (s, 3H), 0.74 (s, 3H).

Step 2a (Compound 3). To a solution of **B1** (180 mg, 0.561 mmol) in THF (5 mL) was added KOH (94.2 mg, 1.68 mmol) and Me_2SO_4 (0.282 mg, 0.211 mL, 2.24 mmol) at 0°C. Then the mixture was warmed to 25°C and stirred at the same temperature for 16 h. The mixture was quenched with 50 mL of water and extracted with EtOAc (2 x 30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc=0-10/1) to give **Compound 3** (21 mg, 11%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.34 (s, 3H), 3.22 (t, *J* = 8.0 Hz, 1H), 2.04-1.96 (m, 1H), 1.88-1.71 (m, 3H), 1.63-1.56 (m, 2H), 1.54-1.34 (m, 7H), 1.32-1.17 (m, 8H), 1.16-0.97 (m, 5H), 0.90 (d, *J* = 4.0 Hz, 2H), 0.76 (s, 3H), 0.74 (s, 3H).

LCMS Rt = 2.050 min in 3.0 min chromatography, 10-80 AB_3MIN_E.M, purity 100%, MS ESI calcd. for $C_{22}H_{37}O$ $[M+H-H_2O]^+$ 317, found 317.

Step 1b (B2). To a solution of **A8** (200 mg, 0.627 mmol) in MeOH (5 mL) was added $NaBH_4$ (47.2 mg, 1.25 mmol) at 25°C. After stirring at 25°C for 30 mins, the reaction was quenched by adding water (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum to give **B2** (170 mg, crude) as a solid, which was directly used for next step without further purification.

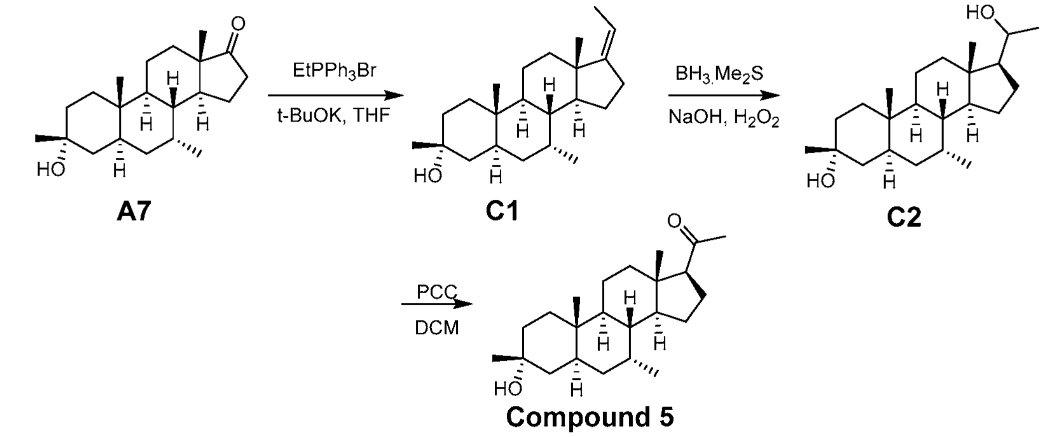
^{1}H NMR (400MHz, $CDCl_3$) δ 3.62-3.56 (m,1H), 2.08-1.99 (m,1H), 1.81-1.76 (m, 2H), 1.68-1.62 (m, 1H), 1.58-1.38 (m, 7H), 1.33-0.99 (m, 15H), 0.94 (d, *J*=8.0 Hz, 2H), 0.84-0.77 (m, 1H), 0.75 (s, 3H), 0.73 (s, 3H).

Step 2b (Compound 4). To a solution of **B2** (170 mg, 0.530 mmol) in THF (5 mL) was added KOH (88.6 mg, 1.58 mmol) and Me_2SO_4 (0.266 mg, 0.2 mL, 2.11 mmol) at 0°C. Then the mixture was warmed to 25°C and stirred at the same temperature for 16 h. The mixture was quenched with the addition of 50 mL of water and extracted with EtOAc (2 x 30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give a crude product, which was purified by a silica gel column (PE/EtOAc=0-10/1) to give **Compound 4** (21 mg, 11%) as a solid. **^{1}H NMR** (400MHz, $CDCl_3$) δ 3.34 (s, 3H), 3.16 (t, *J* = 8.0 Hz, 1H), 2.02-1.93 (m, 1H), 1.88 (dt, *J* = 4.0, 12.0 Hz, 1H), 1.77-1.74 (m, 1H), 1.64-1.39 (m, 9H), 1.33-1.08 (m, 12H), 1.03-0.96 (m, 1H), 0.93 (d, *J* = 8.0 Hz, 2H), 0.80-0.74 (m, 1H), 0.75 (s, 3H), 0.71 (s, 3H).

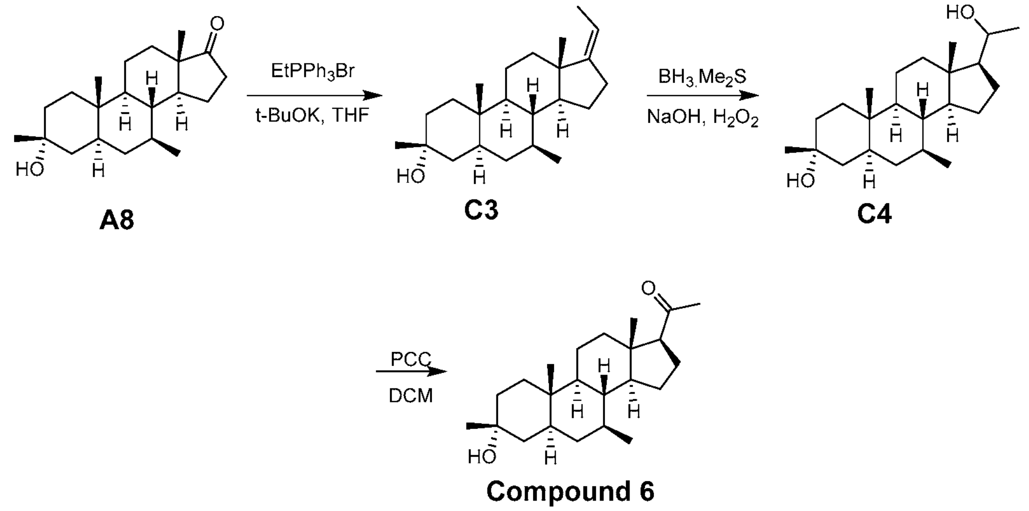
LCMS Rt = 2.079 min in 3.0 min chromatography, 10-80 AB_3MIN_E.M, purity 100%, MS ESI calcd. for $C_{22}H_{37}O$ [M+H-H_2O]+ 317, found 317.

Example 3. Syntheses of Compounds 5 and 6.

a.



b.



Step 1. To a suspension of PPh_3EtBr (1.91 g, 5.15 mmol) in THF (10 mL) was added t-BuOK (0.577 g, 5.15 mmol) at 10°C. The color of the suspension turned dark red. After stirring at 40°C for 30 min, a solution of **A7** (0.55 g, 1.72 mmol) in THF (2 mL) was added at 40°C. After stirring at 40°C for 1 h, the reaction mixture was poured into 20 g of crushed ice and stirred for 15 minutes. The organic layer was separated and the water phase was extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered concentrated and purified by flash column (0~10% of EtOAc in PE) to give **C1** (350 mg, 62%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 5.14-5.08 (m, 1H), 2.41-2.32 (m, 1H), 2.26-2.12 (m, 2H), 1.87-1.70 (m, 2H), 1.67-1.44 (m, 10H), 1.40-1.08 (m, 11H), 1.07-1.03 (m, 1H), 1.05-0.99 (m, 1H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 3H), 0.77 (s, 3H).

Step 2. To a solution of **C1** (200 mg, 0.605 mmol) in THF (3 mL) was added drop-wise a solution of BH_3-Me_2S (0.605 mL, 6.05 mmol) at 0°C. The solution was stirred at 15°C for 3 h. After cooling to 0°C, a solution of NaOH solution (3.62 mL, 2 M) was added very slowly. After addition, H_2O_2 (683 mg, 6.05 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. After stirring at 15°C for 2 h, the saturated aqueous $Na_2S_2O_3$ (50 mL) was added until the reaction solution became clear. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic solution was washed with saturated aqueous $Na_2S_2O_3$ (2 x 20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum to give the crude product (180 mg) as a solid, which was used in next step without further purification.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.77-3.66 (m, 1H), 1.82-1.71 (m, 3H), 1.54-1.42 (m, 8H), 1.32-1.06 (m, 19H), 0.91 (d, *J* = 8.0 Hz, 3H), 0.75 (s, 3H), 0.65 (s, 3H).

Step 3. To a solution of **C3** (180 mg, 0.516 mmol) in DCM (5 mL) was added silica gel (222 mg) and PCC (222 mg, 1.03 mmol) at 25°C. The reaction mixture was stirred at 25°C for 1 h. The resulting mixture was filtered and the filtrate concentrated in vacuum. To a solution of the crude product in DCM (20 mL) was added silica gel (20 g) and PE (100 mL). The mixture was stirred at 25°C for 30 mins and filtered and the filtrate was concentrated in vacuum to give crude product, which was purified by flash column (0~10% of EtOAc in PE) to give **Compound 5** (29 mg, 16%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (t, J = 8.0 Hz, 1H), 2.20-2.14 (m, 1H), 2.11(s, 3H), 2.01-1.94 (m, 1H), 1.83-1.73 (m, 2H), 1.70-1.59 (m, 3H), 1.55-1.43 (m, 5H), 1.39-1.12 (m, 12H), 1.04-1.01 (m, 1H), 0.92 (d, J = 8.0 Hz, 3H), 0.76 (s, 3H), 0.60 (s, 3H).

LCMS Rt = 2.150 min in 3.0 min chromatography, 10-80 AB_3MIN_E.M, purity 100%, MS ESI calcd. for $C_{23}H_{37}O$ $[M+H-H_2O]^+$ 329, found 329.

Step 4. To a suspension of PPh_3EtBr (1.21 g, 3.27 mmol) in THF (10 mL) was added t-BuOK (0.366 g, 3.27 mmol) at 10°C. The color of the suspension turned dark red. After stirring at 40°C for 30 min, a solution of **A8** (0.35 g, 1.09 mmol) in THF (2 mL) was added at 40°C and the reaction mixture was stirred at 40°C for 1 h. The reaction mixture was poured into 20 g of crushed ice and stirred for 15 minutes. The organic layer was separated and the water phase was extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered concentrated and purified by flash column (0~10% of EtOAc in PE) to give **C3** (140 mg, 39%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15-5.12 (m, 1H), 2.31-2.22 (m, 3H), 1.81-1.73 (m, 1H), 1.70-1.61 (m, 4H), 1.56-1.40 (m, 7H), 1.34-1.18 (m, 12H), 0.95 (d, J=4.0 Hz, 3H), 0.89 (s, 3H), 0.87-0.79 (m, 1H), 0.72 (s, 3H).

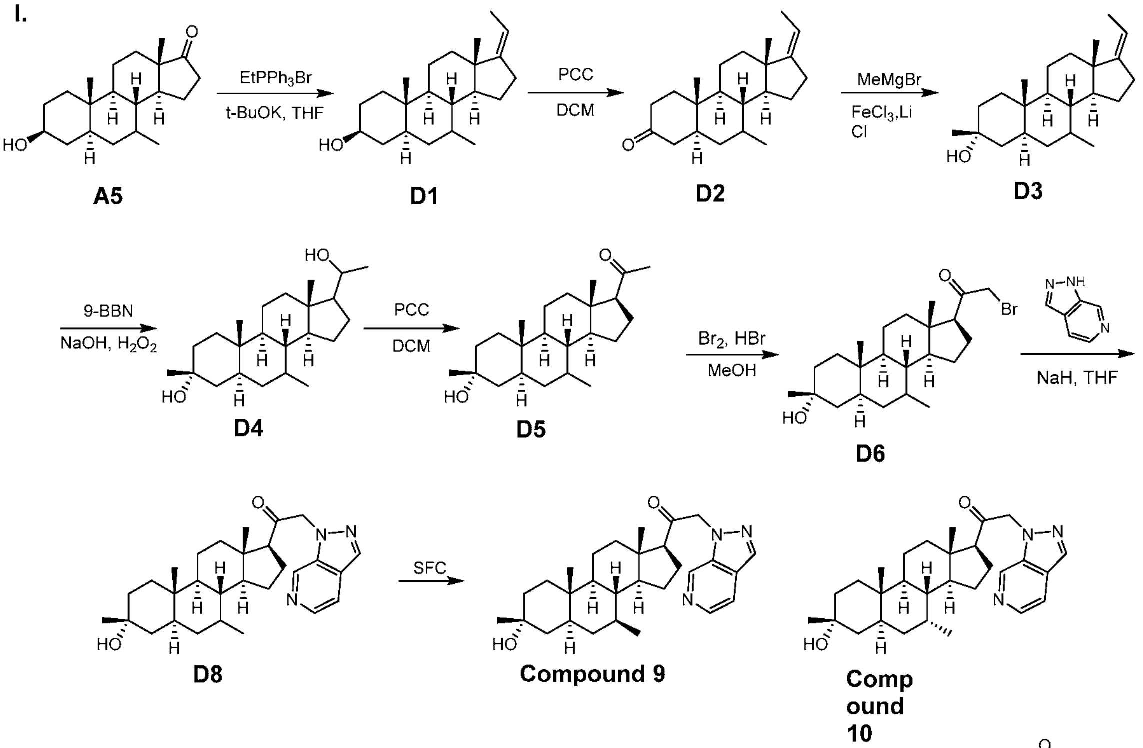
Step 5. To a solution of **C3** (120 mg, 0.363 mmol) in THF (3 mL) was added drop-wise a solution of BH_3-Me_2S (0.363 mL, 3.63 mmol) at 0°C. The solution was stirred at 15°C for 3 h. After cooling to 0°C, a solution of NaOH solution (2.17 mL, 2M) was added very slowly. After addition, H_2O_2 (410 mg, 3.63 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 2 h. Then saturated aqueous $Na_2S_2O_3$ (50 mL) was added until the reaction solution became clear. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic solution was washed with saturated aqueous $Na_2S_2O_3$ (2 x 20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum to give the crude product (100 mg) as a solid, which was used in next step without further purification.

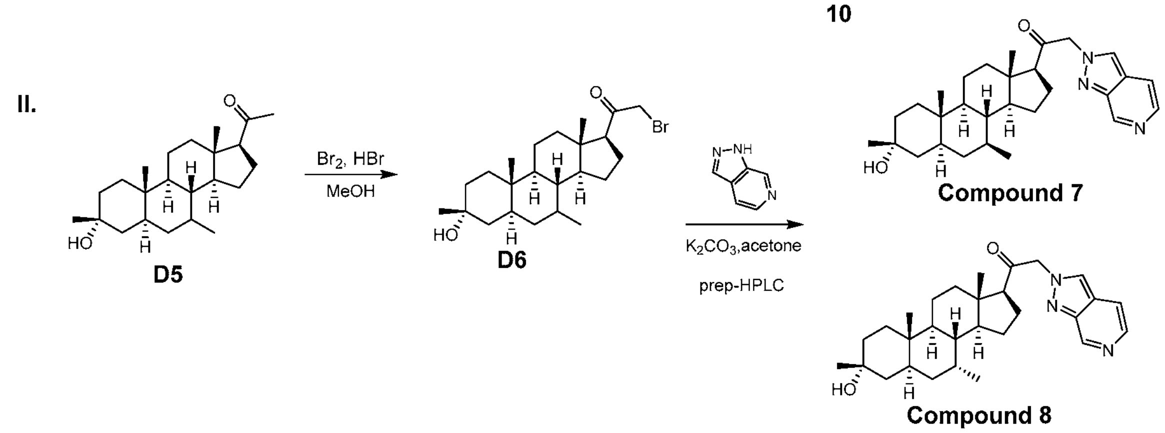
^{1}**H NMR** (400MHz, $CDCl_3$) δ 3.76-3.64 (m, 1H), 1.86-1.79 (m, 3H), 1.54-1.39 (m, 8H), 1.28-1.17 (m, 17H), 0.95 (d, J = 6.0 Hz, 3H), 0.82-0.74 (m, 2H), 0.71 (s, 3H), 0.67 (s, 3H).

Step 6. To a solution of **C4** (100 mg, 0.286 mmol) in DCM (5 mL) was added silica gel (123 mg) and PCC (123 mg, 0.572 mmol) at 25°C. The reaction mixture was stirred at 25°C for 1 h. The resulting mixture was filtered and the filtrate concentrated by vacuum. To a solution of the crude product in DCM (20 mL) was added silica gel (20 g) and PE (100 mL). The mixture was stirred at 25°C for 30 mins and filtered and the filtrate was concentrated in vacuum to give crude product. The crude product was purified by flash column (0~10% of EtOAc in PE) to give **Compound 6** (13 mg, 13%) as a solid. ^{1}**H NMR** (400MHz, $CDCl_3$) δ 2.48 (t, J = 9.2 Hz, 1H), 2.16-2.09 (m, 4H), 2.01-1.95 (m, 1H), 1.86-1.82 (m, 1H), 1.73-1.59 (m, 2H), 1.54-1.42 (m, 5H), 1.40-1.14 (m, 13H), 1.05-0.96 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H), 0.88-0.80 (m, 1H), 0.71 (s, 3H), 0.62 (s, 3H)

LCMS Rt = 2.184 min in 3.0 min chromatography, 10-80 AB_3MIN_E.M, purity 100%, MS ESI calcd. for $C_{23}H_{37}O$ $[M+H-H_2O]^+$ 329, found 329.

Example 4. Syntheses of Compounds 7, 8, 9, and 10.





Example 13. Syntheses of Compounds 7 and 8.

Part I

Step 1. To a suspension of PPh_3EtBr (72.7 g, 196 mmol) in THF (200 mL) was added t-BuOK (21.9 g, 196 mmol) at 10°C. The color of the suspension was turned to dark red. After stirring at 40°C for 30 min, a solution of **A5** (20 g, 65.6 mmol) in THF (20 mL) was added at 40°C and the reaction mixture was stirred at 40°C for 1 h. The reaction mixture was poured into 200 g of crashed ice and stirred for 15 minutes. The organic layer was separated and the water phase was extracted with EtOAc (2 x 200 mL). The combined organic phase was washed with saturated brine (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered concentrated and purified by flash column (0~30% of EtOAc in PE) to give **D1** (19.5 g, 94%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 5.20-5.01 (m, 1H), 3.70-3.50 (m, 1H), 2.48-2.15 (m, 3H), 1.89-1.52 (m, 8H), 1.52-1.09 (m, 7H), 1.09-0.93 (m, 5H), 0.93-0.70 (m, 11H).

Step 2. To a solution of **D1** (10 g, 31.5 mmol) in anhydrous DCM (100 mL) was added silica gel (10 g) and PCC (13.5 g, 63.0 mmol). The mixture was stirred at 15°C for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by flash column (0~30% of EtOAc in PE) to give **D2** (6.6 g, 67%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20-50.8 (m, 1H), 2.49-2.15 (m, 6H), 2.15-1.95 (m, 2H), 1.95-1.72 (m, 2H), 1.72-1.19 (m, 10H), 1.19-0.95 (m, 7H), 0.95-0.75 (m, 6H).

Step 3. Under nitrogen atmosphere, anhydrous THF (100 mL) was cooled to 10°C and anhydrous LiCl (3.54 g, 83.6 mmol) was added in one portion. The mixture was stirred for 30 min to obtain a clear solution. To this solution was added anhydrous $FeCl_3$ (7.44 g, 45.9 mmol) in one portion. The resulting mixture was stirred for additional 30 mins. The reaction mixture was cooled to -35°C and methyl magnesium bromide (3 M in diethyl ether, 55.6 mL, 167 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. A solution of **D2** (6.6 g, 20.9 mmol) in THF (20 mL) was added in one portion. The internal temperature was allowed to -20°C and held between -15°C and -20°C for 2 hrs. The reaction mixture was poured into ice-cooled aqueous HCl (1 M, 200 mL), extracted with EtOAc (2 x 200 mL). The combined organic layer was washed with water (200 mL), aqueous NaOH (10%, 2 x 200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE /EtOAc = 20 /1 to 20 / 1) to give **D3** (6.5 g, 94%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15-5.05 (m, 1H), 2.42-2.11 (m, 3H), 1.90-1.40 (m, 16H), 1.40-1.10 (m, 5H), 1.10-0.81 (m, 10H), 0.81-0.69 (m, 3H).

Step 4. To a solution of **D3** (6 g, 18.1 mmol) in THF (85 mL) was added 9-BBN dimer (13.2 g, 54.3 mmol). The mixture was stirred at 50°C for 2 hrs. After cooling to 0°C, to the reaction mixture was added ethanol (10.3 mL, 181 mmol) and NaOH (36.1 mL, 5 M, 181 mmol) very slowly. After addition, H_2O_2 (18.1 mL, 181 mmol, 30%) was added slowly and the inner temperature was maintained below 15°C. The resulting solution was stirred at 75°C for 1 hrs. The mixture was cooled and added to water (100 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with saturated brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **D4** (5.9 g, crude) as colourless oil which was used directly for the next step without purfication.

Step 5. To a suspension of **D4** (5.9 g, 16.9 mmol) in DCM (100 mL) was added silica gel (3 g) and PCC (5.45 g, 25.3 mmol) at 15°C. The mixture was stirred at 15°C for 2 hrs. The mixture was filtered and the filtrated cake was washed with DCM (50 mL). The combined filtrate was concentrated in vacuum and purified by flash column (0~30% of EtOAc in PE) to afford **D5** (4.3 g, impure) as a solid.

Step 6. To a solution of **D5** (500 mg, 1.44 mmol) in MeOH (10 ml) was added HBr (57.4 mg, 0.29 mmol, 40% in water) and Br_2 (337 mg, 2.15 mmol) at 25°C. The mixture was stirred at 25°C for 2 hrs. The mixture was quenched by sat.aq $NaHCO_3$ (10 mL), treated with water (20 mL), extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum to afford **D6** (480 mg, crude) as light yellow oil, which was used directly for the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97-3.86 (m, 2H), 2.86-2.71 (m, 1H), 2.24-1.96 (m, 2H), 1.93-1.68 (m, 6H), 1.54-1.43 (m, 5H), 1.35-1.23 (m, 5H), 1.21-1.15 (m, 5H), 0.96-0.79 (m, 4H), 0.77-0.58 (m, 7H).

Step 7. To a solution of 1H-pyrazolo[3,4-c]pyridine (139 mg, 1.17 mmol) in THF (10 mL) was added NaH (89.5 g, 2.24 mmol, 60%) in portions at 25°C. The mixture was stirred at 60°C for 10 min. Then **D6** (480 mg, 1.12 mmol) in THF (10 mL) was added drop-wise to the solution. The mixture was stirred at 60°C for 1 h. The mixture was poured into water (50 mL) and extrated with EtOAc (3 x 20 mL). The combined organe layer was washed with brine (50 mL), dried over with Na_2SO_4 and concentrated to afford crude product. The residue was purified by silica gel chromatography (100-200 mesh silica gel, Petroleum ether/Ethyl acetate=0/1) to afford the mixture of **D7** and **D8** (290 mg, crude) as a solid.

Step 8 (Compounds 9 and 10). **D8** (290 mg, 0.62 mmol) was purified by SFC (column: OD(250mm*30mm,10um)), gradient: 40-40% B (A= 0.1%NH_3/H_2O, B= EtOH), flow rate: 80 mL/min) to give pure **Compound 9** (48 mg, 16%) and pure **Compound 10** (18 mg, 6%) as a solid.

Compound 9:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.8 (s, 1H), 8.39-8.29 (m, 1H), 8.1 (s, 1H), 7.68-7.61 (d, J = 4.8 Hz, 1H), 5.32-5.19 (m, 2H), 2.76-2.62 (m, 1H), 2.27-2.06 (m, 2H), 1.84-1.67 (m, 4H), 1.53-1.26 (m, 11H), 1.23-1.09 (m, 7H), 1.08-1.01 (m, 1H), 0.96-0.89 (d, J = 7.2 Hz, 3H), 0.77 (s, 3H), 0.71 (s, 3H).

LCMS Rt = 0.885 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{29}H_{42}N_3O_2$ $[M+H]^+$ 464, found 464.

SFC Rt = 1.785 min in 3 min chromatography, OD-H_3UM_3_5_40_4ML_3MIN, purity: 100%.

Compound 10:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.39-8.28 (m, 1H), 8.09 (s, 1H), 7.69-7.61 (d, J = 4.8 Hz, 1H), 5.34-5.17 (m, 2H), 2.68-2.57 (m, 1H), 2.24-2.09 (m, 2H), 1.96-1.71 (m, 4H), 1.47-1.13 (m, 15H), 1.07-0.81 (m, 7H), 0.73 (s, 6H).

LCMS Rt = 0.908 min in 2 min chromatography, 30-90AB_2MIN_E, purity 98%, MS ESI calcd. for $C_{29}H_{42}N_3O_2$ $[M+H]^+$ 464, found 464.

SFC Rt = 2.132 min in 3 min chromatography, OD-H_3UM_3_5_40_4ML_3MIN, purity: 99%.

Part II

Step 1. To a solution of **D5** (500 mg, 1.44 mmol) in MeOH (10 ml) was added HBr (57.4 mg, 0.288 mmol, 40% in water) and Br_2 (229 mg, 1.46 mmol) at 25°C. The mixture was stirred at 25°C for 16 hrs. The mixture was quenched by sat.aq $NaHCO_3$ (10 mL), treated with water (20 mL), extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum to afford **D6** (500 mg, crude) as a solid used directly for the next step.

Step 2 (Compounds 7 and 8). To a mixture of **D6** (500 mg, 1.17 mmol) and K_2CO_3 (323 mg, 2.34 mmol) in acetone (3 mL) was added 1H-pyrazolo[3,4-c]pyridine (1.45 mg, 1.22 mmol) at 25°C. The mixture was stirred at 25°C for 12 h. The mixture was poured into water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (50 mL), dried over with Na_2SO_4, filtered and concentrated to afford crude product, which was purified by prep-HPLC separation (column: Phenomenex Synergi C18 150*30mm*4um)), gradient: 28-58% B (A = 0.1%HCl, B = ACN), flow rate: 30 mL/min) and then SFC (column: OJ(250mm*30mm,10um)), gradient: 35-35% B (A = 0.1%NH_3H_2O , B = ETOH), flow rate: 80 mL/min) to afford **Compound 8** (15 mg, yield 75%) as a solid and **Compound 7** (5 mg, yield 25%) as a solid.

Compound 7:

^{1}H NMR (400MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.27-8.17 (m, 1H), 7.98 (s, 1H), 7.58-7.49 (m, 1H), 5.32 (d, *J* = 16.0 Hz, 1H), 5.22 (d, *J* = 16.0 Hz, 1H), 2.62 (t, *J* = 8.0 Hz, 1H), 2.24-2.09 (m, 2H), 1.97-1.89 (m, 1H), 1.81-1.72 (m, 2H), 1.52-1.42 (m, 4H), 1.37-1.13 (m, 14H), 1.05-0.98 (m, 1H), 0.96 (d, *J* = 8.0 Hz, 3H), 0.90-0.82 (m, 1H), 0.74-0.71 (m, 6H).

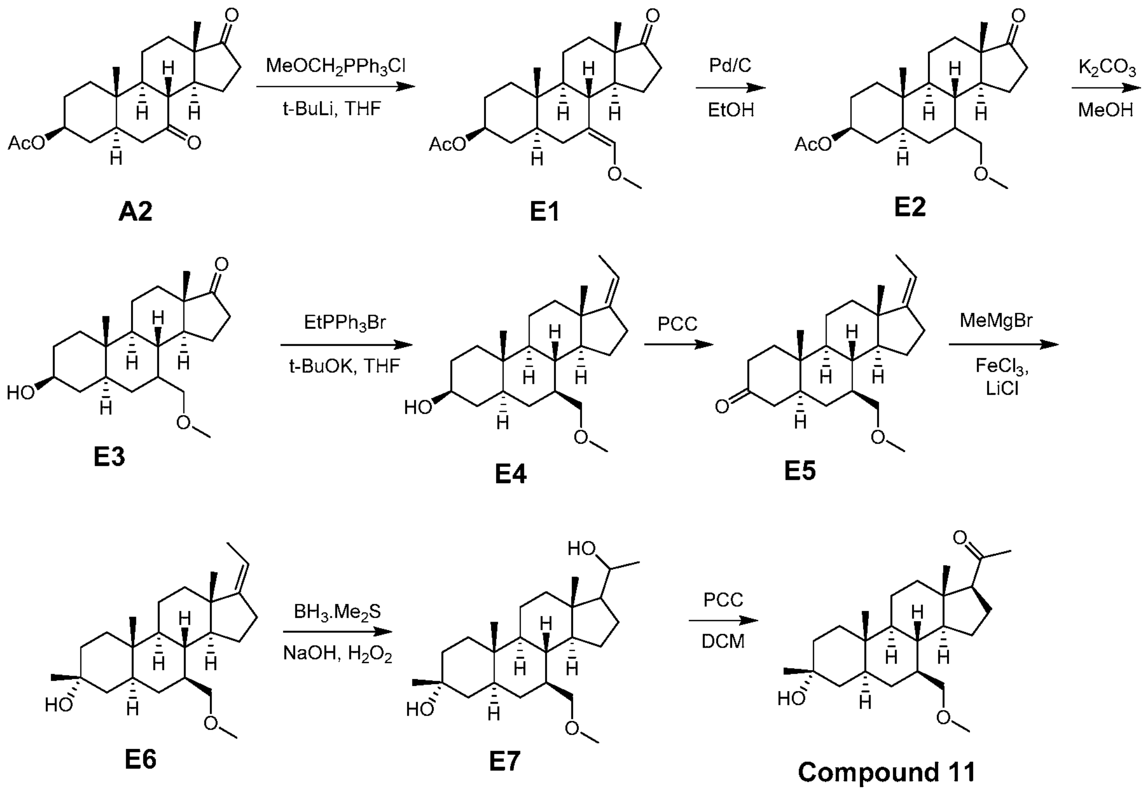
LCMS Rt = 2.406 in in 4.0 min chromatography, 10-80AB.lcm, purity 99.3%, MS ESI calcd. for $C_{29}H_{42}N_3O_2$ $[M+H]^+$ 464, found 464.

Compound 8:

^{1}H NMR (400MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.98 (s, 1H), 7.52 (dd, *J*=1.0, 8.0 Hz, 1H), 5.32 (d, *J* = 16.0 Hz, 1H), 5.22 (d, *J* = 16.0 Hz, 1H), 2.67 (t, *J* = 8.0 Hz, 1H), 2.28-2.18 (m, 1H), 2.11-2.08 (m, 1H), 1.85-1.67 (m, 5H), 1.65-1.36 (m, 10H), 1.27-1.12 (m, 7H), 1.04 (br d, *J*=13.3 Hz, 1H), 0.93 (d, *J* = 8.0 Hz, 3H), 0.77 (s, 3H), 0.71 (s, 3H).

LCMS Rt = 2.358 in in 4.0 min chromatography, 10-80AB.lcm, purity 99.7%, MS ESI calcd. for $C_{29}H_{42}N_3O_2$ $[M+H]^+$ 464, found 464.

Example 5. Synthesis of Compound 11.



Step 1. To a solution of chloro(methoxymethyl)triphenylphosphorane (19.7 g, 57.7 mmol) in THF (200 mL) was added t-BuLi (44.3 mL, 57.7 mmol, 1.3 M in n-hexane) at -10°C, after addition, the reaction mixture was stirred for 1 hour. Then the mixture was added to **A2** (20 g, 57.7 mmol) in THF (200 mL) at 0°C and the reaction mixture was stirred at 15°C for 2h. The mixture was treated with NH_4Cl (100 mL, 10%), EtOAc (2 x 200 mL) was added. The organic phase was separated, concentrated in vacuum to afford crude product. The residue was purified by flash column (0~30% of EtOAc in PE) to give **E1** (5 g, 23%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (s, 1H), 4.75-4.60 (m, 1H), 3.56 (s, 3H), 2.60-2.42 (m, 2H), 2.31-1.98 (m, 8H), 1.80-1.38 (m, 6H), 1.38-1.19 (m, 4H), 1.19-0.80 (m, 9H).

Step 2. To a solution of **E1** (5 g, 13.3 mmol) in MeOH (50 mL) was added Pd-C (dry, 10%, 1 g) under N_2. The suspension was degassed under vacuum and purged with H_2 for three times. The mixture was stirred under H_2 (15 psi) at 15°C for 16 hours to give a black suspension. The reaction mixture was filtered through a pad of Celite and washed with EtOH (3 x 20 mL). The filtrate was concentrated to **E2** (3.8 g, 76%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78-4.60 (m, 1H), 3.42-3.35 (m, 1H), 3.35-3.28 (m, 4H), 2.50-2.38 (m, 1H), 2.20-1.95 (m, 5H), 1.85-1.60 (m, 7H), 1.60-1.18 (m, 8H), 1.18-0.91 (m, 2H), 0.91-0.76 (m, 7H).

Step 3. To a solution of **E2** (3.8 g, 10.0 mmol) in MeOH (50 mL) was added K_2CO_3 (5.52 g, 40.0 mmol) in one portion at 15°C under N_2. The mixture was stirred at 15°C for 2 h. Water (20 mL) was added. The aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford **E3** (3 g, 90%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68-3.51 (m, 1H), 3.51-3.39 (m, 1H), 3.35-3.28 (m, 4H), 2.50-2.38 (m, 1H), 2.20-2.01 (m, 2H), 1.85-1.70 (m, 5H), 1.70-1.46 (m, 5H), 1.46-1.12 (m, 7H), 1.12-0.91 (m, 1H), 0.91-0.70 (m, 7H).

Step 4. To a suspension of PPh_3EtBr (11.5 g, 31.2 mmol) in THF (50 mL) was added t-BuOK (3.5 g, 31.2 mmol) at 10°C. The color of the suspension turned dark red. After stirring at 40°C for 1 hour, a solution of **E3** (3.5 g, 10.4 mmol) in THF (20 mL) was added at 40°C and the reaction mixture was stirred at 40°C for 16 h. The mixture was added saturated NH_4Cl solution (20 mL) and extracted with EtOAc (2 x 20 mL). The organic layer was separated and the water phase was extracted with EtOAc (2 x 10 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered concentrated and purified by flash column (0~30% of EtOAc in PE) to give **E4** (1.5 g, 42%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15-5.05 (m, 1H), 3.68-3.55 (m, 1H), 3.51-3.39 (m, 1H), 3.35-3.28 (m, 4H), 2.40-2.31 (m, 1H), 2.22-2.10 (m, 2H), 2.01-1.49 (m, 8H), 1.49-1.11 (m, 6H), 1.11-0.75 (m, 14H).

The stereochemistry at C7 of **E4** was confirmed by NOE.

Step 5. To a suspension of **E4** (1.5 g, 4.32 mmol) in DCM (30 mL) was added silica gel (2 g) and PCC (1.86 g, 8.64 mmol) at 15°C. The mixture was stirred at 15°C for 2 hrs. The mixture was filtered and the filtrated cake was washed with DCM (2 x 20 mL). The combined filtrate was concentrated in vacuum and purified by flash column (0~30% of EtOAc in PE) to give crude product **E5** (1.3 g, 87%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19-5.10 (m, 1H), 3.52-3.45 (m, 1H), 3.31-3.28 (m, 3H), 3.28-3.19 (m, 1H), 2.45-2.15 (m, 7H), 2.15-2.02 (m, 3H), 1.85-1.75 (m, 1H), 1.75-1.62 (m, 4H), 1.62-1.25 (m, 7H), 0.99 (s, 3H), 0.98-0.80 (m, 5H).

Step 6. Under nitrogen atmosphere, anhydrous THF (20 mL) was cooled to 10°C and anhydrous LiCl (589 mg, 13.9 mmol) was added in one portion. The mixture was stirred for 30 min to obtain a clear solution. To this solution was added anhydrous $FeCl_3$ (1.24 g, 7.65 mmol) in one portion. The resulting mixture was stirred for additional 30 mins. The reaction mixture was cooled to -35°C and methyl magnesium bromide (9.26 mL, 27.8 mmol, 3 M in diethyl ether,) was added dropwise maintaining the internal temperature between -35°C and -30°C. The above mixture was stirred for 30 min at -30°C. **E5** (1.2 g, 3.48 mmol) in THF (20 mL) was added in one portion. The internal temperature was allowed to -20°C and held between -15°C and -20°C for 2 hrs. The reaction mixture was poured to ice-cooled aqueous HCl (1 M, 20 mL), extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with water (20 mL), aqueous NaOH (10%, 2 x 20mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 20/1 to 5/1) to give **E6** (1 g, 80%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19-5.10 (m, 1H), 3.52-3.45 (m, 1H), 3.29 (s, 3H), 3.20-3.19 (m, 1H), 2.42-2.10 (m, 3H), 1.85-1.76 (m, 1H), 1.76-1.62 (m, 5H), 1.62-1.40 (m, 3H), 1.40-1.11 (m, 13H), 1.01-0.82 (m, 6H), 0.72 (s, 3H).

Step 7. To a solution of **E6** (1 g, 2.77 mmol) in THF (15 mL) was added dropwise a solution of BH_3-Me_2S (2.77 mL, 27.7 mmol, 10M in THF) at 0°C. The solution was stirred at 15°C for 3h. After cooling to 0°C, a solution of NaOH solution (16.6 mL, 2M) was added very slowly. After addition, H_2O_2 (2.76 mL, 27.7 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 $Na_2S_2O_3$ (20 mL) was added until the reaction solution became clear. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic solution was washed with saturated aqueous $Na_2S_2O_3$ (2 x 10 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum to give **E7** (0.9 g, crude) as a solid, which was used in next step without further purification.

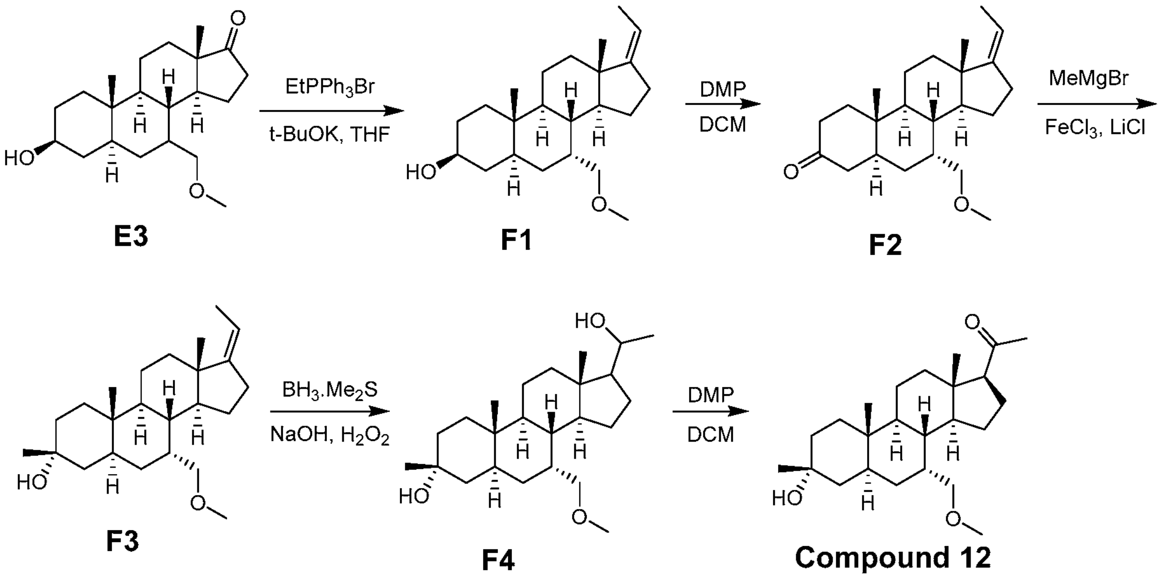
Step 8. To a suspension of **E7** (0.9 g, 1.37 mmol) in DCM (20 mL) was added silica gel (1 g) and PCC (1.02 g, 4.74 mmol) at 15°C. The mixture was stirred at 15°C for 2 hrs. The mixture was filtered and the filtrated cake was washed with DCM (2 x 20mL). The combined filtrate was concentrated in vacuum, purified by flash column (0~20% of EtOAc in PE) and re-crystallized from DCM/n-hexane (2 mL/20 mL) at 15°C to give **Compound 11** (130 mg, 14%) as solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45-3.38 (m, 1H), 3.29-3.20 (m, 4H), 2.55-2.45 (m, 1H), 2.19-2.09 (m, 4H), 2.05-1.85 (m, 2H), 1.75-1.55 (m, 2H), 1.55-1.35 (m, 9H), 1.35-1.15 (m, 10H), 0.94-0.82 (m, 1H), 0.72 (s, 3H), 0.63 (s, 3H).

LCMS Rt = 1.134 min in 2 min chromatography, 30-90AB_2MIN_E, purity 87%, MS ESI calcd. for $C_{24}H_{39}O_2$ $[M+H-H_2O]^+$ 359, found 359.

HPLC Rt = 4.54 min in 8 min chromatography, 30-90_AB_1.2ml_E.met, purity: 100%.

Example 6. Synthesis of Compound 12.



Step 1. To a suspension of PPh_3EtBr (26.5 g, 71.6 mmol) in THF (100mL) was added t-BuOK (8.03 g, 71.6 mmol) at 10°C. The color of the suspension turned dark red. After stirring at 40°C for 1 hour, a solution of **E3** (8 g, 23.9 mmol) in THF (20 mL) was added at 40°C and the reaction mixture was stirred at 40°C for 16 h. The mixture was added saturated NH_4Cl solution (20 mL) and EtOAc (2 x 30 mL). The organic layer was separated and the water phase was extracted with EtOAc (2 x 30 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered concentrated and purified by flash column (0~20% of EtOAc in PE) to give **F1** (2.1 g, 25%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15-5.05 (m, 1H), 3.68-3.55 (m, 1H), 3.40-3.35 (m, 1H), 3.31 (s, 3H), 2.43-2.32 (m, 1H), 2.22-2.10 (m, 2H), 2.01-1.89 (m, 1H), 1.89-1.50 (m, 8H), 1.50-1.22 (m, 9H), 1.10-0.82 (m, 11H).

The stereochemistry at C7 of **F1** was confirmed by NOE.

Step 2. To a solution of **F1** (2 g, 5.77 mmol) in DCM (50 mL) was added DMP (4.87 g, 11.5 mmol). After that, the reaction was stirred at 15°C for 30min. The reaction mixture was added aqueous saturated $NaHCO_3$ (50 mL) solution, aqueous saturated $Na_2S_2O_3$ (50 mL) solution, extracted with DCM (2 x 50 mL). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (2 x 20 mL) solution and brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give **F2** (1.95 g, 98%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19-5.10 (m, 1H), 3.50-3.35 (m, 2H), 3.30 (s, 3H), 2.46-2.15 (m, 7H), 2.15-1.98 (m, 3H), 1.78-1.50 (m, 9H), 1.50-1.21 (m, 4H), 1.05-1.12 (m, 4H), 0.89 (s, 3H).

Step 3. Under a nitrogen atmosphere, anhydrous THF (10 mL) was cooled to 10°C and anhydrous LiCl (958 mg, 22.6 mmol) was added in one portion. The mixture was stirred for 30 min to obtain a clear solution. To this solution was added anhydrous $FeCl_3$ (2.01 mg, 12.4 mmol) in one portion. The resulting mixture was stirred for additional 30 mins. The reaction mixture was cooled to -35°C and methyl magnesium bromide (15.0 mL, 45.2 mmol, 3 M in diethyl ether,) was added dropwise maintaining the internal temperature between -35°C and -30°C. The above mixture was stirred for 30 min at -30°C. A solution of **F2** (1.95 g, 5.65 mmol) in THF (10 mL) was added in one portion. The internal temperature was allowed to -20°C and held between -15°C and -20°C for 2 hrs. The reaction mixture was poured into ice-cooled aqueous HCl (1 M, 20 mL), extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with water (20 mL), aqueous NaOH (10%, 2 x 20mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column (0~30% of EtOAc in PE) to give **F3** (1.6 g, 79%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19-5.10 (m, 1H), 3.55-3.49 (m, 1H), 3.40-3.35 (m, 1H), 3.31 (s, 3H), 2.42-2.30 (m, 1H), 2.30-2.15 (m, 2H), 1.99-1.90 (m, 1H), 1.80-1.55 (m, 8H), 1.55-1.40 (m, 4H), 1.40-1.20 (m, 9H), 1.20-0.95 (m, 2H), 0.95-0.82 (m, 4H), 0.79 (s, 3H).

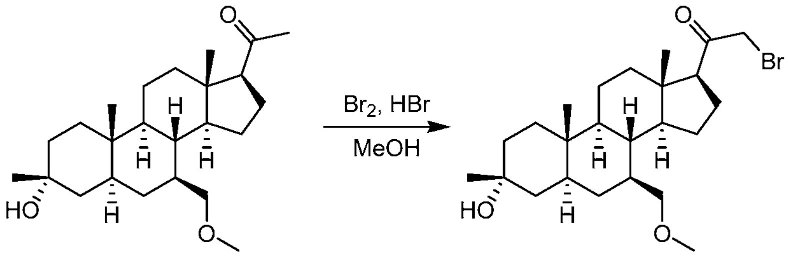
Step 3. To a solution of **F3** (1.6 g, 4.43 mmol) in THF (25 mL) was added dropwise a solution of BH_3-Me_2S (4.43 mL, 44.3 mmol, 10M in THF) at 0°C. The solution was stirred at 15°C for 3h. After cooling to 0°C, a solution of NaOH solution (26.5 mL, 53.1 mmol, 2M) was added very slowly. After addition, H_2O_2 (4.42 mL, 44.3 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 $Na_2S_2O_3$ (20 mL) was added until the reaction solution became clear. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic solution was washed with saturated aqueous $Na_2S_2O_3$ (2 x 10 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum to give **F4** (1.66 g, crude) as a solid, which was used in next step without further purification.

Step 4. To a solution of **F4** (1.66 g, 4.4 mmol) in DCM (50 mL) was added DMP (3.73 g, 8.80 mmol) at 15°C. The reaction was stirred at 15°C for 10 min. To the reaction mixture was added aqueous saturated $NaHCO_3$ (50 mL) solution, aqueous saturated $Na_2S_2O_3$ (50 mL) solution and extracted with DCM (2 x 20 mL). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (3 x 20 mL) solution and brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum and purified by silica gel chromatography (PE/EtOAc = 15/1 to 10/1) to give **Compound 12** (0.85 g, impure) as a solid. **Compound 12** (0.2 g, impure) was re-crystallized from MeCN (15 mL) at 15°C to give **Compound 12** (150 mg, 48%) as a solid.

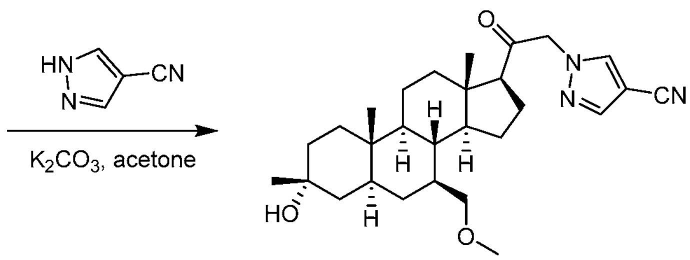
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58-3.50 (m, 1H), 3.45-3.35 (m, 1H), 3.32 (s, 3H), 2.55-2.48 (m, 1H), 2.21-2.05 (m, 4H), 2.01-1.85 (m, 2H), 1.85-1.60 (m, 5H), 1.60-1.45 (m, 4H), 1.45-1.20 (m, 12H), 1.10-1.01 (m, 1H), 0.77 (s, 3H),0.60 (s, 3H).

LCMS Rt = 1.126 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{24}H_{39}O_2$ $[M+H-H_2O]^+$ 359, found 359.

Example 7. Synthesis of Compound 13.



Compound 11 **G1**



Compound 13

Step 1. To a solution of **Compound 11** (300 mg, 0.796 mmol) in MeOH (10 ml) was added HBr (31.7 mg, 0.159 mmol, 40% in water) and Br_2 (131 mg, 0.835 mmol) at 25°C. The mixture was stirred at 25°C for 16 hrs and quenched by adding sat.aq $NaHCO_3$ (10 mL) and water (20 mL). The mixture was extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford **G1** (400 mg) as a solid, which used directly for the next step.

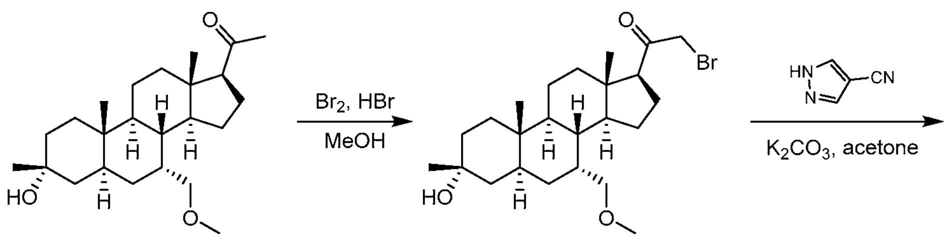
^{1}H NMR (400MHz, $CDCl_3$) δ 3.96-3.87 (m, 2H), 3.46-3.34 (m, 1H), 3.34-3.20 (m, 5H), 2.77 (t, J = 8 Hz, 1H), 2.23-2.06 (m, 1H), 1.98-1.83 (m, 2H), 1.80-1.61 (m, 3H), 1.49-1.40 (m, 5H), 1.38-1.19 (m, 12H), 0.91-0.82 (m, 1H), 0.74-0.64 (m, 6H).

Step 2. To a mixture of **G1** (60 mg, 0.131 mmol) and K_2CO_3 (36.2 mg, 0.2.62 mmol) in acetone (5 mL) was added 1H-pyrazole-4-carbonitrile (18.2 mg, 0.196 mmol) at 25°C. The reaction mixture was stirred at 25°C for 16 h and treated with H_2O (50 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined organic solution was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give the crude product, which was purified by flash column (0~30% of EtOAc in PE) twice to give **Compound 13** (15 mg, 25%) as a solid.

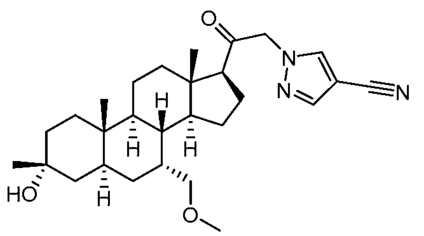
^{1}**H NMR** (400MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.81 (s, 1H), 5.05-4.87 (m, 2H), 2.54 (m, 1H), 3.40-3.38 (m, 1H), 3.37-3.27 (m, 4H), 2.55 (d, J = 8 Hz, 1H), 2.23-2.15 (m, 1H), 2.041.96 (m, 1H), 1.76-1.72 (m, 2H), 1.52-1.49 (m, 8H), 1.32-1.21 (m, 10H), 1.11 (s, 1H), 0.88-0.85 (m, 1H), 0.73 (s, 3H), 0.69 (s, 3H).

LCMS Rt = 1.054 in in 2.0 min chromatography, 30-90AB_2MIN_E.M.lcm, purity 100%, MS ESI calcd. for $C_{28}H_{42}N_3O_3$ $[M+H]^+$ 468, found 468.

Example 8. Syntheses of Compound 14.



Compound 12 H1



Compound 14

Step 1. To a solution of **Compound 12** (700 mg, 1.85 mmol) in MeOH (10 ml) was added HBr (74 mg, 0.370 mmol, 40% in water) and Br_2 (304 mg, 1.94 mmol) at 25°C. After stirring at 25°C for 16 hrs, the mixture was quenched with sat.aq $NaHCO_3$ (10 mL) and water (20 mL), extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum to afford **H1** (900 mg) as a solid, which was used directly for the next step.

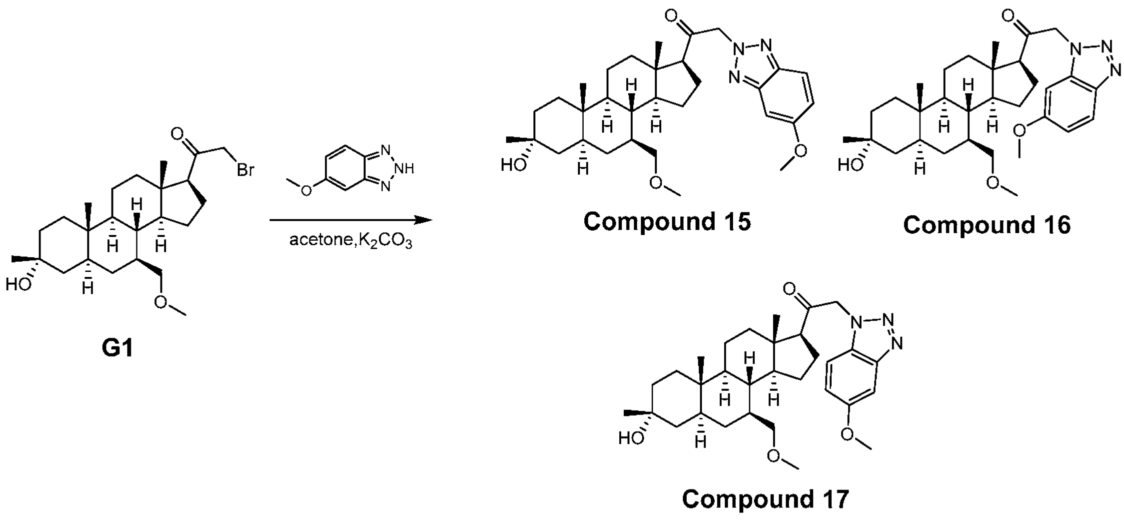
^{1}**H NMR** (400MHz, $CDCl_3$) δ 3.92-3.88 (m, 2H), 3.58-3.46 (m, 1H), 3.41 (s, 3H), 3.37-3.27 (m, 3H), 2.84-2.80 (m, 1H), 1.91-1.89 (m, 2H), 1.78-1.65 (m, 3H), 1.54-1.40 (m, 5H), 1.40-1.17 (m, 12H), 0.91 (s, 1H), 0.79-0.75 (m, 3H), 0.62 (s, 3H).

Step 2. To a mixture of **H1** (80 mg, 0.175 mmol) and K_2CO_3 (48.3 mg, 0.350 mmol) in acetone (5 mL) was added 1H-pyrazole-4-carbonitrile (24.3 mg, 0.262 mmol) at 25°C. The reaction mixture was stirred at the 25°C for 16 h and treated with H_2O (50 mL), extracted with EtOAc (3 x 50 mL). The combined organic solution was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum to give the crude product, which was purified by flash column (0~30% of EtOAc in PE) to give **Compound 14** (23 mg, 28%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.83 (d, J = 18.8 Hz, 2H), 5.04-4.86 (m, 2H), 3.55-3.50 (m, 1H), 3.42-3.41 (m, 1H), 3.32 (s, 3H), 2.59 (t, J = 9.2 Hz, 1H), 2.27-2.14 (m, 1H), 2.03-1.98 (m, 1H), 1.95-1.83 (m, 2H), 1.80-1.64 (m, 4H), 1.53-1.47 (m, 3H), 1.45-1.23 (m, 9H), 1.20 (s, 3H), 1.14-1.00 (m, 2H), 0.78 (s, 3H), 0.65 (s, 3H).

LCMS Rt = 2.901 in in 4.0 min chromatography, 10-80AB.lcm, purity 100%, MS ESI calcd. for $C_{28}H_{40}N_3O_2$ $[M-H_2O+H]^+$ 450, found 450.

Example 9. Syntheses of Compounds 15, 16, and 17.



To a solution of **G1** (200 mg, 0.439 mmol) in acetone (5 mL) was added 5-methoxy-2H-benzo[d][1,2,3]triazole (98.1 mg, 0.658 mmol), followed by adding K_2CO_3 (121 mg, 0.878 mmol) at 25 °C. The resulting reaction mixture was stirred at 25 °C for 16 hrs, treated with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic solution was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum to give the crude product, which was purified by flash column (0~30% of EtOAc in PE) to give impure

Compound 15 (50 mg). The impure **Compound 15** was purified by prep. HPLC separation (column: YMC-Actus Triart C18 150*30mm*5um), gradient: 65-95% B (A = water(0.05%HCl)-ACN, B = ACN), flow rate: 25 mL/min) to give **Compound 15** (18 mg, 8%) as a solid; and a mixture of **Compound 16** and **Compound 17** (100 mg, crude). The mixture of **Compound 16** and **Compound 17** (100 mg, crude) was purified by SFC separation (column: OJ(250mm*30mm,5um)),gradient: 40-40% B (A = 0.1%NH_3H_2O, B = ETOH), flow rate: 60 mL/min) to give **Compound 16** (33 mg, 14%) as solid and **Compound 17** (16 mg, 7%) as solid.

Compound 15:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.08-7.06 (m, 2H), 5.50-5.39 (m, 2H), 3.88 (s, 3H), 3.41-3.35 (m, 1H), 3.27 (s, 4H), 2.58 (t, *J* = 8.0 Hz, 1H), 2.27-2.07 (m, 2H), 2.01-1.88 (m, 1H), 1.81-1.69 (m, 2H), 1.53-1.47 (m, 5H), 1.46-1.12 (m, 14H), 0.94 - 0.82 (m, 1H), 0.76 (s, 3H), 0.74 (s, 3H).

LCMS Rt = 3.240 min in 4.0 min chromatography, 10-80AB.lcm, purity 100%, MS ESI calcd. for $C_{31}H_{46}N_3O4$ $[M+H]^+$ 524, found 524.

Compound 16:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.01 (dd, *J* = 4.0, 8.0 Hz, 1H), 6.60 (d, *J* = 4.0 Hz, 1H), 5.40-5.29 (m, 2H), 3.86 (s, 3H), 3.41-3.35 (m, 1H), 3.30-3.25 (m, 4H), 2.64 (t, *J* = 8.0 Hz, 1H), 2.28-2.09 (m, 2H), 2.00-1.90 (m, 1H), 1.76-1.75 (m, 2H), 1.54-1.43 (m, 7H), 1.42-1.20 (m, 11H), 1.13 (s, 1H), 0.92-0.87 (m, 1H), 0.75 (s, 3H), 0.74 (s, 3H).

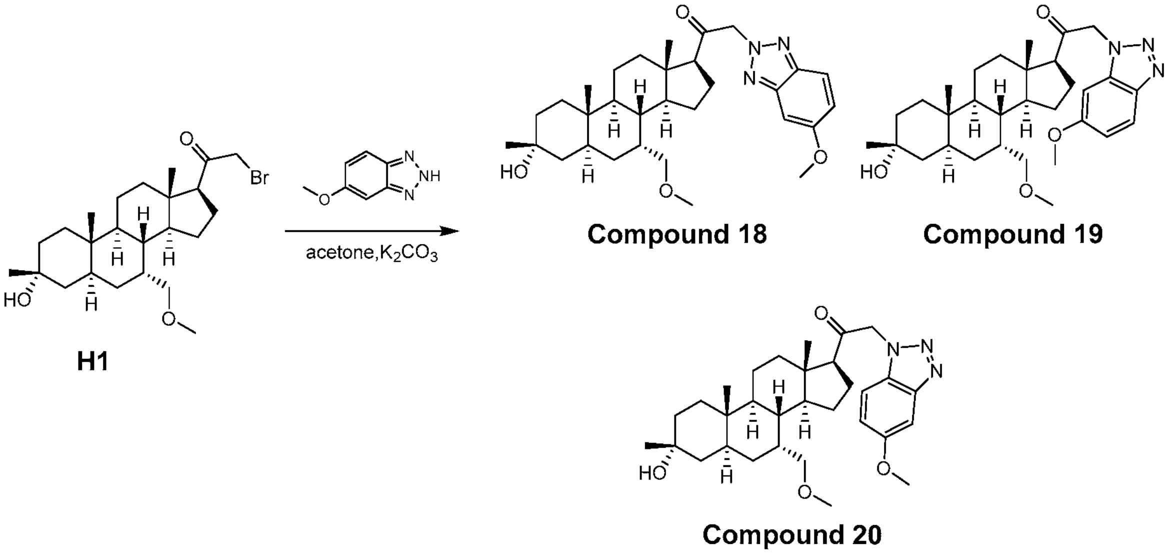
LCMS Rt = 3.025 min in 4.0 min chromatography, 10-80AB.lcm, purity 100%, MS ESI calcd. for $C_{31}H_{46}N_3O4$ $[M+H]^+$ 524, found 524.

Compound 17:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.39 (d, *J* = 4.0 Hz, 1H), 7.24-7.13 (m, 2H), 5.43-5.32 (m, 2H), 3.89 (s, 3H), 3.39-3.37 (m, 1H), 3.27 (s, 4H), 2.63 (t, *J* = 12.0 Hz, 1H), 2.25-2.09 (m, 2H), 1.97-1.95 (m, 1H), 1.83-1.71 (m, 2H), 1.54-1.44 (m, 7H), 1.43-1.20 (m, 11H), 1.12 (s, 1H), 0.91-0.87 (m, 1H), 0.74 (s, 6H)

LCMS Rt = 3.033 min in 4.0 min chromatography, 10-80AB.lcm, purity 100%, MS ESI calcd. for $C_{31}H_{46}N_3O_4$ $[M+H]^+$ 524, found 524.

Example 10. Syntheses of Compounds 18, 19, and 20.



To a solution of **H1** (200 mg, 0.439 mmol) in acetone (5 mL) was added 5-methoxy-2H-benzo[d][1,2,3]triazole (98.1 mg, 0.658 mmol), followed by adding K_2CO_3 (121 mg, 0.878 mmol) at 25 °C. The resulting reaction mixture was stirred at 25 °C for 16 hours, treated with water (20 mL), extracted with EtOAc (3 x 20 mL). The combined organic solution was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum to give the crude product, which was purified by flash column (0~30% of EtOAc in PE) to give **Compound 18** (10 mg, 4%) as a solid and a mixture of **Compound 19** and **Compound 20** (100 mg, crude). The mixture of **Compound 19** and **Compound 20** was purified by SFC separation (column:OD(250mm*30mm,5um)),gradient: 40-40% B (A = 0.1%NH_3H_2O, B = ETOH), flow rate: 50 mL/min) to give **Compound 19** (32 mg, 13%) as a solid and **Compound 20** (27 mg, 12%) as a solid.

Compound 18:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.74-7.71 (m, 1H), 7.08-7.06 (m, 2H), 5.48-5.38 (m, 2H), 3.88 (s, 3H), 3.55-3.50 (m, 1H), 3.42-3.38 (m, 1H), 3.32 (s, 3H), 2.64-2.60 (m, 1H), 2.29-2.18 (m, 1H), 2.14-2.06 (m, 1H), 1.92 (m, 1H), 1.68 (m, 5H), 1.53-1.41 (m, 4H), 1.41-1.19 (m, 12H), 1.09-1.02 (m, 1H), 0.79 (s, 3H), 0.73 (s, 3H)

LCMS Rt = 3.215 min in 4.0 min chromatography, 10-80AB.lcm, purity 100%, MS ESI calcd. for $C_{31}H_{46}N_3O4$ $[M+H]^+$ 524, found 524.

Compound 19:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.01 (m, 1H), 6.61-6.59 (m, 1H), 5.37-5.28 (m, 2H), 3.86 (s, 3H), 3.53 (t, *J* = 8.0 Hz, 1H), 3.43-3.37 (m, 1H), 3.32 (s, 3H), 2.68 (t, *J* = 8.0 Hz, 1H), 2.27-2.17 (m, 1H), 2.13-2.070 (m, 1H), 1.97-1.82 (m, 2H), 1.77-1.68 (m, 3H), 1.55-1.27 (m, 12H), 1.21 (s, 3H), 1.10-1.05 (m, 1H), 0.94 (s, 2H), 0.79 (s, 3H), 0.72 (s, 3H).

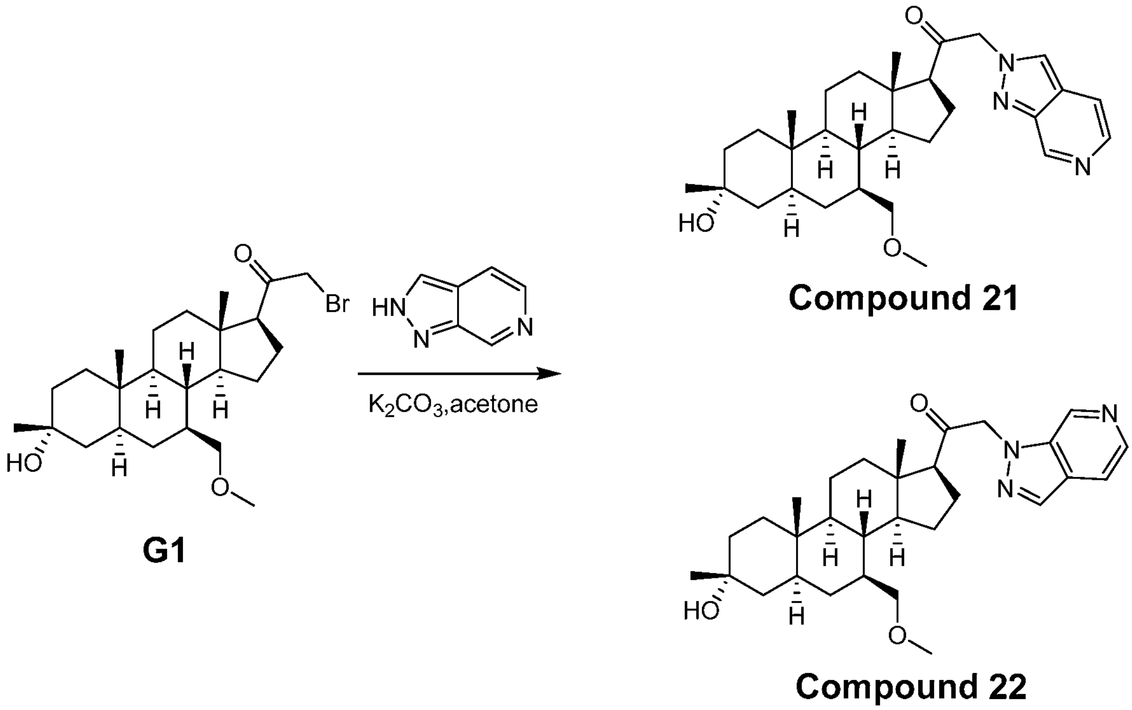
LCMS Rt = 2.344 min in 3.0 min chromatography, 10-80AB.lcm, purity 96.15%, MS ESI calcd. for $C_{31}H_{46}N_3O4$ $[M+H]^+$ 524, found 524.

Compound 20:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.39 (d, *J* = 4 .0 Hz, 1H), 7.23-7.11 (m, 2H), 5.36 (s, 2H), 3.89 (s, 3H), 3.53 (t, *J* = 8.0 Hz, 1H), 3.42-3.37 (m, 1H), 3.32 (s, 3H), 2.67 (t, *J* = 8.0 Hz, 1H), 2.26-2.17 (m, 1H), 2.12-2.06 (m, 1H), 1.97-1.81 (m, 2H), 1.77-1.67 (m, 3H), 1.55-1.46 (m, 4H), 1.46-1.22 (m, 9H), 1.21 (s, 3H), 1.12 (s, 1H), 1.09-1.02 (m, 1H), 0.79 (s, 3H), 0.71 (s, 3H).

LCMS Rt = 1.095 min in 2.0 min chromatography, 30-90AB_2MIN_E_M, purity 100%, MS ESI calcd. for $C_{31}H_{46}N_3O_4$ $[M+H]^+$ 524, found 524.

Example 11. Syntheses of Compounds 21 and 22.

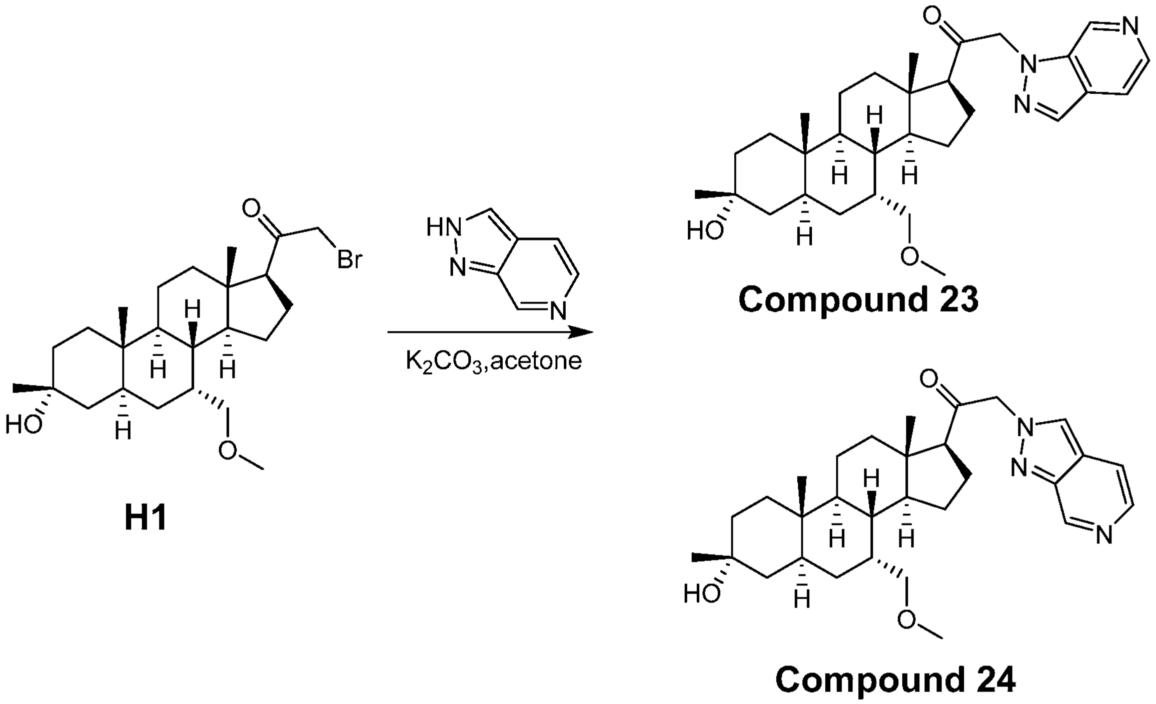


To a solution of the **G1** (150 mg, 0.329 mmol) and 1H-pyrazolo[3,4-c]pyridine (41 mg, 0.345 mmol) in acetone (3 mL) was added K_2CO_3 (26.1 g, 0.658 mmol) at 25°C. After stirring at 25°C for 10 hrs, the mixture was poured into water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (50 mL), dried over with Na_2SO_4, filtered and concentrated to afford crude product, which was purified by *prep.* HPLC (column: YMC-Actus Triart C18 150*30mm*5um)), gradient: 30-60% B (A = 0.1%HCl, B = ACN), flow rate: 25 mL/min) to afford **Compound 22** (3 mg, impure) as a solid and **Compound 21** (20 mg, impure). **Compound 21** (20 mg, impure) was purified by flash column (0~30% of EtOAc in PE) to give **Compound 21** (9 mg, 6%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.17 (d, *J* = 4.8 Hz, 1H), 7.98 (s, 1H), 7.53 (d, *J* = 6.8 Hz, 1H), 5.36-5.20 (m, 2H), 3.38-3.36 (m, 1H), 3.32-3.31 (m, 1H), 3.27 (s, 3H), 2.70-2.61 (m, 1H), 2.30-2.19 (m, 1H), 2.17-2.13 (m, 1H), 2.04-1.95 (m, 1H), 1.85-1.74 (m, 2H), 1.56-1.49 (m, 6H), 1.45-1.22 (m, 12H), 1.17-1.14 (m, 1H), 0.93-0.88 (m, 1H), 0.73 (s, 6H).

LCMS Rt = 1.771 min in 3.0 min chromatography, 10-80AB, purity 100%, MS ESI calcd. For $C_{30}H_{44}N_3O_3$ $[M+H]^+$ 494, found 494.

Example 12. Syntheses of Compounds 23 and 24.



To a mixture of **H1** (150 mg, 0.329 mmol) and K_2CO_3 (90.9 mg, 0.658 mmol) in acetone (3 mL) was added 1H-pyrazolo[3,4-c]pyridine (41 mg, 0.345 mmol) at 25°C. After stirring at 25°C for 12 h, the mixture was poured into water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (50 mL), dried over with Na_2SO_4, filtered and concentrated to afford crude product, which was purified by preparative HPLC (column: YMC-Actus Triart C18 150 * 30 mm * 5 um)), gradient: 35-65% B (A = 0.1% HCl, B = ACN), flow rate: 25 mL/min) to afford **Compound 23** (50 mg, 31%) as a solid and **Compound 24** (20 mg, impure). **Compound 24** (20 mg, impure) was purified by SFC separation (column: AD (250 mm * 30 mm, 10 um)), gradient: 45-45% B (A = 0.1% NH_3H_2O, B = EtOH), flow rate: 80 mL/min) to afford **Compound 24** (8 mg, 5%) as a solid.

Compound 23:

^{1}H NMR (400MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.34 (d, J = 5.6 Hz, 1H), 8.09 (s, 1H), 7.66-7.63 (m, 1H), 5.23-5.30 (m, 2H), 3.56-3.48 (m, 1H), 3.42-3.37 (m, 1H), 3.33 (s, 3H), 2.69-2.66 (m, 1H), 2.27-2.17 (m, 1H), 2.14-2.07 (m, 1H), 1.97-1.84 (m, 2H), 1.80-1.65 (m, 4H), 1.55-1.28 (m, 13H), 1.21 (s, 3H), 1.10-1.04 (m, 1H), 0.80 (s, 3H), 0.71 (s, 3H).

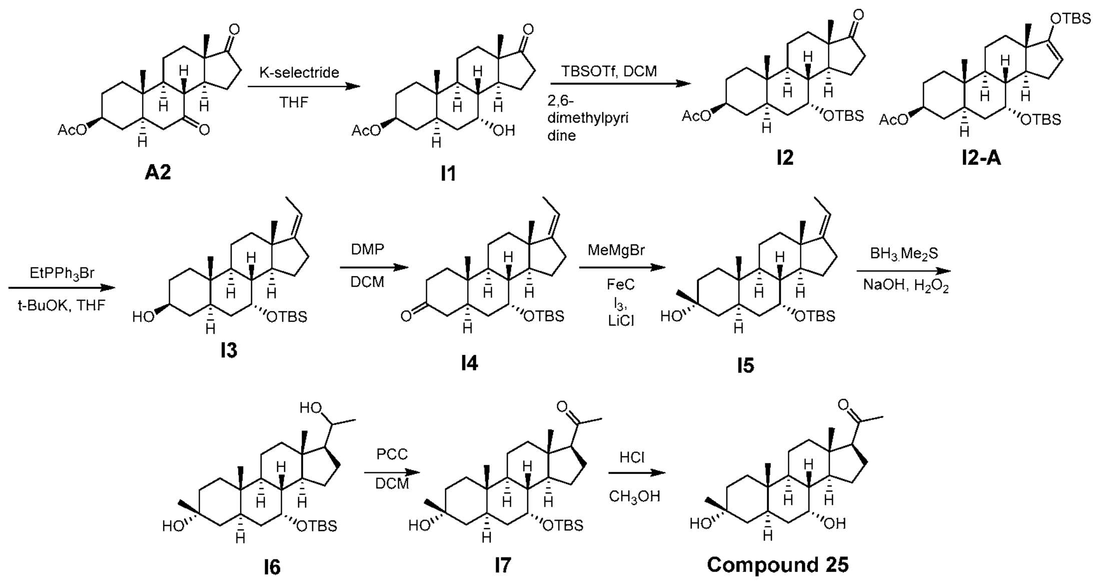
LCMS Rt = 2.290 min in 4.0 min chromatography, 10-80AB, purity 99.1%, MS ESI calcd. For $C_{30}H_{44}N_3O_3$ $[M+H]^+$ 494, found 494.

Compound 24:

^{1}H NMR (400MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.17 (d, J = 6.4 Hz, 1H), 7.98 (s, 1H), 7.56-7.50 (m, 1H), 5.35-5.19 (m, 2H), 3.56-3.50 (m, 1H), 3.44-3.39 (m, 1H), 3.33 (s, 3H), 2.66 (t, J = 8.8 Hz, 1H), 2.25-2.22 (m, 1H), 2.10-2.07 (m, 1H), 1.97-1.67 (m, 6H), 1.52-1.38 (m, 7H), 1.36-1.25 (m, 6H), 1.21 (s, 3H), 1.15-1.03 (m, 1H), 0.79 (s, 3H), 0.70 (s, 3H).

LCMS Rt = 2.155 min in 4.0 min chromatography, 10-80AB, purity 100%, MS ESI calcd. For $C_{30}H_{44}N_3O_3$ $[M+H]^+$ 494, found 494.

Example 13. Synthesis of Compound 25.



Step 1. To a solution of **A2** (20 g, 57.7 mmol) in THF (100 mL) was added dropwise K-selectride (57.7 mL, 57.7 mmol, 1M in THF) at -70°C. The reaction mixture was stirred 2 h at -70°C. The mixture was quenched with sat.NH_4Cl (20 mL) at -20°C and extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine (2 x 30 mL), dried over

Na_2SO_4, filtered and concentrated and purified by flash column (0~30% of EtOAc in PE) to give **I1** (12.5 g, 62%) as a solid.

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 4.75-4.65 (m, 1H), 4.02-3.90 (m, 1H), 2.51-2.40 (m, 1H), 2.22-2.01 (m, 1H), 1.98-1.40 (m, 15H), 1.40-1.08 (m, 7H), 1.08-0.78 (m, 6H).

Step 2. To a solution of **I1** (12 g, 34.4 mmol) in DCM (100 mL) was added TBSOTf (11.8 mL, 51.6 mmol) and 2,6-dimethylpyridine (7.37 g, 68.8 mmol) in one portion at 15°C. The mixture was refluxed at 15°C for 7 hrs. Then sat.NH_4Cl (50 mL) was added to the reaction mixture. The aqueous phase was extracted with DCM (3 x 50 mL). The combined organic phase was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give residue, which was purified by flash column (0~5% of EtOAc in PE) to afford **I2** (8.35 g, crude) combined with another batch of **I2-A** (7.5 g, crude, **I2-A/I2** = 1/1) as an oil, which was used directly for the next step.

Step 3. To a suspension of PPh_3EtBr (37.8 g, 102 mmol) in THF (100mL) was added *t*-BuOK (11.4 g, 102 mmol) at 10°C. The color of the suspension turned dark red. After stirring at 40°C for 1 h, a solution of **I2** (15.85 g, crude, containing **I2-A**) in THF (20 mL) was added at 40°C and the reaction mixture was stirred at 40°C for 16 h. To the mixture was added saturated NH_4Cl solution (20 mL) and EtOAc (60 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column (0~20% of EtOAc in PE) to give **I3** (10 g, crude) as colorless oil.

Step 4. To a solution of **I3** (12 g, 27.7 mmol) in DCM (100 mL) was added DMP (23.4 g, 55.4 mmol) followed by H_2O (2.48 mg, 0.138 mmol). The reaction mixture was stirred at 15°C for 30 min. The reaction mixture was added aqueous saturated $NaHCO_3$ (50 mL) solution, aqueous saturated $Na_2S_2O_3$ (50 mL) solution, extracted with DCM (2 x 50 mL). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (2 x 20 mL) solution and brine (20 mL), dried over Na_2SO_4, filtered, concentrated in vacuum and purified by flash column (0~10% of EtOAc in PE) to give **I4** (6 g, 50%) as a solid.

[1]**H NMR** (400 MHz, $CDCl_3$) δ 5.20-5.00 (m, 1H), 3.88 (s, 1H), 2.48-1.97 (m, 10H), 1.80-1.35 (m, 8H), 1.35-1.11 (m, 2H), 1.11-0.80 (m, 18H), 0.02 (s, 6H).

Step 5. Under nitrogen atmosphere, anhydrous THF (20 mL) was cooled to 15°C and anhydrous LiCl (2.35 g, 55.6 mmol) was added in one portion. The mixture was stirred for 30 min to obtain a clear solution. To the solution was added anhydrous $FeCl_3$ (4.94 g, 30.5 mmol) in one portion. The resulting mixture was stirred for additional 30 mins. The reaction mixture was cooled to -35°C and methyl magnesium bromide (3 M in diethyl ether, 37.0 mL, 111 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. **I4** (6 g, 13.9 mmol) in THF (20 mL) was added in one portion. The internal temperature was allowed to 15°C and the reaction mixture was stirred for 2 hrs. The reaction mixture was poured into ice-cooled aqueous HCl (1 M, 20 mL), extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with water (20 mL), aqueous NaOH (10%, 2 x 20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column (0~5% of EtOAc in PE) to give **I5** (3.5 g, 56%) as a solid.

[1]**H NMR** (400 MHz, $CDCl_3$) δ 5.15-5.00 (m, 1H), 3.87 (s, 1H), 2.41-2.00 (m, 4H), 1.80-1.49 (m, 7H), 1.49-1.25 (m, 7H), 1.25-1.08 (m, 6H), 1.08-0.81 (m, 14H), 0.81-0.69 (m, 4H), 0.05-0.01 (m, 6H).

Step 6. To a solution of **I5** (3.5 g, 7.83 mmol) in THF (20 mL) was added dropwise $BH_3.Me_2S$ (7.83 mL, 10M, 78.3 mmol) at 0°C. The resulting solution was stirred at 15°C for 3 h. After cooling to 0°C, a solution of aqueous NaOH (46.9 mL, 93.9 mmol, 2 M) was added very slowly. After the addition, H_2O_2 (7.84 mL, 78.3 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 1 h. Then saturated aqueous $Na_2S_2O_3$ (20 mL) was added until the reaction solution became clear. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with saturated aqueous $Na_2S_2O_3$ (2 x 10 mL), brine (20 mL), dried over Na_2SO_4 , filtered and concentrated in vacuum to give **I6** (3.4 g, crude) as a solid, which was used in next step without further purification.

Step 7. To a solution of **I6** (3.4 g, 7.31 mmol) in DCM (20 mL) was added DMP (6.19 g, 14.6 mmol) followed by H_2O (2.62 mg, 0.146 mmol). The reaction mixture was stirred at 15°C for 30 min. To the reaction mixture was added aqueous saturated $NaHCO_3$ (50 mL) solution and aqueous saturated $Na_2S_2O_3$ (10 mL) solution. The mixture was extracted with DCM (2 x 20 mL). The combined organic layer was washed with saturated $NaHCO_3$ (2 x 20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, concentrated in vacuum and purified by flash column (0~10% of EtOAc in PE) to give **I7** (2.2 g, 65%) as a solid.

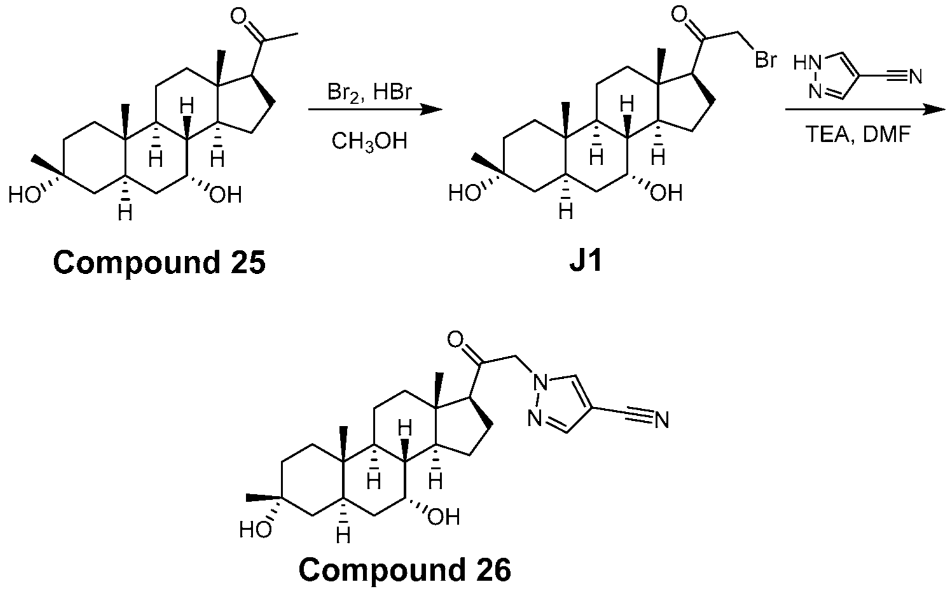
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83-3.80 (m, 1H), 2.59-2.50 (m, 1H), 2.21-1.90 (m, 6H), 1.78-1.49 (m, 9H), 1.49-1.09 (m, 12H), 0.90 (s, 9H), 0.73 (s, 3H), 0.58 (s, 3H), 0.06-0.01 (m, 6H).

Step 8. To a solution of **I7** (1.80 g, 3.88 mmol) in CH_3OH (50 mL) was added concentrated HCl (0.966 mL, 12 M) 15°C under N_2. The mixture was stirred at 15°C for 16 hrs. To the mixture was added saturated $NaHCO_3$ (5 mL) and stirred for 20 min. The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give a solid, which was purified by flash column (0~ 70% of EtOAc in PE) to give **Compound 25** (1.20 g, impure) as a solid. The impure **Compound 25** (600 mg, impure) was triturated with hexane (30 mL) at 68°C to give **Compound 25** (510 mg, 64%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (brs, 1H), 2.58-2.52 (m, 1H), 2.21-2.06 (m, 4H), 2.03-1.92 (m, 2H), 1.85-1.58 (m, 3H), 1.58-1.45 (m, 4H), 1.45-1.14 (m, 15H), 0.75 (s, 3H), 0.61 (s, 3H).

LCMS Rt = 0.893 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. for $C_{22}H_{33}O$ $[M+H-2H_2O]^+$ 313, found 313.

Example 14. Synthesis of Compound 26.



Step 1. To a solution of **Compound 25** (497 mg, 1.42 mmol) in MeOH (10 ml) was added HBr (57.2 mg, 0.284 mmol, 40% in water) and Br_2 (230 mg, 1.75 mmol) at 15°C. After stirring at 15°C for 4 hrs, the mixture was quenched by $NaHCO_3$ (10 mL), treated with water (20 mL), extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum to give **J1** (600 mg, crude) as a solid.

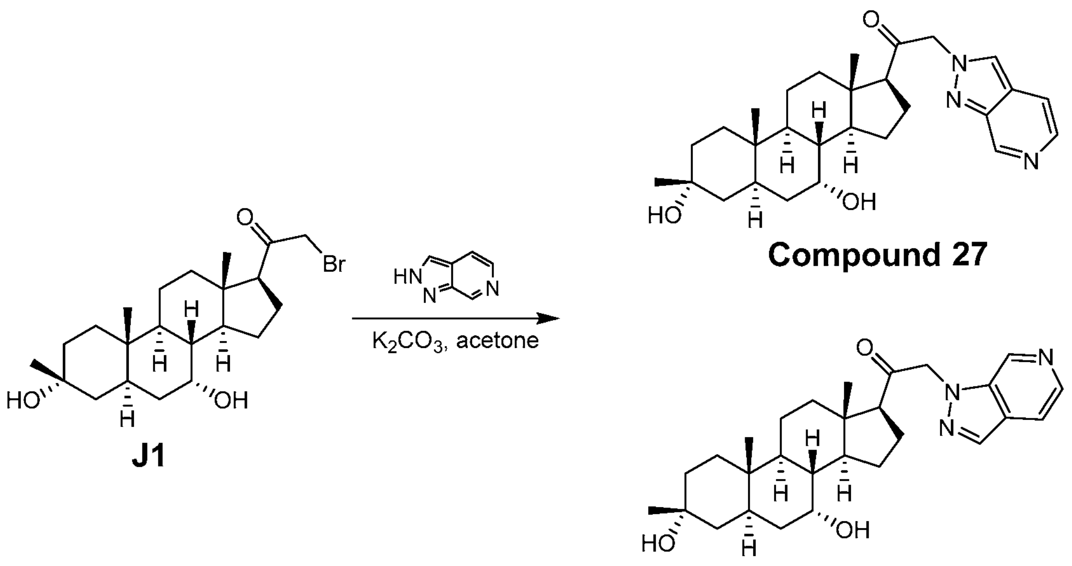
^{1}**H NMR** (400 MHz, $CDCl_3$) δ 3.95-3.86 (m, 2H), 2.86-2.80 (m, 1H), 2.40-2.05 (m, 3H), 2.05-1.57 (m, 6H), 1.55-1.13 (m, 16H), 1.05-0.95 (m, 1H), 0.75 (s, 3H), 0.65-0.55 (m, 3H).

Step 2. To a suspension of TEA (35.2 mg, 0.348 mmol) and 1H-pyrazole-4-carbon (12.9 mg, 0.139 mmol) in DMF (5 mL) was added **J1** (50 mg, 0.116 mmol) at 25°C under N_2. The mixture was stirred at 25°C for 16 h. The mixture was concentrated to give a light yellow soild. The solid was purified by pre-HPLC (Column:YMC-Actus Triart C18 100*30mm*5um; Condition: water(0.05%HCl)-ACN; Gradient 53%-83%B; Gradient Time(min):9.5) to afford **Compound 26** (22 mg, 43%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.81 (s, 1H), 5.05-4.87 (m, 2H), 3.88-3.82 (m, 1H), 2.70-2.58 (m, 1H), 2.28-2.15 (m, 1H), 2.05-1.56 (m, 7H), 1.48-1.15 (m, 17H), 0.76 (s, 3H), 0.66 (s, 3H).

LCMS Rt = 0.828 min in 1.5 min chromatography, 5-95 AB, purity 100 %, MS ESI calcd. for $C_{26}H_{34}N_3O$ $[M+H-2H_2O]^+$ 404, found 404.

Example 15. Syntheses of Compounds 27 and 28.



To a suspension of 2H-pyrazolo[3,4-c]py (125 mg, 1.05 mmol) and K_2CO_3 (193 mg, 1.40 mmol) in acetone (10 mL) was added **J1** (300 mg, 0.701 mmol) at 15°C under N_2. The mixture was stirred at 15°C for 16 hrs. The mixture was filtered and concentrated to give a solid, which was purified by pre-HPLC (Column:Xtimate C18 150*25mm*5um; Condition: water(0.05%HCl)-ACN; Gradient 16%-41%B; Gradient Time(min):9.5) to afford **Compound 27** (8.00 mg, 2%) as a solid and **Compound 28** (6.00 mg, 2%) as a solid.

Compound 27:

^{1}H NMR (400 MHz, CDC13) δ 9.25 (s, 1H), 8.19-8.14 (m, 1H), 7.98 (s, 1H), 7.55-7.50 (m, 1H), 5.36-5.20 (m, 2H), 3.87-3.85 (m, 1H), 2.75-2.70 (m, 1H), 2.33-1.72 (m, 5H), 1.50-1.12 (m, 19H), 0.90-0.77 (m, 4H), 0.71 (s, 3H).

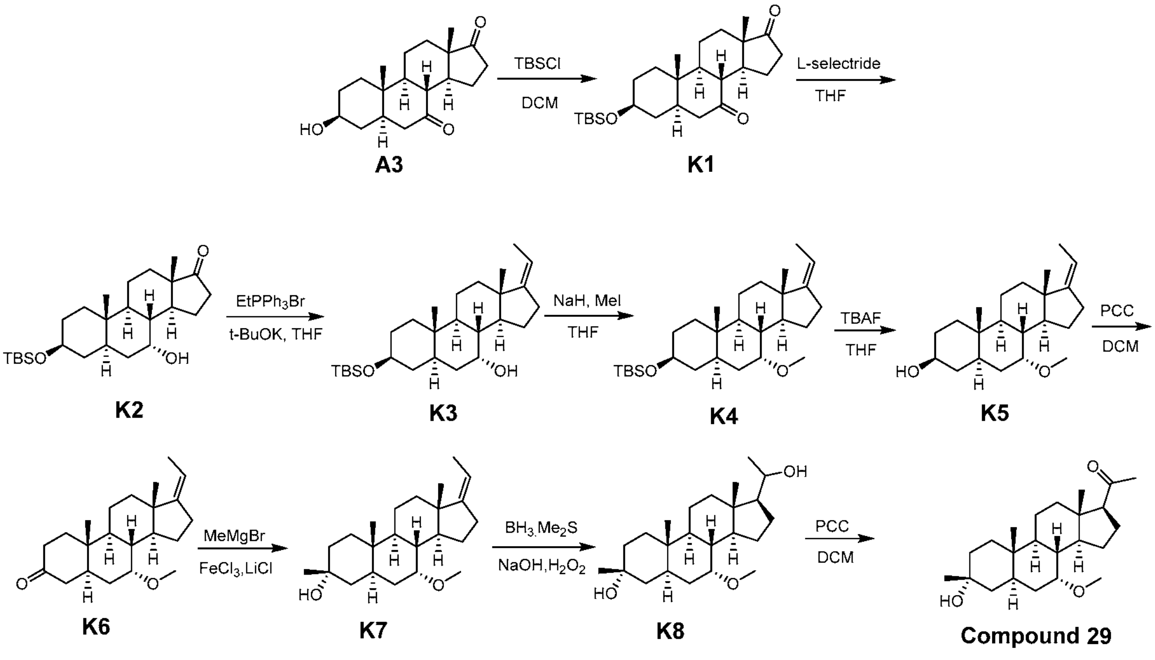
LCMS Rt = 0.725 min in 1.5 min chromatography, 5-95 AB, purity 100 %, MS ESI calcd. for $C_{28}H_{40}N_3O_3$ $[M+H]^+$ 466, found 466.

Compound 28:

^{1}**H NMR** (400 MHz, CDC13) δ 8.80 (s, 1H), 8.36-8.32 (m, 1H), 8.09 (s, 1H), 7.65-7.60 (m, 1H), 5.32-5.20 (m, 2H), 3.87-3.85 (m, 1H), 2.75-2.68 (m, 1H), 2.33-1.68 (m, 7H), 1.50-1.18 (m, 18H), 0.77 (s, 3H), 0.72 (s, 3H).

LCMS Rt = 0.748 min in 1.5 min chromatography, 5-95 AB, purity 100 %, MS ESI calcd. for $C_{28}H_{40}N_3O_3$ $[M+H]^+$ 466, found 466.

Example 16. Synthesis of Compound 29.



Step 1. To a solution of **A3** (82 g, 269 mmol) in DCM (500 mL) was added imidazole (27.4 g, 403 mmol) and TBSCl (60.7 g, 403 mmol) at 25°C. The reaction mixturewas stirred at 25°C for 5 hours. The reaction mixture was concentrated under reduced pressure. The residue was triturated from MeOH (500 mL) to give **K1** (102 g, 91%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62-3.50 (m, 1H), 2.65-2.29 (m, 4H), 2.20-2.01 (m, 2H), 1.85-1.63 (m, 6H), 1.56-1.38 (m, 6H), 1.26-0.93 (m, 5H), 0.92-0.80 (m, 12H), 0.04 (s, 6H).

Step 2. To a solution of **K1** (25 g, 59.7 mmol) in THF (50 mL) was added L-selectride (65.6 mL, 1 M in THF, 65.6 mmol) at -70°C under N_2, The reaction mixture was stirred at -70°C for 5 hours. The reaction mixture was quenched by water (50 mL). The mixture was extracted with EtOAc (3 x 150 mL). The combined organic phase was washed with saturated brine (2 x 150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc = 30/1 to 3/1) to afford **K2** (16 g, crude) as a solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 1H), 3.64-3.52 (m, 1H), 2.52-2.38 (m, 1H), 2.18-1.97 (m, 2H), 1.86-1.43 (m, 11H), 1.42-1.13 (m, 6H), 1.08-0.96 (m, 1H), 0.93-0.79 (m, 15H), 0.044 (s, 6H).

Step 5. To a solution of $EtPPh_3Br$ (39.3 g, 106 mmol) in THF (100 mL) was added t-BuOK (11.8 g, 106 mmol) at 25°C under N_2. The reaction mixture was stirred at 25°C for 0.5 hour. **K2** (15 g, 35.6 mmol) was added to the reaction mixture under N_2. The reaction mixture was stirred at 50°C for 5 hours. The reaction mixture was quenched by water (50 mL). The mixture was extracted with EtOAc (3 x 150 mL). The combined organic phase was washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (PE/EtOAc = 30/1 to 10/1) to afford **K3** (5.5 g, 36%) and **K3** (6 g, crude) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19-5.05 (m, 1H), 3.88 (s, 1H), 3.63-3.52 (m, 1H), 2.45-2.17 (m, 3H), 1.79-1.51 (m, 10H), 1.51-1.23 (m, 10H), 1.10-0.99 (m, 1H), 0.91-0.83 (m, 12H), 0.83-0.78 (m, 3H), 0.07-0.02 (m, 6H).

Step 6. To a solution of **K3** (5 g, 11.5 mmol) in THF (50 mL) was added NaH (2.28 g, 60%, 57.4 mmol) at 0°C. The reaction mixture was stirred at 0°C for 0.5 hour under N_2. MeI (44 g , 309 mmol) was added to the reaction mixture at 0°C. The reaction mixture was stirred at 40°C for 20 hours. The reaction mixture was quenched with ice-water (30 mL) and stirred for 20 mins. The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated.

The residue was purified by silica gel chromatography (PE/EtOAc = 50/1 to 10/1) to afford **K4** (1.8 g, 35%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15-5.07 (m, 1H), 3.64-3.54 (m, 1H), 3.28 (s, 3H), 3.26-3.21 (m, 1H), 2.41-2.12 (m, 3H), 1.72-1.51 (m, 10H), 1.49-1.15 (m, 9H), 1.06-0.97 (m, 1H), 0.97-0.77 (m, 15H), 0.05 (s, 6H).

Step 7. To a solution of **K4** (1.8 g, 4.02 mmol) in THF (30 mL) was added TBAF (12 mL, 1M in THF, 12.0 mmol) at 25°C, the reaction mixture was stirred at 40°C for 15 hours. The reaction mixture was quenched with water (20 mL), The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was triturated from water (40 mL) at 80°C to give **K5** (1.6 g, crude) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13-5.03 (m, 1H), 3.64-3.50 (m, 1H), 3.26-3.20 (m, 4H), 2.40-2.10 (m, 3H), 1.84-1.73 (m, 1H), 1.68-1.58 (m, 14H), 1.35-1.14 (m, 5H), 1.11-1.03 (m, 1H), 0.86-0.81 (m, 6H).

Step 8. To a solution of **K5** (1.3 g, 3.90 mmol) in DCM (20 mL) was added silica gel (4 g) and PCC (1.68 g, 7.8 mmol) 25°C. The mixture was stirred at 25°C for 3 hrs. The mixture was filtered though a pad of silica gel and the solid was washed with EtOAc/DCM (30/30 mL). filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (PE/EtOAc =10/1 to 1/1) to afford **K6** (1 g, 78 %) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16-5.07 (m, 1H), 3.32-3.19 (m, 4H), 2.48-2.09 (m, 6H), 2.09-1.87 (m, 3H), 1.78-1.10 (m, 14H), 1.00 (s, 3H), 0.87 (s, 3H).

Step 9. Under nitrogen atmosphere, anhydrous THF (30 mL) was cooled to 10°C and anhydrous LiCl (508 mg, 12.0 mmol) was added in one portion. The mixture was stirred for 30 mins to obtain a clear solution. To this solution was added anhydrous $FeCl_3$ (1.07 g, 6.64mmol) in one portion. The resulting mixture was stirred for additional 30 mins. The reaction mixture was cooled to -35°C and methyl magnesium bromide (8.03 mL, 3 M in ether, 24.1 mmol) was added dropwise maintaining the internal temperature between -35°C and -30°C. The above mixture was stirred for 30 mins at -30°C. **K6** (1 g, 3.02 mmol) in THF (10 mL) was added in one portion. The internal temperature was allowed to -20°C and held between -15°C and -20°C for 2 hrs. The reaction mixture was poured into ice-cooled aqueous HCl (1 M, 50 mL), extracted with EtOAc (2 x 100mL). The combined organic layer was washed with water (50 mL), aqueous NaOH (10%, 2 x 100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE /EtOAc = 20 /1 to 2 / 1) to give **K7** (800 mg, 77%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17-5.07 (m, 1H), 3.25 (s, 4H), 2.42-2.15 (m, 3H), 1.90-1.80 (m, 1H), 1.67-1.57 (m, 6H), 1.55-1.37 (m, 7H), 1.35-1.14 (m, 10H), 0.84 (s, 3H), 0.76(s, 3H).

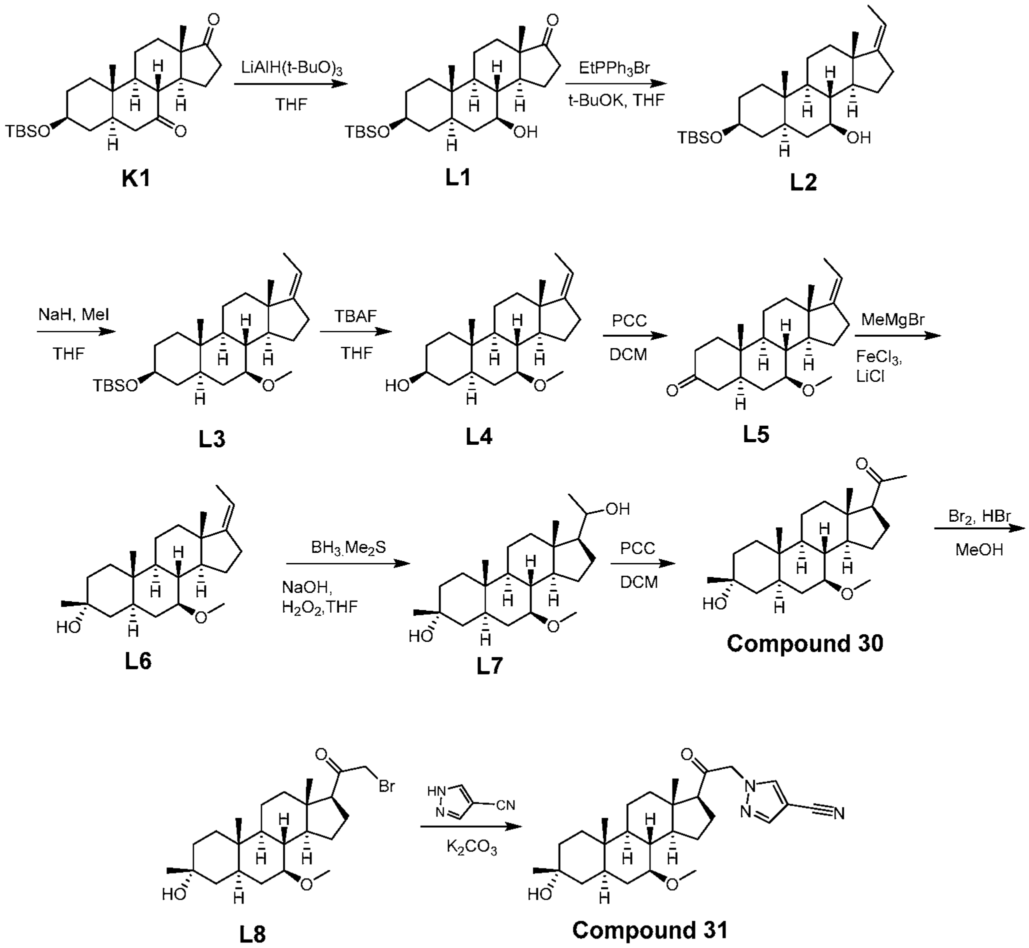
Step 10. To a solution of **K7** (0.8 g, 2.3 mmol) in THF (25 mL) was added $BH_3.Me_2S$ (2.3 mL, 10 M in THF , 23 mmol) slowly at 0°C under N_2. The reaction mixture was stirred at 25°C for 12 hrs. After the mixture was cooled to 0°C, a solution of NaOH (7.66 mL, 3 M in H_2O, 23.0 mmol) was added into the mixture very slowly. After the addition was complete, H_2O_2 (2.6 g, 30%) was added slowly and the inner temperature was maintained below 10°C. The mixture was stirred at 25°C for 2 hrs. The resulting solution was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with aqueous $Na_2S_2O_3$ (40 mL), brine (50 mL), dried over Na_2SO_4. The mixture was filtered. The filtrate was concentrated in vacuum to give **K8** (650 mg, crude) as a solid. The crude product was used next step without further purification.

Step 11. To a solution of **K8** (0.65 g, 1.78 mmol) in DCM (20 mL) was added silica gel (1.71 g) and PCC (0.765 g, 3.56 mmol) at 25°C. The reaction mixture was stirred at 25°C for 4 hours. The solution was filtered and the filter cake was washed with EtOAc(10 mL). The solution was filtered and the filter cake was washed with EtOAc (30 mL). The solution was concentrated in vacuo. The residue was purified by silica gel chromatography (PE/EtOAc = 50/1 to 1/1) to afford **Compound 29** (0.12 g, 19%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (s, 3H), 3.24-3.19 (m, 1H), 2.62-2.54 (m, 1H), 2.12-2.14 (m, 1H), 2.11(s, 3H) , 2.03-1.84 (m, 2H), 1.74-1.59 (m, 5H), 1.56-1.35 (m, 7H), 1.32-1.11 (m, 9H), 0.75 (s, 3H), 0.59 (s, 3H).

LCMS Rt = 0.991 min in 2 min chromatography, 30-90AB_ELSD, purity 97.6.0%, MS ESI calcd. for $C_{22}H_{33}O$ $[M\text{-}H_2O\text{-}CH_3OH]^+$ 313, found 313.

Example 17. Syntheses of Compounds 30 and 31.



Step 1. To a solution of **K1** (15 g, 35.8 mmol) in THF (100 mL) was added LiAlH(t-BuO)$_3$ (27.2 g, 107 mmol) at -70°C , the reaction mixture was stirred at -70°C for 5 hours. The reaction mixture was poured into ice-water (50 mL) and stirred for 20 min. The organic layer was separated. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with saturated brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~10% of EtOAc in PE) to afford **L1** (8 g, crude) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65-3.41 (m, 2H), 2.53-2.38 (m, 1H), 2.30-1.95 (m, 2H), 1.95-1.65 (m, 6H), 1.65-1.38 (m, 8H), 1.38-0.99 (m, 4H), 0.99-0.78 (m, 14H), 0.78-0.65 (m, 1H), 0.046 (m, 6H).

Step 2. To a solution of bromo(ethyl)triphenylphosphorane (28.2 g, 76.0 mmol) in THF (100 mL) was added t-BuOK (8.52 g, 76.0 mmol) at 25°C. The mixture was heated to 60°C and stirred for 1 h. A solution of **L1** (8 g, 19.0 mmol) in THF (20 mL) was added. The mixture was stirred at 60°C for 16 hrs. The mixture was treated with NH_4Cl (50 mL, sat. aq.). The organic layer was separated. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phase was washed with saturated brine (2 x 50 mL), dried over anhydrous Na2SO4, filtered, concentrated. The residue was purified by flash column (0~5% of EtOAc in PE) to give **L2** (5 g, 61 %) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22-5.05 (m, 1H), 3.65-3.49 (m, 1H), 3.49-3.30 (m, 1H), 2.48-2.35 (m, 1H), 2.35-2.19 (m, 2H), 1.98-1.85 (m, 1H), 1.75-1.55 (m, 11H), 1.55-1.25 (m, 9H), 1.25-1.10 (m, 1H), 0.95-0.80 (m, 14H), 0.047 (s, 6H).

Step 3. To a solution of **L2** (5 g, 11.5 mmol) in THF (50 mL) was added NaH (2.28 g, 57.4 mmol, 60% in mineral oil) in one portion at 0°C under N_2. After 30 min, MeI (16.1 g, 114 mmol) was added dropwise at 20°C. The reaction mixture was stirred for 6 hours at 40°C. The mixture was quenched with saturated aqueous NH_4Cl (20 mL, sat. aq.) at 0°C. The organic layer was separated. The aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases was washed with saturated brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford **L3** (5 g, crude) as a solid which used directly for the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20-5.10 (m, 1H), 3.60-3.55 (m, 1H), 3.28 (s, 3H), 2.90-2.75 (m, 1H), 2.41-2.05 (m, 3H), 1.85-1.35 (m, 14H), 1.35-1.00 (m, 6H), 1.00-0.65 (m, 15H), 0.05 (m, 6H).

Step 4. To a solution **L3** (5 g, 11.1 mmol) in THF (10 mL) was added TBAF (55.5 mL, 55.5 mmol, 1 M in THF). The reaction mixture was stirred at 80°C for 16 h. The reaction mixture was poured into water (50 mL). The organic layer was separated. The aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **L4** (3.6 g, impure) as a solid.

Step 5. To a solution of **L4** (3.6 g, 10.8 mmol) in DCM (20 mL) was added silica gel (3 g) and PCC (4.64 g, 21.6 mmol) at 20°C. The mixture was stirred at 20°C for 2 hrs. The mixture was filtered and the filter cake was washed with DCM (2 x 10mL). The combined filtrate was concentrated in vacuum to give **L5** (3 g, crude) as a solid.

Step 6. Under N_2, anhydrous THF (10 mL) was cooled to 15°C and anhydrous LiCl (1.53 g, 36.2 mmol) was added in one portion. The mixture was stirred for 30 min to obtain a clear solution. To this solution was added anhydrous $FeCl_3$ (3.22 g, 19.9 mmol) in one portion. The resulting mixture was stirred for additional 30 mins. The reaction mixture was cooled to -35°C and methyl magnesium bromide (3 M in diethyl ether, 12.0 mL, 36.2 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. **L5** (3 g, 9.07 mmol) in THF (10 mL) was added in one portion. The internal temperature was allowed to -20°C and held between -15°C and -20°C for 2 hrs. The reaction mixture was poured to ice-cooled aqueous HCl (1 M, 20 mL), extracted with EtOAc (2 x 20 mL). The organic layer was separated. The combined organic layer was washed with water (20 mL), aqueous NaOH (10%, 2 x 20mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column (0~10% of EtOAc in PE) to give **L6** (2.8 g, 89 %) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20-5.00 (m, 1H), 3.27 (s, 3H), 2.90-2.80 (m, 1H), 2.45-2.10 (m, 4H), 2.90-1.45 (m, 11H), 1.45-1.05 (m, 11H), 0.95-0.72 (m, 7H).

Step 7. To a solution of **L6** (2.8 g, 8.07 mmol) in THF (15 mL) was added dropwise a solution of $BH_3.Me_2S$ (8.07 mL, 10M, 80.7 mmol) at 0°C. The solution was stirred at 15°C for 3h. After cooling to 0°C, a solution of NaOH solution (48.4 mL, 2M, 96.8 mmol) was added very slowly. After addition, H_2O_2 (8.07 mL, 80.7 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 $Na_2S_2O_3$ (20 mL) was added until the reaction solution became clear. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic solution was washed with saturated aqueous $Na_2S_2O_3$ (2 x 10 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give **L7** (3.1 g, crude) as a solid which was used in next step without further purification.

Step 8. To a solution of **L7** (3.1 g, 8.50 mmol) in DCM (20 mL) was added PCC (3.65 g, 17.0 mmol) and silica gel (3 g) at 25°C. The solution was stirred at 25°C for 3h. The reaction mixture was filtered and the filter cake was washed with anhydrous DCM (2 x 20 mL). The combined filtrate was concentrated in vacuum. The residue purified by flash column (0~20% of EtOAc in PE) to give **Compound 30** (2 g, impure) as a solid. The residue **Compound 30** (2 g, 5.51 mmol) was re-crystallized from MeCN (20 mL) at 65°C to give **Compound 30** (24 mg, 1 %, pure) as a solid. The mother liquid was concentrated to give **Compound 30** (1776 mg, impure) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (s, 3H), 2.90-2.80 (m, 1H), 2.50-2.41 (m, 1H), 2.20-2.08 (m, 4H), 2.08-1.95 (m, 1H), 1.82-1.70 (m, 2H), 1.70-1.60 (m, 3H), 1.60-1.45 (m, 5H), 1.45-1.20 (m, 9H), 1.20-1.05 (m, 2H), 0.90-0.80 (m, 1H), 0.76 (s, 3H), 0.62 (s, 3H).

LCMS t_R = 0.905 min in 2 min chromatography, 30-90AB_ELSD, purity 100.0%, MS ESI calcd. for $C_{22}H_{33}O$ $[M-H_2O-CH_3O]^+$ 313, found 313.

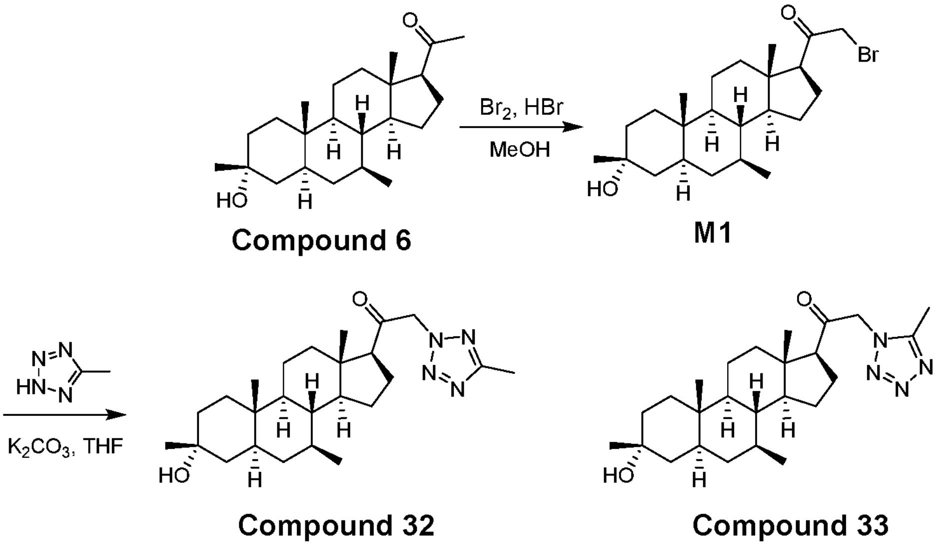
Step 9. To a solution of **Compound 30** (200 mg, 551 μmol) in MeOH (10 mL) was added HBr (11.1 mg, 0.0551 mmol, 40% in water) and Br_2 (105 mg, 0.661 mmol) at 25°C. The mixture was stirred at 25°C for 2 hrs. The mixture was quenched by sat.aq $NaHCO_3$ (10 mL), treated with water (20 mL). The mixture was extracted with DCM (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum to afford **L8** (230 mg, crude) as a pale yellow oil, which was used directly in next step without further purification.

Step 10. To a solution of **L8** (230 mg, 0.521 mmol) in acetone (5 mL) was added K_2CO_3 (143 mg, 1.04 mmol) and 1H-pyrazole-4-carbonitrile (58.1 mg, 0.625 mmol) at 25°C. The mixture was stirred at 25°C for 16 hrs. The mixture was treated with water (20 mL). The mixture was extracted with DCM (2 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated. The residue was purified by flash column (0~50% of EtOAc in PE) to give **Compound 31** (63 mg, 27%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.80 (s, 1H), 5.08-4.85 (m, 2H), 3.27 (s, 3H), 2.85-2.75 (m, 1H), 2.55-2.45 (m, 1H), 2.22-2.12 (m, 1H), 2.12-2.00 (m, 1H), 1.90-1.65 (m, 5H), 1.65-1.1.28 (m, 11H), 1.28-1.20 (m, 3H), 1.20-1.05 (m, 2H), 0.90-0.80(m, 1H), 0.77 (s, 3H), 0.68 (s, 3H).

LCMS t_R = 0.912 min in 2 min chromatography, 30-90AB_ELSD, purity 100.0%, MS ESI calcd. for $C_{27}H_{40}N_3O_3$ $[M+H]^+$ 454, found 454.

Example 18. Syntheses of Compounds 32 and 33.



Compound 6 → M1 → Compound 32, Compound 33

Step 1. To a solution of **Compound 6** (1 g, 2.88 mmol) in MeOH (10 ml) was added HBr (0.1 mL, 40% in water) and Br_2 (551 mg, 3.45 mmol) at 25°C. The mixture was stirred at 25°C for 3 hrs. The mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), treated with water (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic phase was washed with Sat $Na_2S_2O_3$ (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography eluting with (petroleum ether/ethyl acetate = 5/1) to give **M1** (800 mg, 66%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.95-3.88 (m, 2H), 2.76 (t, J = 8Hz, 1H), 2.20-2.11 (m, 1H), 1.95-1.84 (m, 2H), 1.78-1.67 (m, 2H), 1.53-1.43 (m, 4H), 1.42-1.38 (m, 1H), 1.34-1.08 (m, 13H), 1.03-0.93 (m, 4H), 0.87-0.80 (m, 1H), 0.71 (s, 3H), 0.65 (s, 3H).

Step 2. To a solution of **M1** (200 mg, 0.47 mmol) in acetone (2 mL) was added K_2CO_3 (161 mg, 1.17 mmol) and 5-methyl-2H-tetrazole (59.2 mg, 0.705 mmol). The mixture was stirred at 25°C for 16 hours. To the mixture was added water (10 mL) and ethyl acetate (20 mL). The organic layer was separated. The aqueous phase was extracted with ethyl acetate (50 mL). The combined organic layers was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography eluting with (petroleum ether/ethyl acetate = 2/1) to give **Compound 32** (56 mg, 28%) and **Compound 33** (82 mg, 41%) as a solid.

Compound 32:

^{1}HNMR (400 MHz, $CDCl_3$) δ 5.40-5.31 (m, 2H), 2.59-2.54 (m, 4H), 2.23-2.13 (m, 1H), 2.10-2.02 (m, 1H), 1.98-1.85 (m, 1H), 1.82-1.68 (m, 2H), 1.54-1.39 (m, 5H), 1.37-1.15 (m, 13H), 1.04-0.94 (m, 4H), 0.90-0.81 (m, 1H), 0.72 (s, 6H).

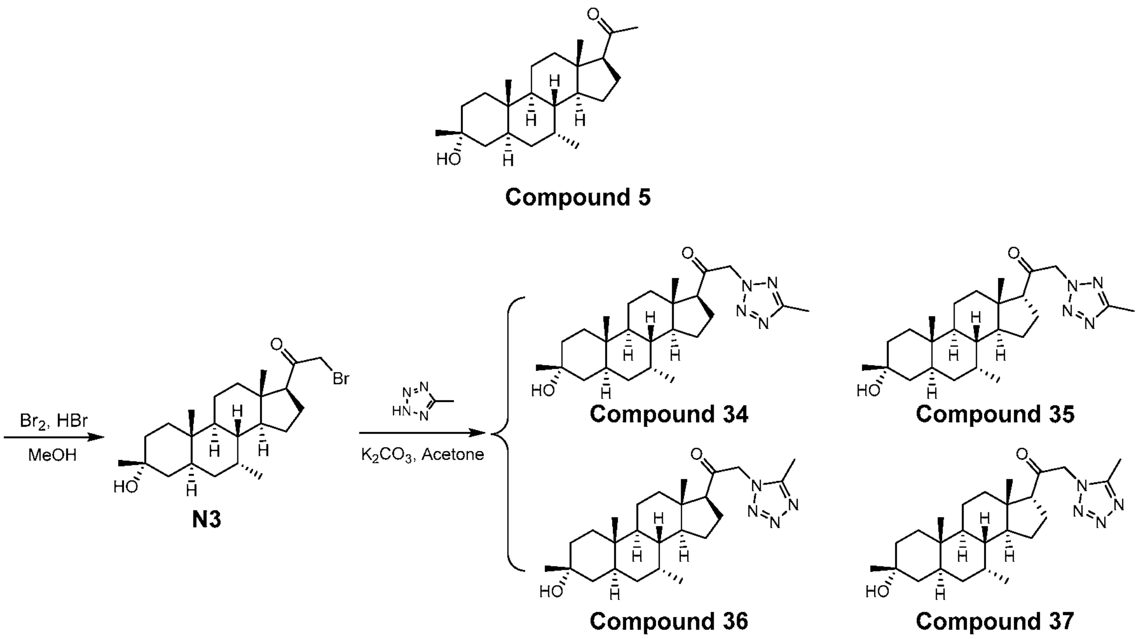
LCMS Rt = 1.103 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{25}H_{41}N_4O_2$ $[M+H]^+$ 429, found 429.

Compound 33:

^{1}**HNMR** (400 MHz, $CDCl_3$) δ 5.17-5.03 (m, 2H), 2.60 (t, *J* = 8Hz, 1H), 2.46 (s, 3H), 2.25-2.13 (m, 1H), 2.07-1.87 (m, 1H), 1.83-1.70 (m, 2H), 1.56-1.42 (m, 6H), 1.40-1.11 (m, 13H), 1.05-0.95 (m, 4H), 0.90-0.81 (m, 1H), 0.73 (s, 3H), 0.69 (s, 3H).

LCMS Rt = 1.043 min in 2.0 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{25}H_{41}N_4O_2$ $[M+H]^+$ 429, found 429.

Example 19. Syntheses of Compounds 34, 35, 36, and 37.



Step 1. To a solution of **Compound 5** (1.1 g, 3.17 mmol) in MeOH (20 mL) was added HBr (126 mg, 0.634 mmol, 40% in water) and Br_2 (608 mg, 3.80 mmol) at 25°C. The mixture was stirred at 25°C for 1 h. The mixture was quenched by sat.$NaHCO_3$ (20 mL), and treated with water (20 mL). The mixture was extracted with DCM (2 x 30 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum to afford **N3** (1.2 g, impure) as a solid used directly for the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95-3.85 (m, 2H), 2.85-2.75 (m, 1H), 2.25-2.10 (m, 1H), 1.95-1.69 (m, 7H), 1.69-1.41 (m, 8H), 1.41-0.98 (m, 12H), 0.98-0.75 (m, 3H), 0.63 (s, 3H).

Step 2. To a solution of **N3** (350 mg, 0.822 mmol) in acetone (10 mL) was added K_2CO_3 (226 mg, 1.64 mmol) and 5-methyl-2H-tetrazole (137 mg, 1.64 mmol) at 25°C. The mixture was stirred at 25°C for 16 hrs. The reaction mixture was treated with water (20 mL). The mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum. The residue was purified by flash column (0~100% of EtOAc in PE) to afford **Compound 35** (5 mg, 1%) as a solid, **Compound 34** (49 mg, 14%) as a solid, **Compound 37** (6 mg, 2%) as a solid and **Compound 36** (41 mg, 12%) as a solid.

Compound 34:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40-5.30 (m, 2H), 2.65-2.60 (m, 1H), 2.56 (s, 3H), 2.30-2.15 (m, 1H), 2.09-2.00 (m, 1H), 1.89-1.55 (m, 6H), 1.55-1.01 (m, 17H), 1.01-0.90 (m, 3H), 0.77 (s, 3H), 0.70 (s, 3H).

LCMS Rt = 1.084 min in 2 min chromatography, 30-90AB_ELSD, purity 100.0%, MS ESI calcd. for $C_{25}H_{41}N_4O_2$ $[M+H]^+$ 429, found 429.

Compound 35:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45-5.25 (m, 2H), 2.80-2.70 (m, 1H), 2.57 (s, 3H), 2.00-1.65 (m, 7H), 1.50-1.40 (m, 5H), 1.40-1.22 (m, 6H), 1.22-1.15 (m, 5H), 1.15-1.00 (m, 2H), 0.94 (s, 3H), 0.94-0.89 (m, 3H), 0.75 (s, 3H).

LCMS Rt = 1.094 min in 2 min chromatography, 30-90AB_ELSD, purity 100.0%, MS ESI calcd. for $C_{25}H_{39}N_4O$ $[M+H-H2O]^+$ 411, found 411.

Compound 36:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20-5.00 (m, 2H), 2.70-2.60 (m, 1H), 2.47 (s, 3H), 2.25-2.15 (m, 1H), 2.10-2.00 (m, 1H), 1.90-1.65 (m, 5H), 1.65-1.25 (m, 10H), 1.25-1.11 (m, 7H), 1.11-1.05 (m, 1H), 1.05-0.95 (m, 3H), 0.77 (s, 3H), 0.67 (s, 3H).

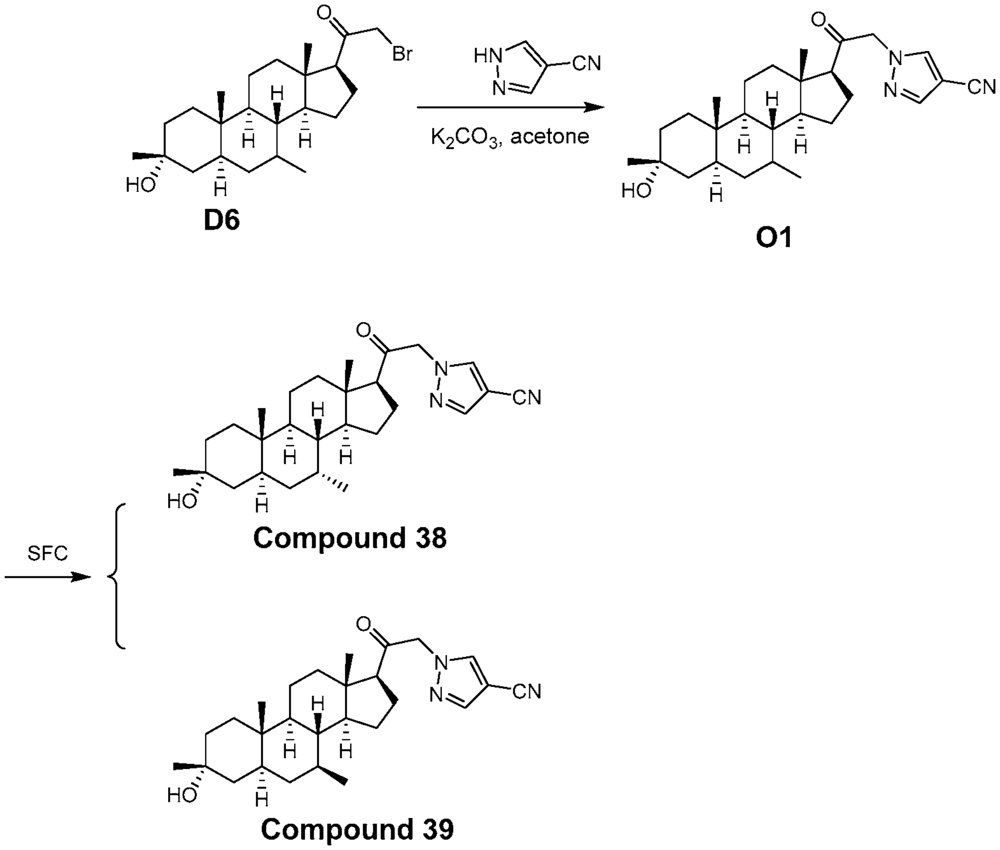
LCMS Rt = 1.007 min in 2 min chromatography, 30-90AB_ELSD, purity 100.0%, MS ESI calcd. for $C_{25}H_{41}N_4O_2$ $[M+H]^+$ 429, found 429.

Compound 37:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30-5.20 (m, 1H), δ 5.00-4.90 (m, 1H), 2.90-2.80 (m, 1H), 2.48 (s, 3H), 1.95-1.65 (m, 7H), 1.45-1.40 (m, 3H), 1.40-1.22 (m, 7H), 1.22-1.10 (m, 6H), 1.10-1.06 (m, 2H), 0.97 (s, 3H), 0.96-0.93 (m, 3H), 0.75 (s, 3H).

LCMS Rt = 1.021 min in 2 min chromatography, 30-90AB_ELSD, purity 100.0%, MS ESI calcd. for $C_{25}H_{39}N_4O$ $[M+H-H2O]^+$ 411, found 411.

Example 20. Syntheses of Compounds 38 and 39.



Step 1. To a solution of **D6** (500 mg, 1.17 mmol) in acetone (10 mL) was added K_2CO_3 (322 mg, 2.34 mmol) and 1H-pyrazole-4-carbonitrile (162 mg, 1.75 mmol).After stirring at 25°C for 12 hours, the mixture was poured in to water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers was washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash column (0~15% of EtOAc in PE) to afford **O1** (340 mg, 60%) as a solid.

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.99-7.78 (m, 2H), 5.07-4.84 (m, 2H), 2.67-2.49 (m, 1H), 2.26-2.13 (m, 1H), 2.02-1.81 (m, 2H), 1.64-1.38 (m, 10H), 1.34-0.99 (m, 12H), 0.98-0.91 (m, 3H), 0.76 (s, 2H), 0.72 (s, 1H), 0.69-0.63 (m, 3H).

Step 2. **O1** (340 mg, 0.77 mmol) was purified by SFC (column: OD(250mm*30mm,5um)), gradient: 45-45% B (A= 0.1%NH_3/H_2O, B= EtOH), flow rate: 50 mL/min) to give **Compound 38** (145 mg, 43%) and **Compound 39** (84 mg, 24%) as a solid.

Compound 38:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.78 (d, *J* = 19.2 Hz, 2H), 5.06-4.84 (m, 2H), 2.64-2.56 (m, 1H), 2.26-2.15 (m, 1H), 2.04-1.96 (m, 1H), 1.84-1.64 (m, 5H), 1.55-1.24 (m, 11H), 1.22-1.09 (m, 6H), 1.07-0.99 (m, 1H), 0.96-0.89 (m, 3H), 0.76 (s, 3H), 0.66 (s, 3H).

LCMS Rt = 1.037 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{27}H_{40}N_3O_2$ $[M+H]^+$ 438, found 438.

SFC Rt = 4.998 min in 10 min chromatography, OD_3_EtOH_DEA_5_40_25ML, purity: 99.8%.

Note: The structure of **Compound 38** was confirmed by X-ray.

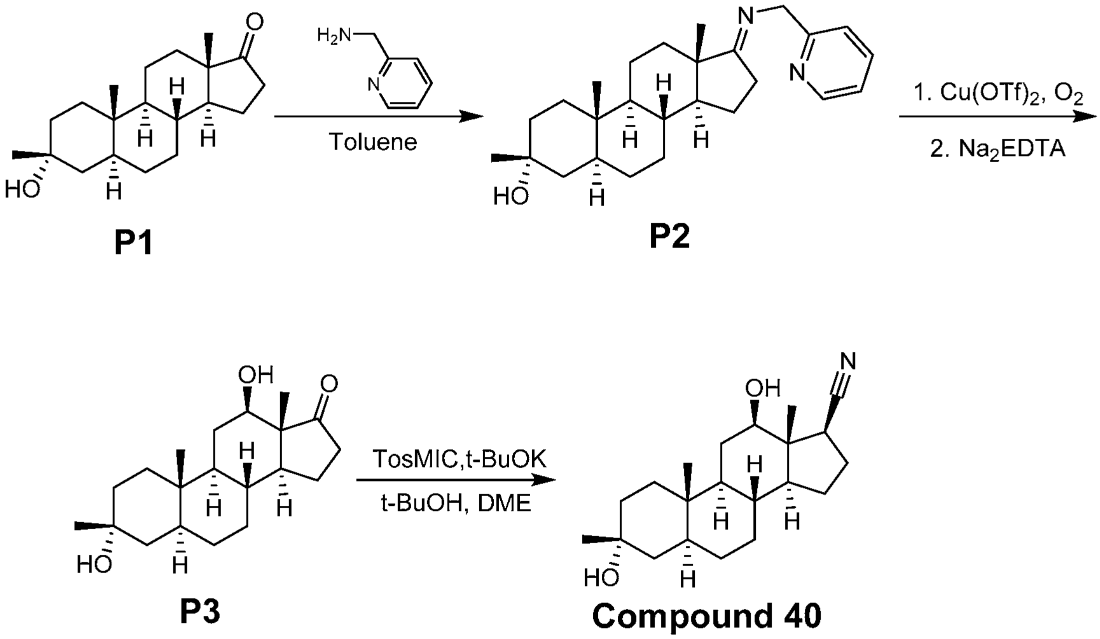
Compound 39:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.78 (d, *J* = 17.2 Hz, 2H), 5.07-4.86 (m, 2H), 2.57-2.49 (m, 1H), 2.23-2.13 (m, 1H), 2.06-1.99 (m, 1H), 1.97-1.86 (m, 1H), 1.79-1.67 (m, 2H), 1.55-1.36 (m, 6H), 1.35-1.13 (m, 12H), 1.05-0.92 (m, 4H), 0.89-0.81 (m, 1H), 0.72 (s, 3H), 0.68 (s, 3H).

LCMS Rt = 1.051 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{27}H_{39}N_3O_2Na$ $[M+Na]^+$ 460, found 460.

SFC Rt = 6.270 min in 10 min chromatography, OD_3_EtOH_DEA_5_40_25ML, purity: 100%.

Example 21. Synthesis of Compound 40.



Step 1. To a solution of **P1** (2 g, 6.56 mmol) in toluene (20 mL) was added p-toluenesulfonic acid (20 mg, 0.116 mmol) and pyridin-2-ylmethanamine (1.55 g, 14.4 mmol) at 25°C. The reaction mixture was heated to 130°C in a Dean-Stark apparatus for 16 h. The reaction was cooled to 25°C and diluted with EtOAc (30 mL). The organic layer was washed sequentially with sat. NH_4Cl (2 x 20 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL) and dried over Na_2SO_4, then concentrated in vacuum to give crude product **P2** (3 g, crude) as yellow oil, which was used directly for the next.

Step 2. **P2** (1 g, 2.53 mmol), $Cu(OTf)_2$ (1.18 g, 3.28 mmol) and L-ascorbic acid, sodium salt (1 g, 5.06 mmol) were added to a round-bottom-flask under N_2. Acetone (dry, 8 mL) and MeOH (dry, 8 mL) were added at 25°C and stirred for 5 min (reaction mixture may turn brown). O_2 from a balloon was bubbled through the reaction mixture for 5 min (resulting in a blue/green solution). After that, the reaction was heated to 50°C under an O_2 atmosphere for 1.5 h. The reaction mixture was then cooled to 25°C, EtOAc (30 mL) and sat. Na_4EDTA (30 mL, pH~10) were added and the reaction mixture was stirred for 1 h. The layers were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL), dried over Na_2SO_4 and concentrated in vacuum to give crude product, which was purified by a silica gel column (PE/EtOAc = 3/1) to give **P3** (230 mg, 28%) as a solid which was triturated with MeCN (5 mL) at 25°C to give **P3** (110 mg, 48% yield) as a solid and **P3** (100 mg, impure) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.78-3.73 (m, 1H), 2.98 (d, J = 1.4 Hz, 1H), 2.49-2.41 (m, 1H), 2.16-2.03 (m, 1H), 2.02-1.92 (m, 1H), 1.87-1.76 (m, 2H), 1.68-1.56 (m, 1H), 1.55-1.45 (m, 5H), 1.42-1.22 (m, 7H), 1.21 (s, 3H), 1.11 (s, 1H), 1.04-0.86 (m, 5H), 0.78 (s, 3H).

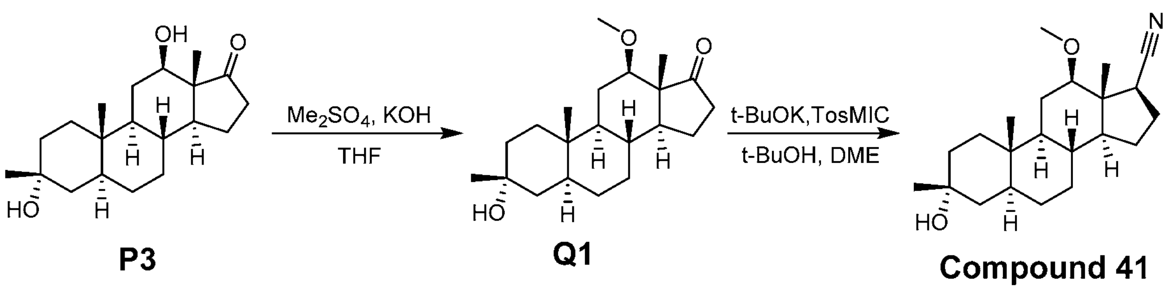
Step 3. Into a over-dried bottom was added t-BuOH (2 mL) and t-BuOK (348 mg, 3.11 mmol). It was degassed and filled with N_2. A solution of **P3** (100 mg, 0.312 mmol) in DME (2 mL) was added into the suspension. After 30 min, a solution of TosMIC (121 mg, 0.624 mmol) in DME (2 mL) was added. The mixture became yellow. The resulting mixture was stirred at 25°C for 16 h. Water was added and the mixture was stirred and the mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluting with (petroleum ether/ethyl acetate = 4/1) to give **Compound 40** (60 mg, 58% yield) as a pale solid, which was triturated with MeCN (2 mL) to give **Compound 40** (30 mg) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.51-3.44 (m, 1H), 2.46-2.37 (m, 1H), 2.23-2.11 (m, 1H), 2.00-1.91 (m, 1H), 1.84-1.74 (m, 2H), 1.70-7.67 (m, 1H), 1.62-1.57 (m, 1H), 1.53-1.31 (m, 8H), 1.30-1.22 (m, 4H), 1.21-1.15 (s, 3H), 1.09 (s, 1H), 1.04-0.84 (m, 6H), 0.77 (s, 3H)

LCMS Rt = 0.747 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{21}H_{30}N$ $[M+H-2H_2O]^+$ 296, found 296.

Note: the structure of **Compound 40** was confirmed by X-ray.

Example 23. Synthesis of Compound 41.



Step 1. To a solution of **P3** (1.2 g, 3.74 mmol) in THF (12 mL) was added KOH (632 mg, 11.3 mmol) and Me_2SO_4 (966 mg, 0.725 mL, 7.66 mol) at 0°C. Then the mixture was warmed to

25°C and stirred at the same temperature for 16 h. The mixture was quenched with the addition of 50 mL of water and extracted with EtOAc (2 x 30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product, which was purified by a silica gel column (PE/EtOAc=10/1-5:1) to give **Q1** (600 mg, 48%) as a solid and the starting material **P3** (600 mg) as a solid.

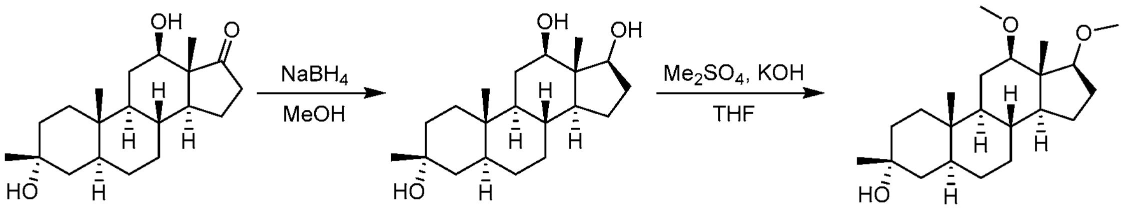
^{1}H NMR (400MHz, $CDCl_3$) δ 3.49 (s, 3H), 3.20-3.15 (m, 1H), 2.48-2.40 (m, 1H), 2.12-1.90 (m, 3H), 1.83-1.75 (m, 1H), 1.59-1.46 (m, 8H), 1.38-1.26 (m, 4H), 1.23-1.15 (m, 5H), 1.01-0.91 (m, 4H), 0.86-0.76 (m, 4H).

Step 2. Into an over-dried bottom was added t-BuOH (2 mL) and t-BuOK (334 mg, 2.98 mmol). It was evaporated and filled with N_2. **Q1** (100 mg, 0.299 mmol) in DME (1 mL) was added into the suspension. After 30 min, TosMIC (116 mg, 0.598 mmol) in DME (1 mL) was added. The mixture became yellow. The resulting mixture was stirred at 25°C for 16 h. Water was added and the mixture was stirred. Then it was extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluting with (petroleum ether: ethyl acetate= 4/1) to give **Compound 41** (25 mg, impure) as a pale yellow oil, which was triturated with MeCN (1 mL) to give **Compound 41** (10 mg, 10%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.41 (s, 3H), 2.92-2.88 (m, 1H), 2.43-2.35 (m, 1H), 2.23-2.09 (m, 1H), 2.02-1.89 (m, 2H), 1.81-1.64 (m, 2H), 1.49-1.32 (m, 5H), 1.27-1.24 (m, 5H), 1.22-1.20 (m, 4H), 1.00-0.85 (m, 7H), 0.83-0.79 (m, 1H), 0.77 (s, 3H).

LCMS Rt = 0.903 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{22}H_{32}N$ $[M+H-2H_2O]^+$ 296, found 296.

Example 24. Synthesis of Compound 42.



P3 **R1** **Compound 42**

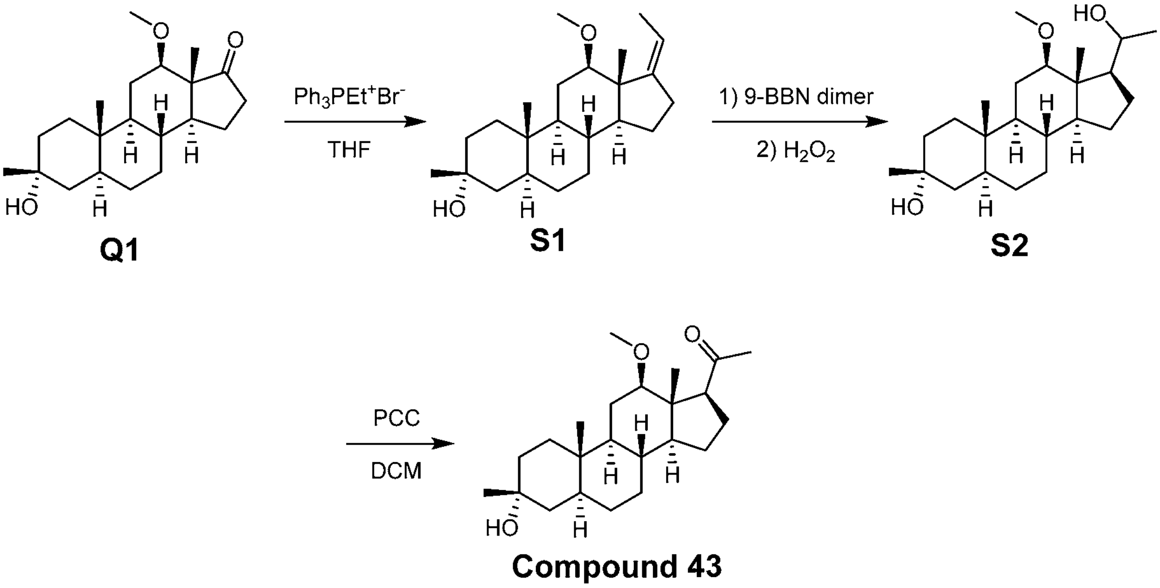
Step 1. To a solution of **P3** (200 mg, 0.624 mmol) in MeOH (5 mL) was added $NaBH_4$ (46.9 mg, 1.24 mmol) at 25°C. The reaction was stirred at 25°C for 30 mins. The reaction was quenched with water (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum to give **R1** (180 mg, crude) as a colourless oil, which was used directly for next step without further purification.

Step 2. To a solution of **R1** (200 mg, 0.620 mmol) in THF (3 mL) was added KOH (211 mg, 3.77 mmol) and Me_2SO_4 (320 mg, 0.24 mL, 2.54 mmol) at 0°C. Then the mixture was warmed to 25°C and stirred at the same temperature for 16 h. The mixture was quenched with the addition of 50 mL of water and extracted with EtOAc (2 x 30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc=10/1-5:1) to give **Compound 42** (30 mg, 14%) as a solid, which was triturated with n-hexane (3 mL) at 25°C to give **Compound 42** (6 mg, 3%) as a solid.

^{1}H NMR (400MHz, CDCl3) δ 3.39-3.33 (m, 7H), 2.91-2.86 (m, 1H), 2.08-2.02 (m, 1H), 1.91-1.86 (m, 5H), 1.55-1.20 (m, 7H), 1.18-1.14 (m, 8H), 0.92-0.79 (m, 3H), 0.77 (s, 6H).

LCMS Rt = 0.952 min in 2 min chromatography, 30-90 AB, purity 99%, MS ESI calcd. For $C_{22}H_{38}O_3Na^+$ $[M+Na]^+$ 373, found 373.

Example 25. Synthesis of Compound 43.



Step 1. To a suspension of EtPPh$_3$Br (3.32 g, 8.95 mmol) in THF (40 mL) was added t-BuOK (1 g, 8.95 mmol) at 25°C under N_2. After stirring at 60°C for 30 min, a solution of **Q1** (600 mg, 1.79 mmol) in THF (10 mL) was added at 60°C. The mixture was stirred at 60°C for 16 h. The mixture was quenched with NH_4Cl (80 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated in vacuum to give a crude product, which was purified by a silica gel column (PE/EtOAc=10/1-5/1) to give **S1** (340 mg, 55%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 5.25-5.18 (m, 1H), 3.33 (s, 3H), 3.17-3.12 (m, 1H), 2.42-2.36 (m, 1H), 2.25-2.10 (m, 2H), 1.79-1.76 (m, 6H), 1.75-1.56 (m, 5H), 1.54-1.23 (m, 6H), 1.21-0.98 (m, 5H), 0.90-0.84 (m, 5H), 0.77 (s, 3H).

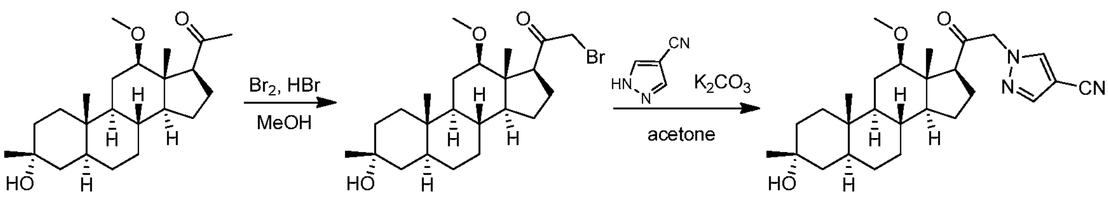
Step 2. To a solution of **S1** (340 mg, 0.981 mmol) in THF (4 mL) was added 9-BBN dimer (597 mg, 2.45 mmol) at 0°C under N_2. The solution was stirred at 60°C for 16 h. After cooling to 0°C, a solution of EtOH (15 mL) and NaOH (1.96 mL, 5M, 9.81 mmol) was added very slowly. After addition, H_2O_2 (0.981 ml, 9.81 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. The mixture was stirred at 60°C under N_2 for 1 hour. The mixture was re-cooled to 30°C. Water washed (100 mL) was added to the solution and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give **S2** (400 mg, crude) as colorless oil which was directly used for next step.

Step 3. To a solution of **S2** (350 mg, 0.960 mmol) in DCM (10 mL) was added PCC (413 mg, 1.92 mmol) and silica gel (454 mg) at 25°C. Then the solution was stirred at 25°C for 3 h. The reaction mixture was filtered and the residue was washed with anhydrous DCM (2 x 30 mL). The combined filtrate was concentrated in vacuum to give a crude product, which was purified by a silica gel column (PE/EtOAc=8/1~4/1) to give **Compound 43** (270 mg, impure) as pale solid. The solid was triturated with MeCN (5 mL) at 25°C to give **Compound 45** (10 mg, 4%) as a solid for delivery and **Compound 43** (250 mg, crude) as pale yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.08-3.03 (m, 1H), 2.71-2.66 (m, 1H), 2.21 (s, 3H), 2.17-1.97 (m, 2H), 1.58-1.55 (m, 3H), 1.54-1.21 (m, 12H), 1.20-1.00 (m, 5H), 0.98-0.75 (m, 5H), 0.65 (s, 3H).

LCMS Rt = 0.960 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{23}H_{39}O_3$ $[M+H]^+$ 363, found 363.

Example 26. Synthesis of Compound 44.



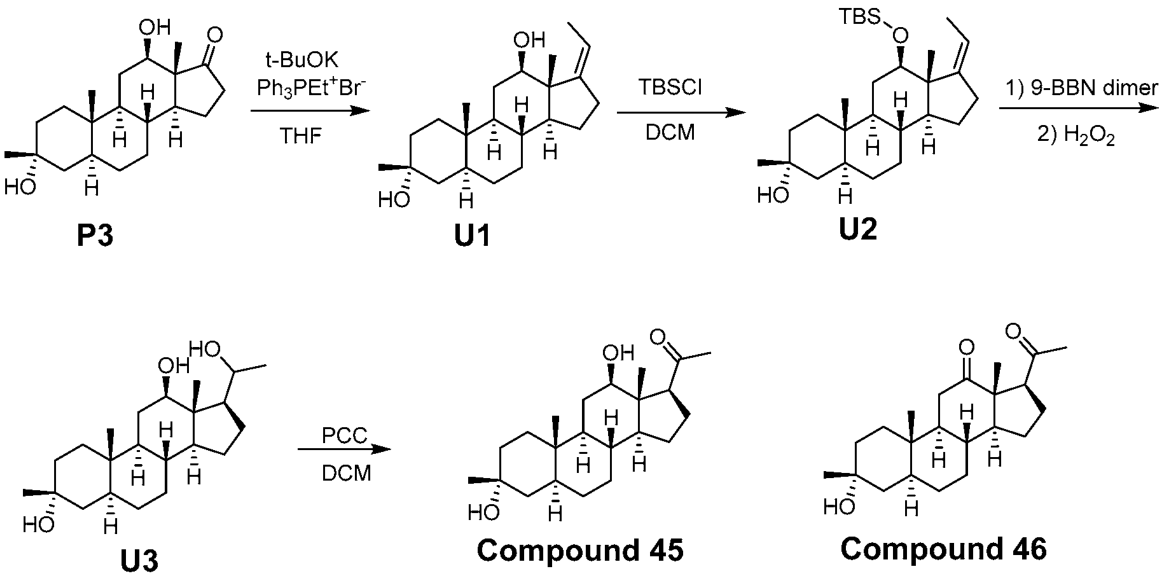
Step 1. To a solution of **Compound 43** (1 g, 2.75 mmol) in MeOH (15 ml) was added HBr (44.5 mg, 0.55 mmol, 40% in water) and Br_2 (439 mg, 0.140 mmol) at 25°C. The mixture was stirred at 25°C for 16 hrs. The mixture was quenched by sat.aq $NaHCO_3$ (10 mL), treated with water (20 mL), extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum to afford **T1** (1.3 g, crude) as light yellow oil which was used directly for the next step.

Step 2. To a mixture of **T1** (300 mg, 0.680 mmol) and K_2CO_3 (186 mg, 1.35 mmol) in acetone (5 mL) was added 1H-pyrazole-4-carbonitrile (94 mg, 1.01 mmol) at 25°C. The reaction mixture was stirred at the 25°C for 16 h. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give crude product, which was purified by a silica gel column (PE/EtOAc= 2/1) to give **Compound 44** (37 mg, 12%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.80 (s, 2H), 5.45 (d, J=17.8 Hz, 1H), 4.93 (d, J=17.8 Hz, 1H), 3.38 (s, 3H), 3.19-3.14 (m, 1H), 2.73-2.67 (m, 1H), 2.20-2.02 (m, 2H), 1.80-1.65 (m, 3H), 1.50-1.32 (m, 5H), 1.31-1.11 (m, 11H), 1.00-0.80 (m, 3H), 0.77 (s, 3H), 0.66 (s, 3H)

LCMS Rt = 1.113 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{27}H_{39}N_3O_3Na^+$ $[M+Na]^+$ 476, found 476.

Example 27. Syntheses of Compounds 45 and 46.



Step 1. To a suspension of $EtPPh_3Br$ (11.5 g, 31.2 mmol) in THF (50 mL) was added t-BuOK (3.50 g, 31.2 mmol) at 25°C under N_2. After stirring at 60°C for 30 min, a solution of **P3** (2 g, 6.24 mmol) in THF (20 mL) was added at 60°C. The mixture was stirred at 60°C for 16 h and quenched with NH_4Cl (100 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc = 10/1-5/1) to give **U1** (1.8 g, 87%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 5.18-5.14 (m, 1H), 3.68-3.63 (m, 1H), 2.47-2.35 (m, 1H), 2.21-2.09 (m, 1H), 1.89-1.70 (m, 5H), 1.69-1.59 (m, 1H), 1.51-1.45 (m, 4H), 1.41-1.19 (m, 8H), 1.16 (s, 3H), 1.12-0.88 (m, 2H), 1.12-0.88 (m, 1H), 1.12-0.88 (m, 1H), 0.86 (s, 3H), 0.84-0.81 (m, 1H), 0.80 (s, 3H).

Step 2. To a solution of **U1** (1.8 g, 5.41 mmol) in DCM (40 mL) was added TBSCl (1.22 g, 8.11 mmol) and 1H-Imidazole (735 mg, 10.8 mmol) at 25°C. The reaction was stirred at 50°C for 16 h, quenched by water (30 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc = 10/1-5/1) to give **U2** (1.6 g, 66%) as a solid.

Step 3. To a solution of **U2** (1.6 g, 3.58 mmol) in THF (40 mL) was added 9-BBN dimer (4.36 g, 17.9 mmol) at 0°C under N_2. The solution was stirred at 60°C for 16 h. After cooling to 0°C, a solution of EtOH (40 mL) and NaOH (7.15 mL, 5M, 35.8 mmol) was added very slowly. After addition, H_2O_2 (3.56 ml, 35.8 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. The mixture was stirred at 60°C under N_2 for 1 hour. The mixture was re-cooled to 30°C, treated with water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give **U3** (2.3 g, crude) as colourless oil, which was directly used for next step.

^{1}H NMR (400MHz, $CDCl_3$) δ 4.15-4.06 (m, 1H), 3.40-3.30 (m, 1H), 1.76-1.68 (m, 3H), 1.56-1.43 (m, 6H), 1.40-1.30 (m, 4H), 1.29-1.15 (m, 13H), 1.04-0.80 (m, 4H), 0.78-0.73 (m, 6H).

Step 4. To a solution of **U3** (300 mg, 1.72 mmol) in DCM (15 mL) was added silica gel (404 mg) and PCC (368 mg, 1.71 mmol) at 25°C. The reaction was stirred at 25°C for 1 h. The mixture was filtered and the filtrate was concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc= 6/1-2/1) to give **Compound 46** (10 mg, 3%) and **Compound 45** (10 mg, 3%) as a solid.

Compound 45:

^{1}H NMR (400MHz, $CDCl_3$) δ 4.86 (s, 1H), 3.45-3.40 (m, 1H), 2.50-2.34 (m, 1H), 2.21-2.05 (m, 4H), 2.03-1.89 (m, 1H), 1.88-1.63 (m, 3H), 1.48-1.22 (m, 9H), 1.21-1.12 (m, 6H), 1.11-0.98 (m, 1H), 0.97-0.80 (m, 3H), 0.75-0.70 (m, 6H).

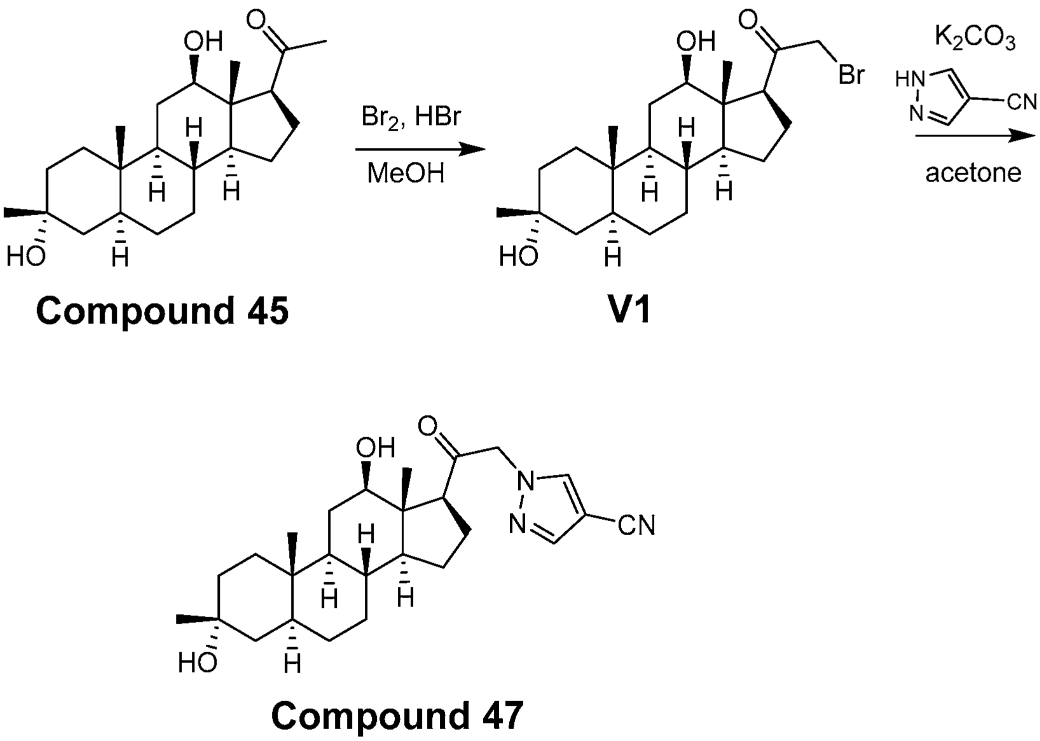
LCMS Rt = 0.969 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{22}H_{35}O_2$ $[M+H-H_2O]^+$ 331, found 331.

Compound 46:

^{1}**H NMR** (400MHz, $CDCl_3$) δ 3.35-3.10 (m, 1H), 2.54-2.38 (m, 1H), 2.34-2.09 (m, 5H), 1.89-1.62 (m, 4H), 1.60-1.53 (m, 2H), 1.47-1.24 (m, 9H), 1.21-1.12 (m, 4H), 1.09 (s, 1H), 1.03-0.89 (m, 4H), 0.83 (s, 3H).

LCMS Rt = 0.977 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{22}H_{35}O_3$ $[M+H]^+$ 347, found 347.

Example 28. Synthesis of Compound 47.



Step 1. To a solution of **Compound 45** (560 mg, 1.60 mmol) in MeOH (15 ml) was added HBr (25.9 mg, 0.32 mmol, 40% in water) and Br_2 (255 mg, 1.60 mmol) at 25°C. The mixture

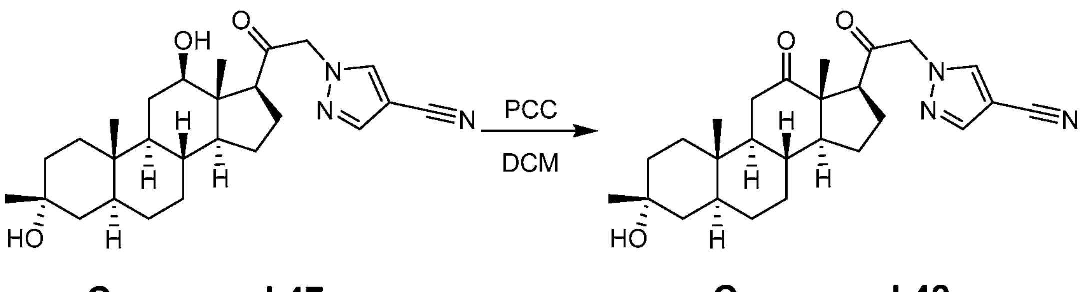
was stirred at 25°C for 16 hrs. The mixture was quenched by sat.aq $NaHCO_3$ (10 mL), treated with water (20 mL), extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum to afford **V1** (700 mg, crude) as light yellow oil which was used directly for the next step.

Step 2. To a mixture of **V1** (150 mg, 0.351 mmol) and K_2CO_3 (96.9 mg, 0.702 mmol) in acetone (5 mL) was added 1H-pyrazole-4-carbonitrile (48.9 mg, 0.526 mmol) at 25°C. The reaction mixture was stirred at the 25°C for 16 h. The reaction mixture was quenched by water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product (50 mg) which was triturated with MeCN (5 mL) to give **Compound 47** (41 mg, 27%) as a solid.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.05 (s, 1H), 5.87 (d, *J*= 18.2 Hz, 1H), 5.22 (d, *J*= 18.2 Hz, 1H), 4.92-4.88 (m, 1H), 3.88 (s, 1H), 3.56-3.49 (m, 1H), 2.86-2.76 (m, 1H), 1.96-1.92 (m, 1H), 1.73-1.58 (m, 4H), 1.57-1.44 (m, 1H), 1.42-1.22 (m, 7H), 1.19-1.11 (m, 5H), 1.07 (s, 3H), 0.92-0.77 (m, 2H), 0.70 (s, 3H), 0.54 (s, 3H)

LCMS Rt = 0.980 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{26}H_{37}N_3O_3Na^+$ $[M+Na]^+$ 462, found 462.

Example 29. Synthesis of Compound 48.



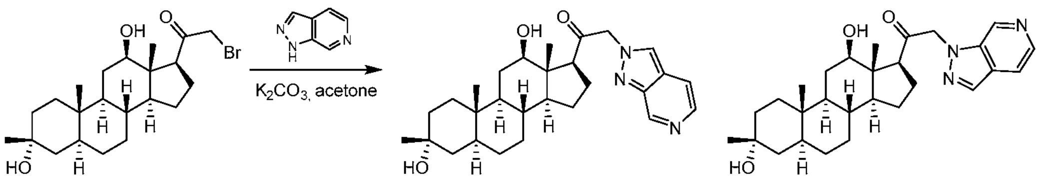
Compound 47 **Compound 48**

To a solution of **Compound 47** (50 mg, 0.114 mmol) in DCM (10 mL) was added PCC (98.0 mg, 0.455 mmol) and silica gel (150 mg) at 25°C. Then the solution was stirred at 25°C for 5 h. The reaction mixture was filtered and the residue was washed with anhydrous DCM (2 x 30 mL). The combined filtrate was concentrated in vacuum to give a crude product, which was purified by a silica gel column (PE/EtOAc=1/1) to give **Compound 48** (13 mg, 26%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.83-7.79 (m, 2H), 5.55 (d, *J* = 18.4 Hz, 1H), 5.08 (d, *J* = 18.4 Hz, 1H), 3.27 (t, *J* = 9.0 Hz, 1H), 2.52-2.39 (m, 1H), 2.39-2.29 (m, 1H), 2.26-2.14 (m, 1H), 1.89-1.68 (m, 3H), 1.58-1.43 (m, 4H), 1.40-1.23 (m, 9H), 1.21 (s, 3H), 1.07-0.99 (m, 1H), 1.07-0.99 (m, 1H), 0.96 (s, 3H), 0.84 (s, 3H).

LCMS Rt = 0.983 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{26}H_{36}N_3O_3$ $[M+H]^+$ 438, found 438.

Example 30. Syntheses of Compounds 49 and 50.



V1   Compound 49   Compound 50

To a mixture of **V1** (400 mg, 0.936 mmol) and K_2CO_3 (258 mg, 1.87 mmol) in acetone (5 mL) was added 1H-pyrazole-4-carbonitrile (166 mg, 1.40 mmol) at 25°C. The reaction mixture was stirred at the 25°C for 16 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product, which was purified by *prep.* HPLC (column: Boston Green ODS 150 * 30 5u, gradient: 34-44% B (A= 0.1% TFA-ACN, B= acetonitrile), flow rate: 30 mL/min) to give mixture of **Compound 49** and **Compound 50** (120 mg, crude) as yellow oil. The oil was purified by SFC (column: OD (250 mm * 30 mm, 5 um); Mobile phase: Supercritical CO_2 /MeOH + NH_3H_2O = 40/40; Flow rate: 50 ml/min; Wavelength: 220 nm) to give **Compound 49** (20 mg, 17%) as a solid and **Compound 50** (50 mg, 42%) as a solid.

Compound 49:

^{1}H NMR (400MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.17 (d, *J* = 5.6 Hz, 1H), 7.99 (s, 1H), 7.52 (d, *J* = 5.6 Hz, 1H), 5.81 (d, *J* = 17.6 Hz, 1H), 5.37 (d, *J* = 17.6 Hz, 1H), 3.61-3.56 (m, 1H), 2.66-2.60

(m, 2H), 2.21-2.08 (m, 1H), 1.92-1.64 (m, 4H), 1.54-1.44 (m, 4H), 1.42-1.31 (m, 4H), 1.30-1.25 (m, 3H), 1.21 (s, 3H), 1.18-1.05 (m, 3H), 0.97-0.85 (m, 2H), 0.77 (s, 3H), 0.73 (s, 3H).

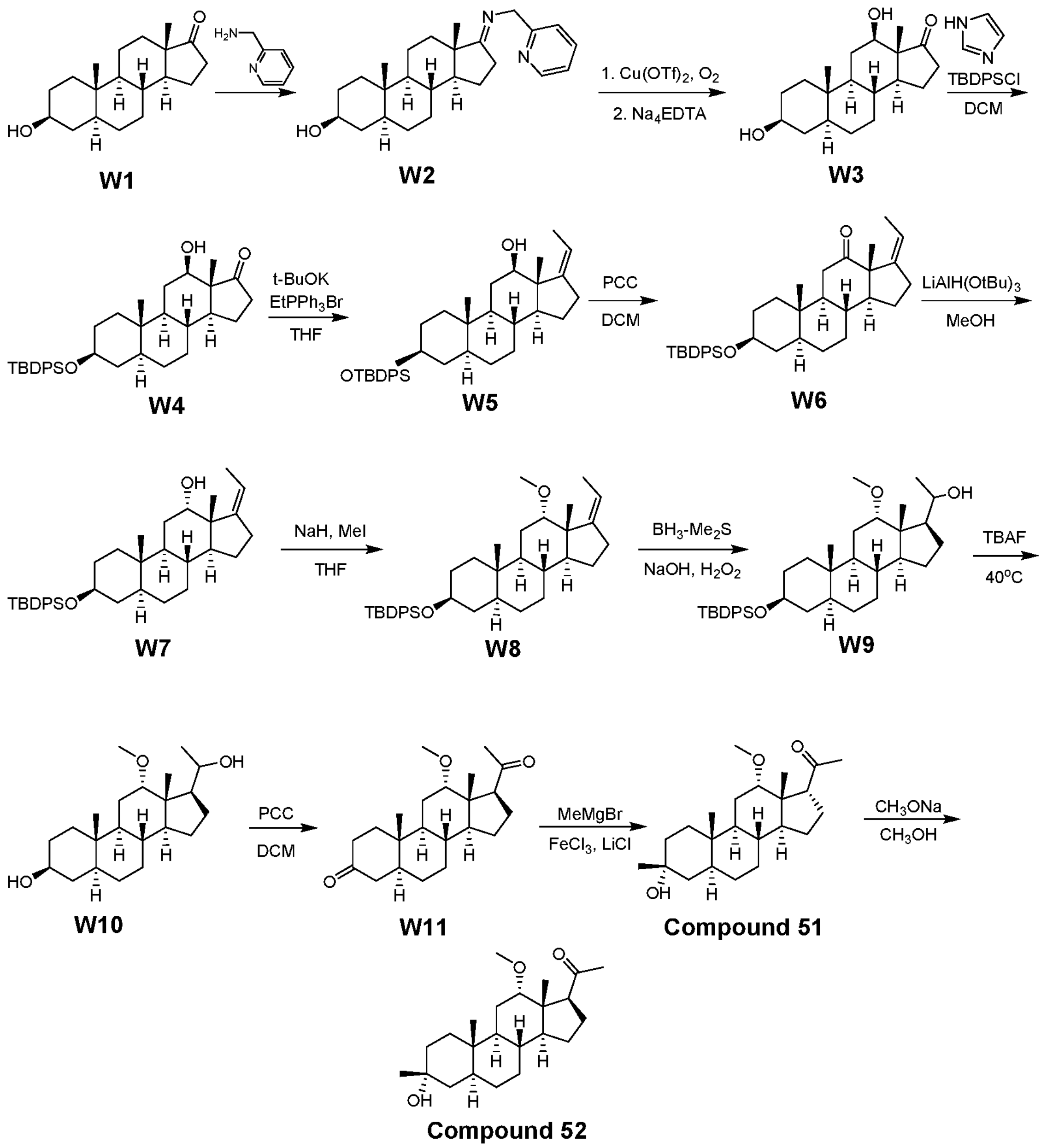
LCMS Rt = 0.655 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{28}H_{40}N_3O_3$ $[M+H]^+$ 466, found 466.

Compound 50:

^{1}H NMR (400MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.33-8.31 (m, 1H), 8.11 (s, 1H), 7.65-7.63 (m, 1H), 5.91 (d, J = 18.4 Hz, 1H), 5.35 (d, J = 18.4 Hz, 1H), 3.65-3.61 (m, 1H), 2.73-2.67 (m, 1H), 2.62-2.60 (m, 1H), 2.19-2.07 (m, 1H), 1.90-1.64 (m, 4H), 1.54-1.44 (m, 4H), 1.43-1.32 (m, 4H), 1.31-1.22 (m, 4H), 1.21 (s, 3H), 1.19-1.07 (m, 2H), 0.97-0.86 (m, 2H), 0.77 (s, 3H), 0.73 (s, 3H).

LCMS Rt = 0.690 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{28}H_{40}N_3O_3$ $[M+H]^+$ 466, found 466.

Example 31. Syntheses of Compounds 51 and 52.



Step 1. To a solution of **W1** (50 g, 172 mmol) in toluene (400 mL) was added p-toluenesulfonic acid (532 mg, 3.09 mmol) and pyridin-2-ylmethanamine (40.8 g, 378 mmol) at 25°C. The reaction mixture was heated to 140°C with a Dean-Stark apparatus for 16 hrs. The reaction mixture was cooled to 25°C and then diluted with EtOAc (300 mL) and water (200 mL). The combined organic layer was washed sequentially with sat. NH_4Cl (2 x 200 mL), sat. $NaHCO_3$ (200 mL), brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated

under reduced pressure to give the crude product, which was triturated from (EtOAc, 200 mL) at 25°C to give **W2** (54 g, 83%) as a pale solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 8.50-8.43 (m, 1H), 7.60-7.55 (m, 1H), 7.36-7.33 (m, 1H), 7.21-7.06 (m, 1H), 7.18-7.11 (m, 2H), 4.58-4.45 (m, 2H), 3.61-3.40 (m, 1H), 2.40-2.34 (m, 1H), 2.22-2.18 (m, 1H), 1.98-1.95 (m, 2H), 1.93-1.60 (m, 5H), 1.57-1.33 (m, 4H), 1.21-1.17 (m, 3H), 1.05-0.96 (m, 2H), 0.95-0.84 (m, 2H), 0.82 (s, 3H), 0.78 (s, 3H), 0.70-0.65 (s, 1H).

Step 2. **W2** (20 g, 52.5 mmol), $Cu(OTf)_2$ (24.6 g, 68.2 mmol) and L-ascorbic acid sodium salt (20.8 g, 105 mmol) were added to a round-bottom-flask under N_2. Acetone (160 mL) and MeOH (160 mL) were added at 25°C and stirred for 5 mins (reaction mixture may turn brown). O_2 from a balloon was bubbled through the reaction mixture for 5 mins (resulting in a blue/green solution), after which the reaction was heated to 60°C under an O_2 atmosphere for 18 hrs. The reaction mixture was cooled to 25°C, EtOAc (300 mL) and sat. Na_4EDTA (300 mL, PH~10) were added and the reaction mixture was stirred for 2 hrs. The layer was separated. The aqueous layer was extracted with EtOAc (2 x 300 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc=1/1) to give **W3** (12.5 g, 77%) as a solid.

^{1}H NMR (400MHz, MeOD) δ3.74-3.64 (m, 1H), 3.60-3.47 (m, 1H), 2.48-2.41 (m, 1H), 2.14-2.05 (m, 1H), 2.01-1.91 (m, 1H), 1.89-1.62 (m, 6H), 1.62-1.51 (m, 2H), 1.49-1.28 (m, 7H), 1.22-1.11 (m, 1H), 1.10-0.97 (m, 2H), 0.94 (s, 3H), 0.89 (s, 3H), 0.87-0.80 (m, 1H).

Step 3. To a solution of **W3** (10.3 g, 33.6 mmol) in DCM (150 mL) was added TBDPSCl (13.8 g, 50.4 mmol) and imidazole (4.57 g, 67.2 mmol) at 25°C. The reaction was stirred at 25°C for 16 h. The reaction was quenched with H_2O (100 mL) and extracted with DCM (2 x 100 mL). The combined organic layer was washed with saturated brine solution (100 mL). The organic phase was then dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum and the resulting solid was purified by column chromatography (PE/EtOAc=15/1-10/1) to give **W4** (6 g, 33%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H), 7.45-7.33 (m, 6H), 3.70-3.65 (m, 1H), 3.60-3.53 (m, 1H), 2.94 (d, *J*= 0.8 Hz, 1H), 2.46-2.39 (m, 1H), 2.13-2.05 (m, 1H), 2.04-2.01 (m, 2H), 1.98-1.87 (m, 2H), 1.78-1.68 (m, 2H), 1.68-1.57 (m, 2H), 1.54-1.38 (m, 4H), 1.23-1.11 (m, 3H), 1.04 (s, 9H), 0.91 (s, 3H), 0.90-0.84 (m, 1H), 0.82 (s, 3H), 0.79-0.63 (m, 2H).

Step 4. To a suspension of $EtPh_3PBr$ (16.7 g, 45.2 mmol) in anhydrous THF (60 mL) under N_2 was added t-BuOK (5.07 g, 45.2 mmol) at 25°C. The color of the suspension turned dark red. Then the reaction mixture was heated to 40°C. After stirring at 40°C for 30 mins, **W4** (6.2 g, 11.3 mmol) was added. The reaction mixture was stirred at 40°C for 1.5 hrs. The reaction mixture was quenched with aq.NH_4Cl solution (100 mL) and then extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to get the crude product, which was purified with flash column (0-20% of EtOAc in PE) to give **W5** (6 g, 95%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.71-7.63 (m, 4H), 7.45-7.31 (m, 6H), 5.20-5.14 (m, 1H), 3.71-3.65 (m, 1H), 3.59-3.54 (m, 1H), 2.48-2.34 (m, 1H), 2.16-2.12 (m, 1H), 1.83-1.80 (m, 4H), 1.78-1.70 (m, 1H), 1.69-1.57 (m, 4H), 1.45-1.40 (m, 2H), 1.29-1.21 (m, 3H), 1.20-1.14 (m, 2H), 1.04 (s, 9H), 1.00-0.93 (m, 1H), 0.91-0.85 (m, 2H), 0.83 (s, 3H), 0.80 (s, 3H), 0.79-0.68 (m, 2H), 0.67-0.57 (m, 1H).

Step 5. To a solution of **W5** (6 g, 10.7 mmol) in DCM (60 mL) was added silica gel (10 g) and PCC (9.22 g, 42.8 mmol) at 25°C. Then the reaction was stirred at 25°C for 2 hrs. The reaction mixture was filtered and the residue was washed with DCM (2 x 80 mL). The combined filtrate was concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc=10/1) to give **W6** (5 g, 84%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.71-7.61 (m, 4H), 7.46-7.31 (m, 6H), 5.46-5.42 (m, 1H), 3.60-3.54 (m, 1H), 2.57 (t, J= 13.2 Hz, 1H), 2.39-2.12 (m, 3H), 1.90-1.71 (m, 2H), 1.71-1.62 (m, 3H), 1.61-1.56 (m, 4H), 1.52-1.33 (m, 6H), 1.32-1.22 (m, 2H), 1.20 (s, 3H), 1.04 (s, 9H), 0.92-0.75 (m, 5H).

Step 6. To a solution of **W6** (5 g, 9.01 mmol) in THF (50 mL) was added lithium tri-tert-butoxyaluminum hydride (11.4 g, 45 mmol) in THF (100 mL) was added dropwise at 0°C. The reaction was warmed to 25°C and stirred at 25°C for 16 hrs. The reaction was quenched by adding aqueous HCl (1 M, 100 mL) and the mixture was diluted with EtOAc (100 mL). The phases were separated and the organic phase was washed sequentially with water (100 mL) and saturated brine solution (100 mL). The organic phase was then dried over anhydrous Na_2SO_4

and filtered. The filtrate was concentrated under vacuum to give **W7** (5 g, crude) as pale yellow oil.

Step 7. To a solution of **W7** (5 g, 8.97 mmol) in THF (50 mL) was added NaH (1.07 g, 26.9 mmol, 60%) in one portion at 0°C under N_2. After 30 mins, MeI (12.7 g, 5.57 mL, 89.7 mmol, actual dosage: 13.6 g) was added dropwise at 25°C. The reaction mixture was stirred for 16 hrs at 40°C. The mixture was quenched with saturated aqueous NH_4Cl (100 mL). Then the mixture was extracted with EtOAc (200 mL) and H_2O (2 x 150 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was evaporated to afford crude product. The crude product was purified by column chromatography on silica gel (PE/EtOAc= 20/1-10/1) to give **W8** (4.7 g, 92%) as an oil.

^{1}H NMR (400MHz, CDCl3) δ 7.70-7.65 (m, 4H), 7.45-7.34 (m, 6H), 5.23-5.18 (m, 1H), 3.83-3.77 (m, 1H), 3.63-3.55 (m, 1H), 3.26 (s, 3H), 2.46-2.09 (m, 2H), 1.92-1.85 (m, 1H), 1.76-1.73 (m, 6H), 1.54-1.30 (m, 8H), 1.23-1.09 (m, 6H), 1.05 (m, 9H), 0.86 (s, 3H), 0.80 (s, 3H).

Step 8. To a solution of **W8** (4.7 g, 8.23 mmol) in THF (50 mL) was added dropwise a solution of BH_3-Me_2S (8.22 mL, 82.3 mmol) at 0°C. The solution was stirred at 25°C for 16 hrs. After cooling to 0°C, a solution of EtOH (4.79 mL, 82.3 mmol) and NaOH solution (39.4 g, 10% in water) was added very slowly. After addition, H_2O_2 (8.23 mL, 82.3 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. The resulting solution was stirred at 25°C for 1 h. The mixture was quenched with saturated aqueous $Na_2S_2O_3$ (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with saturated aqueous $Na_2S_2O_3$ (2 x 50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated in vacuum to give **W9** (5.1 g, crude) as a solid, which was used directly for next step without further purification.

Step 9. To a solution of **W9** (5.1 g, 8.65 mmol) in THF (10 mL) was added TBAF (43.2 mL, 1 M in THF) at 25°C. The reaction was stirred at 40°C for 48 hrs. The reaction was quenched with water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give **W10** (5 g, crude) as pale yellow oil which was used directly for next step without further purification.

Step 10. To a solution of **W10** (5 g, crude) in DCM (50 mL) was added silica gel (13.4 g) and PCC (12.2 g, 56.8 mmol) at 25°C. The reaction was stirred at 25°C for 4 hrs. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc= 5/1) to give **W11** (1.2 g, impure) as a pale yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.42-3.38 (m, 1H), 3.13 (s, 3H), 2.56-2.52 (dd, J= 8.8 Hz, 1H), 2.43-2.21 (m, 4H), 2.05 (s, 3H), 2.04-1.65 (m, 8H), 1.55-1.23 (m, 5H), 1.18-1.01 (m, 3H), 1.00 (s, 3H), 0.94 (s, 3H).

Step 11. A suspension of LiCl (307 mg, 7.26 mmol, anhydrous) in THF (20 mL, anhydrous) was stirred at 10°C for 30 mins under N_2. $FeCl_3$ (616 mg, 3.80 mmol, anhydrous) was added at 10°C. The mixture was cooled to -30°C. To the mixture was added MeMgBr (4.60 mL, 13.8 mmol, 3M in diethyl ether) dropwise at -30°C. The mixture was stirred at -30°C for 10 mins. **W11** (1.2 g, impure) was added at -30°C. The mixture was stirred at -15°C for 2 hrs. To the mixture was added citric acid (40 mL, 10% aq.). The mixture was extracted with EtOAc (2 x 60 mL). The combined organic phase was washed with saturated brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc=1/10~1/5) to give **Compound 51** (650 mg, 52%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.38-3.36 (m, 1H), 3.11 (s, 3H), 2.53-2.48 (dd, *J*= 8.8 Hz, 1H), 2.04 (s, 3H), 2.01-1.94 (m, 1H), 1.70-1.59 (m, 4H), 1.55-1.46 (m, 4H), 1.42-1.23 (m, 6H), 1.19 (s, 3H), 1.18-0.98 (m, 6H), 0.91 (s, 3H), 0.74 (s, 3H).

LCMS Rt = 1.058 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{23}H_{39}O_3$ $[M+H]^+$ 363, found 363.

The stereochemistry at C17 of **Comound 51** was confirmed by NOE.

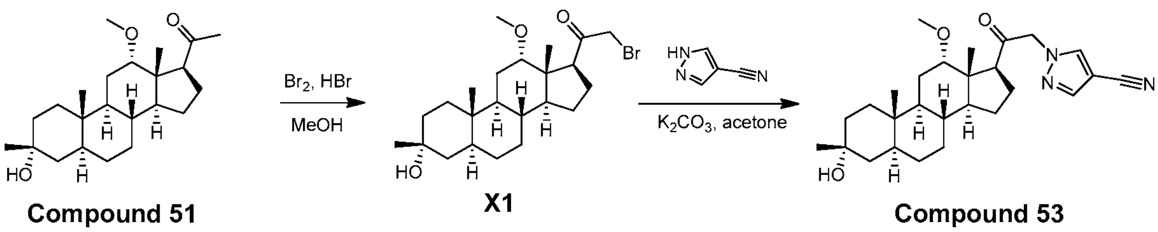
Step 12. To a solution of **Compound 51** (600 mg, 1.65 mmol) in MeOH (6 mL) was added CH_3ONa (891 mg, 16.5 mmol) at 25°C. The reaction was stirred at 50°C for 16 hrs. The reaction mixture was quenched with HCl (2 mL, 2 M) to adjust the pH to about 7, diluted with water (20 mL) and extracted with DCM (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc=5/1~3/1) to give **Compound 52** (420 mg, 70%, 10 mg for delivery) as a solid.

^{1}H NMR (400MHz, CDCl3) δ 3.45-3.42 (m, 1H), 3.35 (s, 3H), 3.27 (t, *J*= 9.2 Hz, 1H), 2.08 (s, 3H), 2.01-1.94 (m, 1H), 1.70-1.59 (m, 4H), 1.55-1.46 (m, 4H), 1.42-1.23 (m, 6H), 1.20 (s, 3H), 1.19-1.17 (m, 3H), 1.16-0.92 (m, 3H), 0.75 (s, 3H), 0.63 (s, 3H).

LCMS Rt = 1.033 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{22}H_{35}O_2$ $[M -CH_3OH+H]^+$ 331, found 331.

The stereochemistry at C17 of Comound 52 was confirmed by NOE during the pilot reaction..

Example 32. Synthesis of Compound 53.



Step 1. To a solution of **Compound 51** (400 mg, 1.10 mmol) in MeOH (4 mL) was added HBr (44.5 mg, 0.220 mmol, 40% in water) and the solution of Br_2 (0.06 mL, 1.21 mmol) in MeOH (4 mL) at 25°C. The mixture was stirred at 25°C for 16 hrs. The mixture was quenched by sat.aq $NaHCO_3$ (10 mL) and treated with water (20 mL). The reaction mixture was filtered and the residue was washed with water (10 mL), concentrated in vacuum to give **X1** (430 mg, 89%) as a solid.

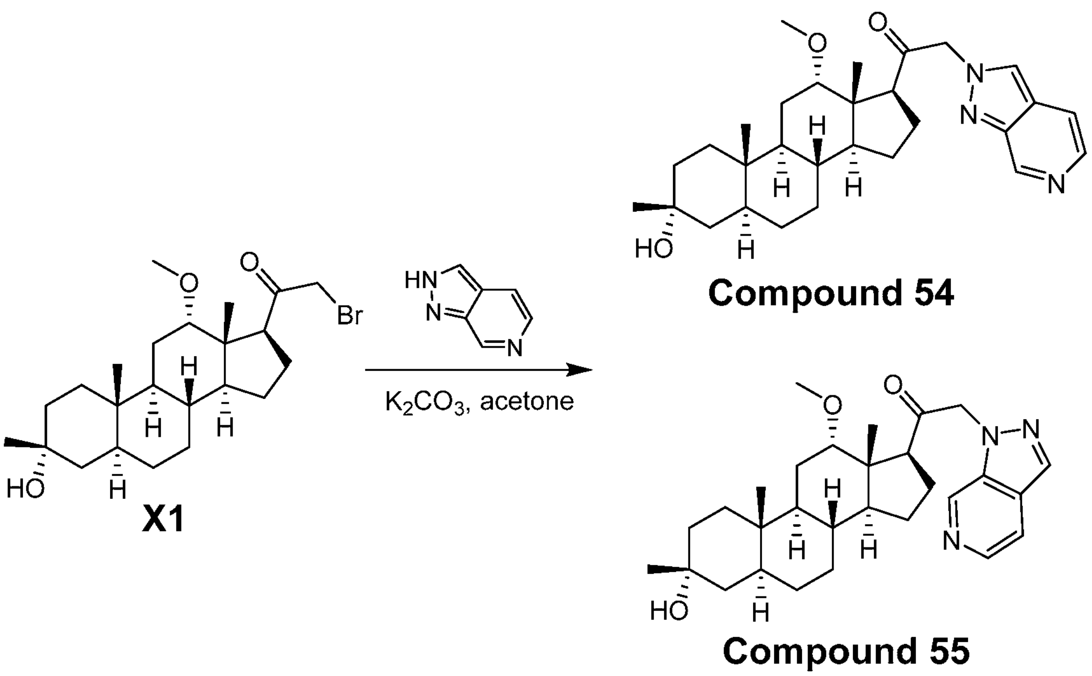
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96-3.82 (m, 2H), 3.47 (t, *J*= 8.8 Hz, 1H), 3.38-3.36 (m, 1H), 3.35 (s, 3H), 2.19-1.93 (m, 2H), 1.78-1.60 (m, 4H), 1.53-1.45 (m, 3H), 1.45-1.33 (m, 3H), 1.32-1.22 (m, 5H), 1.20 (s, 3H), 1.15 (s, 1H), 1.13-0.91 (m, 3H), 0.75 (s, 3H), 0.67 (s, 3H).

Step 2. To a solution of 1H-pyrazole-4-carbonitrile (31.6 mg, 0.3397 mmol) and K_2CO_3 (78.2 mg, 0.5662 mmol) in acetone (2 mL) was added **X1** (100 mg, 0.2265 mmol) at 25°C. The mixture was stirred at 25°C for 2 h. The mixture was poured into water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with saturated brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give **Compound 53** (106 mg, crude) as a solid, which was further purified by HPLC (column: Gemini 150*25 5u, gradient: 56-81% B, condition: water(0.05%HCl)-ACN, flow rate: 30 mL/min) to give **Compound 53** (57 mg, 54%) as solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.79 (s, 1H), 5.00-4.80 (m, 2H), 3.53-3.50 (m, 1H), 3.41-3.36 (m, 4H), 2.20-2.05 (m, 2H), 1.80-1.65 (m, 4H), 1.60-1.50 (m, 7H), 1.48-0.90 (m, 11H), 0.75 (s, 3H), 0.67 (s, 3H).

LCMS Rt = 1.053 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{27}H_{40}N_3O_3$ $[M+H]^+$ 454, found 454.

Example 33. Syntheses of Compounds 54 and 55.



To a solution of **X1** (150 mg, 0.339 mmol) in acetone (2 mL) was added 2H-pyrazolo [3,4-c]pyridine (60.5 mg, 0.508 mmol) and K_2CO_3 (92.8 mg, 0.678 mmol). After stirring at 15°C for 16 hrs, the reaction mixture was treated with water (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by HPLC (column: Waters Xbridge 150*25 5u), water (10mM NH4HCO3)-ACN, gradient: 45-65% B, flow rate: 25 mL/min)) to give **Compound 55** (20 mg, 12%) as a solid and **Compound 54** (15 mg, impure) as a solid, which was combined with another batch prepared from 50 mg of **X1**. The impure sample was further purified by *prep*-TLC (PE/EtOAc = 1/1) to give **Compuond 54** (8 mg) as a solid.

Compound 54:

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40-9.20 (m, 1H), 8.25-8.10 (m, 1H), 8.10-8.00 (m, 1H), 7.70-7.55 (m, 1H), 5.39-5.12 (m, 2H), 3.63-3.10 (m, 1H), 3.52-3.48 (m, 1H), 3.42 (s, 3H), 2.34-2.01 (m, 3H), 2.00-1.62 (m, 10H), 1.62-1.48 (m, 5H), 1.48-0.97 (m, 6H), 0.82 -0.63 (m, 6H).

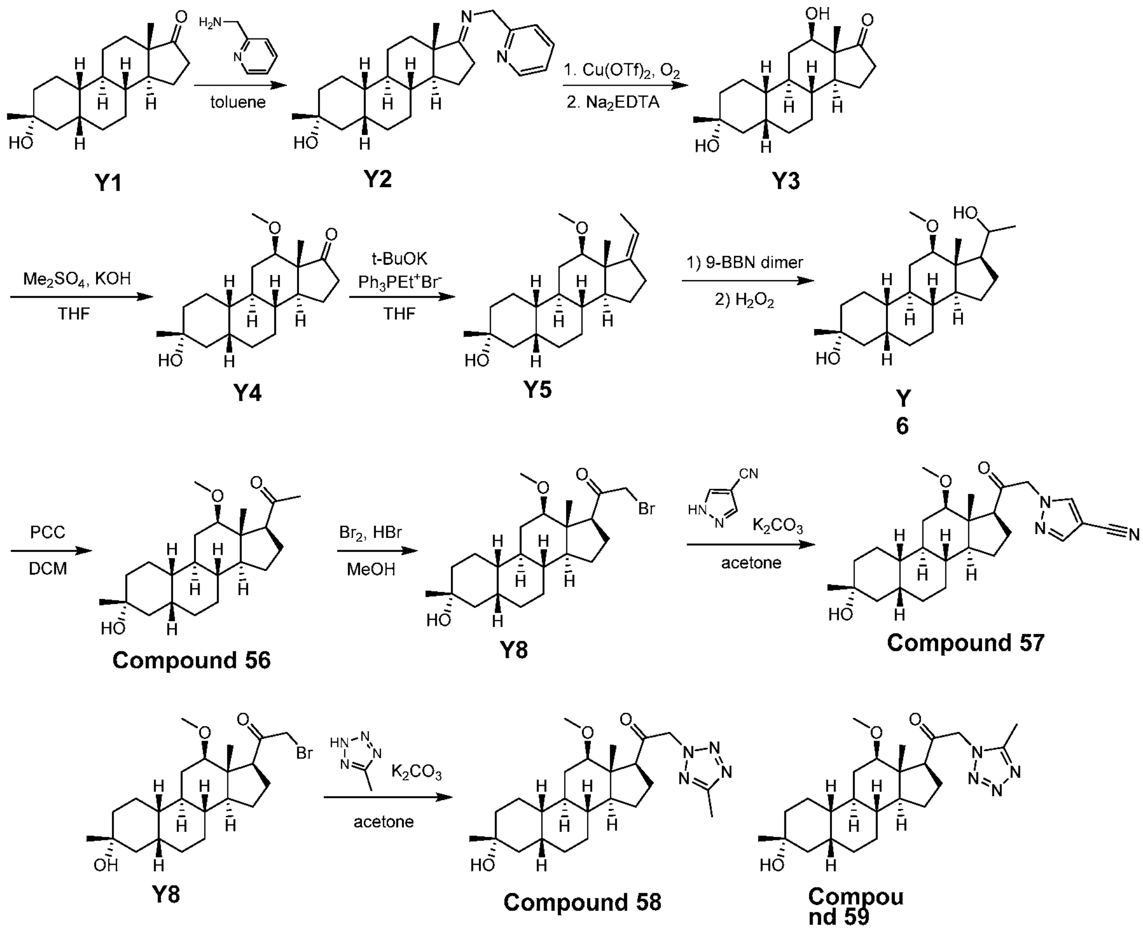
LCMS Rt = 0.766 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{29}H_{42}N_3O_3$ $[M+H]^+$ 480 found 480.

Compound 55:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81-8.78 (m, 1H), 8.36-8.32 (m, 1H), 8.08 (s, 1H), 7.65-7.61 (m, 1H), 5.28-5.12 (m, 2H), 3.70-3.60 (m, 1H), 3.52-3.48 (m, 1H), 3.41 (s, 3H), 2.21-2.01 (m, 2H), 1.84-1.65 (m, 4H), 1.65-1.48 (m, 6H), 1.48-1.19 (m, 10H), 1.19-0.98 (m, 2H), 0.82 -0.70 (m, 6H).

LCMS Rt = 0.793 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{29}H_{42}N_3O_3$ $[M+H]^+$ 480 found 480.

Example 34. Syntheses of Compounds 56, 57, 58, and 59.



Step 1. To a solution of **Y1** (10 g, 34.4 mmol) in toluene (100 mL) was added *p*-toluenesulfonic acid (106 mg, 0.6 mmol) and pyridin-2-ylmethanamine (8.17 g, 75.6 mmol) at 25°C. The reaction mixture was heated to 140°C with a Dean-Stark apparatus for 16 hrs. The reaction was cooled to 25°C and diluted with EtOAc (200 mL). The organic layer was washed sequentially with sat. NH_4Cl (2 x 200 mL), sat. $NaHCO_3$ (200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and then concentrated in vacuum to give a crude product. The residual was triturated with EtOAc (20 mL) to give **Y2** (8.7 g, 66%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57-8.49 (m, 1H), 7.72-7.61 (m, 1H), 7.44-7.38 (m, 1H), 7.17-7.09 (m, 1H), 4.69-4.52 (m, 2H), 2.49-2.22 (m, 2H), 2.06-1.63 (m, 8H), 1.54-1.44 (m, 3H), 1.41 (s, 3H), 1.40-1.32 (m, 3H), 1.30-1.24 (m, 5H), 1.21-1.07 (m, 3H), 0.90 (s, 3H).

Step 2. Y2 (8.7 g, 22.8 mmol), $Cu(OTf)_2$ (10.6 g, 29.6 mmol) and L-ascorbic acid sodium salt (9.03 g, 45.6 mmol) were added to a round-bottom-flask under N_2. Acetone (dry, 50 mL) and

MeOH (dry, 50 mL) were added at 25°C and stirred for 5 mins (reaction mixture may turn brown). O_2 from a balloon was bubbled through the reaction mixture for 5 min (resulting in a blue/green solution).The reaction mixture was heated at 50°C under an O_2 atmosphere for 24 hrs. The reaction mixture was then cooled to 25°C. EtOAc (100 mL) and sat. Na_4ETDA (200 mL, pH~10) were added and the reaction mixture was stirred for 1 h. The layers were separated. The aqueous layer was extracted with EtOAc (2 x 200 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product, which was purified by flash column (0~40% of EtOAc in PE) to give **Y3** (4 g, 57%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.82-3.74 (m, 1H), 2.98 (brs, 1H), 2.49-2.40 (m, 1H), 2.17-2.03 (m, 1H), 2.01-1.71 (m, 5H), 1.67-1.29 (m, 12H), 1.26 (s, 3H), 1.23-1.01 (m, 3H), 0.93 (s, 3H).

Step 3. To a solution of **Y3** (2 g, 6.52 mmol) in THF (20 mL) was added KOH (2.21 g, 39.6 mmol) and Me_2SO_4 (1.85 g, 14.6 mmol) at 0°C. Then the mixture was warmed to 25°C and stirred at the same temperature for 16 hrs. Me_2SO_4 (4.08 g, 32.4 mmol) was added at 0°C and the mixture was stirred at 40°C for 16 hrs. The mixture was quenched with the addition of 50 mL of water and extracted with EtOAc (2 x 30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product, which was purified by a silica gel column (PE/EtOAc=10/1-5/1) to give **Y4** (1.2 g, 58%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.50 (m, 1H), 3.19 (dd, J = 6.8 Hz, J = 4.8 Hz, 1H), 2.48-2.40 (m, 1H), 2.12-2.00 (m, 2H), 1.98-1.51 (m, 7H), 1.48-1.28 (m, 10H), 1.27 (s, 3H), 1.23-1.01 (m, 4H), 0.93 (s, 3H).

Step 4. To a suspension of $EtPPh_3Br$ (4.15 g, 11.2 mmol) in THF (20 mL) was added t-BuOK (1.25 g, 11.2 mmol) at 25°C under N_2. The mixture was stirred at 50°C for 30 mins. To the mixture was added **Y4** (1.2 g, 3.74 mmol) in THF (12 mL) at 50°C. The mixture was stirred at 50°C for 16 hrs. The mixture was quenched with sat.NH_4Cl solution (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc=5/1~3/1) to give **Y5** (1.1 g, 89%) as colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 5.26-5.18 (m, 1H), 3.34 (s, 3H), 3.16 (dd, J = 10.6 Hz, J = 5.0 Hz, 1H), 2.44-2.39 (m, 1H), 2.20-2.15 (m, 4H), 1.80-1.76 (m, 5H), 1.75-1.23 (m, 9H), 1.27 (s, 3H), 1.25-0.95 (m, 6H), 0.86 (s, 3H).

Step 5. To a solution of **Y5** (1.1 g, 3.30 mmol) in THF (30 mL) was added 9-BBN dimer (2.01 g, 8.25 mmol) at 25°C under N_2. The solution was stirred at 50°C for 16 hrs. After cooling to 0°C, a solution of EtOH (30 mL) and NaOH (6.60 mL, 5M in H_2O, 33.0 mmol) was added very slowly. After the addition, H_2O_2 (3.30 mL, 33.0 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. The mixture was stirred at 50°C under N_2 for 1 h. The mixture was re-cooled to 30°C. Water (100 mL) was added to the solution and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed sat. $Na_2S_2O_3$ (100 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give **Y6** (3 g, crude) as colorless oil, which was used directly for the next step.

Step 6. To a solution of **Y6** (3 g, 8.55 mmol) in DCM (30 mL) was added silica gel (6.1 g) and PCC (5.51 g, 25.6 mmol) at 25°C. The reaction was stirred at 25°C for 2 hrs. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give crude product, which was purified by a silica gel column (PE/EtOAc= 5/1) to give **Compound 56** (1.2 g, impure) as colourless oil. **Compound 56** (1.2 g, impure) was purified by combi-flash (DCM/acetone=30/1-20/1) to give **Compound 56** (250 mg, pure) as a solid and **Compound 56** (420 mg, impure) as a solid. **Compound 56** (250 mg, 0.717 mmol) was triturated with (PE/EtOAc= 3/1, 120 mL) to afford **Compound 56** (240 mg, 96%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 3.34 (m, 1H), 3.08 (dd, J = 10.8 Hz, J = 4.4 Hz, 1H), 2.69 (t, J = 8.8 Hz, 1H), 2.22 (s, 3H), 2.11-2.05 (m, 2H), 1.80-1.55 (m, 8H), 1.53-1.29 (m, 5H), 1.28 (s, 3H), 1.19-0.85 (m, 9H), 0.66 (s, 3H).

LCMS Rt = 0.924 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{22}H_{37}O_3$ $[M+H]^+$ 349, found 349.

Step 7. To a solution of **Compound 56** (420 mg, 1.20 mmol) in MeOH (8 ml) was added HBr (48.5 mg, 0.240 mmol, 40% in water) and Br_2 (210 mg, 1.32 mmol) in MeOH (8 mL) at 25°C. The mixture was stirred at 25°C for 16 hrs. The mixture was quenched by sat.$NaHCO_3$ (10 mL) and water (20 mL), extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford **Y8** (500 mg, 98%) as light yellow oil, which was used directly for the next step.

^{1}H NMR (400MHz, $CDCl_3$) δ 4.15-3.99 (m, 2H), 3.34 (s, 3H), 3.11 (dd, *J* = 11.0 Hz, *J* = 4.6 Hz, 1H), 3.01 (t, *J* = 9.2 Hz, 1H), 2.58 (s, 1H), 2.19-2.05 (m, 3H), 1.90-1.59 (m, 6H), 1.51-1.32 (m, 7H), 1.28 (s, 3H), 1.13-1.01 (m, 3H), 0.94-0.82 (m, 2H), 0.65 (s, 3H).

Step 8. To a mixture of **Y8** (250 mg, 0.585 mmol) and K_2CO_3 (160 mg, 1.16 mmol) in acetone (4 mL) was added 1H-pyrazole-4-carbonitrile (81.6 mg, 0.877 mmol) at 25°C. The reaction mixture was stirred at the 25°C for 16 hrs. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give crude product, which was purified by a silica gel column (PE/EtOAc= 2/1~1/1) to give **Compound 57** (125 mg, 49%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.81 (s, 2H), 5.45 (d, J=17.6 Hz, 1H), 4.94 (d, J=17.6 Hz, 1H), 3.40 (s, 3H), 3.19 (dd, *J* = 11 Hz, *J* = 4.6 Hz, 1H), 2.75-2.65 (m, 1H), 2.22-2.07 (m, 2H), 1.92-1.59 (m, 6H), 1.52-1.41 (m, 7H), 1.40-1.30 (m, 3H), 1.29 (s, 3H), 1.15-1.04 (m, 2H), 0.99-0.82 (m, 2H), 0.67 (s, 3H).

LCMS Rt = 0.981 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{26}H_{37}N_3O_3Na$ $[M +Na]^+$ 462, found 462.

Step 9. To a solution of **Y8** (250 mg, 0.585 mmol) in acetone (5 mL) was added 5-methyl-2H-tetrazole (73.7 mg, 0.877 mmol), followed by K_2CO_3 (160 mg, 1.16 mmol). The resulting reaction mixture was stirred at 25°C for 16 hrs. The mixture was filtered and the filtrate was concentrated in vacuum to give crude product, which was purified by a silica gel column (PE/EtOAc= 3/1-1/1) to give **Compound 58** (60 mg, impure) as a solid and **Compound 59** (54 mg, 22%) as a solid. **Compound 58** (60 mg, impure) was re-purified by combi-flash (EtOAc in PE, 40%-50%) to afford **Compound 58** (45 mg, 75%) as a solid.

Compound 58:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (d, *J* = 16.8 Hz, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 3.45 (s, 3H), 3.18 (dd, *J* =11 Hz, *J* = 4.2 Hz, 1H), 2.74-2.64 (m, 1H), 2.56 (s, 3H), 2.23-2.06 (m, 2H), 1.91-1.67 (m, 6H), 1.53-1.36 (m, 8H), 1.37-1.29 (m, 3H), 1.28 (s, 3H), 1.15-1.02 (m, 2H), 0.99-0.87 (m, 1H), 0.69 (s, 3H).

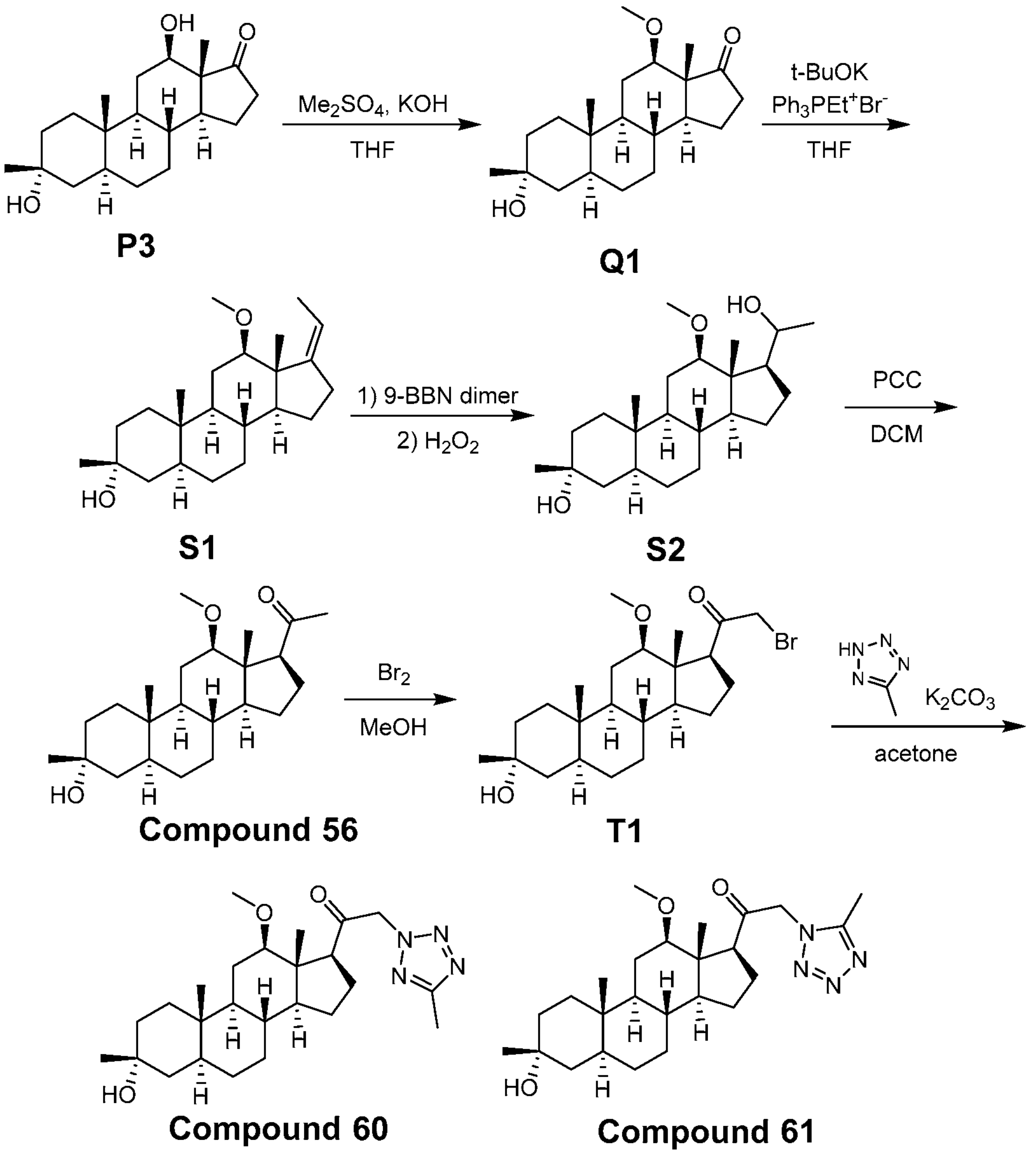
LCMS Rt = 0.951 min in 2 min chromatography, 30-90 AB, purity 99.42%, MS ESI calcd. For $C_{23}H_{33}N_4O$ $[M +H-CH_3OH-H_2O]^+$ 381, found 381.

Compound 59:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (d, *J* = 18.0 Hz, 1H), 5.24 (d, *J* = 18.4 Hz, 1H), 3.42 (s, 3H), 3.24 (dd, *J* = 11.2 Hz, *J* = 4.4 Hz, 1H), 2.84-2.72 (m, 1H), 2.45 (s, 3H), 2.22-2.06 (m, 2H), 1.91-1.72 (m, 5H), 1.52-1.37 (m, 7H), 1.38-1.30 (m, 3H), 1.29 (s, 3H), 1.17-1.03 (m, 3H), 1.01-0.83 (m, 2H), 0.69 (s, 3H).

LCMS Rt = 0.912 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{24}H_{39}N_4O_3$ $[M+H]^+$ 431, found 431.

Example 35. Syntheses of Compounds 60 and 61.



Step 1. To a solution of **P3** (2 g, 6.24 mmol) in THF (20 mL) was added KOH (1.05 g, 18.9 mmol) and Me_2SO_4 (1.60 g, 1.20 mL, 12.7 mmol) at 0°C. Then the mixture was warmed to 25°C and stirred at this temperature for 16 hrs. Me_2SO_4 (1.60 g, 1.20 mL, 12.7 mmol) at 0°C was added and the mixture was stirred at 25°C for 16 hrs. The mixture was quenched with 50 mL of water and extracted with EtOAc (2 x 30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product, which was purified by a silica gel column (PE/EtOAc=10/1-5/1) to give **Q1** (1.7 g, 82%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3H), 3.17 (dd, J = 11.2 Hz, J = 4.8 Hz, 1H), 2.48-2.39 (m, 1H), 2.12-1.88 (m, 3H), 1.84-1.74 (m, 1H), 1.54-1.49 (m, 3H), 1.42-1.33 (m, 2H), 1.32-1.22 (m, 6H), 1.21 (s, 3H), 1.14-1.11 (m, 2H), 1.13 (s, 1H), 1.02-0.94 (m, 1H), 0.93 (s, 3H), 0.87-0.79 (m, 1H), 0.77 (s, 3H).

Step 2. To a suspension of $EtPPh_3Br$ (5.64 g, 15.2 mmol) in THF (60 mL) was added t-BuOK (1.70 g, 15.2 mmol) at 25°C under N_2. The mixture was stirred at 50°C for 30 mins. To the mixture was added **Q1** (1.7 g, 5.08 mmol) in THF (20 mL) at 50°C. The mixture was stirred at 50°C for 16 hrs. The reaction was cooled to 25°C and the mixture was quenched with sat.NH_4Cl (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product, which was purified by a silica gel column (PE/EtOAc= 5/1~3/1) to give **S1** (1.6 g, 91%) as a solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27-5.16 (m, 1H), 3.33 (s, 3H), 3.14 (dd, J = 10.4 Hz, J = 4.8 Hz, 1H), 2.46-2.33 (m, 1H), 2.26-2.06 (m, 2H), 1.80-1.75 (m, 3H), 1.73-1.70 (m, 1H), 1.55-1.51 (m, 2H), 1.42-1.32 (m, 3H), 1.28-1.22 (m, 5H), 1.20 (s, 3H), 1.19-1.16 (m, 2H), 1.15-1.02 (m, 2H), 0.97-0.87 (m, 1H), 0.86 (s, 3H), 0.82-0.78 (m, 1H), 0.82-0.78 (m, 1H), 0.77 (s, 3H).

Step 3. To a solution of **S1** (1.6 g, 4.61 mmol) in THF (20 mL) was added 9-BBN dimer (2.80 g, 11.5 mmol) at 0°C under N_2. The solution was stirred at 50°C for 16 hrs. After cooling to 0°C, a solution of EtOH (30 mL) and NaOH (9.22 mL, 5M in H_2O, 46.1 mmol) was added in sequence very slowly. After the addition, H_2O_2 (4.60 mL, 46.1 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. The mixture was stirred at 50°C under N_2 for 1 h. The mixture was cooled to 30°C, diluted with water (100 mL) and extracted with EtOAc (2 x100 mL). The combined organic layer was washed with sat. $Na_2S_2O_3$ (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give **S2** (3.5 g, crude) as colorless oil, which was directly used in next step without further purification.

Step 4. To a solution of **S2** (3.5 g, 9.60 mmol) in DCM (35 mL) was added silica gel (5.6 g) and PCC (5.15 g, 23.9 mmol) at 25°C. The reaction was stirred at 25°C for 2 hrs. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc= 5/1) to give **Compound 56** (950 mg, 27%) as a solid.

^{1}**H NMR** (400MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.06 (dd, *J* = 10.8 Hz, *J* = 4.4 Hz, 1H), 2.68 (t, *J* = 9.0 Hz, 1H), 2.21 (s, 3H), 2.11-1.95 (m, 2H), 1.74-1.62 (m, 3H), 1.54-1.43 (m, 3H), 1.42-1.22 (m, 7H), 1.21 (s, 3H), 1.18-1.02 (m, 4H), 0.96-0.78 (m, 2H), 0.76 (s, 3H), 0.65 (s, 3H).

Step 5. To a solution of **Compound 56** (200 mg, 0.552 mmol) in MeOH (4 ml) was added HBr (22.3 mg, 0.11 mmol, 40% in water) and Br_2 (96.9 mg, 0.607 mmol) in MeOH (4 mL) at 25°C. The mixture was stirred at 25°C for 16 hrs. The mixture was quenched by sat.$NaHCO_3$ (10 mL), treated with water (20 mL), extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum to afford **T1** (230 mg, crude) as light yellow oil, which was used directly for the next step.

^{1}**H NMR** (400MHz, $CDCl_3$) δ 4.18-4.09 (m, 1H), 4.06-3.97 (m, 1H), 3.32 (s, 3H), 3.08 (dd, *J* = 10.8 Hz, *J* = 4.4 Hz, 1H), 3.03-2.96 (m, 1H), 2.15-1.97 (m, 4H), 1.79-1.64 (m, 6H), 1.54-1.49 (m, 5H), 1.21 (s, 3H), 1.19-1.01 (m, 6H), 0.76 (s, 3H), 0.64 (s, 3H).

Step 6. To a solution of **T1** (230 mg, 0.521 mmol) in acetone (5 mL) was added 5-methyl-2H-tetrazole (65.7 mg, 0.782 mmol), followed by K_2CO_3 (143 mg, 1.04 mmol). The resulting reaction mixture was stirred at 25°C for 16 hrs. The mixture was filtered and the filtrate was concentrated in vacuum to give crude product which was purified by a silica gel column (PE/EtOAc= 3/1-1/1) to give **Compound 60** (70 mg, 30%, impure) as colourless oil and **Compound 61** (45 mg, 19%, impure) as colourless oil. **Compound 60** (70 mg, impure) was purified by a silica gel column (PE/EtOAc= 3/1) to give **Compound 61** (54 mg, 77%) as a solid. **Compound 61** (45 mg, impure) was purified by a silica gel column (PE/EtOAc= 2/1-1/1) to give **Compound 61** (28 mg, 62%) as a solid.

Compound 60:

^{1}**H NMR** (400MHz, $CDCl_3$) δ 5.92-5.86 (m, 1H), 5.37-5.32 (m, 1H), 3.44 (s, 3H), 3.16 (dd, *J* = 10.8 Hz, *J* = 4.4 Hz, 1H), 2.68 (t, *J* = 8.8 Hz, 1H), 2.56 (s, 3H), 2.23-2.03 (m, 2H), 2.01 (s, 1H), 1.74-1.66 (m, 3H), 1.54-1.49 (m, 3H), 1.39-1.24 (m, 6H), 1.21(s, 3H), 1.19-1.09 (m, 3H), 0.98-0.80 (m, 3H), 0.77 (s, 3H), 0.68 (s, 3H).

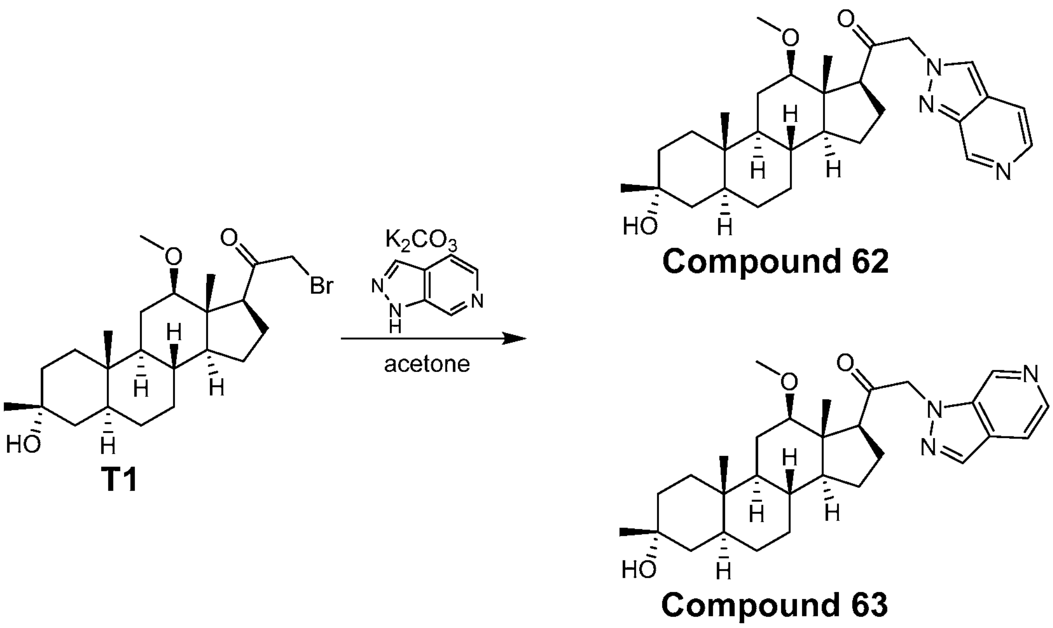
LCMS Rt = 1.030 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{24}H_{37}N_4O_2$ $[M +H\text{-}CH3OH]^+$ 413, found 413.

Compound 61:

^{1}H NMR (400MHz, $CDCl_3$) δ 5.65-5.59 (m, 1H), 5.26-5.20 (m, 1H), 3.41 (s, 3H), 3.22 (dd, J = 11.2 Hz, J = 4.4 Hz, 1H), 2.76 (t, J = 8.4 Hz, 1H), 2.44 (s, 3H), 2.20-2.04 (m, 2H), 1.84-1.65 (m, 3H), 1.54-1.50 (m, 2H), 1.46-1.24 (m, 8H), 1.22 (s, 3H), 1.20-1.07 (m, 3H), 1.00-0.81 (m, 3H), 0.78 (s, 3H), 0.68 (s, 3H).

LCMS Rt = 0.983 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{25}H_{41}N_4O_3$ $[M+H]^+$ 445, found 445.

Example 52. Syntheses of Compounds 62 and 63.



To a mixture of **T1** (500 mg, 1.13 mmol) and K_2CO_3 (312 mg, 2.26 mmol) in acetone (5 mL) was added 1H-pyrazolo[3,4-b]pyridine (201 mg, 1.69 mmol) at 25°C. The reaction mixture was stirred at the 25°C for 16 h. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give crude product which was purified by *prep.* HPLC (column: Agela Durashell C18 150* 25 5u, gradient: 30-60% B (A= 0.05% HCl- ACN, B= acetonitrile), flow rate: 30 mL/min) to give **Compound 62** (30 mg, impure) as a solid and **Compound 63** (10 mg, 2%) as a solid. The impure **Compound 62** (30 mg, impure) was purified by SFC separation (Column: AS (250 mm * 30 mm, 5 um), Mobile phase: Supercritical CO_2 /MeOH+ NH_3H_2O = 25/25, Flow rate: 50 ml/min, Wavelength: 220 nm) to give **Compound 62** (5 mg, 1%) as a solid.

Compound 62:

^{1}H NMR (400MHz, CDCl3) δ 9.28-9.26 (m, 1H), 8.20-8.14 (m, 1H), 7.95 (s, 1H), 7.64-7.43 (m, 1H), 5.74 (d, *J*= 17.4 Hz, 1H), 5.29 (d, *J*= 17.4 Hz, 1H), 3.46 (s, 3H), 3.25-3.20 (m, 1H), 2.82-2.73 (m, 1H), 2.22-2.06 (m, 2H), 1.80-1.67 (m, 4H), 1.43-1.33 (m, 4H), 1.30-1.11 (m, 11H), 1.00-0.82 (m, 3H), 0.78 (s, 3H), 0.71 (s, 3H)

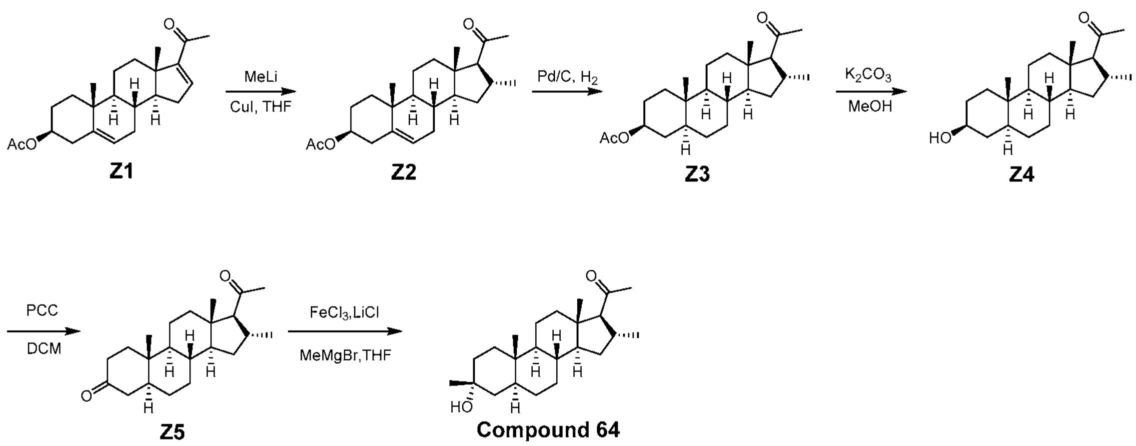
LCMS Rt = 0.794 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{29}H_{42}N_3O_3$ $[M+H]^+$ 480, found 480.

Compound 63:

^{1}H NMR (400MHz, CDCl3) δ 9.52-9.30 (m, 1H), 8.45-8.32 (m, 1H), 8.20-8.12 (m, 1H), 6.13-6.09 (m, 1H), 5.80-5.60 (m, 1H), 3.50 (s, 3H), 3.35-3.30 (m, 1H), 2.96-2.92 (m, 1H), 2.15-2.08 (m, 2H), 1.90-1.67 (m, 4H), 1.43-1.33 (m, 6H), 1.30-1.11 (m, 10H), 1.00-0.82 (m, 3H), 0.78 (s, 3H), 0.71 (s, 3H)

LCMS Rt = 0.816 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{29}H_{42}N_3O_3$ $[M+H]^+$ 480, found 480.

Example 36. Synthesis of Compound 64.



Step 1. To a stirred slurry of CuI (13.7 g,72.2 mmol) in dry THF (90 mL) at 0°C was added a solution of MeLi (87 mL,1.6 M in ether) in ether until the initially formed yellow precipitate just rediseolved to give a dear solution. Then a solution of **Z1** (10 g.27.8 mmol) in dry THF (200 mL) was added at 0°C, during which a bright yellow precipitate formed in the solution. The mixture was stired at 0°C for 30 mins and quenched with NH_4Cl (300 mL). The aqueous phase was extracted with EtOAc (3 x 400 mL). The combined organic phase was washed with saturated brine (2 x 400 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0~30% of EtOAc in PE) to give **Z2** (7.1 g, 68%) as a solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.38-5.36 (m, 1H), 4.62-4.58 (m, 1H), 2.68-2.66 (m, 1H), 2.33-2.27 (m, 2H), 2.12 (s, 4H), 2.03 (s, 3H), 2.00-1.95 (m, 2H), 1.96-1.85 (m, 2H), 1.65-1.50 (m, 2H), 1.50-1.45 (m, 5H), 1.47-1.35 (m, 4H), 1.01 (s, 3H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.65 (s, 3H).

The stereochemistry at C16 of **Z2** was confirmed by NOE.

Step 2. To a solution of **Z2** (7 g, 18.7 mmol) in MeOH (50 mL) and THF (50 mL) was added dry Pd/C (2 g) under N_2. The mixture was degassed under vacuum and purged with H_2 several times. The mixture was stirred for 20 hrs at 25°C under 30 psi of H_2. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give **Z3** (6.5 g, 92%) as a solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.77-4.64 (m, 1H), 2.65-2.60 (m, 1H), 2.11-2.10 (m, 4H), 2.00 (s, 3H), 1.95-1.70 (m, 4H), 1.69-1.48 (m, 9H), 1.40-1.10 (m, 8H), 1.10-0.95 (m, 5H), 0.61 (s, 3H).

Step 3. To a solution of **Z3** (6.5 g, 17.3 mmol) in MeOH (50 mL) was added K_2CO_3 (4.77 g, 34.6 mmol) at 20°C under N_2. The mixture was stirred at 20°C for 2 hrs and quenched with water (40 mL). The aqueous phase was extracted with DCM (3 x 60 mL). The combined organic phase was washed with saturated brine (2 x 60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **Z4** (4.7 g, crude) as a solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.65-3.55 (m, 1H), 2.65-2.62 (m, 1H), 2.14-2.11 (m, 4H), 1.93-1.90 (m, 1H), 1.85-1.80 (m, 1H), 1.70-1.55 (m, 1H), 1.50-1.45 (m, 4H), 1.43-1.30 (m, 3H), 1.20-1.19 (m, 7H), 1.15-1.05 (m, 1H), 1.05-1.00 (m, 1H), 1.00-0.80 (m, 4H), 0.82 (s, 3H), 0.64 (m, 4H).

Step 4. To a solution of **Z4** (4.7 g, 14.1 mmol) in DCM (70 mL) was added silica gel (7.2 g) and PCC (6.07 g, 28.2 mmol) at 20°C. After stirring at 20°C for 1 h, the resulting mixture was filtered and the filtrate concentrated by vacuum. The crude product was re-dissolved in DCM (80 mL) and treated with silica gel (20 g) and PE (80 mL). The mixture was stirred at 20°C for 30 mins and filtered. The filtrate was concentrated in vacuum to give **Z5** (3.4 g, crude) as a solid.

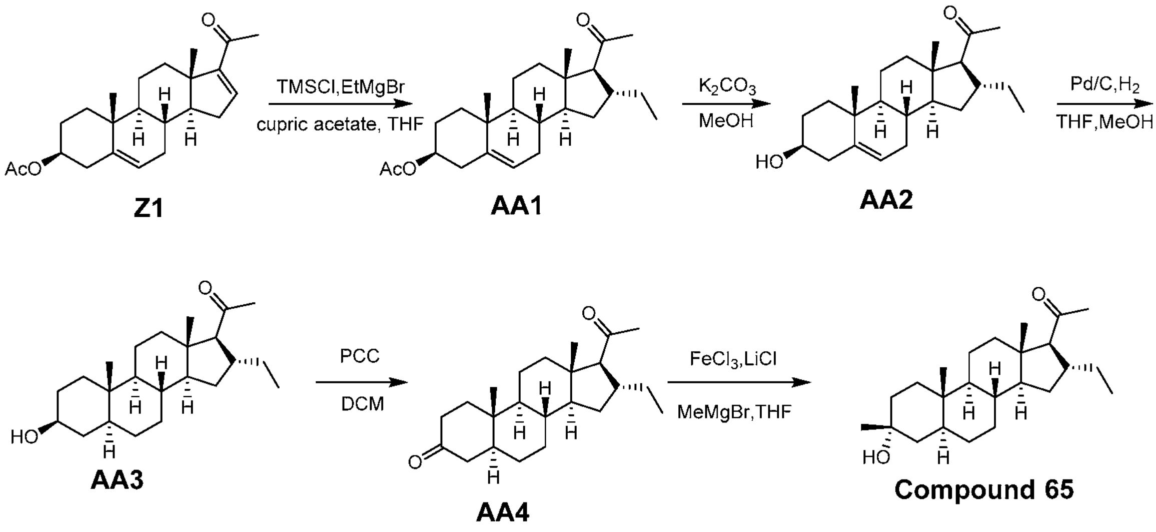
^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.65-2.62 (m, 1H), 2.45-2.20 (m, 3H), 2.15-2.10 (m, 5H), 2.10-1.90 (m, 2H), 1.70-1.15 (m, 12H), 1.00 (s, 3H), 0.94-0.92 (m, 4H), 0.80-0.70 (m, 1H), 0.65 (s, 3H).

Step 5. Under nitrogen atmosphere, anhydrous THF (40 mL) was cooled to 10°C and anhydrous LiCl (907 mg, 21.4 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 $FeCl_3$ (1.81 g, 11.2 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, 13.6 mL, 40.8 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. **Z5** (3.4 g, 10.2 mmol) was added in one portion. The internal temperature was allowed to -20°C and held 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, 20 mL), extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with aqueous NaOH (10%, 2 x 30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column (0-20% of EtOAc in PE) to give **Compound 64** (0.56 g, 13%) as a solid and 2.5 g impure product. The 2.5 g impure product was purified by flash column (5%-20% of EtOAc in PE) to give **Compound 64** (2.4 g, 56%) as a solid.

^{1}H NMR ($CDCl_3$, 400MHz) δ 2.64-2.62 (m, 1H), 2.27-2.10 (m, 4H), 1.93-1.89 (m, 1H), 1.70-1.60 (m, 3H), 1.59-1.30 (m, 6H), 1.30-1.10 (m, 12H), 0.94-0.92 (m, 4H), 0.80-0.75 (m, 1H), 0.74 (m, 3H), 0.62 (m, 3H).

LCMS Rt = 1.263 min in 2 min chromatography, 30-90 AB, purity 98%, MS ESI calcd. For $C_{23}H_{37}O$ $[M+H-H_2O]^+$ 329, found 329.

Example 37. Synthesis of Compound 65.



Step 1. A solution of copper(II) acetate (503 mg, 2.78 mmol) in anhydrous THF (350 mL) was cooled to 0°C. After adding ethyl magnesium bromide (27 mL, 8.10 mmol) dropwise, a solution of **Z1** (10 g, 27.8 mmol) together with chlorotrimethyl silane (15 g, 139 mmol) in THF (50 mL) was added dropwise, keeping the temperature below 10°C. After an hour at 0°C, ethyl magnesium bromide (10 mL, 30 mmol) was added and the reaction was stirred for 30 mins. The reaction was quenched by the addition of NH_4Cl (300 mL).extracted with EtOAc (3 x 400 mL). The combined organic phase was washed with saturated brine (2 x 800 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0-25% of EtOAc in PE) to give **AA1** (4.8 g, 44%) as a solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.36-5.34 (m, 1H), 4.60-4.56 (m, 1H), 2.50-2.48 (m, 1H), 2.31-2.28 (m, 2H), 2.21-2.20 (m, 1H), 2.01 (s, 3H), 2.00-1.83 (m, 6H), 1.56-1.50 (m, 7H), 1.47-1.45 (m, 3H), 1.30-1.10 (m, 3H), 1.05-0.95 (m, 4H), 0.79 (t, J = 6.8 Hz, 3H), 0.63 (s, 3H).

Step 2. To a solution of **AA1** (4.8 g, 12.8 mmol) in MeOH (80 mL) was added K_2CO_3 (3.52 mg, 25.6 mmol) at 20°C under N_2. The mixture was stirred at 20°C for 2 hrs and quenched with water (40 mL). The aqueous phase was extracted with DCM (3 x 60 mL). The combined organic phase was washed with saturated brine (2 x 60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give **AA2** (3.6 g, 84%) as a solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.36-5.34 (m, 1H), 3.53-3.51 (m, 1H), 2.60-2.45 (m, 1H), 2.30-2.20 (m, 3H), 2.12 (s, 3H), 1.97-1.95 (m, 2H), 1.87-1.83 (m, 2H), 1.60-1.30 (m, 9H), 1.25-1.10 (m, 4H), 1.05-0.95 (m, 4H), 0.83-0.79 (m, 3H), 0.65 (s, 3H).

Step 3. To a solution of **AA2** (3.6 g, 10.4 mmol) in MeOH (100 mL) and THF (100 mL) was added dry Pd/C (1 g) under N_2. The mixture was degassed under vacuum and purged with H_2 several times. The mixture was stirred for 20 hrs at 30°C under 30 psi of H_2. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give **AA3** (3.5 g, 96%) as a solid.

^{1}H NMR (methanol-*d4*, 400 MHz) δ 3.54-3.52 (m, 1H), 2.47-2.46 (m, 1H), 2.34-2.33 (m, 1H), 2.14 (s, 3H), 1.98-1.94 (m, 1H), 1.80-1.65 (m, 4H), 1.60-1.20 (m, 14H), 1.10-0.90 (m, 3H), 0.85-0.70 (m, 7H), 0.65 (s, 3H).

Step 4. To a solution of **AA3** (3.5 g, 10.5 mmol) in DCM (50 mL) was added silica gel (5 g) and PCC (4.52 g, 21 mmol) at 20°C. After stirring at 20°C for 1 h, the resulting mixture was filtered and the filtrate concentrated by vacuum. The crude product was re-dissolved in DCM (50 mL) and treated with silica gel (30 g) and PE (50 mL). The mixture was stirred at 20°C for 30 mins and filtered. The filtrate was concentrated in vacuum to give **AA4** (2.89 g, 83%) as a solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55-2.20 (m, 5H), 2.12 (s, 3H), 2.00-2.93 (m, 3H), 1.65-1.55 (m, 2H), 1.50-1.20 (m, 12H), 1.00 (s, 3H), 0.98-0.85 (m, 1H), 0.82-0.78 (m, 4H), 0.65 (s, 3H).

Step 5. Under nitrogen atmosphere, anhydrous THF (40 mL) was cooled to 10°C and anhydrous LiCl (741 mg, 17.5 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 $FeCl_3$ (1.49 g, 9.21 mmol) in one portion. The resulting mixture was stirred for an additional 30 min. The reaction mixture was cooled to -35°C and methyl magnesium bromide (3 M in diethyl ether, 11.1 mL, 33.5 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. **AA4** (2.89 g, 8.38 mmol) was added in one portion. The internal temperature was allowed to -20 °C and held between -

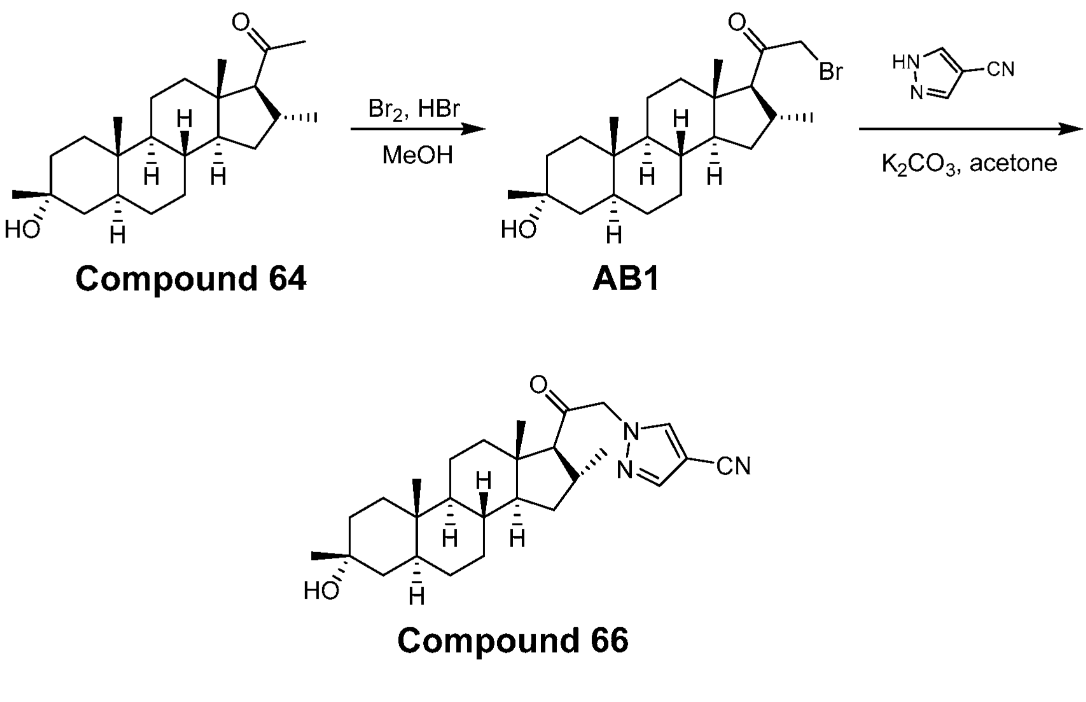
15 °C and -20 °C for 2 hours. The reaction mixture was quenched with aqueous HCl (2 M, 20 mL), extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with aqueous NaOH (10%, 2 x 30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was triturated from EtOAc to give **Compound 65** (0.25 g, 8%) as a solid, and 2 g of impure product.

^{1}H NMR ($CDCl_3$, 400MHz) δ 2.51-2.44 (m, 1H), 2.21-2.18 (m, 1H), 2.11 (s, 3H), 1.91-1.88 (m, 1H), 1.70-1.60 (m, 3H), 1.60-1.78 (m, 4H), 1.75-1.65 (m, 5H), 1.60-1.05 (m, 11H), 1.00-1.80 (m, 1H), 0.79-0.75 (m, 4H), 0.73 (s, 3H), 0.62 (s, 3H).

LCMS Rt = 1.315 min in 2 min chromatography, 30-90 AB, purity 100%, MS ESI calcd. For $C_{24}H_{39}O$ $[M+H-H_2O]^+$ 343, found 343.

The stereochemistry at C16 of **Compound 65** was confirmed by NOE.

Example 38. Synthesis of Compound 66.



Step 1. To a solution of **Compound 64** (900 mg, 2.59 mmol) in MeOH (10 ml) was added HBr (103 mg, 0.518 mmol, 40% in water) and Br_2 (406 mg, 2.59 mmol) at 25°C. After stirring at 25°C for 16 hrs, the mixture was quenched by sat.aq $NaHCO_3$ (10 mL), treated with water (20 mL), extracted with EtOAc (2x20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum to afford **AB1** (1.2 g) as a solid used directly for the next step.

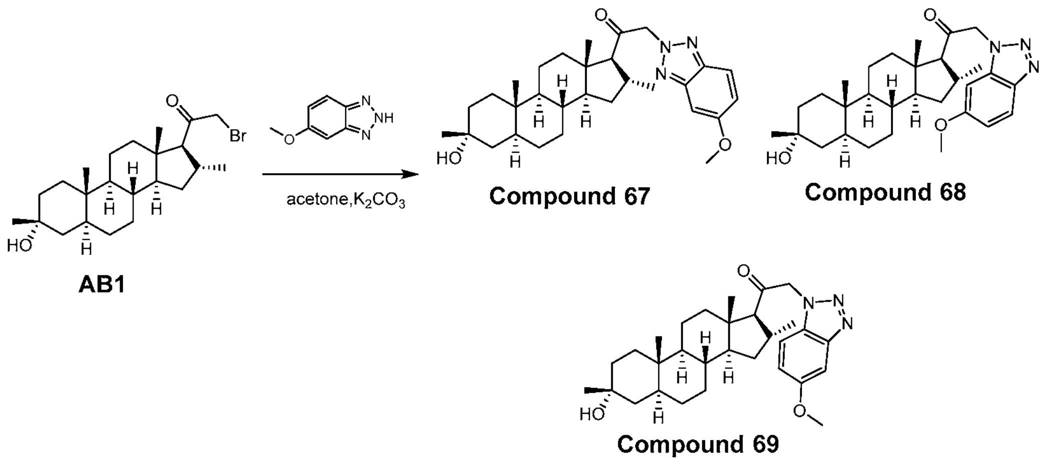
^{1}H NMR (400MHz, $CDCl_3$) δ 3.89 (d, J = 12.0 Hz, 1H), 3.85 (d, J = 12.0 Hz, 1H) 2.68-2.67 (m, 1H), 2.46 (d, J = 12 Hz, 1H), 1.82-1.80 (m, 1H), 1.66-1.59 (m, 2H), 1.52-1.44 (m, 5H), 1.37-1.18 (m, 14H), 0.96 (d, J = 8.0 Hz, 4H), 0.84-0.77 (m, 1H), 0.74 (s, 3H), 0.65 (s, 3H)

Step 2. To a mixture of **AB1** (100 mg, 0.235 mmol) and K_2CO_3 (64.9 mg, 0.47 mmol) in acetone (5 mL) was added 1H-pyrazole-4-carbonitrile (32.7 mg, 0.352 mmol) at 25°C. The reaction mixture was stirred at the 25°C for 16 h. Then saturated aqueous H_2O (50 mL) was added .The mixture was extracted with EtOAc (3 x 50 mL). The combined organic solution was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum to give the crude product .The crude product was purified by flash column (0~30% of EtOAc in PE) to give **Compound 66** (38 mg, 37%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.81 (s, 1H), 5.00 (d, J = 16.0 Hz, 1H), 4.85 (d, J = 16.0 Hz, 1H), 2.71-2.68 (m, 1H), 2.18-2.09 (m, 1H), 1.98-1.96 (m, 1H), 1.65-1.53 (m, 2H), 1.52-1.50 (m, 5H), 1.37-1.14 (m, 14H), 0.97 (d, J = 8 Hz, 4H), 0.85-0.81 (m, 1H), 0.75 (s, 3H), 0.68 (s, 3H).

LCMS Rt = 2.594 min in 4.0 min chromatography, 30-90AB_220&254.lcm, purity 100%, MS ESI calcd. for $C_{27}H_{38}N_3O$ $[M+H-H_2O]^+$ 420, found 420.

Example 39. Syntheses of Compounds 67, 68, and 69.



To a solution of **AB1** (200 mg, 0.47 mmol) in acetone (2 mL) was added 5-methoxy-2H-benzo[d][1,2,3]triazole (105 mg, 0.705 mmol), followed by K_2CO_3 (129 mg, 0.940 mmol) at 25°C. The resulting reaction mixture was stirred at 25°C for 16 hours. To the mixture was added water (20 mL) and then extracted with EtOAc (3 x 20 mL). The combined organic solution was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum to give the crude product. The crude product was purified by per-HPLC separation (column: DYA-5 C18 150*25mm*5um,gradient: 60-100% B (A = 0.05%HCl-ACN, B = acetonitrile), flow rate: 25 mL/min) to give impure **Compound 67** and a mixture of **Compound 68** and **Compound 69.** The impure **Compound 67** was purified by flash column (0~30% of EtOAc in PE) to give **Compound 67** (23 mg, 10%) as a solid. The mixture of **Compound 68** and **Compound 69**, which were purified by SFC separation (column:AD(250mm*30mm,10um),gradient: 40-40% B (A = 0.1%NH_3H_2O, B = ETOH), flow rate: 80 mL/min) to give **Compound 68** (23 mg, 10%) as solid and **Compound 69** (18 mg, 8%) as solid.

Compound 67:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 5.41 (d, J = 16 Hz, 2H), 3.88 (s, 3H), 2.76-2.78 (m, 1H), 2.22 (d, J = 8.0 Hz, 1H), 2.09-2.06 (m, 1H), 1.66-1.62 (m, 2H), 1.52-1.48 (m, 5H), 1.37-1.21 (m, 14H), 0.98 (d, J = 8.0 Hz, 3H), 0.99-0.97 (m, 2H), 0.76 (s, 6H).

LCMS Rt = 2.963 min in 4.0 min chromatography, 30-90AB.lcm, purity 96.89%, MS ESI calcd. for $C_{30}H_{44}N_3O_3$ $[M+H]^+$ 494, found 494.

Compound 68:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.01 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.58 (d, *J* = 2.0 Hz, 1H), 5.30 (s, 2H), 3.86 (s, 3H), 2.72-2.69 (m, 1H), 2.29 (d, *J* = 8.0 Hz, 1H), 2.08-2.05 (m, 1H), 1.67-1.57 (m, 2H), 1.54-1.51 (m, 5H), 1.37-1.21 (m, 14H), 0.94 (d, *J* = 8 Hz, 4H), 0.88-0.80 (m, 1H), 0.76 (s, 3H), 0.75 (s, 3H).

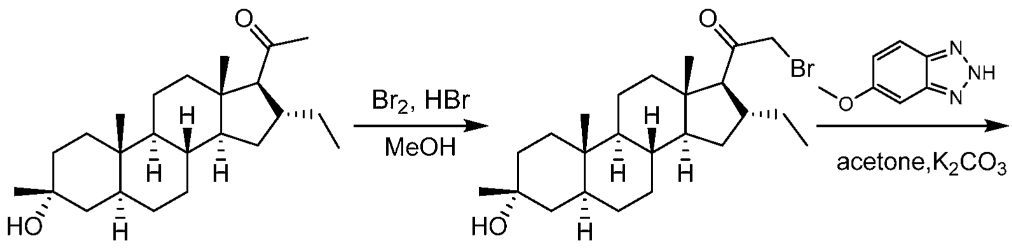
LCMS Rt = 2.718 min in 4.0 min chromatography, 30-90AB.lcm, purity 100%, MS ESI calcd. for $C_{30}H_{44}N_3O_3$ $[M+H]^+$ 494, found 494.

Compound 69:

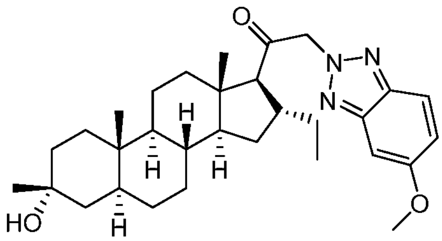
^{1}H NMR (400MHz, $CDCl_3$) δ 7.39 (d, *J* = 2.0 Hz, 1H), 7.18-7.16 (m, 2H), 5.33 (s, 2H), 3.89 (s, 3H), 2.74-2.68 (m, 1H), 2.28 (d, *J* = 8.0 Hz, 1H), 2.10-2.01 (m, 1H), 1.67-1.53 (m, 2H), 1.52-1.51 (m, 5H), 1.37-1.21 (m, 14H), 0.94 (d, *J* = 8 Hz, 4H), 0.88-0.80 (m, 1H), 0.76 (s, 3H), 0.76 (s, 3H).

LCMS Rt = 2.732 min in 4.0 min chromatography, 30-90AB.lcm, purity 100%, MS ESI calcd. for $C_{30}H_{44}N_3O_3$ $[M+H]^+$ 494, found 494.

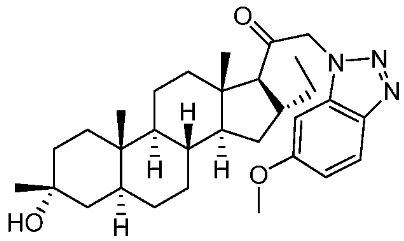
Example 40. Syntheses of Compounds 70, 71, and 72.



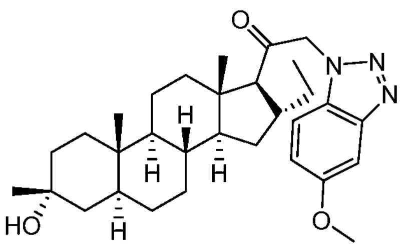
Compound 65 **AC1**



Compound 70



Compound 71



Compound 72

Step 1. To a solution of **Compound 65** (1 g, 2.77 mmol) in MeOH (10 ml) was added HBr (110 mg, 0.554 mmol, 40% in water) and Br_2 (442 mg, 2.82 mmol) at 25°C. The mixture was stirred at 25°C for 16 hrs. The mixture was quenched by sat.aq $NaHCO_3$ (10 mL), treated with water (20 mL), extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuum to afford **AC1** (1.2 g) as a solid used directly for the next step.

Step 2. To a solution of **AC1** (200 mg, 0.486 mmol) in acetone (2 mL) was added 5-methoxy-2H-benzo[d][1,2,3]triazole (108 mg, 0.729 mmol), followed by K_2CO_3 (134 mg, 0.972 mmol) at 25°C. The resulting reaction mixture was stirred at 25°C for 16 hours. To the mixture was added water (20 mL) and then extracted with EtOAc (3 x 20 mL). The combined organic solution was washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum to give the crude product, which was purified by flash column (0~30% of EtOAc in PE) to give **Compound 70** (33 mg, 7%) as a solid; and 100 mg of a mixture of **Compound 71** and **Compound 72.** The mixture was purified by SFC (column: OD(250mm*30mm,5um)), gradient: 45-45% B (A = 0.1%NH_3H_2O, B = ETOH), flow rate: 50 mL/min) to give **Compound 72** (46 mg, 9%) as a solid and **Compound 72** (32 mg, 7%) as a solid.

Compound 70:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 5.41 (d, J = 12 Hz, 2H), 3.87 (s, 3H), 2.56-2.54 (m, 1H), 2.28 (d, J = 8.0 Hz, 1H), 2.09-2.06 (m, 1H), 1.66-1.62 (m, 2H), 1.52-1.48 (m, 5H), 1.37-1.21 (m, 16H), 1.00-0.92 (m, 1H) 0.83 (d, J = 8.0 Hz, 4H), 0.76 (s, 3H), 0.75 (s, 3H).

LCMS Rt = 3.059 in in 4.0 min chromatography, 30-90AB.lcm, purity 96.49%, MS ESI calcd. for $C_{31}H_{46}N_3O_3$ $[M+H]^+$ 508, found 508.

Compound 71:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.39 (d, J = 4.0 Hz, 1H), 7.20-7.13 (m, 2H), 5.41-5.30 (m, 2H), 3.89 (s, 3H), 2.56-2.54 (m, 1H), 2.35 (d, J = 8.0 Hz, 1H), 2.09-2.06 (m, 1H), 1.69-1.62 (m, 2H), 1.52-1.48 (m, 5H), 1.37-1.21 (m, 16H), 1.00-0.92 (m, 1H) 0.85-0.79 (m, 4H), 0.76 (s, 3H), 0.73 (s, 3H).

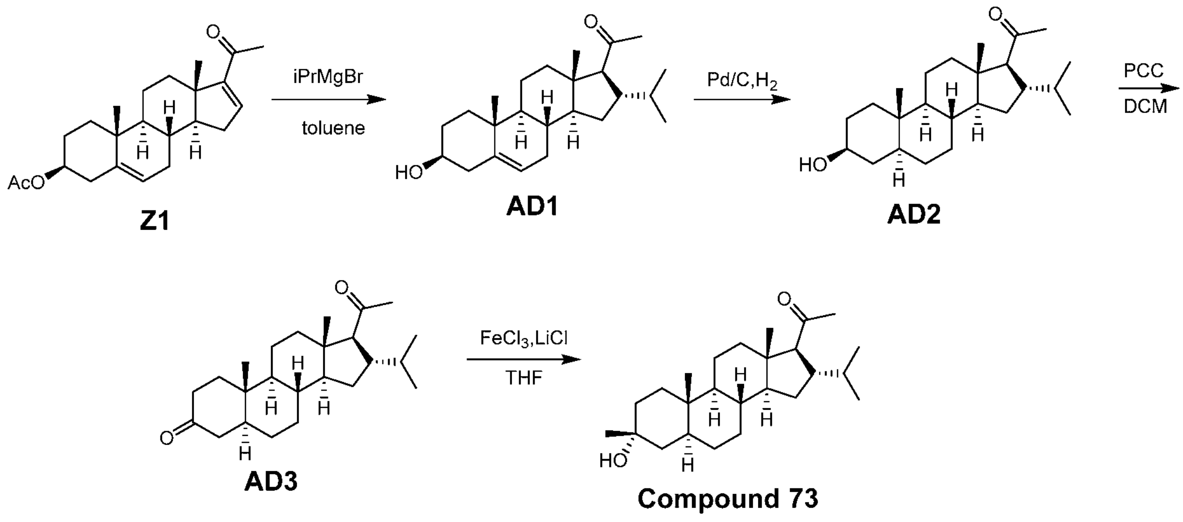
LCMS Rt = 2.822 in in 4.0 min chromatography, 30-90AB.lcm, purity 100%, MS ESI calcd. for $C_{31}H_{46}N_3O_3$ $[M+H]^+$ 508, found 508.

Compound 72:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 1H), 7.01 (dd, J = 4, 8.0 Hz, 1H), 6.57 (d, J = 4 Hz, 1H), 5.38-5.27 (d, J = 12 Hz, 2H), 3.85 (s, 3H), 2.60-2.53 (m, 1H), 2.37 (d, J = 8.0 Hz, 1H), 2.13-2.06 (m, 1H), 1.73-1.65 (m, 2H), 1.56-1.51 (m, 5H), 1.37-1.21 (m, 16H), 0.83-0.80 (m, 1H), 0.82 (d, J = 8.0 Hz, 4H), 0.76 (s, 3H), 0.74 (s, 3H).

LCMS Rt = 2.795 in in 4.0 min chromatography, 30-90AB.lcm, purity 100%, MS ESI calcd. for $C_{31}H_{46}N_3O_3$ $[M+H]^+$ 508, found 508.

Example 41. Synthesis of Compound 73.



Step 1. To a solution of iPrMgCl (420 mL, 2 M in THF) in THF (100 mL) was added a solution of **Z1** (20 g, 56.1 mmol) in toluene (400 mL) at 20°C. After stirring at this temperature for 30 mins, the suspension was allowed to heat at 40°C for 18 hrs. The reaction mixture was quenched with aqueous NH_4Cl (500 mL), extracted with EtOAc (2 x 600 mL). The combined organic layer was washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0-20% of EtOAc in PE) to give **AD1** (7 g, 31%) as a solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.35-5.34 (m, 1H), 3.52 (s, 1H), 2.48-2.20 (m, 4H), 2.13 (s, 3H), 2.00-1.75 (m, 4H), 1.70-1.25 (m, 11H), 1.20-1.05 (m, 2H), 1.00 (s, 3H), 0.95-0.80 (m, 1H), 0.85-0.83 (m, 3H), 0.76-0.73 (m, 3H), 0.64 (s, 2H).

Step 2. To a solution of **AD1** (4 g, 1.87 mmol) in MeOH (100 mL) and THF (100 mL) was added dry $Pd(OH)_2/C$ (1 g) under N_2. The mixture was degassed under vacuum and purged with H_2 several times. The mixture was stirred for 20 hrs at 30°C under 30 psi of H_2. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give **AD2** (3.8 g, 95%) as a solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.58 (s, 1H), 2.45-2.30 (m, 2H), 2.11 (s, 4H), 1.90-1.50 (m, 8H), 1.45-1.25 (m, 5H), 1.25-1.30 (m, 3H), 1.15-1.00 (m, 2H), 0.95-0.85 (m, 3H), 0.84-0.75 (m, 6H), 0.74-0.65 (m, 3H), 0.61 (s, 3H).

Step 3. To a solution of **AD2** (3.8 g, 1.8 mmol) in DCM (15 mL) was added silica gel (1.03 g) and PCC (775 mg, 3.6 mmol) at 25°C. After stirring at 25°C for 1 h, the resulting mixture was filtered and the filtrate concentrated by vacuum. The crude product was re-dissolved in DCM (20 mL) and treated with silica gel (20 g) and PE (30 mL). The mixture was stirred at 25°C for 30 mins and filtered. The filtrate was concentrated in vacuum to give **AD3** (3.4 g, crude) as a solid.

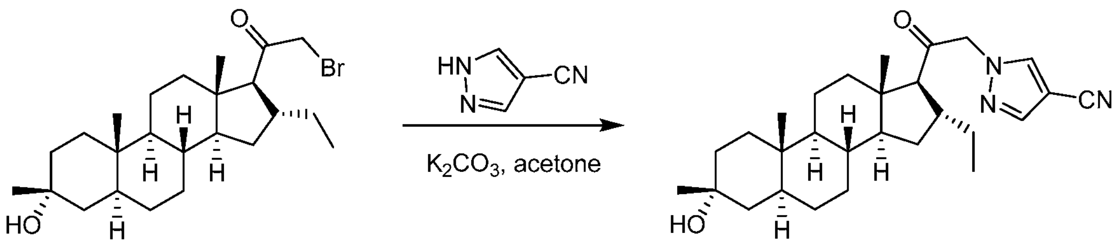
^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.45-2.25 (m, 5H), 2.13 (s, 3H), 2.10-2.00 (m, 2H), 1.90-1.73 (m, 1H), 1.75-1.65 (m, 2H), 1.60-1.55 (m, 1H), 1.64 (m, 1H), 1.59-1.25 (m, 6H), 1.25-1.10 (m, 4H), 1.00 (s, 3H), 0.95-0.90 (m, 1H), 0.85-0.83 (m, 3H), 0.75-0.73 (m, 3H), 0.64 (s, 3H).

Step 4. Under nitrogen atmosphere, anhydrous THF (40 mL) was cooled to 10°C and anhydrous LiCl (491 mg, 11.6 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 $FeCl_3$ (992 mg, 6.12 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, 11.1 mL, 33.5 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. **AD3** (2 g, 5.57 mmol) was added in one portion. The internal temperature was allowed to -20°C and held between -15°C and -20°C for 2 hours. The reaction mixture was quenched with aqueous NH_4Cl (50 mL), extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column (0-20% of EtOAc in PE) to give **Compound 73** (310 mg) as a yellow oil, which was lyophilized to give **Compound 73** (300 mg, 14%) as white powder.

^{1}H NMR ($CDCl_3$, 400MHz) δ 2.35 (s, 2H), 2.12 (s, 3H), 1.90-1.86 (m, 1H), 1.70-1.60 (m, 2H), 1.54-1.45 (m, 6H), 1.45-1.25 (m, 7H), 1.20-1.15 (m, 3H), 0.94-0.85 (m, 4H), 0.85-0.82 (m, 4H), 0.80-0.70 (m, 7H), 0.62 (s, 3H).

LCMS Rt = 1.318 min in 2 min chromatography, 30-90 CD, purity 100%, MS ESI calcd. For $C_{25}H_{41}O^+$ $[M+H-H_2O]^+$ 357, found 357.

Example 42. Synthesis of Compound 74.



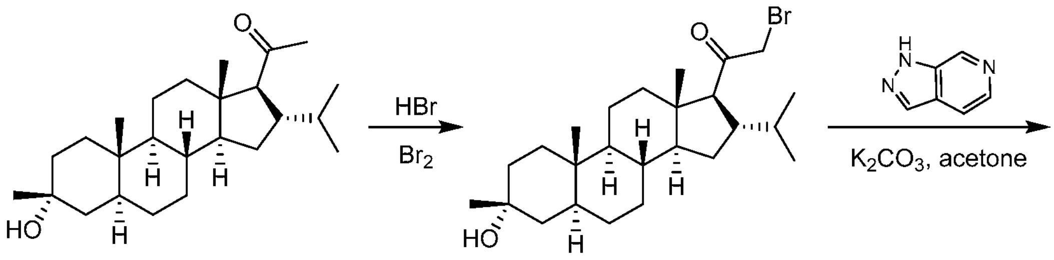
AC1 **Compound 74**

To a mixture of **AC1** (80 mg, 0.182 mmol) and K_2CO_3 (50.3 mg, 0.364 mmol) in acetone (5 mL) was added 1H-pyrazole-4-carbonitrile (25.4 mg, 0.273 mmol) at 25°C. The reaction mixture was stirred at the 25°C for 16 h and treated with H_2O (50 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined organic solution was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give the crude product, which was purified by flash column (0~30% of EtOAc in PE) to give an impure solid (50 mg). The impure product was purified by flash column (0~30% of EtOAc in PE) to give **Compound 74** (32 mg, 39%) as a solid.

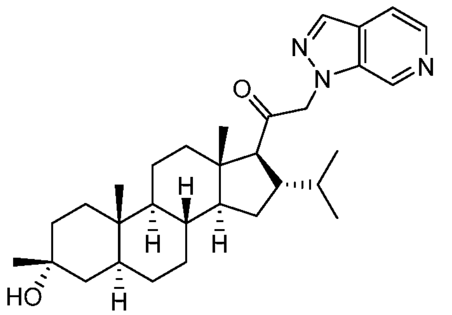
^{1}H NMR (400MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.81 (s, 1H), 5.00 (d, J = 16 Hz, 1H), 4.87 (d, J = 16 Hz, 1H), 2.54 (m, 1H), 2.25 (d, J = 8.0 Hz, 1H), 1.96 (m, 1H), 1.65 (m, 2H), 1.53-1.47 (m, 5H), 1.38-1.12 (m, 16H), 1.01-0.92 (m, 1H), 0.81 (t, J = 8.0 Hz, 4H), 0.75 (s, 3H), 0.68 (s, 3H).

LCMS Rt = 2.682 in in 4.0 min chromatography, 30-90AB.lcm, purity 100%, MS ESI calcd. for $C_{28}H_{40}N_3O$ $[M-H_2O+H]^+$ 434, found 434.

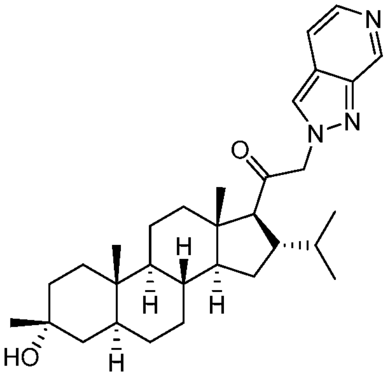
Example 44. Syntheses of Compounds 78 and 79.



Compound 73 **AE1**



Compound 78



Compound 79

Step 1. To a solution of **compound 73** (750 mg, 2 mmol) in MeOH (10 mL) was added HBr (80.7 mg, 0.4 mmol, 40% in water) and Br_2 (326 mg, 2.04 mmol) at 15°C. After stirring at 15°C for 16 hrs, the mixture was quenched by sat.aq $NaHCO_3$ (10 mL) and water (20 mL), extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash column (0-30% of EtOAc in PE) to give **AE1** (660 mg, 69%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99-3.86 (m, 2H), 2.68-2.63 (m, 1H), 1.86-1.76 (m, 1H), 1.72-1.59 (m, 2H), 1.53-1.32 (m, 8H), 1.29-1.23 (m, 4H), 1.21-1.18 (m, 4H), 1.17-1.12 (m, 2H), 1.02-0.83 (m, 6H), 0.81-0.71 (m, 8H), 0.67-0.61 (m, 3H).

Step 2. To a solution of **AE1** (150 mg, 0.33 mmol) in acetone (5 mL) was added K_2CO_3 (91 mg, 0.66 mmol) and 1H-pyrazolo[3,4-c]pyridine (39.3 mg, 0.33 mmol). The mixture was stirred at 15°C for 12 hrs. Second batch of K_2CO_3 (45.5 mg, 0.33 mmol) and 1H-pyrazolo[3,4-c]pyridine (7.86 mg, 0.06 mmol) was added at 15°C. The mixture was stirred at 15°C for another 8 hrs and poured in to water (10 mL), extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash column (0~80% of EtOAc in PE) to afford **Compound 78** (70 mg, impure) as a solid and **Compound 79** (31 mg, 19%) as a solid. The impure **Compound 78** (70 mg, 0.14 mmol) was purified by SFC (column: AS(250mm*30mm,5um)), gradient: 35-35% B (A= 0.1%NH_3/H_2O, B= EtOH), flow rate: 50 mL/min) to give a solid, which was further purified by re-crystallized from MeCN (3 mL) to give **Compound 78** (36 mg, 22%) as a solid.

Compound 78:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.38-8.29 (m, 1H), 8.09 (s, 1H), 7.66-7.61 (m, 1H), 5.33-5.21 (m, 2H), 2.53-2.42 (m, 2H), 2.13-2.04 (m, 1H), 1.75-1.65 (m, 2H), 1.56-1.23 (m, 15H), 1.21 (s, 3H), 1.21-1.14 (m, 2H), 1.03-0.91 (m, 1H), 0.88-0.79 (m, 7H), 0.76 (s, 3H), 0.71 (s, 3H).

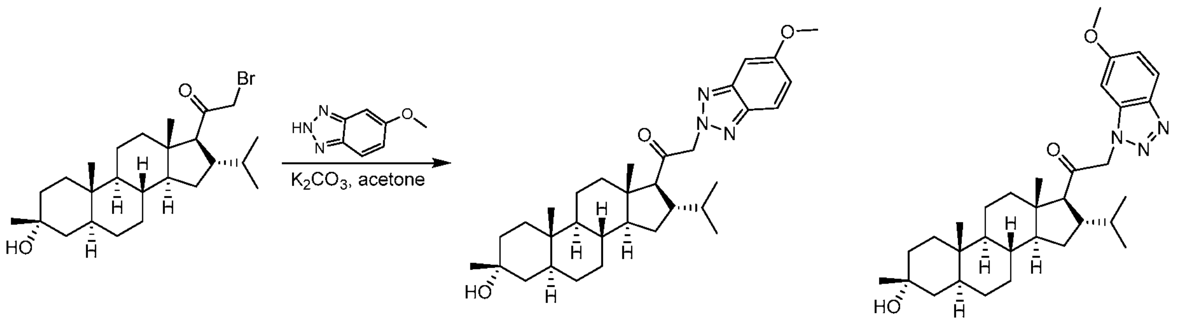
LCMS Rt = 0.968 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{31}H_{46}N_3O_2$ $[M+H]^+$ 492, found 492.

Compound 79:

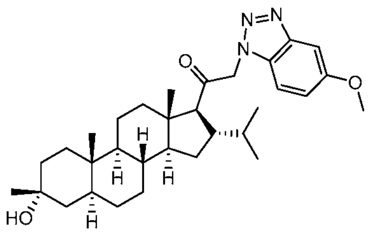
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.18-8.14 (d, J = 6 Hz, 1H), 7.96 (s, 1H), 7.54-7.49 (m, 1H), 5.37-5.18 (m, 2H), 2.53-2.44 (m, 2H), 2.12-2.03 (m, 1H), 1.74-1.66 (m, 2H), 1.52-1.28 (m, 12H), 1.26-1.13 (m, 8H), 1.03-0.92 (m, 1H), 0.87-0.82 (m, 4H), 0.81-0.75 (m, 6H), 0.71 (s, 3H).

LCMS Rt = 0.917 min in 2 min chromatography, 30-90AB, purity 100%, MS ESI calcd. for $C_{31}H_{46}N_3O_2$ $[M+H]^+$ 492, found 492.

Example 44. Syntheses of Compounds 80, 81, and 82.



AE1 Compound 80 Compound 81



Compound 82

To a solution of **AE1** (250 mg, 0.55 mmol) in acetone (10 mL) was added K_2CO_3 (151 mg, 1.1 mmol) and 5-methoxy-2H-benzo[d][1,2,3]triazole (123 mg, 0.83 mmol) and the mixture was stirred at 15°C for 12 hours. A second batch of K_2CO_3 (75.5 mg, 0.55 mmol) and 5-methoxy-2H-benzo[d][1,2,3]triazole (61.5 mg, 0.41 mmol) was added at 15°C and the mixture was stirred at 15°C for 8 hours. The mixture was poured in to water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash column (0~45% of EtOAc in PE) to afford **Compound 80** (44 mg, 15%) as a solid and a mixture of **Compound 81** and **Compound 82** (200 mg, 69%) as a light yellow oil.

The mixture of **Compound 81** and **Compound 82** (200 mg, 0.05 mmol) was purified by SFC (column: OD(250mm*30mm,10um)), gradient: 40-40% B (A= 0.1%NH3/H2O, B= MEOH), flow rate: 80 mL/min) to give **Compound 81** (43 mg, 21%) as a solid and **Compound 82** (26 mg, 13%) as a solid.

Compound 80:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.69 (m, 1H), 7.11-7.03 (m, 2H), 5.49-5.37 (m, 2H), 3.87 (s, 3H), 2.54-2.41 (m, 2H), 2.14-2.05 (m, 1H), 1.73-1.64 (m, 2H), 1.57-1.23 (m, 17H), 1.21 (s, 3H), 1.19-1.07 (m, 2H), 0.86-0.79 (m, 6H), 0.78-0.71 (m, 6H).

LCMS Rt = 1.348 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{32}H_{48}N_3O_3$ $[M+H]^+$ 522, found 522.

Compound 81:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.89 (d, J = 9.6 Hz, 1H), 7.03-6.97 (m, 1H), 6.58-6.54 (m, 1H), 5.46-5.27 (m, 2H), 3.83 (s, 3H), 2.56-2.44 (m, 2H), 2.13-2.05 (m, 1H), 1.75-1.66 (m, 2H), 1.61-1.23 (m, 16H), 1.21 (s, 3H), 1.15 (s,1H), 1.03-0.91 (m, 1H), 0.89-0.79 (m, 7H), 0.76 (s,3H), 0.72 (s, 3H).

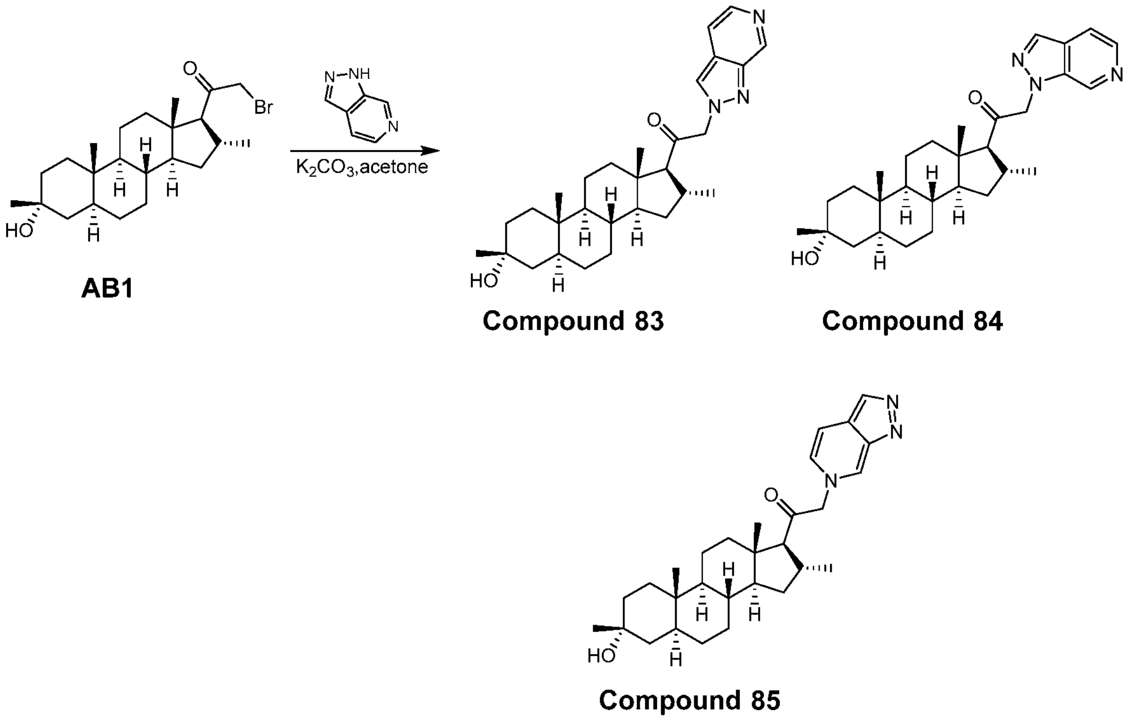
LCMS Rt = 1.273 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{32}H_{48}N_3O_3$ $[M+H]^+$ 522, found 522.

Compound 82:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (d, J = 1.2 Hz, 1H), 7.19-7.11 (m, 2H), 5.45-5.31 (m, 2H), 3.89 (s, 3H), 2.53-2.43 (m, 2H), 2.12-2.04 (m, 1H), 1.75-1.65 (m, 2H), 1.61-1.23 (m, 15H), 1.21 (s, 3H), 1.19-0.91 (m, 3H), 0.88-0.78 (m, 7H), 0.76 (s, 3H), 0.71 (s, 3H).

LCMS Rt = 1.277 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{32}H_{48}N_3O_3$ $[M+H]^+$ 522, found 522.

Example 45. Syntheses of Compounds 83, 84, and 85.



To a solution of **AB1** (150 mg, 0.352 mmol) and 1H-pyrazolo[3,4-c]pyridine (43.9 mg, 0.369 mmol) in acetone (3 mL) was added K_2CO_3 (97.2 g, 0.704 mmol) at 25°C. After stirring at 25°C for 10 hrs, the mixture was poured into water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to afford crude product (100 mg), which was purified by preparative HPLC (column: YMC-Actus Triart C18 150*30mm*5um)), gradient: 40-70% B (A = 0.1%HCl, B = ACN), flow rate: 25 mL/min) to afford **Compound 85** (15 mg, 9%) as a solid, **Compound 84** (17 mg, 10%) as a solid and **Compound 83** (20 mg, impure). **Compound 83** (20 mg, impure) was purified by SFC separation (column: AD (250mm*30mm, 10um)), gradient: 50-50% B (A = 0.1%NH_3H_2O, B = EtOH), flow rate: 80 mL/min) to afford **Compound 83** (3 mg, yield 15%) as a solid.

Compound 83:

^{1}**H NMR** (400MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.17 (d, *J* = 4.8 Hz, 1H), 7.98 (s, 1H), 7.53 (d, *J* = 6.0 Hz, 1H), 5.34-5.16 (m, 2H), 2.78-2.70 (m, 1H), 2.27 (d, *J* = 8.4 Hz, 1H), 2.07-2.01 (m, 1H), 1.73-1.59 (m, 3H), 1.54-1.45 (m, 5H), 1.42-1.24 (m, 11H), 1.21 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.86-0.80 (m, 1H), 0.76 (s, 3H), 0.73 (s, 3H).

LCMS Rt = 2.405 min in 4 min chromatography, 10-80AB, purity 99%, MS ESI calcd. For $C_{29}H_{42}N_3O_2$ $[M+H]^+$ 464, found 464.

Compound 84:

^{1}H NMR (400MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.34 (d, *J* = 5.6 Hz, 1H), 8.10 (s, 1H), 7.65-7.63 (m, 1H), 5.28-5.17 (m, 2H), 2.76-2.65 (m, 1H), 2.29-2.26 (m, 1H), 2.10-2.02 (m, 1H), 1.72-1.60 (m, 3H), 1.55-1.48 (m, 5H), 1.42-1.34 (m, 4H), 1.32-1.19 (m, 10H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.88-0.82 (m, 1H), 0.77 (s, 3H), 0.74 (s, 3H).

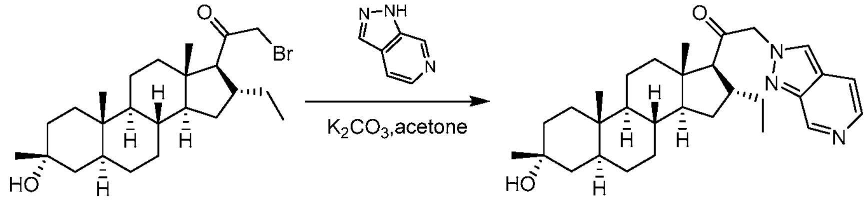
LCMS Rt = 2.014 min in 3 min chromatography, 10-80AB, purity 100%, MS ESI calcd. For $C_{29}H_{42}N_3O_2$ $[M+H]^+$ 464, found 464.

Compound 85:

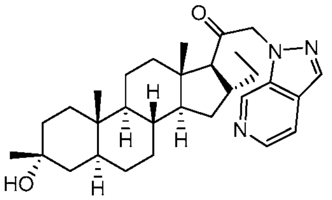
^{1}H NMR (400MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.56 (s, 1H), 7.87 (d, *J* = 6.8 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 5.32-5.18 (m, 2H), 3.80-2.74 (m, 1H), 2.35-2.32 (m, 1H), 2.01-1.98 (m, 1H), 1.71-1.51 (m, 6H), 1.45-1.24 (m, 13H), 1.22 (s, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.91-0.86 (m, 1H), 0.77 (s, 3H), 0.74 (s, 3H).

LCMS Rt = 2.388 min in 4 min chromatography, 10-80AB, purity 98.7%, MS ESI calcd. For $C_{29}H_{42}N_3O_2$ $[M+H]^+$ 464, found 464.

Example 46. Syntheses of Compounds 86 and 87.



AC1 **Compound 86**



Compound 87

To a mixture of **AC1** (150 mg, 0.341 mmol) and K_2CO_3 (94.2 mg, 0.682 mmol) in acetone (3 mL) was added 1H-pyrazolo[3,4-c]pyridine (42.6 mg, 0.358 mmol) at 25°C. After stirring at 25°C for 12 hrs, the mixture was poured into water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (50 mL), dried over with Na_2SO_4, filtered and concentrated to afford crude product, which was purified by prep-HPLC separation (column: YMC-Actus Triart C18 150*30mm*5um)), gradient: 45-75% B (A = 0.1%HCl, B = ACN), flow rate: 25 mL/min) to afford **Compound 87** (36 mg, 22%) as a solid and **Compound 86** (20 mg, impure). The crude **Compound 86** was purified by SFC separation (column: AD(250mm*30mm,10um)), gradient: 45-45% B (A = 0.1%NH_3H_2O , B = ETOH), flow rate: 80 mL/min) to afford **Compound 86** (11 mg, 7%) as a solid.

Compound 86:

^{1}H NMR (400MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.25-8.1 (m, 1H), 8.02 (s, 1H), 7.65-7.55 (m, 1H), 5.37-5.19 (m, 2H), 2.58-2.5 (m, 1H), 2.33 (d, J = 12 Hz, 1H), 2.10-2.05 (m, 1H), 1.72-1.65 (m, 2H), 1.53-1.45 (m, 5H), 1.42-1.23 (m, 12H), 1.21 (s, 3H), 1.16 (s, 1H), 1.01-0.93 (m, 1H), 0.83 (t, J = 8.0 Hz, 4H), 0.77 (s, 3H), 0.73 (s, 3H).

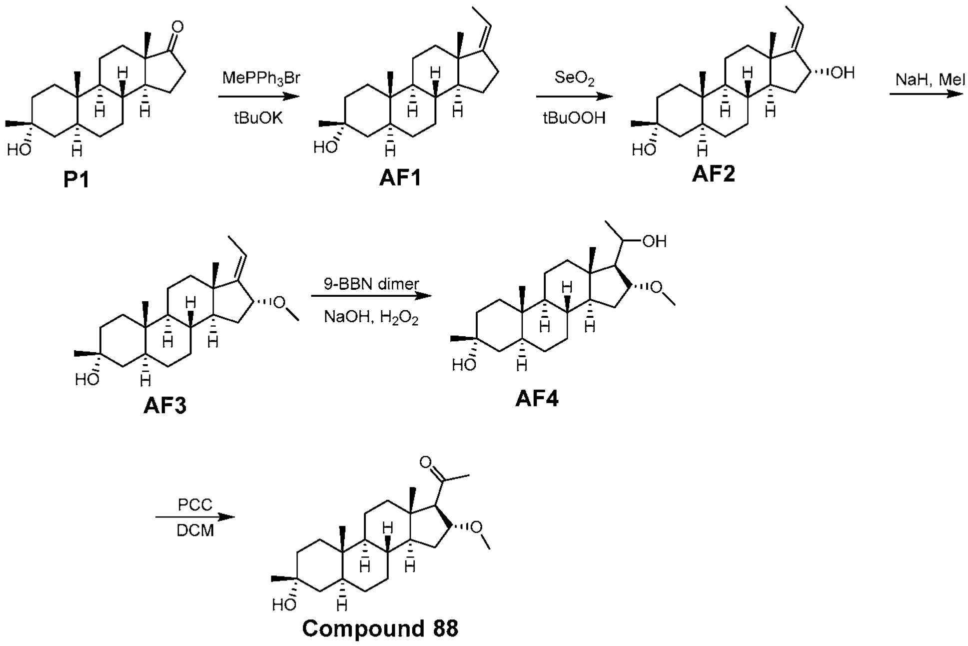
LCMS Rt = 2.502 min in 4.0 min chromatography, 10-80AB.lcm, purity 100%, MS ESI calcd. for $C_{30}H_{44}N_3O_2$ $[M+H]^+$ 478, found 478.

Compound 87:

^{1}H NMR (400MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.17 (d, *J* = 4.0 Hz, 1H), 7.97 (s, 1H), 7.54-7.50 (m, 1H), 5.35-5.17 (m, 2H), 2.60-2.52 (m, 1H), 2.35-2.30 (m, 1H), 2.10-2.04 (m, 1H), 1.69-1.62 (m, 4H), 1.52-1.46 (m, 5H), 1.39-1.26 (m, 11H), 1.21 (s, 3H), 1.12-0.98 (m, 1H), 0.83 (t, *J* = 8.0 Hz, 4H), 0.76 (s, 3H), 0.73 (s, 3H)

LCMS Rt = 1.750 min in 3.0 min chromatography, 10-80AB_3MIN_E.M, purity 100%, MS ESI calcd. for $C_{30}H_{44}N_3O_2$ $[M+H]^+$ 478, found 478.

Example 47. Synthesis of Compound 88.



The synthesis of **P1** is dislosed in WO2016/61527.

Step 1. To a suspension of $MePPh_3Br$ (14.5 g, 39.3 mol) in THF (300 mL) was added t-BuOK (4.4 g, 39.3 mmol) at 15°C under N_2. After stirring at 50°C for 30 min, **P1** (10 g, 32.8 mmol) was added in portions below 65°C. The mixture was stirred at 50°C for 1 h and treated with NH_4Cl (300 mL). The organic layer was separated, concentrated in vacuum to give a cured which was triturated from MeOH/water (150 L, 1:1) at 50°C. The mixture was filtered after cooled and the solid was washed with MeOH/water (2 x 150 mL, 1:1), dried in vacuum to give **AF1** (8 g, 77%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15-5.05 (m, 1H), 2.40-2.10 (m, 3H), 1.80-1.55 (m, 5H), 1.54-1.40 (m, 6H), 1.39-1.25 (m, 4H), 1.24-1.10 (m, 10H), 0.77 (s, 3H), 076-0.70(m, 4H).

Step 2. To a suspension of selenium dioxide (854 mg, 7.70 mmol) in DCM (40 mL) was added dropwise tert-butyl hydro peroxide (3.13 mL, 23.1 mmol 70% solution in water) to give a nearly homogeneous solution after stirring at 0°C for 1 h. Then a solution of **AF1** (4.9 g, 15.4 mmol) in DCM (10 mL) was added dropwise to give a clear solution. The resulting mixture was stirred 20°C for 18 h. The reaction mixture was diluted with PE (100 mL) and a lot of white precipitate appeared. The precipitate was collected by filtration and dried in air to give the product **AF2** (4.9 g, crude) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55-5.50 (m, 1H), 4.45-4.40 (m, 1H), 2.30-2.20 (m, 1H), 1.75-1.55 (m, 8H), 1.54-1.15 (m, 17H), 1.10-1.00 (m, 1H), 0.90-0.80 (m, 4H), 0.75 (s, 3H).

Step 3. To a solution of **AF2** (2.2 g, 6.61 mmol) in dry THF (60 mL) was slowly added to a stirred suspension NaH (791 mg, 19.8 mmol) in dry THF (20 mL) at -5°C. Then MeI (10.2 mL, 165 mmol) was added to reaction mixture and stirred for 24 h at 35°C. The reaction mixture was quenched by water (80 mL) and extracted with DCM (2 x 80 mL). The combined organic layer was washed by brine and dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue (2.5 g). The residue was purified by silica gel chromatography eluted with PE: EtOAc = 5:1 to give **AF3** (1.56 g, 68%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60-5.50 (m, 1H), 4.00-3.90 (m, 1H), 3.30 (m, 3H), 2.30-2.20 (m, 1H), 1.75-1.60 (m, 6H), 1.59-1.15 (m, 18H), 1.05-0.95 (m, 1H), 0.85 (s, 3H), 0.80-0.79 (m, 1H), 0.75 (s, 3H).

Step 4. To a solution of **AF3** (500 mg, 1.44 mmol) in dry THF (5 mL) was added borane-tetrahydrofuran complex (2.88 mL of 1.0 M solution in THF) and the reaction mixture was stirred at 20°C for 1 hour. NaOH (4.76 mL, 14.3 mmol, 3 M in water) was slowly added. The mixture was cooled in ice (0°C) and 30 percent aqueous solution of H_2O_2 (1.62 g, 14.3 mmol) was slowly added. The mixture was stirred at ambient temperature for 1 hour and then extracted with DCM (3 x 50 mL). The combined DCM extracts were washed with 10 percent aqueous $Na_2S_20_3$ (100 mL), brine (100 mL), dried over Na_2S0_4, filtered, and concentrated in vacuum to afford compound **AF4** (500 mg, crude) as a solid, which was used in next step without further purification.

Step 5. To a solution To a solution of **AF4** (500 mg, 1.37 mmol) in DCM (40 mL) was added PCC (590 mg, 2.74 mmol) and silica gel (1 g) at 25°C. Then the solution was stirred at 25°C for 3 h. The reaction mixture was filtered and the residue was washed with anhydrous DCM (2 x 30 mL). The combined filtrate was concentrated in vacuum to give **Compound 88** (200 mg, crude) as a solid, which was purified by silica gel column (PE/EtOAc=1/1) and lyophilization to afford **Compound 88** (20 mg, 10%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40-4.30 (m, 1H), 3.20 (s, 3H), 2.55-2.50 (m, 1H), 2.16 (s, 3H), 1.95-1.90 (m, 1H), 1.70-1.55 (m, 4H), 1.50-1.40 (m, 5H), 1.39-1.15 (m, 12H), 1.05-0.95 (m, 1H), 0.90-0.85 (m, 1H), 0.74 (s, 3H), 0.60 (s, 3H).

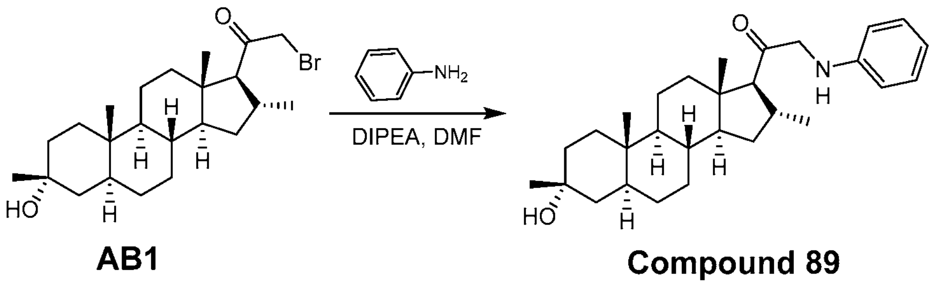
HPLC Rt = 4.28 min in 8.0 min chromatography, 30-90 AB, purity 100%.

LCMS Rt = 1.061 min in 2.0 min chromatography, 30-90 AB, purity 92%, MS ESI calcd. for $C_{23}H_{39}O_3$ $[M+H]^+$363, found 363.

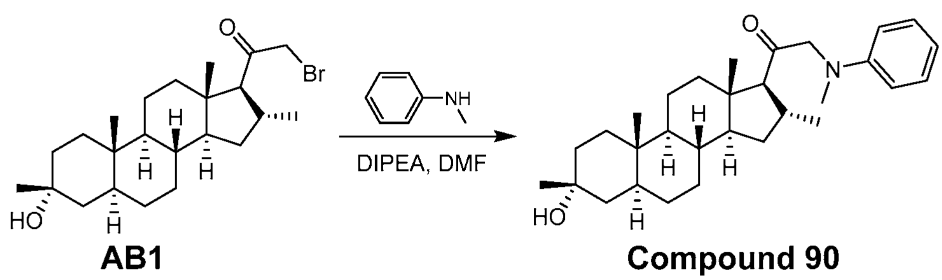
The stereochemistry at C16 of **Compound 88** was confirmed by NOE.

Example 48. Syntheses of Compounds 89 and 90.

a.



b.



Step 1a (Compound 89). To a solution of **AB1** (80 mg, 0.188 mmol), DIEA (60.6 mg, 0.47 mmol) in DMF (2 mL) was added aniline (26.2 mg, 0.282 mmol) at 25°C. The mixture was stirred at 60°C for 16 hours. The mixture was poured into water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by HPLC separation (column: Phenomenex Gemini C18 250*50mm*10 um, gradient: 87-97% B, Condition :(water (0.05% ammonia hydroxide v/v)-ACN), flow rate: 30 mL/min) to give **Compound 89** (12 mg, impure) as a solid. The **Compound 89** (12 mg, impure) was purified by a silica gel column (PE/EtOAc = 5/1) to give **Compound 89** (5 mg, 6%) as a solid.

^{1}HNMR (400 MHz, CDCl3) δ 7.19 (t, *J* = 8 Hz, 2H), 6.72 (t, *J* = 8 Hz, 1H), 6.60 (d, *J* = 8 Hz, 2H), 4.73-4.69 (m, 1H), 4.01-3.85 (m, 2H), 2.79-2.66 (m, 1H), 2.19 (d, *J* = 12 Hz, 1H), 1.89-1.82 (m, 1H), 1.70-1.58 (m, 3H), 1.51-1.34 (m, 6H), 1.31-1.15 (m, 11H), 1.01-0.92 (m, 4H), 0.88-0.78 (m, 2H), 0.74 (s, 3H), 0.67 (s, 3H).

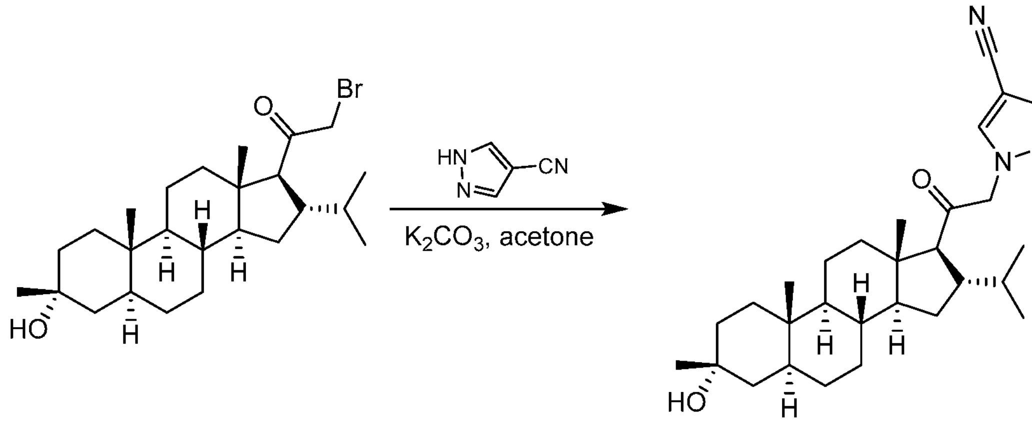
LCMS Rt = 4.893 min in 7.0 min chromatography, 30-90 CD, purity 100%, MS ESI calcd. For $C_{29}H_{44}NO_2$ $[M+H]^+$ 438, found 438.

Step 1b (Compound 90). To a solution of **AB1** (80 mg, 0.188 mmol), DIEA (60.6 mg, 0.47 mmol) in DMF (2 mL) was added N-methylaniline (30.2 mg, 0.282 mmol) at 25°C. The mixture was stirred at 60°C for 16 hours. The mixture was poured into water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by HPLC separation (column: Phenomenex Gemini C18 250*50mm*10 um, gradient: 90-100% B, Condition: (water (0.05% ammonia hydroxide v/v)-ACN), flow rate: 30 mL/min) to give **Compound 90** (10 mg, impure) as a solid. The **Compound 90** (10 mg, impure) was purified by a silica gel column (PE/EtOAc = 5/1) to give **Compound 90** (3 mg, 4%) as a solid.

^{1}HNMR (400 MHz, CDCl3) δ 7.20 (t, *J* = 8 Hz, 2H), 6.71 (t, *J* = 8 Hz, 1H), 6.61 (d, *J* = 8 Hz, 2H), 4.73-4.69 (m, 1H), 4.06-3.95 (m, 2H), 3.01 (s, 3H), 2.75-2.63 (m, 1H), 2.24 (d, *J* = 8 Hz, 1H), 1.91-1.61 (m, 2H), 1.52-1.38 (m, 5H), 1.36-1.15 (m, 13H), 1.01-0.88 (m, 4H), 0.86-0.78 (m, 2H), 0.75 (s, 3H), 0.68 (s, 3H).

LCMS Rt = 5.041 min in 7.0 min chromatography, 30-90 CD, purity 100%, MS ESI calcd. For $C_{30}H_{46}NO_2$ $[M+H]^+$ 452, found 452.

Example 49. Synthesis of Compound 91.



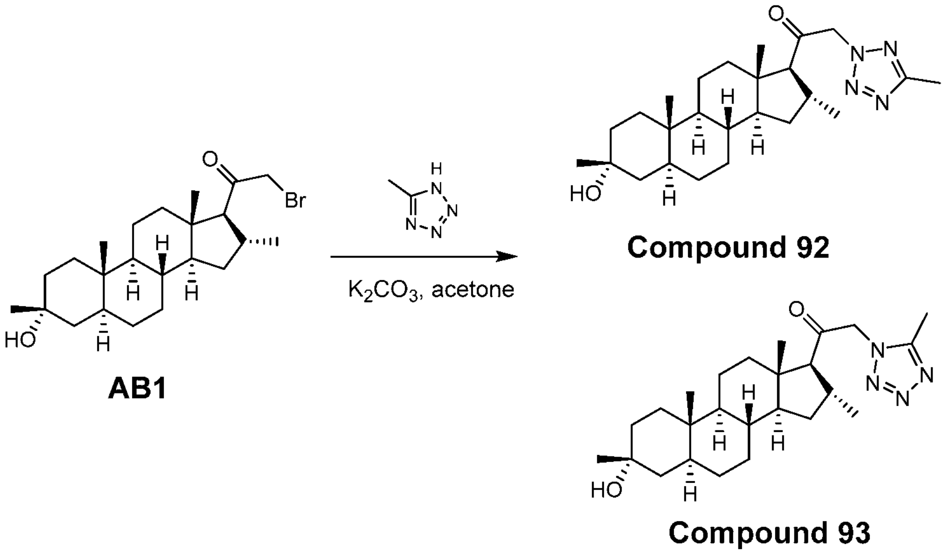
AE1 **Compound 91**

To a solution of **AE1** (100 mg, 0.22 mmol) in acetone (3 mL) was added K_2CO_3 (60.7 mg, 0.44 mmol) and 1H-pyrazole-4-carbonitrile (30.7 mg, 0.33 mmol). The mixture was stirred at 15°C for 12 hours. The mixture was poured in to water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers was washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash column (0~30% of EtOAc in PE) to afford **Compound 91** (90 mg, 88%, impure) as a solid, which was purified by SFC (column: OD(250mm*30mm,10um)), gradient: 40-40% B (A= 0.1%NH_3/H_2O, B= EtOH), flow rate: 50 mL/min) to give **Compound 91** (44 mg, 48%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.79 (d, J = 14 Hz, 2H), 5.04-4.85 (m, 2H), 2.52-2.36 (m, 2H), 1.99-1.92 (m, 1H), 1.73-1.63 (m, 2H), 1.57-1.22 (m, 16H), 1.205 (s, 3H), 1.19-1.13 (m, 2H), 1.02-0.89 (m, 1H), 0.86-0.83 (m, 3H), 0.79-0.73 (m, 6H), 0.66 (s, 3H).

LCMS Rt = 1.227 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{29}H_{44}N_3O_2$ $[M+H]^+$ 466, found 466.

Example 50. Syntheses of Compounds 92 and 93.



To a solution of **AB1** (550 mg, 1.29 mmol) in acetone (10 mL) was added K_2CO_3 (356 mg, 2.58 mmol) and 5-methyl-1H-tetrazole (162 mg, 1.93 mmol) at 25°C. The mixture was stirred at 25°C for 16 hours. To the mixture was added water (50 mL) and ethyl acetate (50 mL). The organic layer was separated. The mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layers was washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography on silica gel with PE:EtOAc=0:1-1:1 to give **Compound 93** (233 mg, 42%) and **Compound 92** (112 mg, 20%) as solid.

Compound 92:

^{1}HNMR (400MHz, $CDCl_3$) δ 5.37-5.26 (m, 2H), 2.74-2.66 (m, 1H), 2.46 (s, 3H), 2.27-2.25 (m, 1H), 2.02-1.98 (m, 1H), 1.70-1.57 (m, 4H), 1.56-1.46 (m, 5H), 1.42-1.16 (m, 13H), 0.98 (m, 3H), 0.86-0.79 (m, 1H), 0.74 (m, 6H).

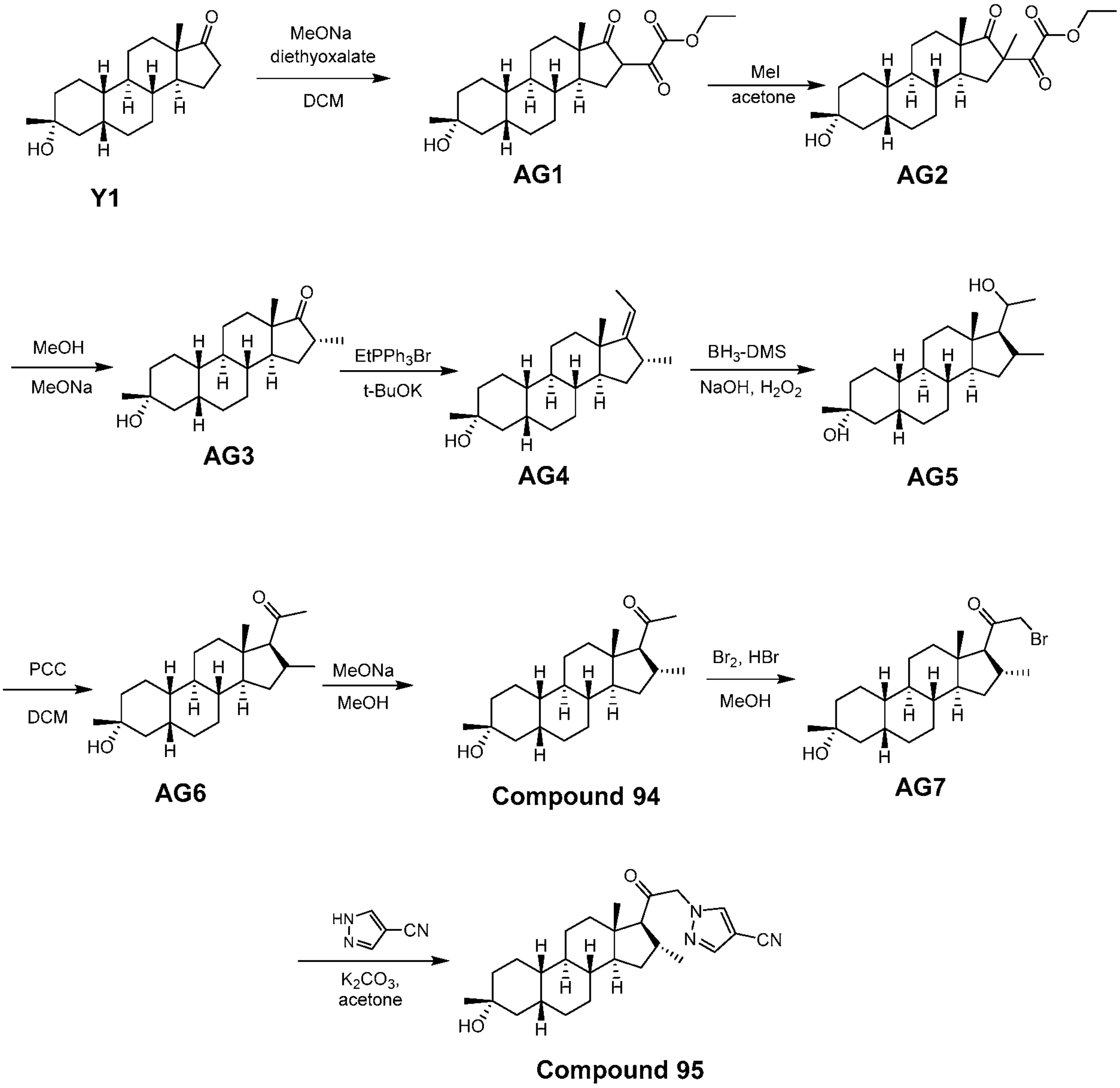
LCMS Rt = 1.108 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{25}H_{41}N_4O_2$ $[M+H]^+$ 429, found 429.

Compound 93:

^{1}HNMR (400MHz, $CDCl_3$) δ 5.16-4.97 (m, 2H), 2.74-2.68 (m, 1H), 2.46 (s, 3H), 2.27-2.25 (m, 1H), 2.00-1.97 (m, 1H), 1.72-1.63 (m, 2H), 1.60 (s, 1H), 1.54-1.41 (m, 4H), 1.41-1.15 (m, 14H), 1.0-0.90 (m, 4H), 0.87-0.81 (m, 1H), 0.76-0.70 (m, 6H).

LCMS Rt = 1.043 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{25}H_{41}N_4O_2$ $[M+H]^+$ 429, found 429.

Example 51. Syntheses of Compounds 94 and 95.



Step 1. To a solution of **Y1** (5 g, 17.2 mmol) in DCM (100 mL) was added diethyoxalate (2.99 g, 20.5 mmol) at 20°C. After cooling to 0°C, MeONa (1.39 g, 25.7 mmol) was added. The mixture was stirred at 20°C for 18 hours and treated with NaHCO3 (1.8 g, solid). The mixture was stirred at 20°C for 10 min and then concentrated in vacuum to give a crude product **AG1** (10 g, crude) as a solid which was used for the next step directly.

Step 2. To a solution of **AG1** (10 g, crude) in acetone (150 mL) was added MeI (32.6 g, 230 mmol) at 20°C. The mixture was warmed to 60°C and stirred at 60°C for 18 hours. The mixture was concentrated in vacuum to give a crude product (13 g, crude) as yellow oil, which was used directly for the next step.

Step 3. To a solution of **AG2** (13 g, crude) in MeOH (100 mL) was added MeONa (1.73 g, 32.1 mmol) at 0°C. The mixture was warmed to 15°C and stirred at 15°C for 18 hours. The reaction was treat with water (30 mL) and EtOAc (20 mL). The mixture was extracted with EtOAc (2 x 30 mL). The combined organic phase was washed with brine (60 mL), dried over Na2SO4, filtered, concentrated in vacuum to give a crude product, which was purified with flash column (EtOAc in PE = 0-35%) to give **AG3** (0.9 g) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60-2.41 (m, 1H), 2.24-2.18 (m, 1H), 1.91-1.72 (m, 6H), 1.70-1.60 (m, 3H), 1.60-1.49 (m, 4H), 1.49-1.39 (m, 3H), 1.39-1.12 (m, 5H), 1.12-1.08 (m, 3H), 1.08-1.02 (m, 1H), 0.99-0.94 (m, 1H), 0.94-0.80 (m, 4H).

Step 4. To suspension of Ph_3PEtBr (1.82 g, 4.92 mmol) in THF (20 mL) under nitrogen was added t-BuOK (552 mg, 4.92 mmol). The mixture became deep orange and stirred at 15°C for 30 min. After that, **AG3** (500 mg, 1.64 mmol) was added. The resulting mixture was stirred at 45°C for 3 hrs. After cooling, the mixture was treated with NH_4Cl (200 mL), extracted with EtOAc (2 x 200 mL). The organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give crude product, which was purified by a silica gel column (PE/EtOAc=0-10%) to give **AG4** (300 mg, impure) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18-5.10 (m, 1H), 2.60-2.49 (m, 1H), 2.30-2.20 (m, 1H), 2.00 (s, 1H),1.90-1.72 (m, 4H), 1.72-1.63(m, 4H), 1.63-1.54 (m, 2H), 1.54-1.50 (m, 1H), 1.50-1.38 (m, 5H), 1.38-1.20 (m, 6H), 1.20-1.02 (m, 4H), 1.02-0.98 (m, 3H), 0.87 (s, 3H).

Step 5. To a solution of **AG4** (300 mg, 0.947 mmol) in THF (10 mL) was added dropwise BH_3-Me_2S (2.84mL, 2.84 mmol) at 0°C. The solution was stirred at 20°C for 2 hrs. After cooling to 0°C, a solution of NaOH solution (1.81 mL, 5 M) was added very slowly. After addition, H_2O_2 (1.07 mL, 10.8 mmol, 30% in water) was added slowly and the inner temperature was maintained below 10°C. The resulting solution was stirred at 20°C for 1 h. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with saturated aqueous $Na_2S_2O_3$ (2 x 10 mL), brine (50 mL), dried over Na_2SO_4 and concentrated in vacuum to give crude product **AG5** (210 mg, crude) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94-1.98 (m, 1H), 1.98-1.71 (m, 4H), 1.71-1.50 (m, 7H), 1.50-1.33 (m, 6H), 1.33-1.19 (m, 10H), 1.19-0.58 (m, 10H).

Step 6. To a solution of **AG5** (600 mg, crude) in DCM (25 mL) was added silica gel (1.65 g) and PCC (773 mg, 3.58 mmol) at 25°C. The reaction mixture was stirred for 1 h and diluted with PE (10 mL). The resulting mixture was filtered though a pad of silica gel. The silica was washed with PE/DCM (50/50 mL), filtered and concentrated in vacuum. The residue was purified by flash column (0-25% of EtOAc in PE) to give **AG6** (520 mg, impure) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70-2.57 (m, 1H), 2.20-2.05 (m, 4H), 1.98-1.75 (m, 4H), 1.75-1.51 (m, 4H), 1.51-1.20 (m, 9H), 1.20-1.00 (m, 5H), 1.00-0.89 (m, 6H), 0.63 (s, 3H).

Step 7. To a solution of **AG6** (520 mg, 1.56 mmol) in MeOH (10 mL) was added MeONa (421 mg, 7.8 mmol). After stirring at 40°C for 18hrs, the reaction was quenched water (5 mL). To the mixture was added water (5 mL) and EtOAc (5 mL). The mixture was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0-10% of EtOAc in PE) to give **Compound 94** (340 mg, impure) as a solid. The impure **Compound 94** (340 mg, impure) was re-crystallized from MeCN to give **Compound 94** (166 mg, 49%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70-2.57 (m, 1H), 2.18-2.05 (m, 4H), 1.98-1.90 (m, 1H), 1.90-1.75 (m, 3H), 1.75-1.58 (m, 3H), 1.52-1.32 (m, 9H), 1.32-1.18 (m, 6H), 1.16-0.98 (m, 3H), 0.98-0.90 (m, 3H), 0.63 (s, 3H).

LCMS Rt = 1.057 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{22}H_{35}O$ $[M+H-H_2O]^+$ 315, found 315.

The stereochemistry at C16 of Comound 94 was confirmed by NOE.)

Step 8. To a solution of **Compound 94** (140 mg, 0.421 mmol) in MeOH (4 ml) was added HBr (17 mg, 0.0842 mmol, 40% in water) and Br_2 (73.9 mg, 0.463 mmol) in MeOH (2 mL) at 20°C. The mixture was stirred at 20°C for 2.5 hrs. The mixture was quenched by sat.aq $NaHCO_3$ (10 mL), treated with water (10 mL), some solid was formed. The suspension was filtered to give **AG7** (150 mg, crude) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95-3.80 (m, 1H), 3.54-3.48 (m, 1H), 2.77-2.60 (m, 1H), 1.90-1.75 (m, 4H), 1.75-1.62 (m, 1H), 1.62-1.49 (m, 4H), 1.49-1.20 (m, 13H), 1.19-0.90 (m, 7H), 0.66 (s, 3H).

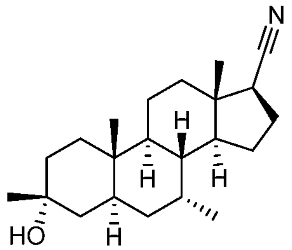
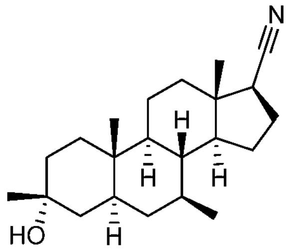
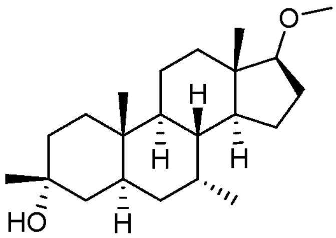
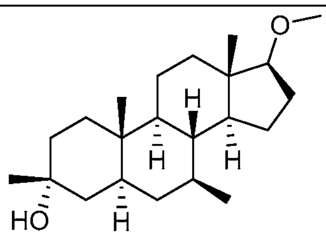
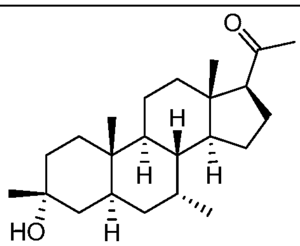
Step 9. To a solution of **AG7** (150 mg, 0.377 mmol) in acetone (2 mL) was added 1H-pyrazole-4-carbonitrile (38.5 mg, 0.414 mmol) and K_2CO_3 (104 mg, 0.754 mmol). After stirring at 20°C for 16 hrs, the reaction mixture was quenched with water (5 mL). The resulting mixture was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column (0-30% of EtOAc in PE) give **Compound 95** (49 mg, 31%) as a solid.

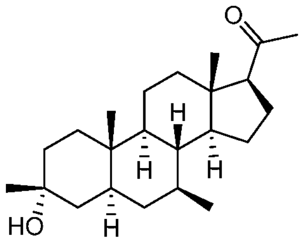
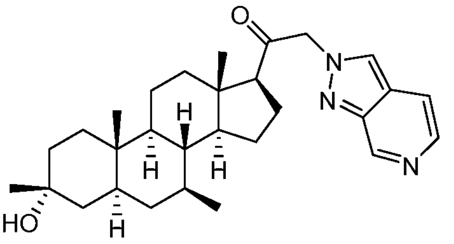
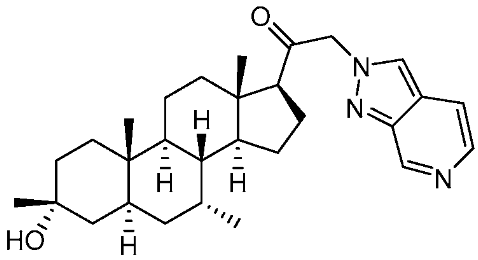
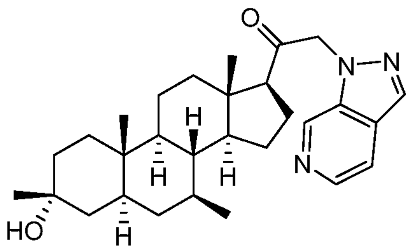
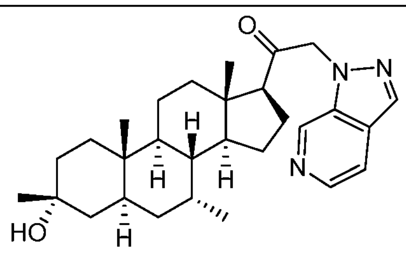
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.95 (m, 2H), 5.02-4.80 (m, 2H), 2.80-2.63 (m, 1H), 2.24-2.18 (m, 1H), 2.05-1.93 (m, 1H), 1.89-1.71 (m, 4H), 1.69-1.51 (m, 5H), 1.51-1.23 (m, 12H), 1.20-1.02 (m, 3H), 1.02-0.91 (m, 3H), 0.69 (s, 3H).

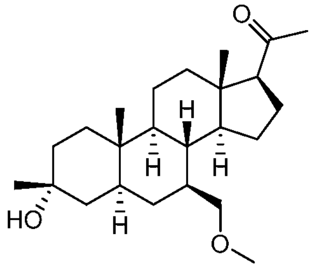
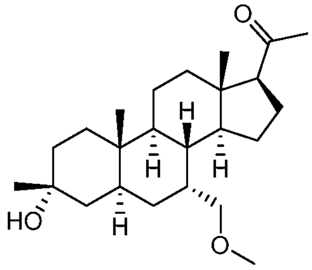
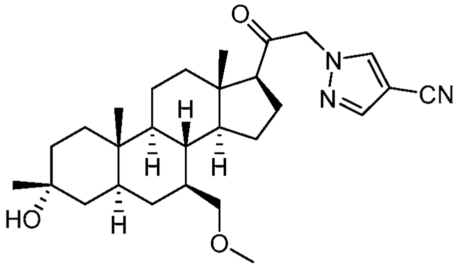
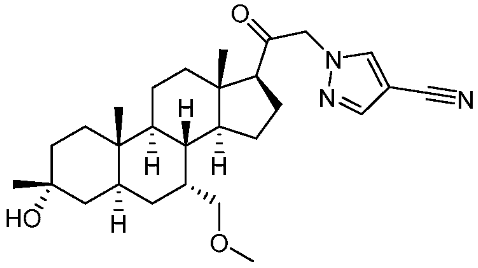
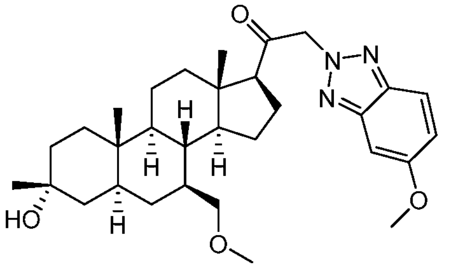
LCMS Rt = 1.042 min in 2 min chromatography, 30-90AB_2MIN_E, purity 100%, MS ESI calcd. for $C_{26}H_{36}N_3O$ $[M+H-H_2O]^+$ 406,

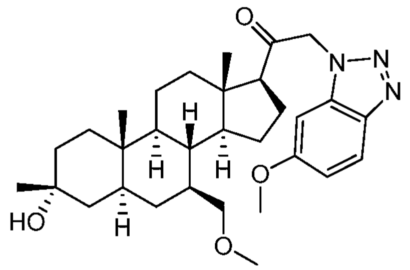
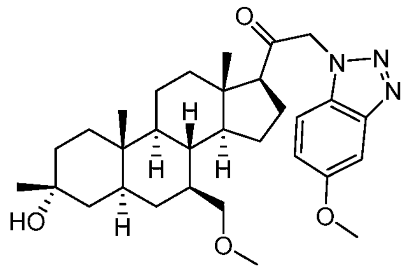
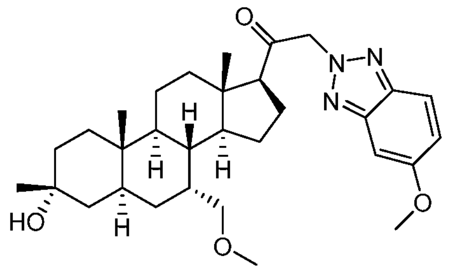
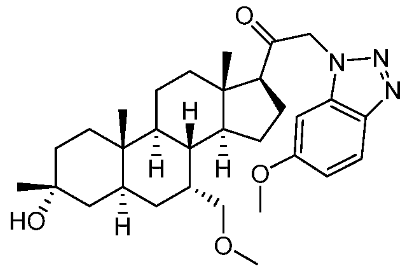
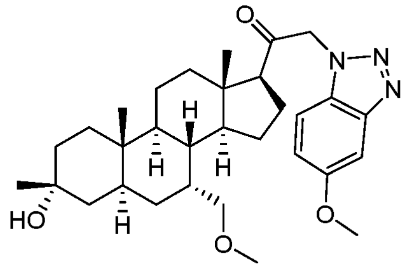
Table 2. TBPS Data

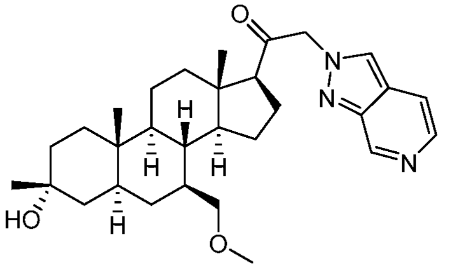
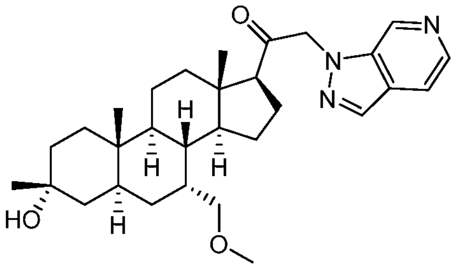
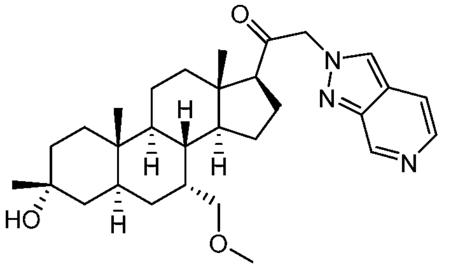
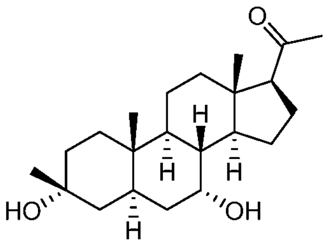
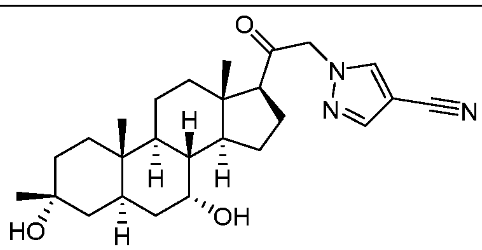
Compound structure	Compound number	TBPS IC_{50} (nM)

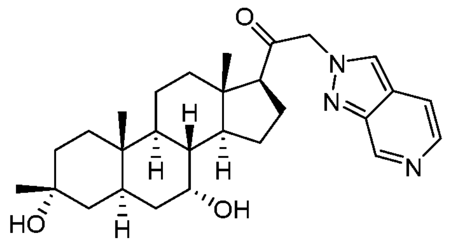
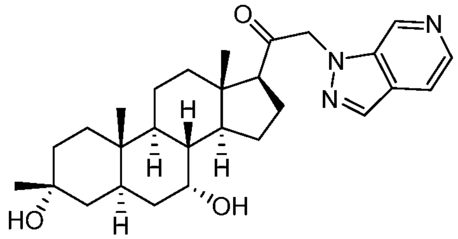
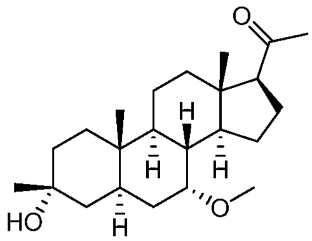
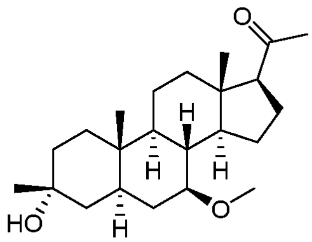
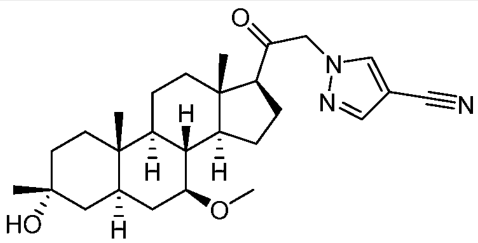
N H H H HO H	1	E
N H H H HO H	2	E
O H H H HO H	3	E
O H H H HO H	4	E
O H H H HO H	5	E

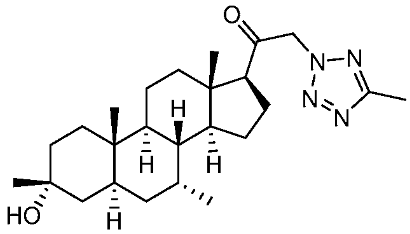
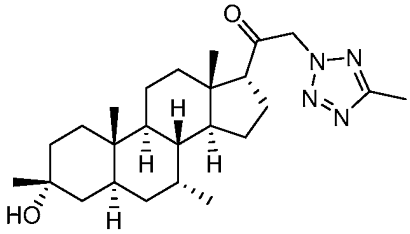
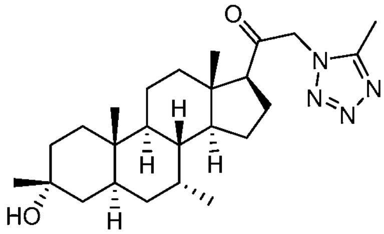
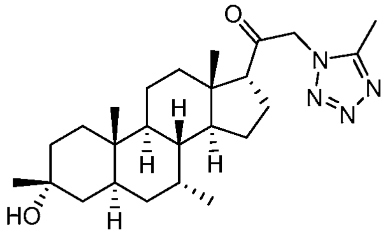
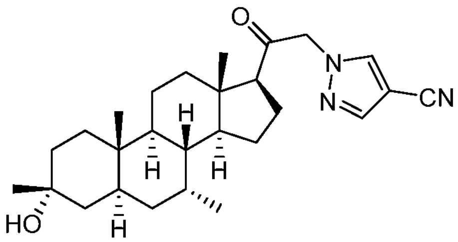
	**6**	**E**
	**7**	**E**
	**8**	**E**
	**9**	**D**
	**10**	**E**

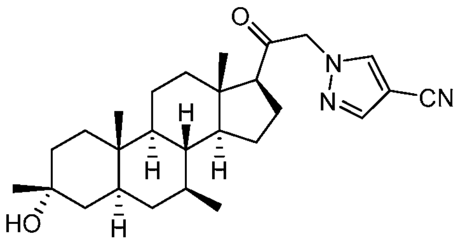
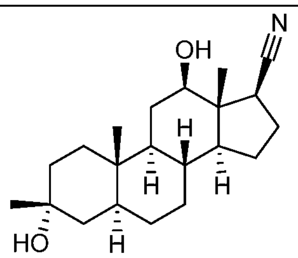
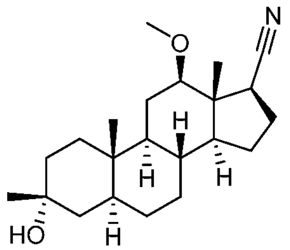
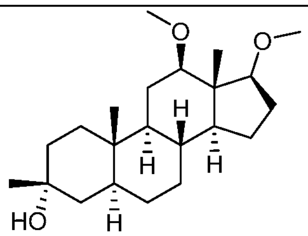
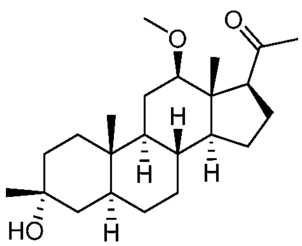
	**11**	**E**
	**12**	**E**
	**13**	**E**
	**14**	**E**
	**15**	**E**

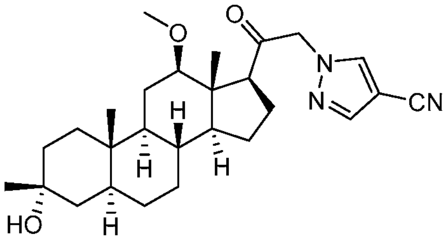
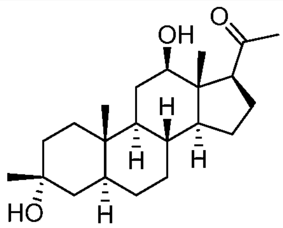
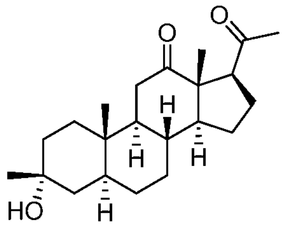
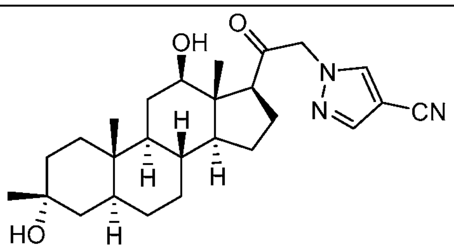
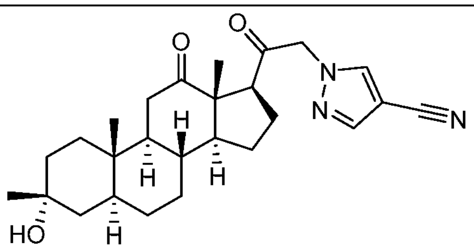
	**16**	**E**
	**17**	**E**
	**18**	**E**
	**19**	**E**
	**20**	**E**

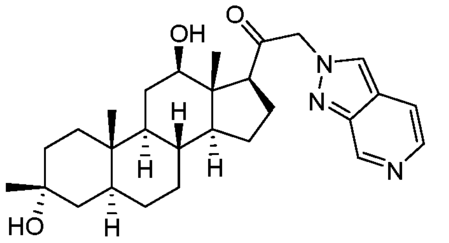
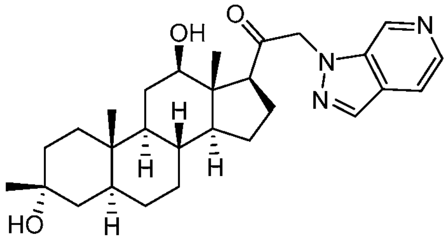
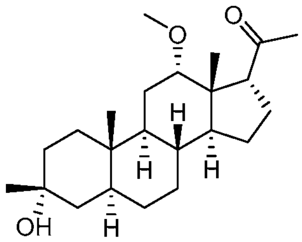
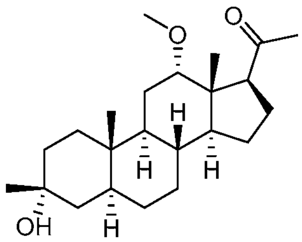
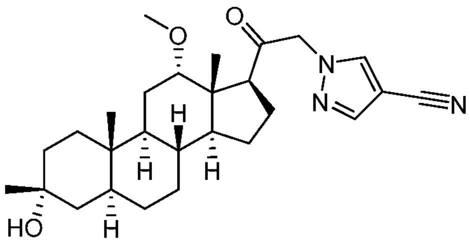
	21	E
	23	E
	24	E
	25	E
	26	E

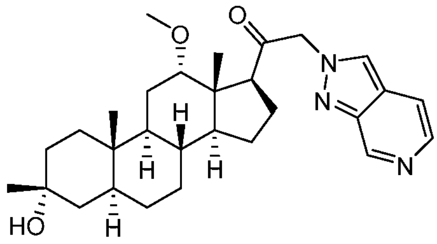
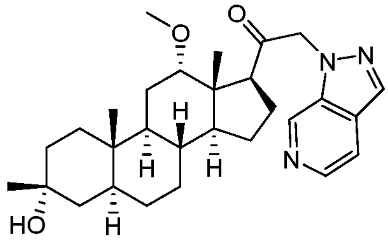
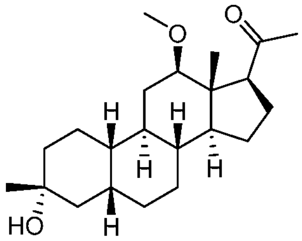
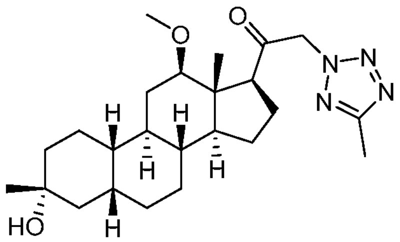
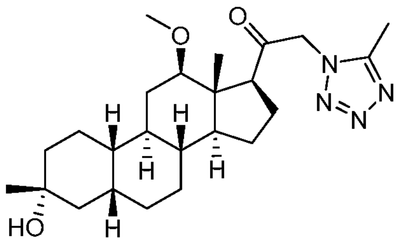
	**27**	**E**
	**28**	**E**
	**29**	**E**
	**30**	**E**
	**31**	**E**

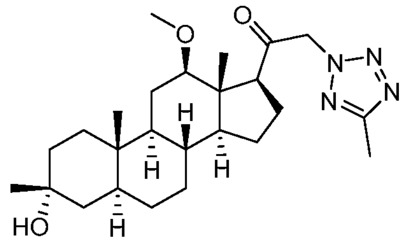
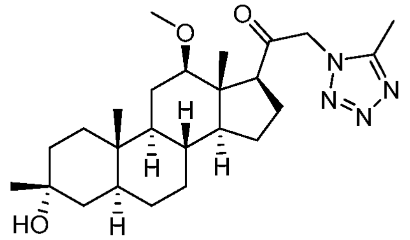
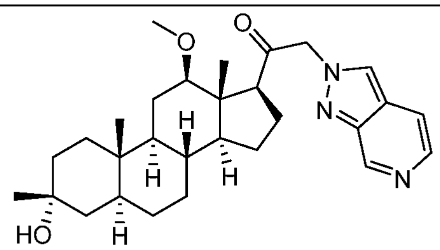
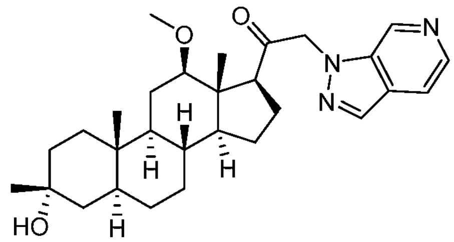
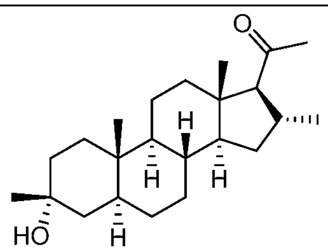
	**34**	**E**
	**35**	**E**
	**36**	**E**
	**37**	**E**
	**38**	**D**

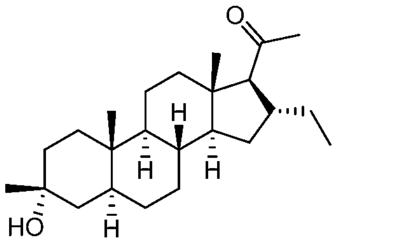
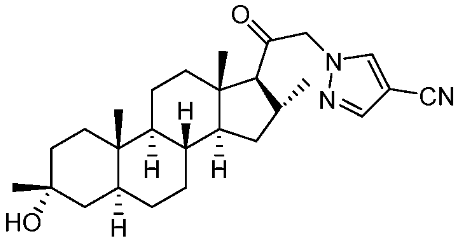
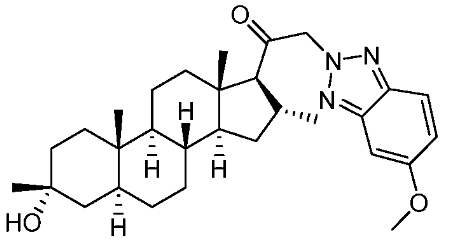
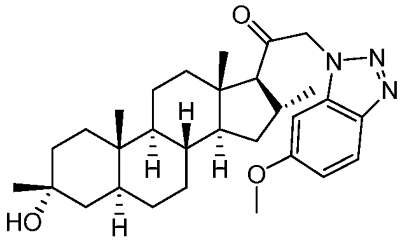
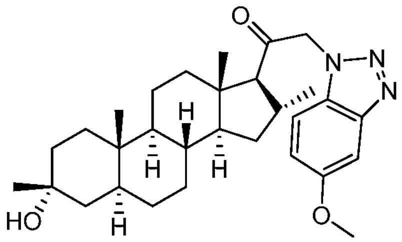
	**39**	**D**
	**40**	**E**
	**41**	**D**
	**42**	**D**
	**43**	**D**

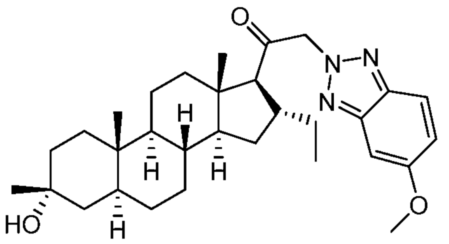
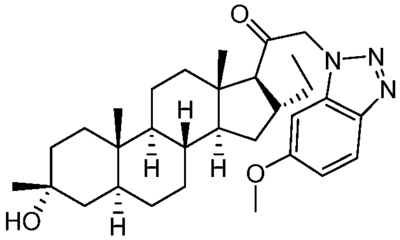
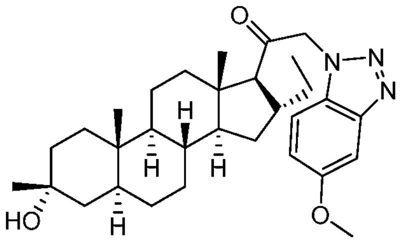
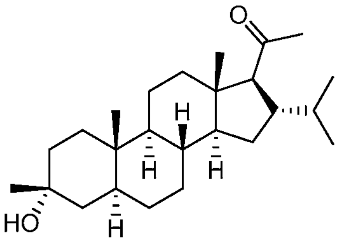
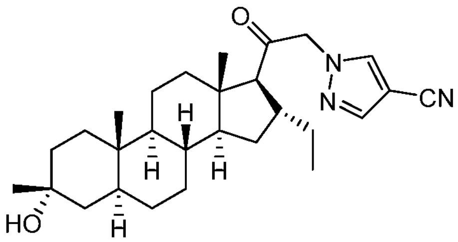
	**44**	**B**
	**45**	**E**
	**46**	**E**
	**47**	**E**
	**48**	**E**

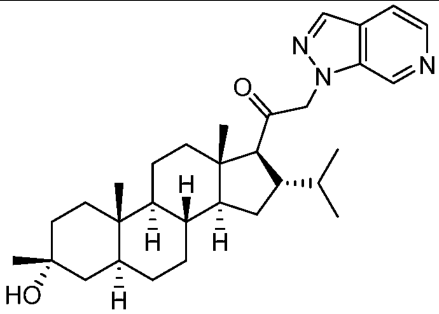
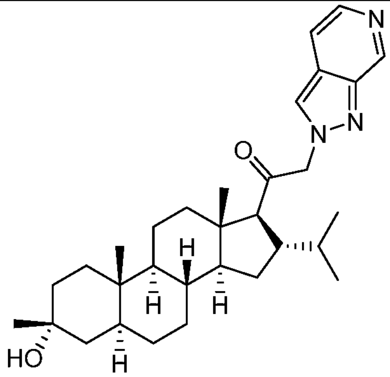
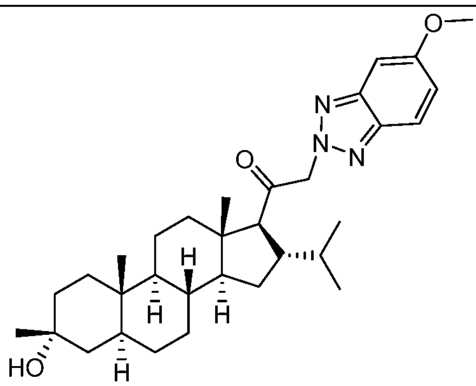
	**49**	**D**
	**50**	**E**
	**51**	**E**
	**52**	**E**
	**53**	**E**

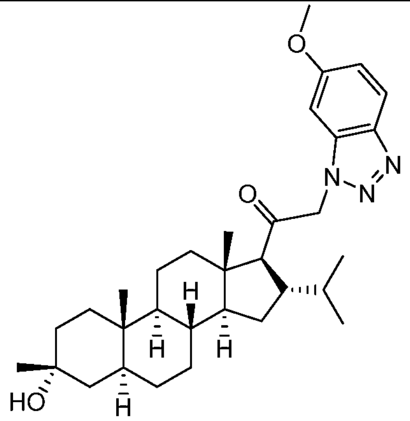
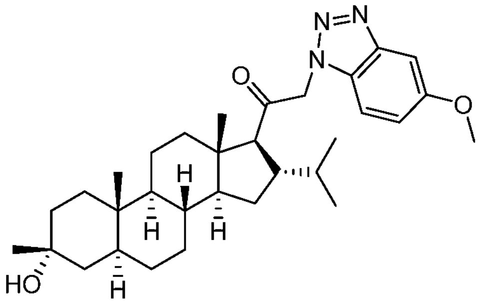
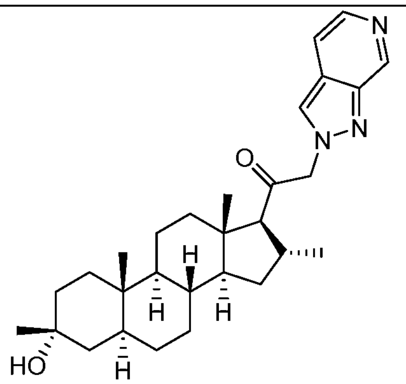
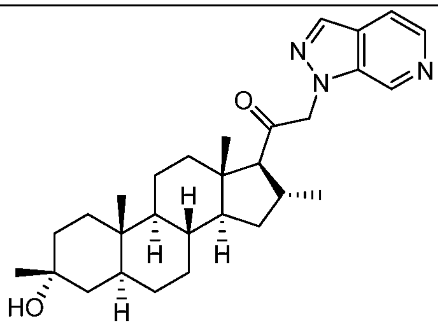
	**54**	**E**
	**55**	**E**
	**56**	**C**
	**58**	**C**
	**59**	**D**

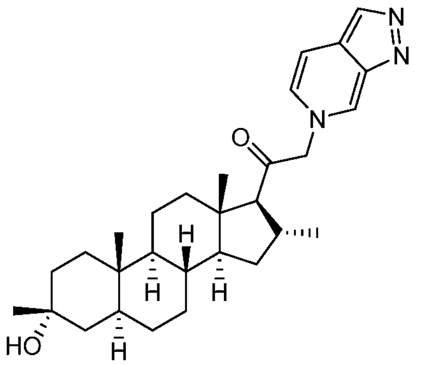
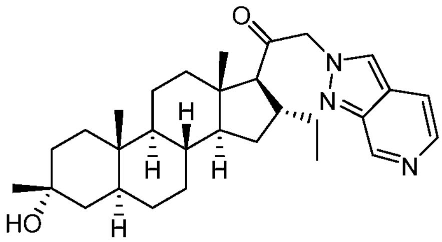
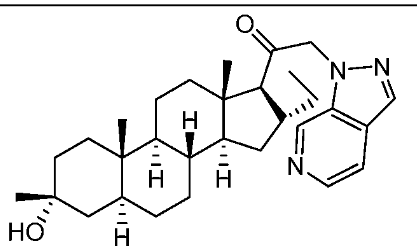
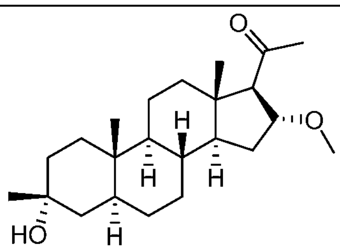
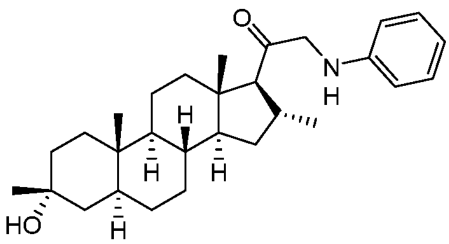
	**60**	**D**
	**61**	**D**
	**62**	**B**
	**63**	**D**
	**64**	**D**

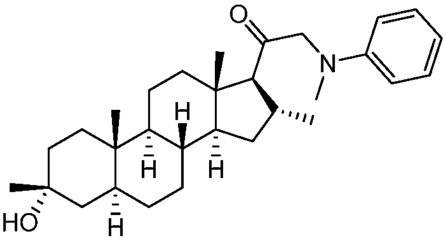
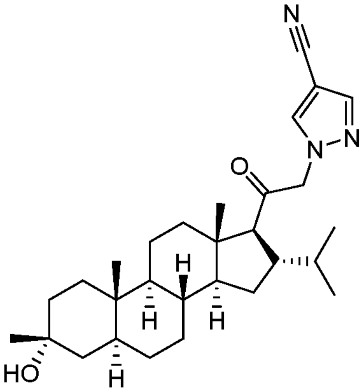
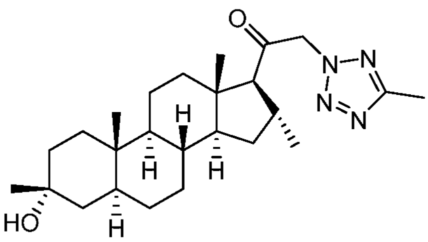
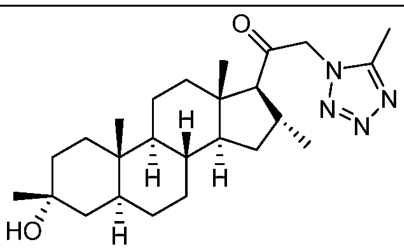
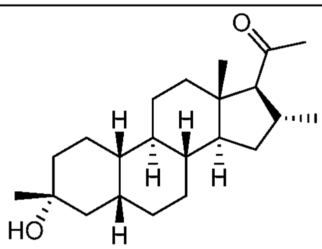
	**65**	**E**
	**66**	**B**
	**67**	**B**
	**68**	**B**
	**69**	**B**

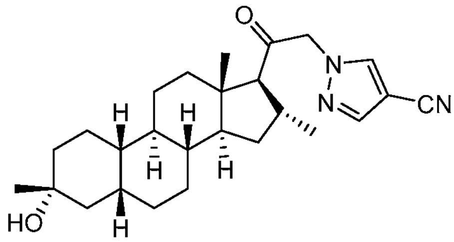
	**70**	**E**
	**71**	**E**
	**72**	**E**
	**73**	**E**
	**74**	**E**

	**75**	**E**
	**76**	**E**
	**77**	**E**

	**78**	**E**
	**79**	**E**
	**80**	**D**
	**81**	**C**

	**82**	**E**
	**83**	**E**
	**84**	**E**
	**85**	**E**
	**86**	**D**

	**87**	**D**
	**88**	**E**
	**89**	**B**
	**90**	**D**
	**91**	**B**

	**92**	**B**

For **Table 2**: **TBPS**: A" indicates an IC_{50} <10 nM, "B" indicates an IC_{50} 10 to <50 nM, "C" indicates an IC_{50} 50 nM to <100 nM, "D" indicates an IC_{50} 100 nM to <500 nM, and "E" indicates IC_{50} greater than or equal to 500 nM.

Equivalents and Scope

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.

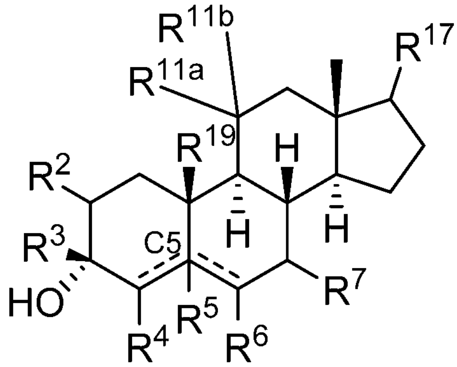
Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub–range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

What is claimed is:

1. A compound of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof, wherein ═ represents a single or double bond as valency permits;

each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $–OR^{A1}$, $–SR^{A1}$, $–N(R^{A1})_2$,$–NHC(=O)R^{A1}$, $–NHC(=O)OR^{A1}$, $–S(=O)R^{A2}$, $–SO_2R^{A2}$, or $–S(=O)_2OR^{A1}$, wherein each instance of R^{A1} is independently hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{A1} groups are joined to form an heterocyclic or heteroaryl ring; and R^{A2} is alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or R^{11a} and R^{11b} together form oxo;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl;

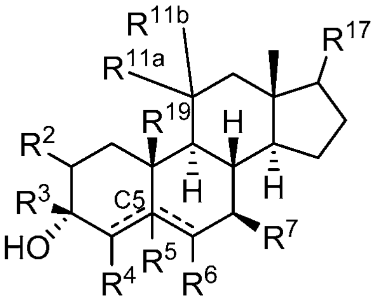
R^5 is absent or hydrogen; and ══ represents a single or double bond, wherein when one of ══ at site is a double bond, the other ══ is a single bond; when both of ══ are single bonds, then R^5 is hydrogen; and when one of the ══ is a double bond, R^5 is absent;

R^{17} is alkoxy, cyano, nitro, aryl, heteroaryl, or $–C(O)R^{B1}$, $–C(O)CH_2R^{B1}$, or $–C(O)CH_2CH_2R^{B1}$, wherein R^{B1} is hydrogen,–OH, alkoxy, aryl, or heteroaryl;

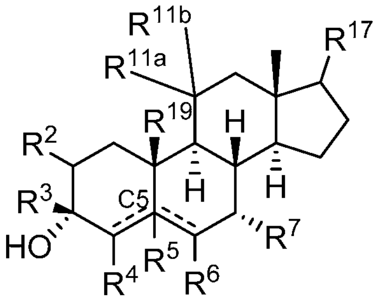
R^{19} is hydrogen or alkyl; and

R^7 is halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $–OR^{A1}$, $–SR^{A1}$, $–N(R^{A1})_2$, $–NHC(=O)R^{A1}$, $–NHC(=O)OR^{A1}$, $–S(=O)R^{A2}$, $–SO_2R^{A2}$, or $–S(=O)_2OR^{A1}$.

2. The compound of claim 1, wherein the compound of Formula **(I)** is a compound of Formula **(I-a)** or **(I-b)**:



(I-a)



(I-b)

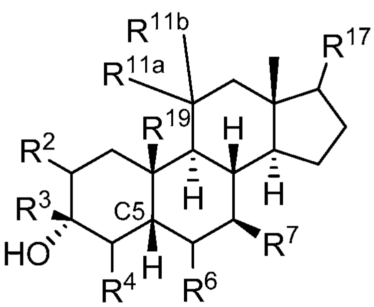
3. The compound of claim 2, wherein each of R^2, R^4, and R^6, R^{11a}, and R^{11b} is independently hydrogen;

4. The compound of claim 2, wherein R^2, R^4, R^6, R^{11a}, and R^{11b} are all hydrogen;

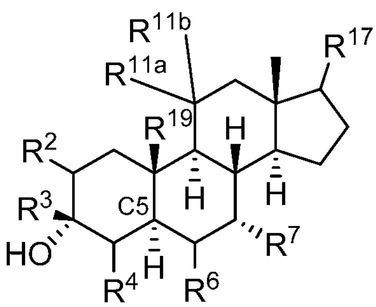
5. The compound of claim 2, wherein each of R^2, R^4, and R^6 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or –OH;

6. The compound of claim 2, wherein R^3 is C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl or $–CH_3$);

7. The compound of claim 2, wherein the compound of Formula **(I)** is a compound of Formula **(II-a)** or **(II-b)**:

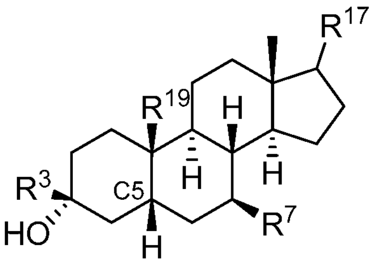


(II-a)

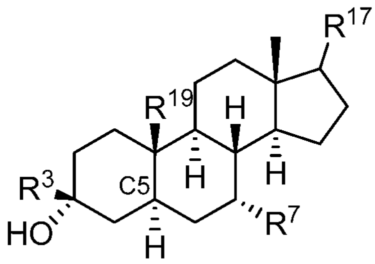


(II-b)

8. The compound of claim 2, wherein the compound of Formula **(I)** is a compound of Formula **(II-c)** or **(II-d)**:



(II-c)



(II-d).

9. The compound of claim 8, wherein R^{19} is $-CH_3$.

10. The compound of claim 8, wherein R^7 is $-CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, or $-CH_2OCH_3$.

11. The compound of claim 8, wherein R^{17} is $-OCH_3$, -CN, or $-C(O)CH_3$.

12. The compound of claim 8, wherein R^{17} is $-C(O)CH_2R^{C1}$.

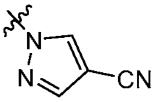
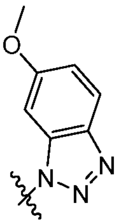
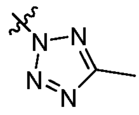
13. The compound of claim 8, wherein R^{17} is $-C(O)CH_2R^{B1}$.

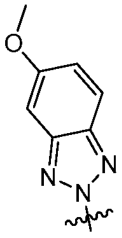
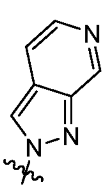
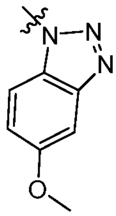
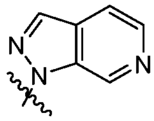
14. The compound of claim 8, wherein R^{17} is alkoxy, cyano, or $-C(O)R^{B1}$.

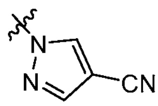
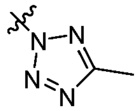
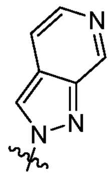
15. The compound of claim 8, wherein R^{B1} is pyrazolyl (e.g., a cyano-substituted pyrazolyl).

16. The compound of claim 8, wherein R^{B1} is tetrazolyl (e.g., a methyl-substituted tetrazolyl).

17. The compound of claim 8, wherein R^{B1} is a bicyclic heteroaryl (e.g., a methoxy-substituted bicyclic heteroaryl.

18. The compound of claim 8, wherein R^{B1} is , , ,

, , , or .

19. The compound of claim 8], wherein R^{B1} is , , or .

20. The compound of claim 2, wherein R^6 is halogen.

21. The compound of claim 2, wherein R^6 is fluorine.

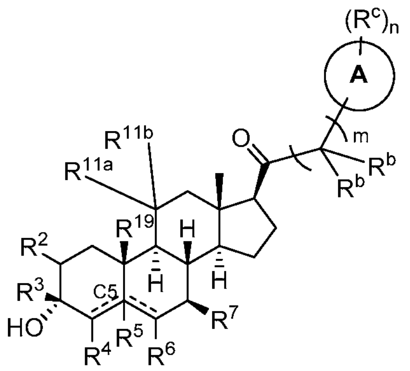
22. The compound of claim 2, wherein each of R^{11a} and R^{11b} is independently hydrogen, C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl), C_1-C_6 alkoxy (*e.g.* C_1-C_6 alkoxyhalo), or –OH.

23. The compound of claim 2, wherein R^{11a} and R^{11b} together form oxo.

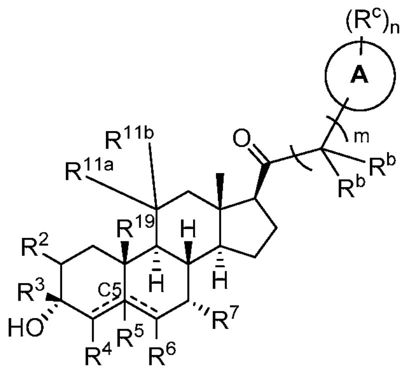
24. The compound of claim 2, wherein R^{17} is C_1-C_6 alkoxy (*e.g.* $-OCH_3$), cyano, or nitro.

25. The compound of claim 2, wherein R^{19} is hydrogen or substituted or unsubtituted C_1-C_6 alkyl (*e.g.* $-CH_2OR^X$, wherein R^X is hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy).

26. The compound of claim 2, wherein the compound of Formula (**I**) is a compound of Formula (**IV-a**) or (**IV-b**):



(IV-a)



(IV-b),

wherein:

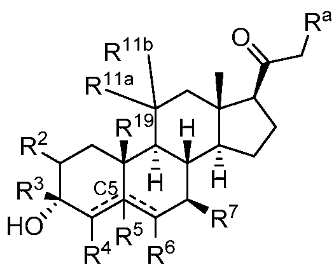
m is 0, 1, or 2;

n is 0, 1, or 2;

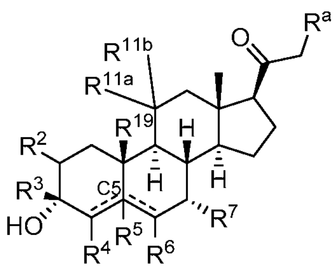
each R^b is independently hydrogen, halogen, or C_1-C_6 alkyl; and

each R^c is independently halogen, C_1-C_6 alkyl (e.g. $-CH_3$ or C_1-C_6 haloalkyl), C_1-C_6 alkoxy, cyano, or –OH.

27. The compound of claim 2, wherein the compound of Formula **(I)** is a compound of Formula **(III-a)** or **(III-b)**:



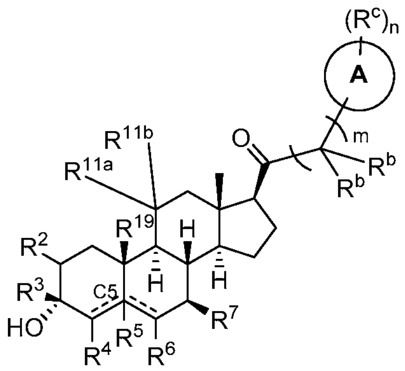
(III-a)



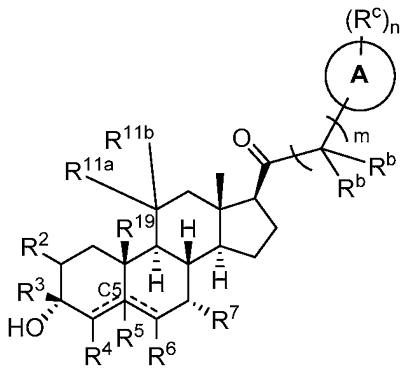
(III-b),

wherein R^a is hydrogen, halogen, C_1-C_6 alkyl (*e.g.* $-CH_3$), or –OH.

28. The compound of claim 2, wherein the compound of Formula **(I)** is a compound of Formula **(IV-a)** or **(IV-b)**:



(IV-a)



(IV-b),

wherein:

m is 0, 1, or 2;

n is 0, 1, or 2;

each R^b is independently hydrogen, halogen, or C_1-C_6 alkyl; and

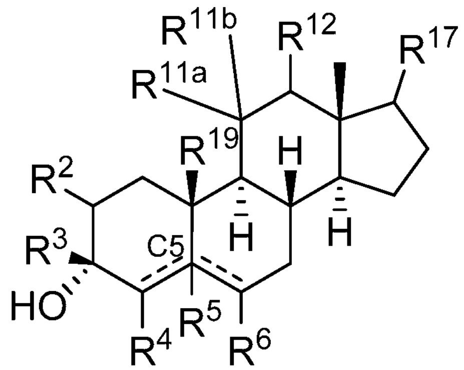
each R^c is independently halogen, C_1-C_6 alkyl (e.g. $-CH_3$ or C_1-C_6 haloalkyl), C_1-C_6 alkoxy, cyano, or –OH.

29. The compound of claim 15, wherein **A** is a 5-10-membered ring.

30. The compound of claim 15, wherein **A** is a fused bicyclic ring.

31. The compound of claim 15, wherein **A** is monocyclic heteroaryl or bicyclic heteroaryl.

32. A compound of Formula (**V**):



(V)

or a pharmaceutically acceptable salt thereof,

wherein ----- represents a single or double bond as valency permits;

each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $–OR^{A1}$, $–SR^{A1}$, $–N(R^{A1})_2$,–NHC(=O)R^{A1}, –NHC(=O)OR^{A1}, –S(=O)R^{A2}, $–SO_2R^{A2}$, or $–S(=O)_2OR^{A1}$, wherein each instance of R^{A1} is independently hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{A1} groups are joined to form an heterocyclic or heteroaryl ring; and R^{A2} is alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or R^{11a} and R^{11b} together form oxo; R^3 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl;

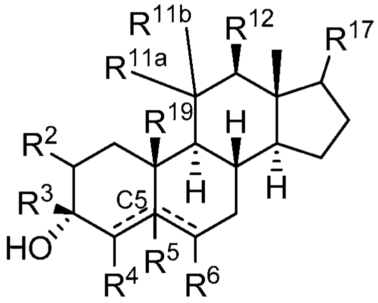
R^5 is absent or hydrogen; and ------ represents a single or double bond, wherein when one of ------ at site is a double bond, the other ------ is a single bond; when both of ------ are single bonds, then R^5 is hydrogen; and when one of the ------ is a double bond, R^5 is absent;

R^{17} is alkoxy, cyano, nitro, aryl, heteroaryl,–C(O)R^{B1}, $–C(O)CH_2R^{B1}$, or –$C(O)CH_2CH_2R^{B1}$, wherein R^{B1} is hydrogen,–OH, alkoxy, aryl, or heteroaryl;

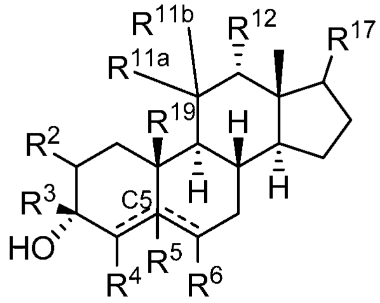
R^{19} is hydrogen or alkyl;

and R^{12} is halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $–OR^{A1}$, $–SR^{A1}$, $–N(R^{A1})_2$, –NHC(=O)R^{A1}, –NHC(=O)OR^{A1}, –S(=O)R^{A2}, $–SO_2R^{A2}$, or $–S(=O)_2OR^{A1}$.

33. The compound of claim 32, wherein the compound of Formula **(V)** is a compound of Formula **(V-a)** or **(V-b)**:



(V-a)



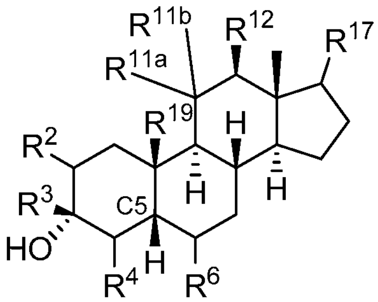
(V-b)

34. The compound of claim 33, wherein each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen. In some embodiments, R^2, R^4, R^6, R^{11a}, and R^{11b} are all hydrogen.

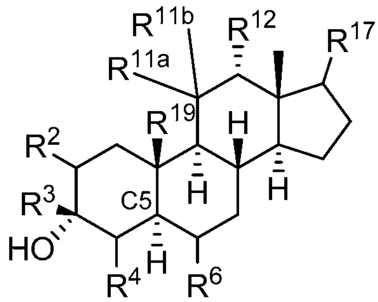
35. The compound of claim 33, wherein each of R^2, R^4, and R^6 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or –OH.

36. The compound of claim 33, wherein R^3 is C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl or $–CH_3$).

37. The compound of claim 33, wherein the compound of Formula **(V)** is a compound of Formula **(VI-a)** or **(VI-b)**:

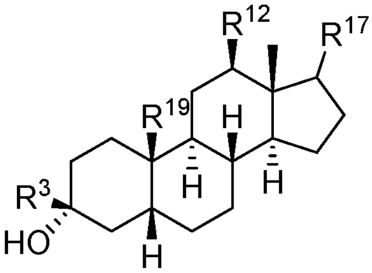
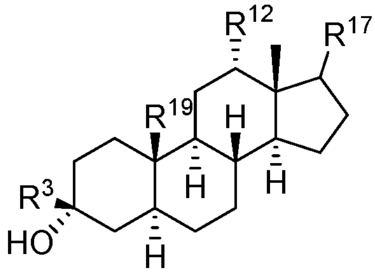


(VI-a)



(VI-b).

38. The compound of claim 33, wherein the compound of Formula **(V)** is a compound of Formula **(VI-c)** or **(VI-d)**:

 **(VI-c)**  **(VI-d)**.

39. The compound of claim 38, wherein R^{19} is $-CH_3$.

40. The compound of claim 38, wherein R^7 is $-CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, or $-CH_2OCH_3$.

41. The compound of claim 38, wherein R^{17} is $-OCH_3$, -CN, or $-C(O)CH_3$.

42. The compound of claim 38, wherein R^{17} is $-C(O)CH_2R^{C1}$.

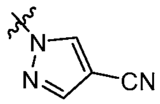
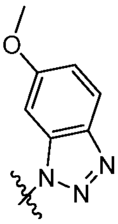
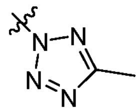
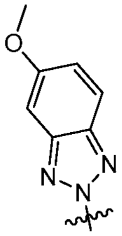
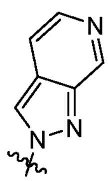
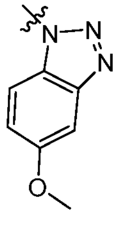
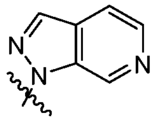
43. The compound of claim 38, wherein R^{17} is $-C(O)CH_2R^{B1}$.

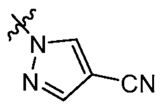
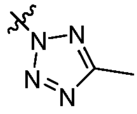
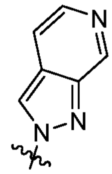
44. The compound of claim 38, wherein R^{17} is alkoxy, cyano, or $-C(O)R^{B1}$.

45. The compound of claim 38, wherein R^{B1} is pyrazolyl (e.g., a cyano-substituted pyrazolyl).

46. The compound of claim 38, wherein R^{B1} is tetrazolyl (e.g., a methyl-substituted tetrazolyl).

47. The compound of claim 38, wherein R^{B1} is a bicyclic heteroaryl (e.g., a methoxy-substituted bicyclic heteroaryl.

48. The compound of claim 38, wherein R^{B1} is , , , , , , or .

49. The compound of claim 38, wherein R^{B1} is , , or .

50. The compound of claim 33, wherein R^6 is halogen.

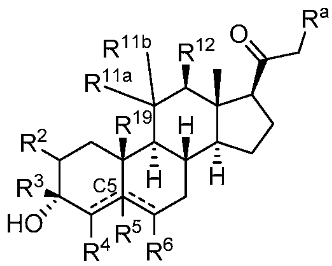
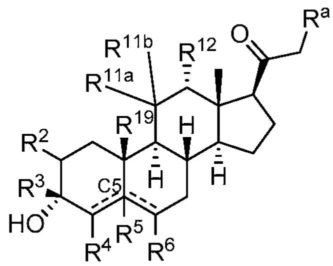
51 The compound of claim 33, wherein R^6 is fluorine.

52. The compound of claim 33, wherein each of R^{11a} and R^{11b} is independently hydrogen, C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl), C_1-C_6 alkoxy (*e.g.* C_1-C_6 haloalkoxy), or –OH. In some embodiments, R^{11a} and R^{11b} together form oxo.

53. The compound of claim 33, wherein R^{17} is C_1-C_6 alkoxy (*e.g.* $-OCH_3$) or cyano.

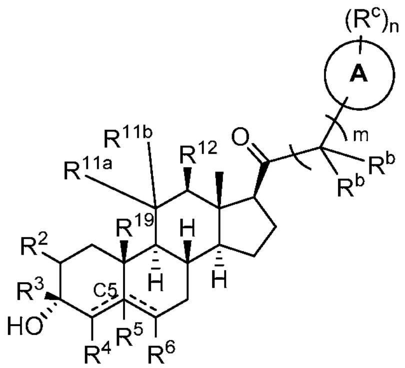
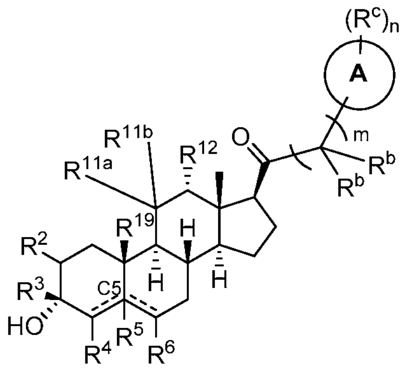
54. The compound of claim 33, wherein R^{19} is hydrogen or substituted or unsubtituted C_1-C_6 alkyl (*e.g.* $-CH_2OR^X$, wherein R^X is hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy).

55. The compound of claim 33, wherein the compound of Formula **(V)** is a compound of Formula **(VII-a)** or **(VII-b)**:

 **(VII-a)**  **(VII-b)**,

wherein R^a is hydrogen, halogen, C_1-C_6 alkyl (*e.g.* $-CH_3$), or –OH.

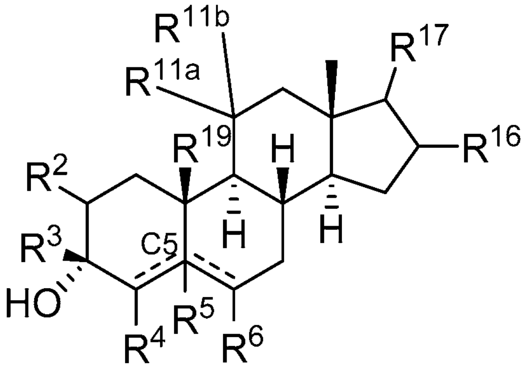
56. The compound of claim 33, wherein the compound of Formula **(V)** is a compound of Formula **(VIII-a)** or **(VIII-b)**:

 **(VIII-a)**  **(VIII-b)**,

wherein m is 0, 1, or 2, n is 0, 1, or 2, and each R^b is independently hydrogen, halogen, or C_1-C_6 alkyl; and each R^c is independently halogen, C_1-C_6 alkyl (e.g. $-CH_3$ or C_1-C_6 haloalkyl), C_1-C_6 alkoxy, cyano, or –OH.

57. The compound of claim 33, wherein **A** is a 5-10-membered ring. In some embodiments, **A** is a fused bicyclic ring. In some embodiments, **A** is monocyclic heteroaryl or bicyclic heteroaryl.

58. A compound of Formula **(IX)**:



(IX),

or a pharmaceutically acceptable salt thereof, wherein ═ represents a single or double bond as valency permits;

each of R^2, R^4, R^6, R^{11a}, and R^{11b} is independently hydrogen, halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-OR^{A1}$, $-SR^{A1}$, $-N(R^{A1})_2$,$-NHC(=O)R^{A1}$, $-NHC(=O)OR^{A1}$, $-S(=O)R^{A2}$, $-SO_2R^{A2}$, or $-S(=O)_2OR^{A1}$, wherein each instance of R^{A1} is independently hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, a nitrogen protecting group when attached to a nitrogen atom, or two R^{A1} groups are joined to form an heterocyclic or heteroaryl ring; and R^{A2} is alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl; or R^{11a} and R^{11b} together form oxo;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl;

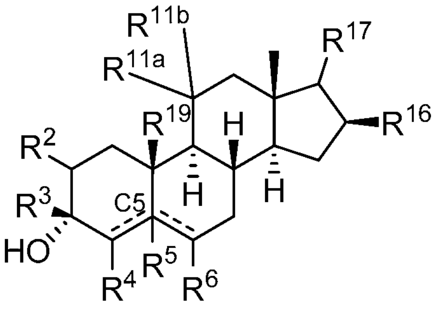
R^5 is absent or hydrogen; and ═ represents a single or double bond, wherein when one of ═ at site is a double bond, the other ═ is a single bond; when both of ═ are single bonds, then R^5 is hydrogen; and when one of the ═ is a double bond, R^5 is absent;

R^{17} is alkoxy, cyano, nitro, aryl, heteroaryl, $-C(O)R^{B1}$, $-C(O)CH_2R^{B1}$, or $-C(O)CH_2CH_2R^{B1}$, wherein R^{B1} is hydrogen,–OH, $-N(R^{A1})_2$, alkoxy, aryl, or heteroaryl;

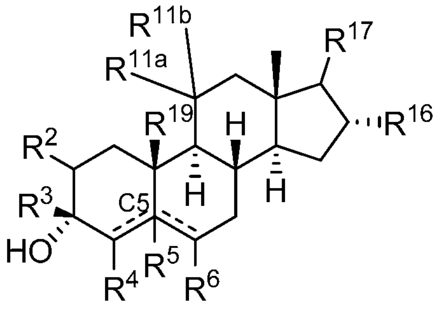
R^{19} is hydrogen or alkyl;

and R^{16} is halogen, cyano, nitro, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-OR^{A1}$, $-SR^{A1}$, $-N(R^{A1})_2$, $-NHC(=O)R^{A1}$, $-NHC(=O)OR^{A1}$, $-S(=O)R^{A2}$, $-SO_2R^{A2}$, or $-S(=O)_2OR^{A1}$.

59. The compound of claim 58, wherein the compound of Formula **(IX)** is a compound of Formula **(IX-a)** or **(IX-b)**:



(IX-a)

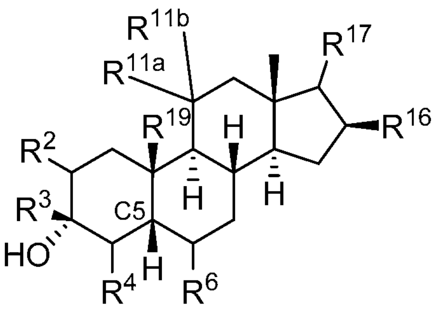


(IX-b).

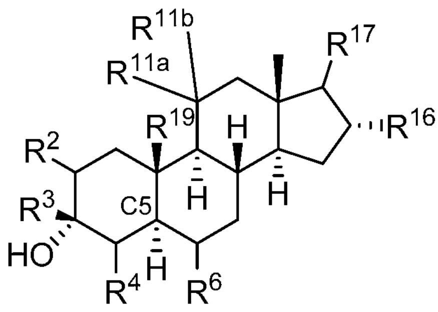
60. The compound of claim 59, wherein each of R^2, R^4, and R^6, R^{11a}, and R^{11b} is independently hydrogen. In some embodiments, R^2, R^4, and R^6, R^{11a}, and R^{11b} are all hydrogen. In some embodiments, each of R^2, R^4, and R^6 is independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or –OH.

61. The compound of claim 59, wherein R^3 is C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl or $-CH_3$).

62. The compound of claim 59, wherein the compound of Formula **(IX)** is a compound of Formula **(X-a)** or **(X-b)**:

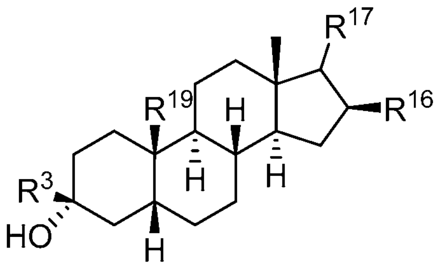


(X-a)

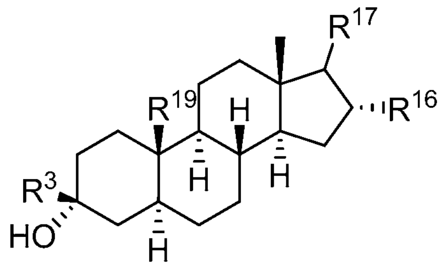


(X-b).

63. The compound of claim 59, wherein the compound of Formula **(IX)** is a compound of Formula **(X-c)** or **(X-d)**:



(X-c)



(X-d).

64. The compound of claim 63, wherein R^{19} is $-CH_3$.

65. The compound of claim 63, wherein R^7 is $-CH_3$, $-CH_2CH_3$, -OH, $-OCH_3$, or $-CH_2OCH_3$.

66. The compound of claim 63, wherein R^{17} is $-OCH_3$, -CN, or $-C(O)CH_3$.

67. The compound of claim 63, wherein R^{17} is $-C(O)CH_2R^{C1}$.

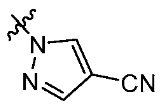
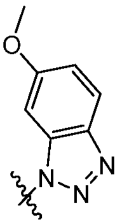
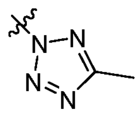
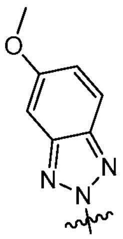
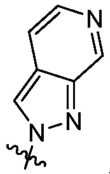
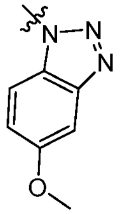
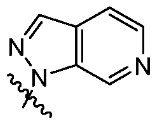
68. The compound of claim 63, wherein R^{17} is $-C(O)CH_2R^{B1}$.

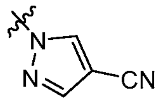
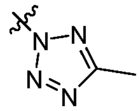
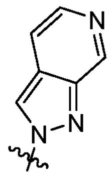
69. The compound of claim 63, wherein R^{17} is alkoxy, cyano, or $-C(O)R^{B1}$.

70. The compound of claim 63, wherein R^{B1} is pyrazolyl (e.g., a cyano-substituted pyrazolyl).

71. The compound of claim 63, wherein R^{B1} is tetrazolyl (e.g., a methyl-substituted tetrazolyl).

72. The compound of claim 63, wherein R^{B1} is a bicyclic heteroaryl (e.g., a methoxy-substituted bicyclic heteroaryl.

73. The compound of claim 63, wherein R^{B1} is , , , , , , or .

74. The compound of claim 63, wherein R^{B1} is , , or .

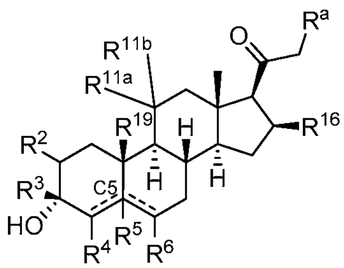
75. The compound of claim 58, wherein R^6 is halogen. In some embodiments, R^6 is fluorine.

76. The compound of claim 58, wherein each of R^{11a} and R^{11b} is independently hydrogen, C_1-C_6 alkyl (*e.g.* C_1-C_6 haloalkyl), C_1-C_6 alkoxy (*e.g.* C_1-C_6 haloalkoxy), or –OH. In some embodiments, R^{11a} and R^{11b} together form oxo.

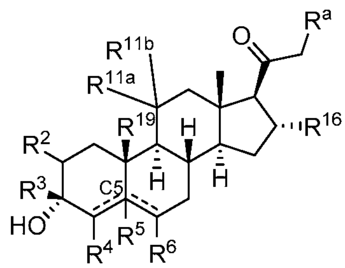
77. The compound of claim 58, wherein R^{17} is C_1-C_6 alkoxy (*e.g.* $–OCH_3$), cyano, or nitro.

78. The compound of claim 58, wherein R^{19} is hydrogen or substituted or unsubtituted C_1-C_6 alkyl (*e.g.* $–CH_2OR^X$, wherein R^X is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy).

79. The compound of claim 58, wherein the compound of Formula **(IX)** is a compound of Formula **(X-a)** or **(X-b)**:



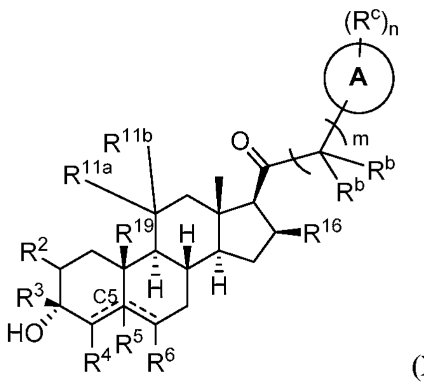
(X-a)



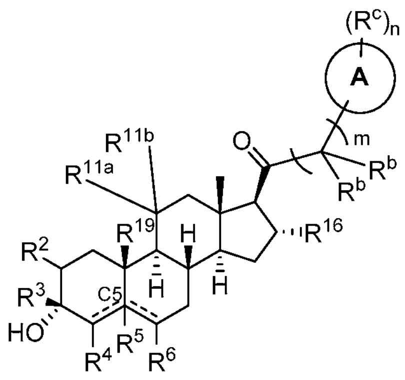
(X-b),

wherein R^a is hydrogen, halogen, C_1-C_6 alkyl (*e.g.* $-CH_3$), or $-OH$.

80. The compound of claim 58, wherein the compound of Formula **(IX)** is a compound of Formula **(XI-a)** or **(XI-b)**:



(XI-a)

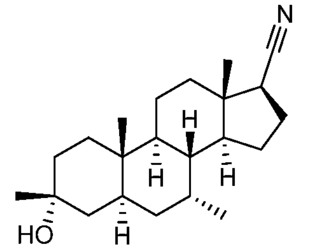


(XI-b),

wherein m is 0, 1, or 2, n is 0, 1, or 2, each R^b is independently hydrogen, halogen, or C_1-C_6 alkyl, and each R^c is independently halogen, C_1-C_6 alkyl (e.g. $-CH_3$ or C_1-C_6 haloalkyl), C_1-C_6 alkoxy, cyano, or $-OH$.

81. The compound of claim 58, wherein **A** is a 5-10-membered ring. In some embodiments, **A** is a fused bicyclic ring. In some embodiments, **A** is monocyclic heteroaryl or bicyclic heteroaryl.

82. A compound selected from the group consisting of: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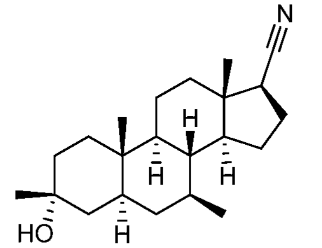
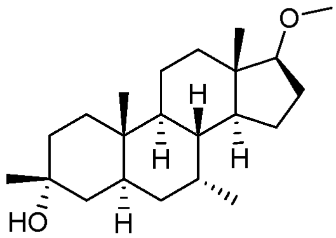
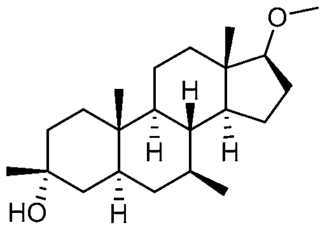
H
H
H
HO
H


N
H
H
H
HO
H


O
H
H
H
HO
H


O
H
H
H
HO
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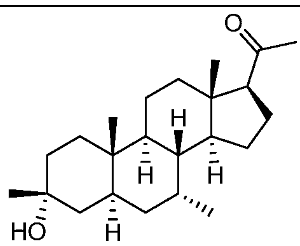
O
H
H
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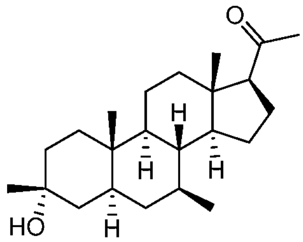
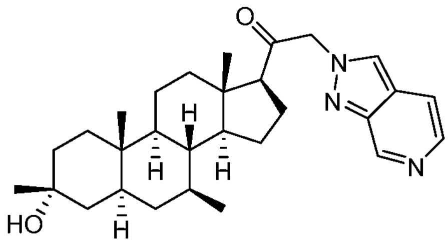
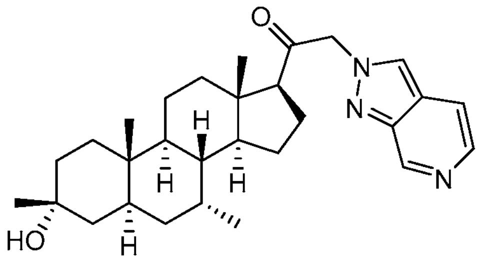
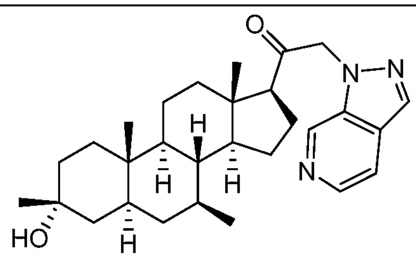
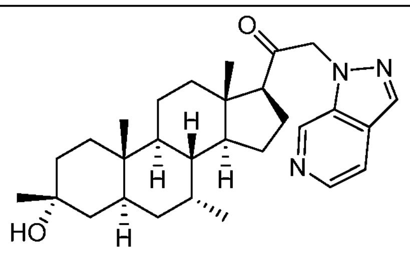
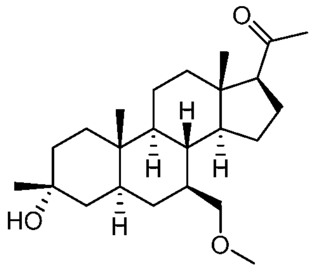
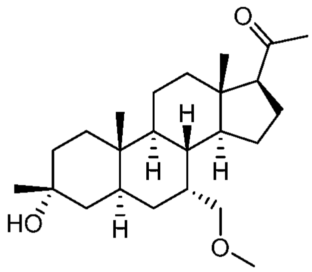
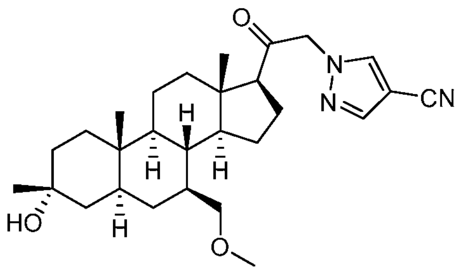
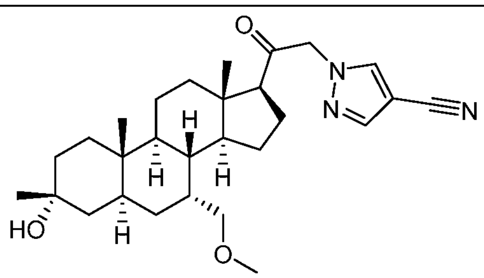
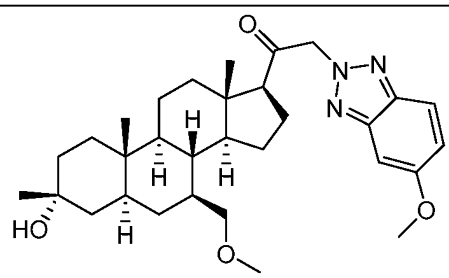






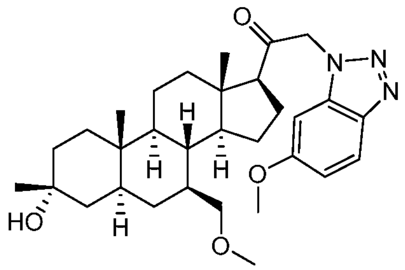


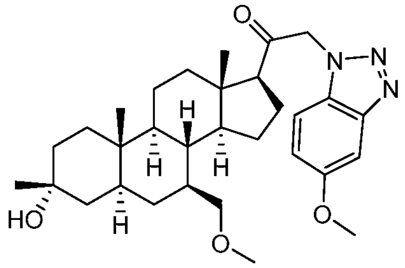









O
N
N
N
HO
O
O


O
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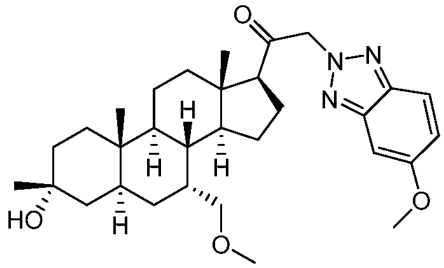
O
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HO
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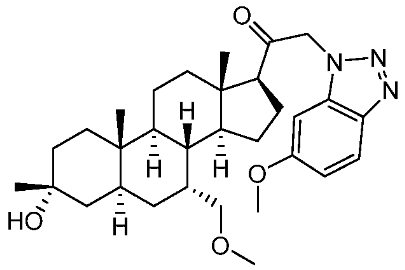
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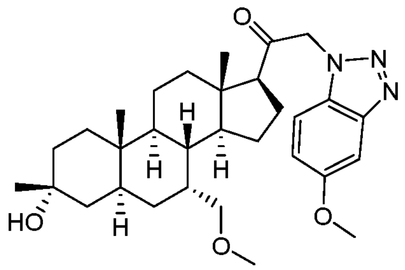
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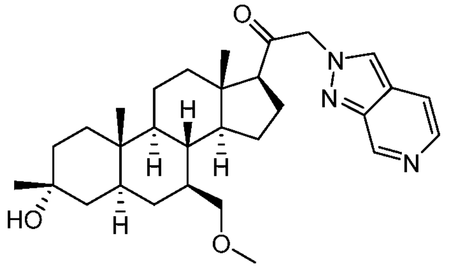

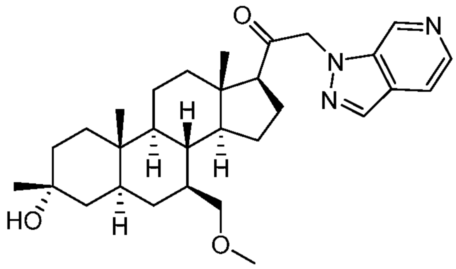

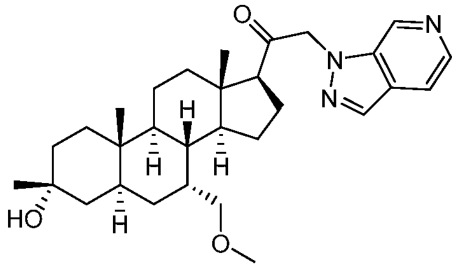

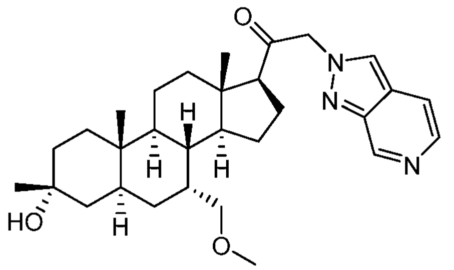

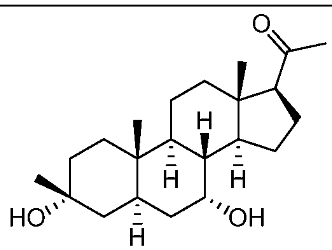

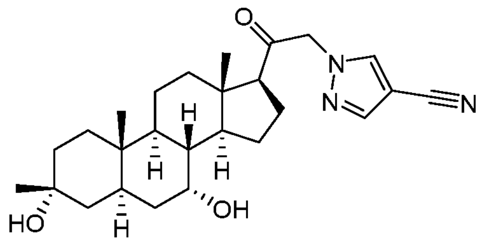
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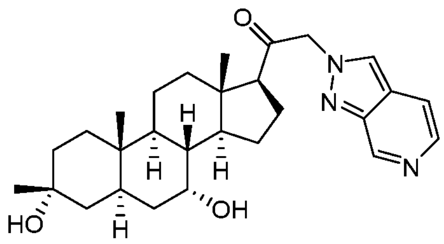
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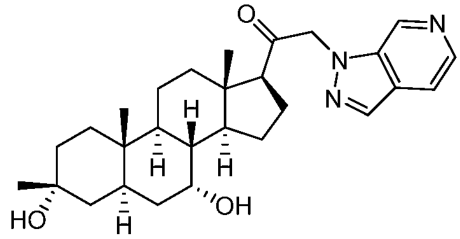
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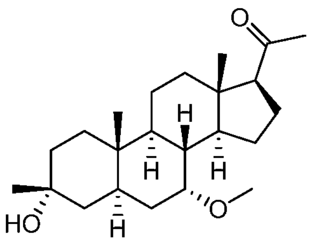
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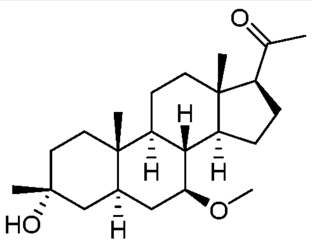
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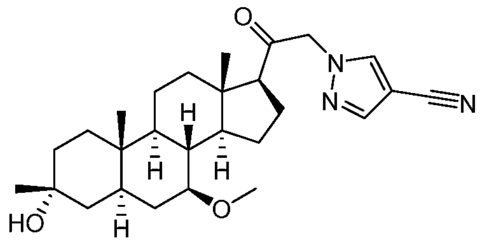
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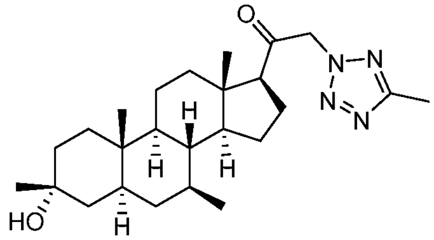
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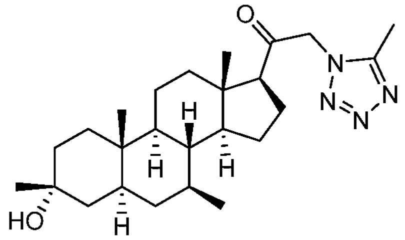
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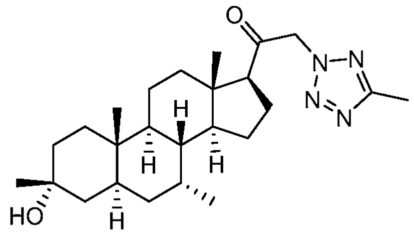
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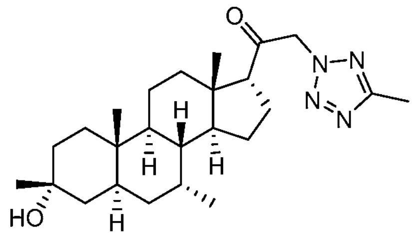
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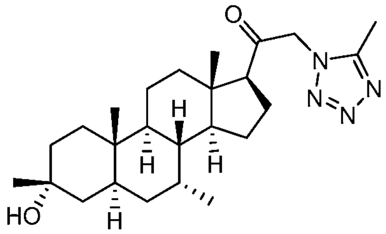
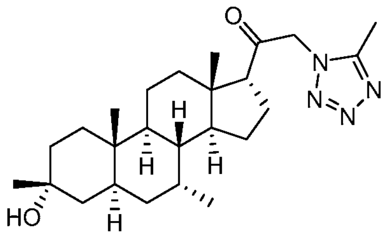
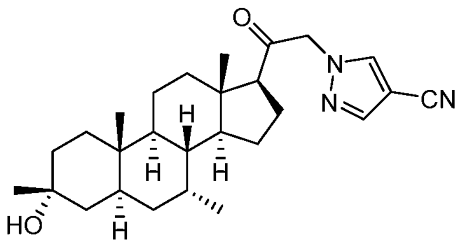
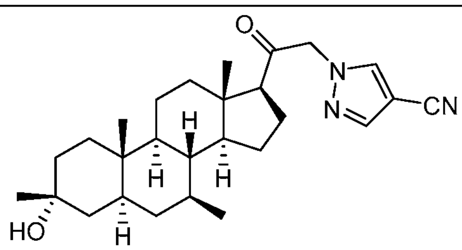
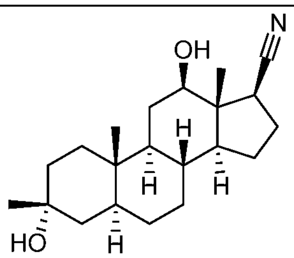

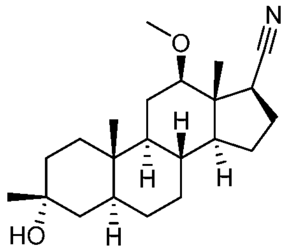

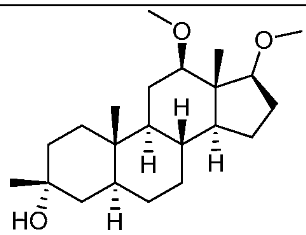

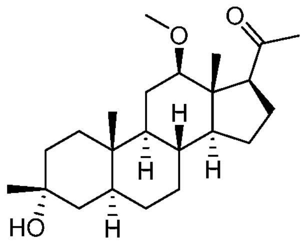

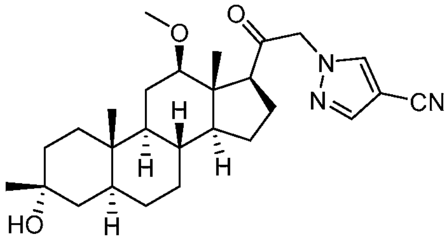

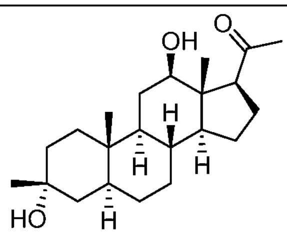

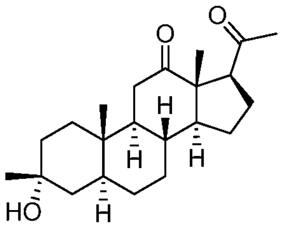
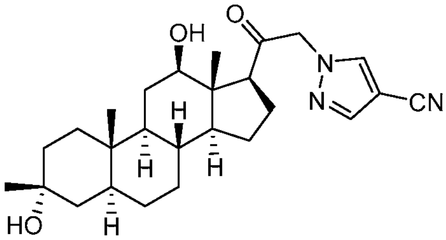
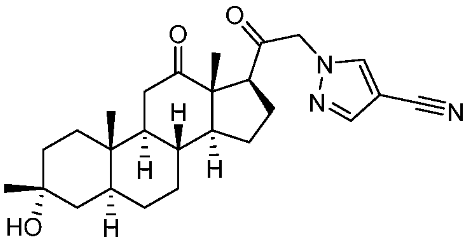
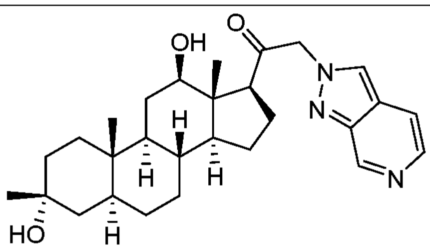
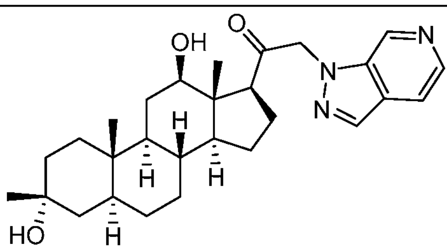

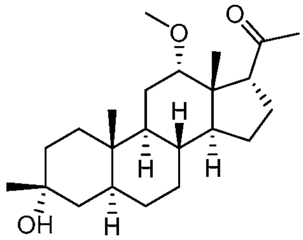

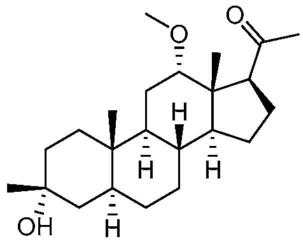

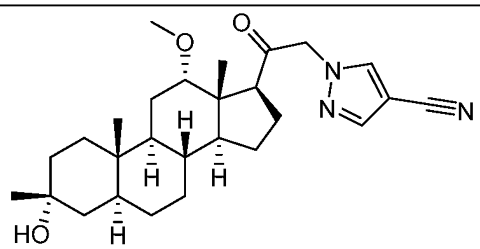

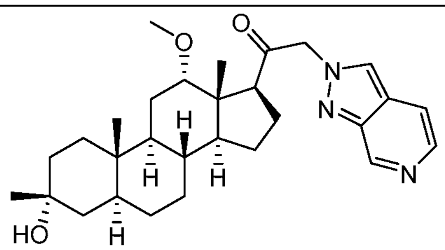

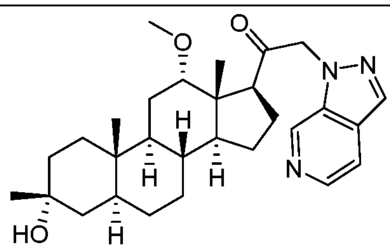

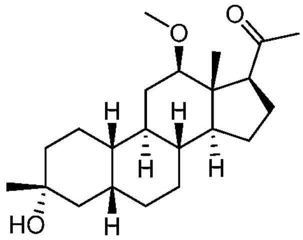
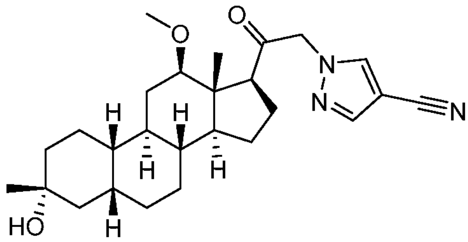
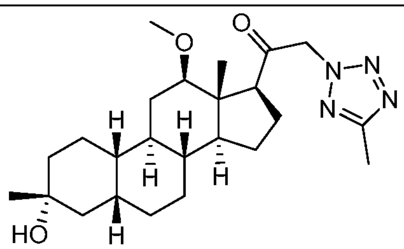
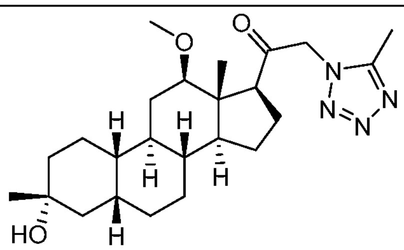
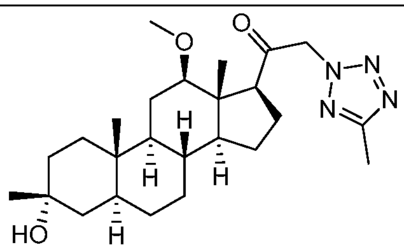

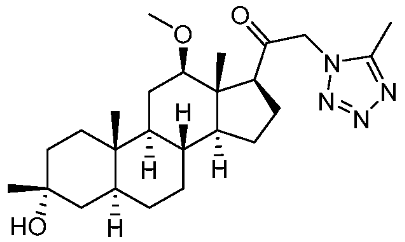

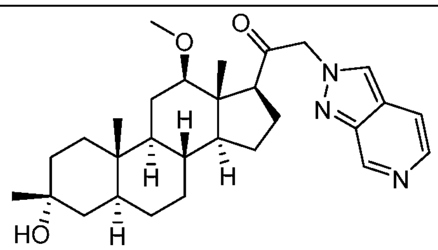

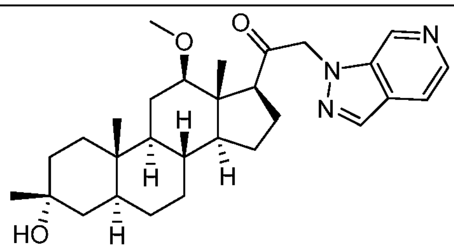

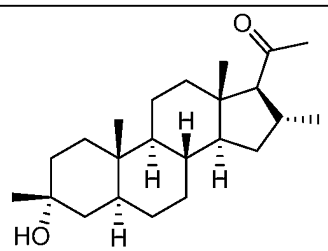

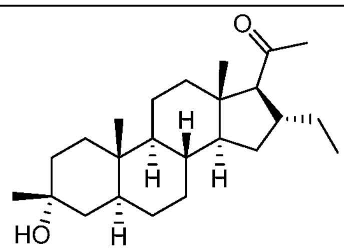

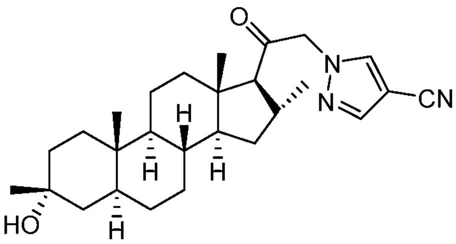

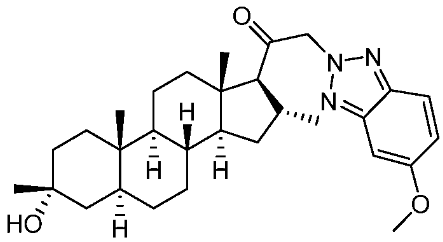

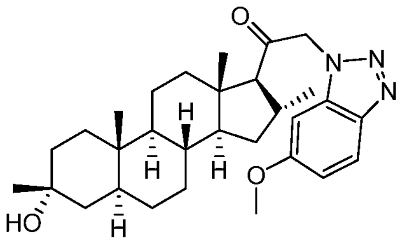

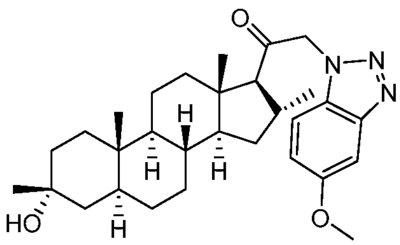

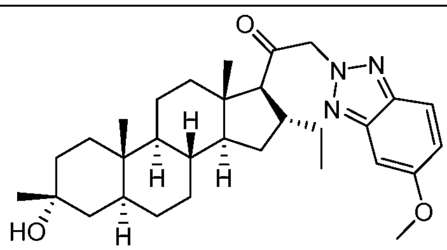

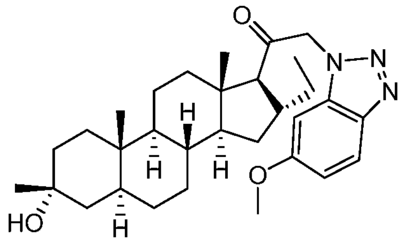

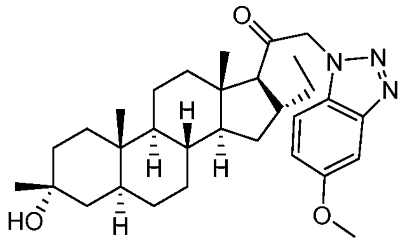

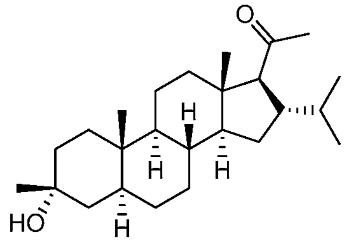

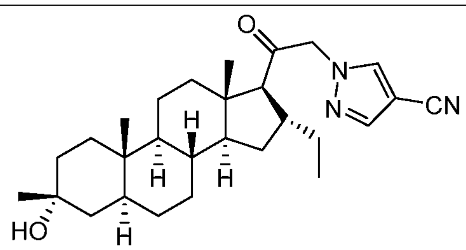

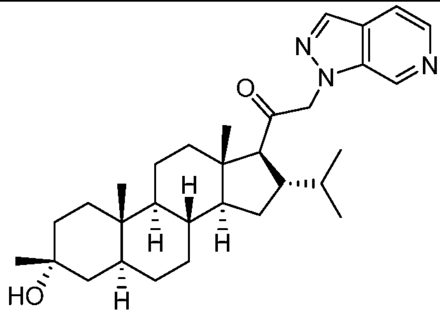

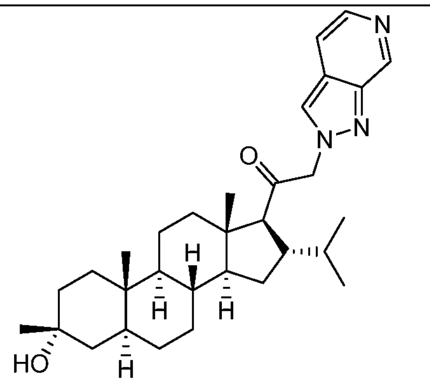

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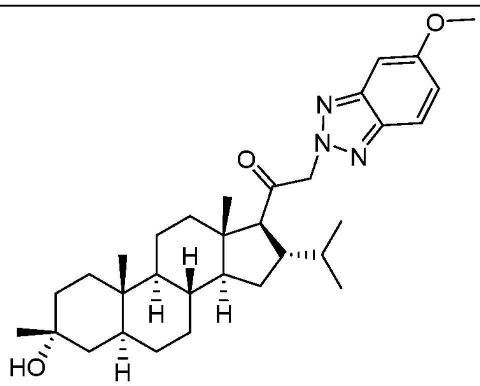

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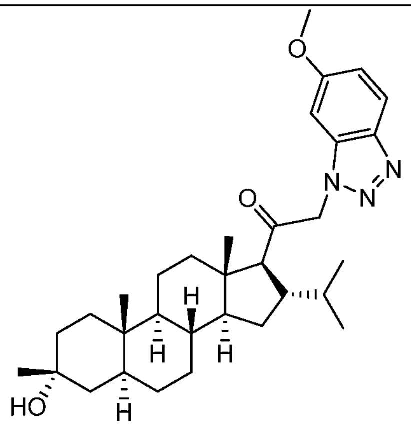

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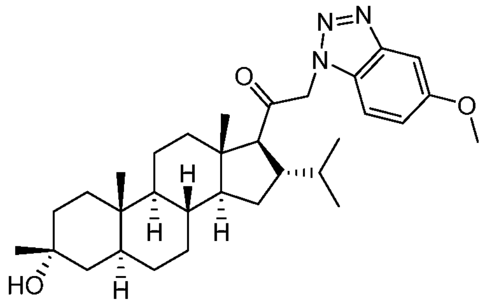
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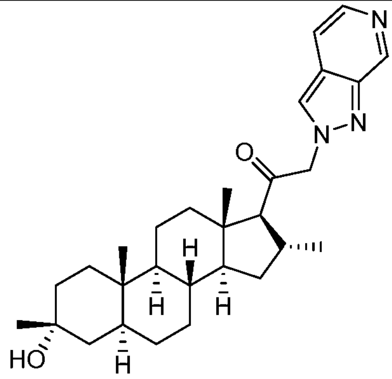
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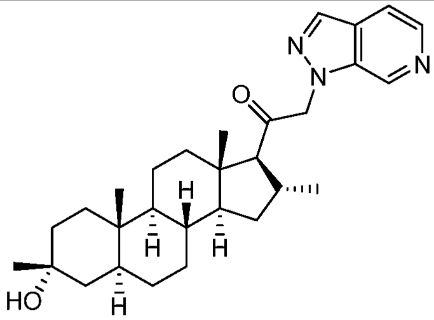
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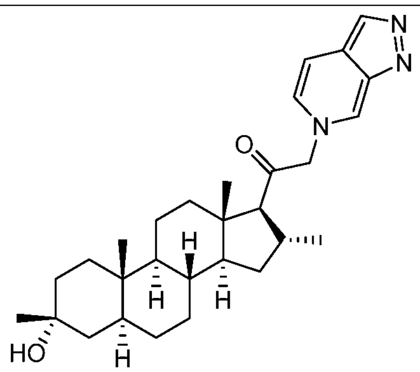
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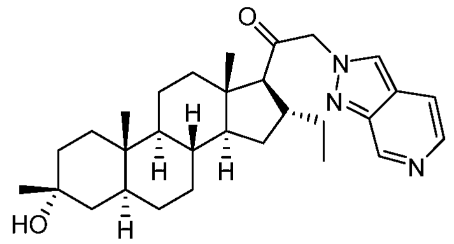
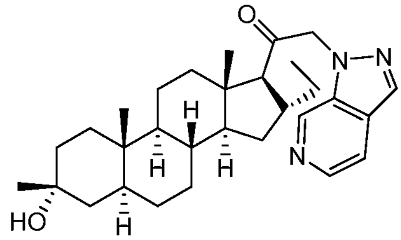
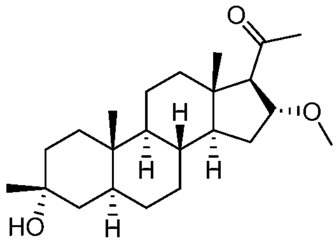
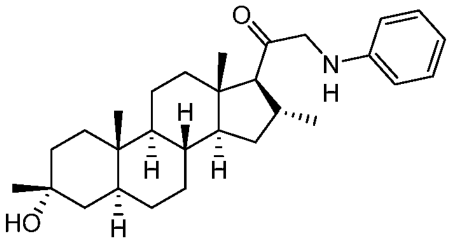
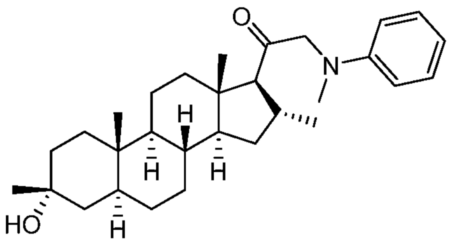
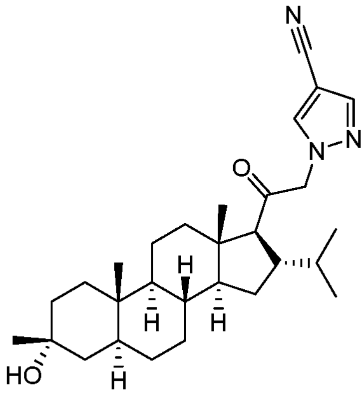
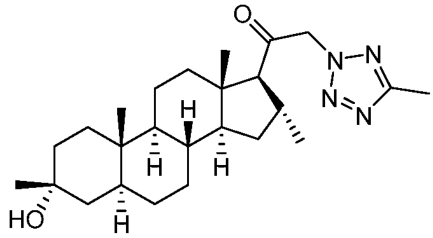
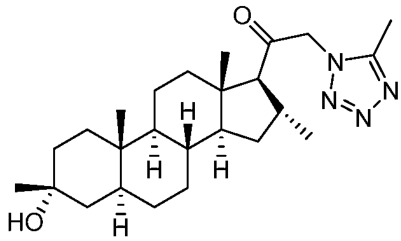
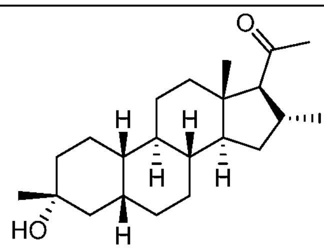
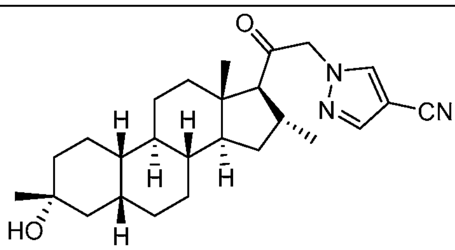
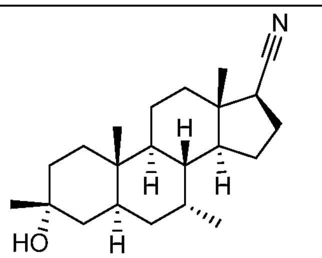
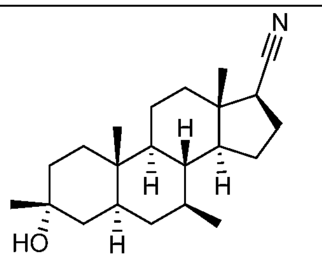
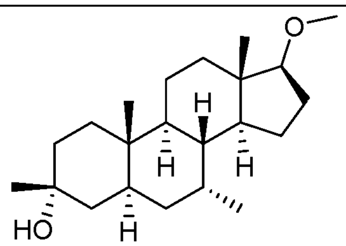






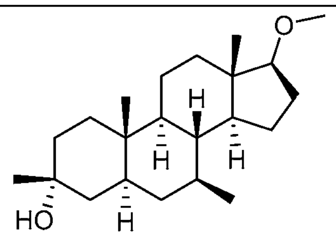
N N N O H H H HO H
O N N N N H H H HO H
O N N N N H H H HO H
O H H H H HO H and
O N N CN H H H H HO H .

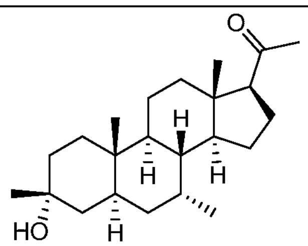
83. A pharmaceutically acceptable salt of a compound selected from the group consisting of:

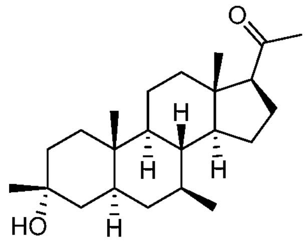












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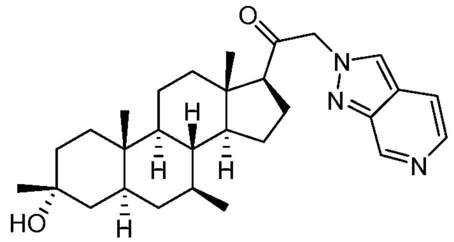

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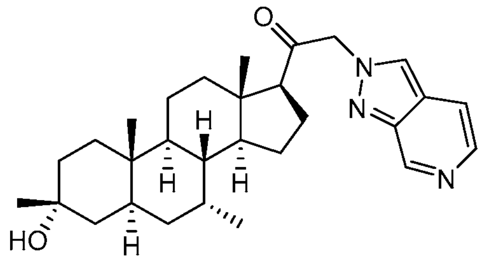

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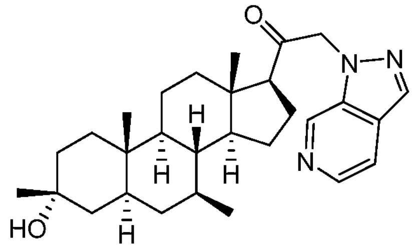

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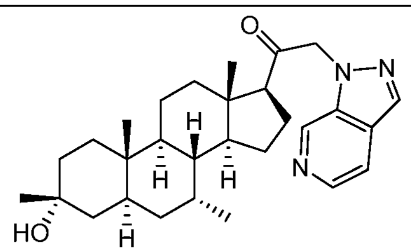

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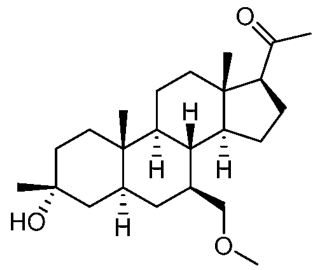
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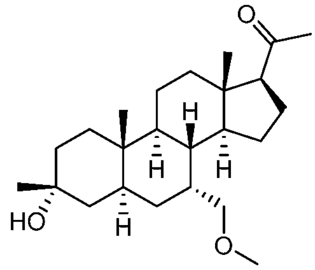
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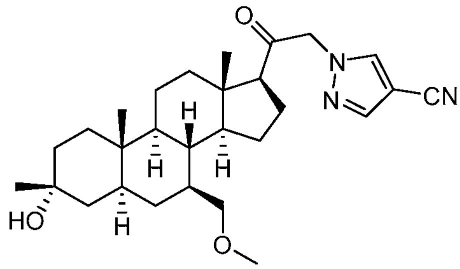
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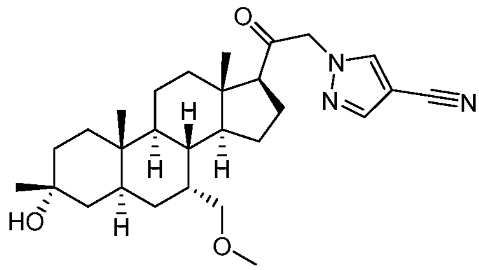
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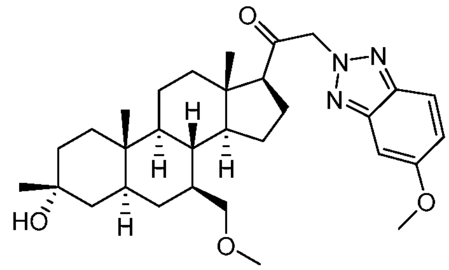
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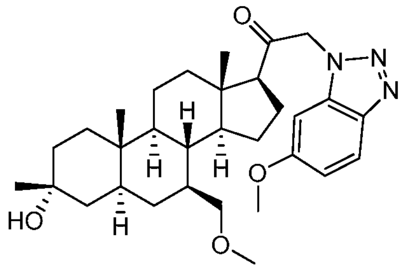

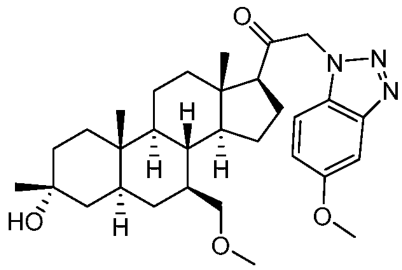

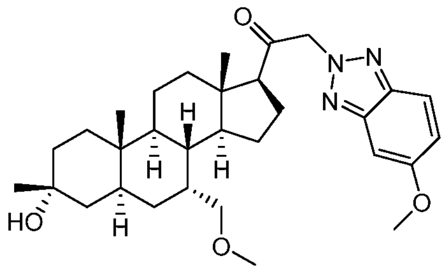

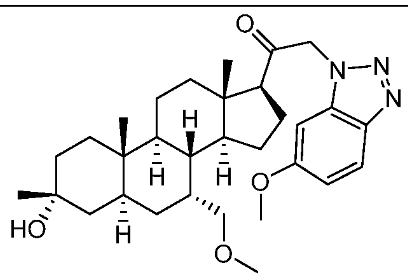

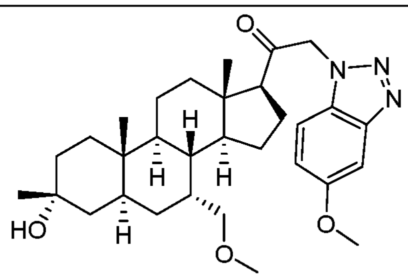

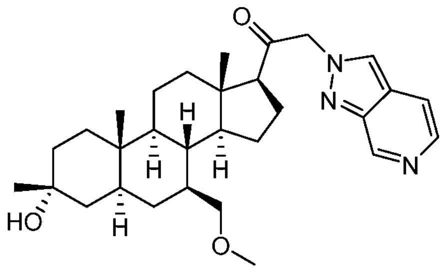
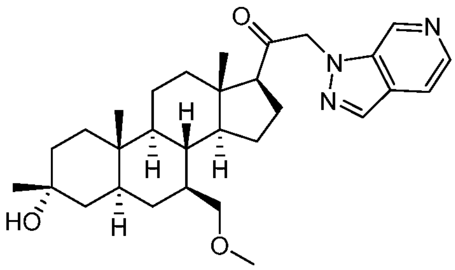
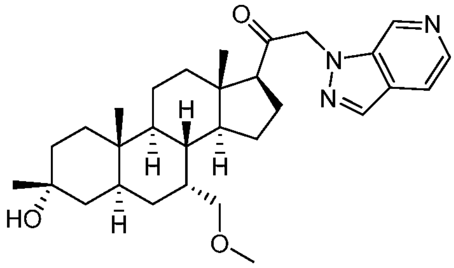
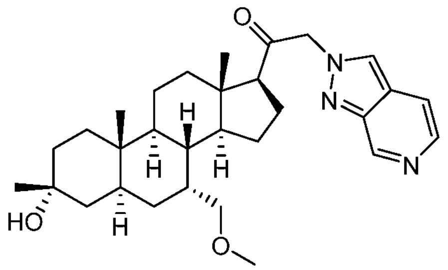
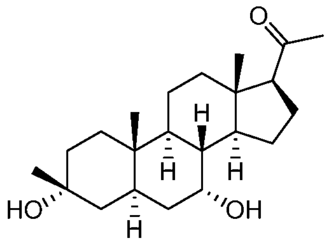

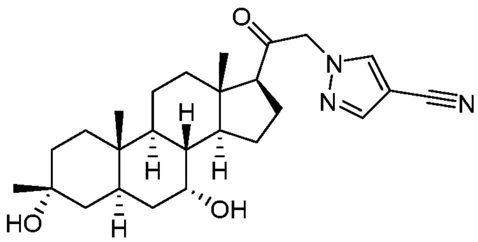
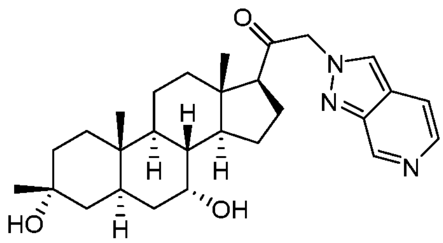
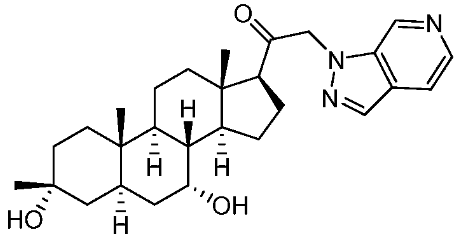
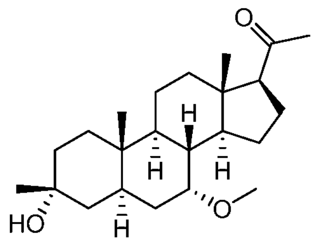
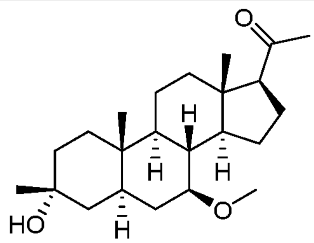

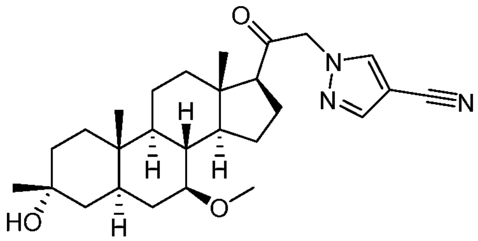

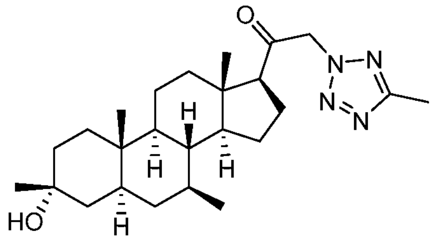

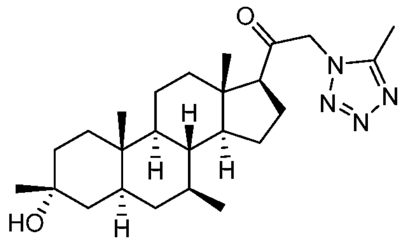

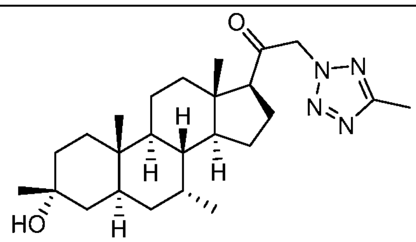

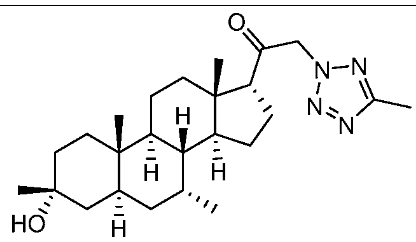

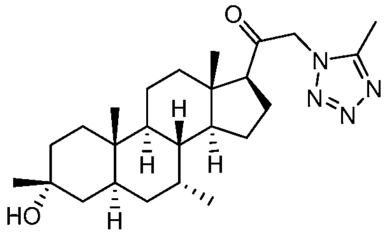
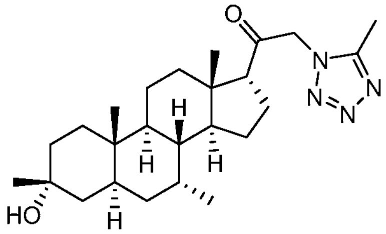
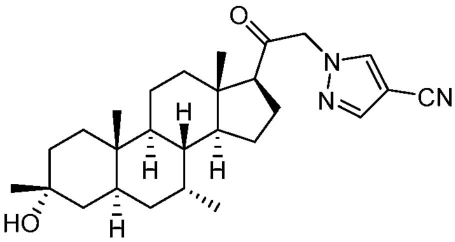
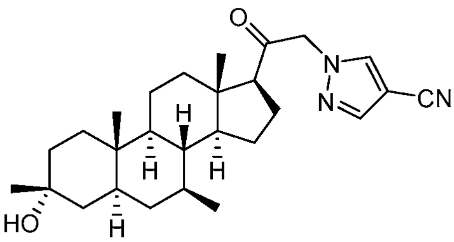
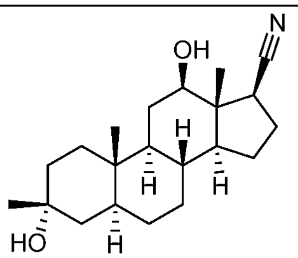

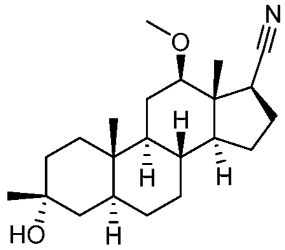
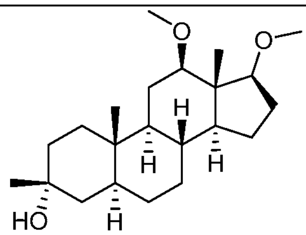
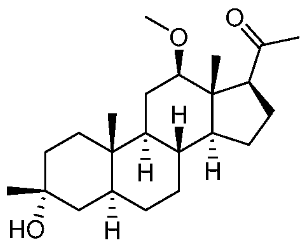
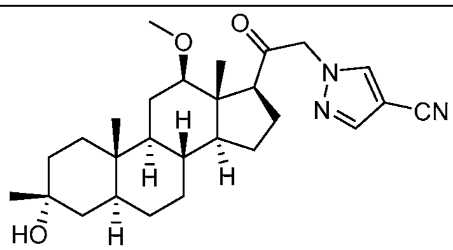
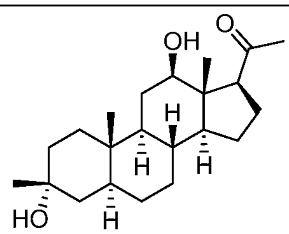

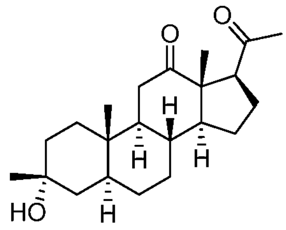
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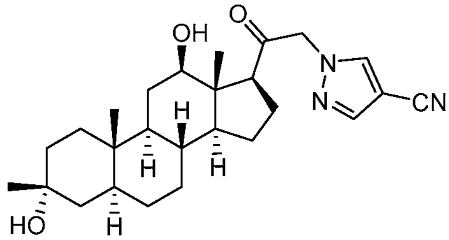
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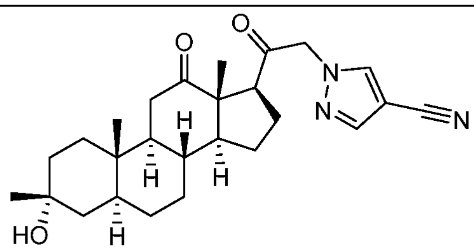
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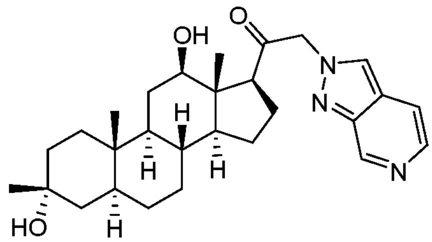
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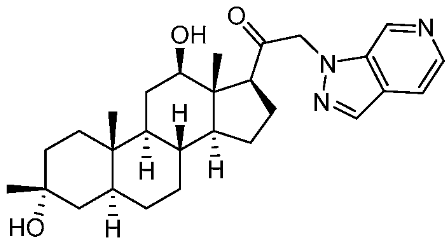
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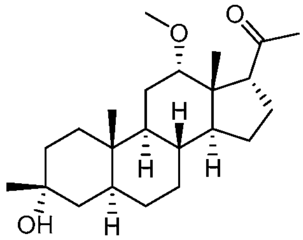
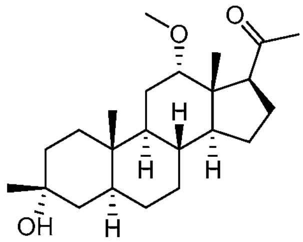
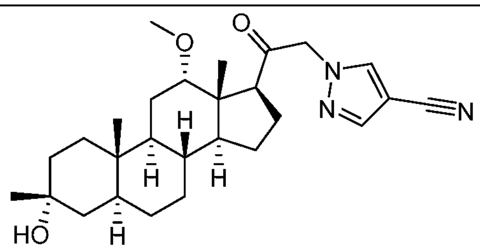
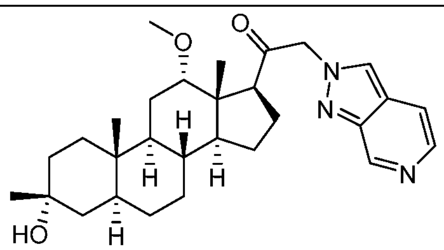
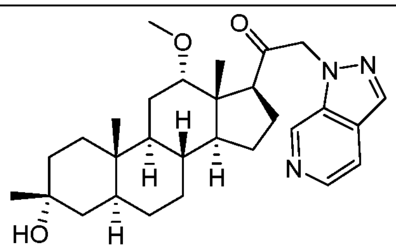
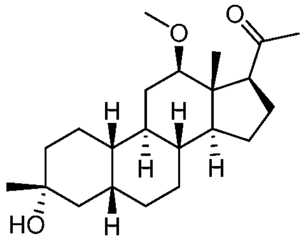
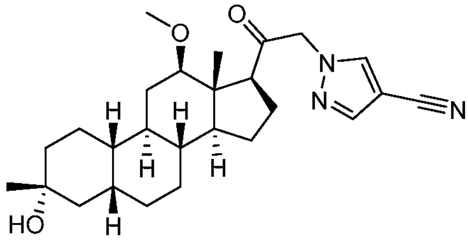
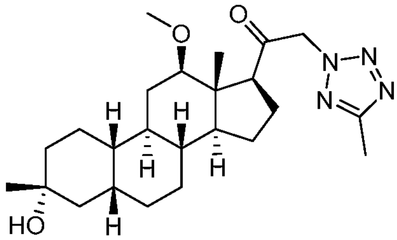
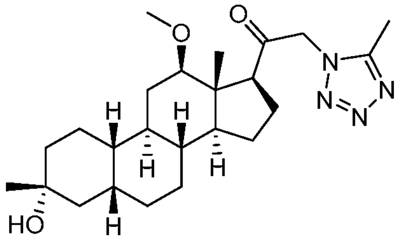
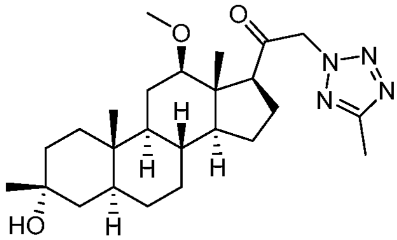


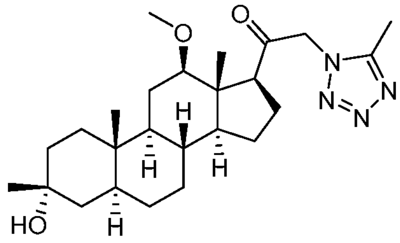








O O H H H H HO H
O O N N N H H H H HO H
O O N N N N H H H H HO H
O O N N N N H H H H HO H
O O N N N N H H H HO H



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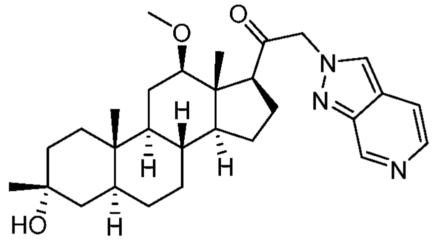

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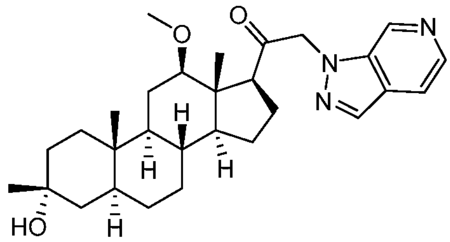

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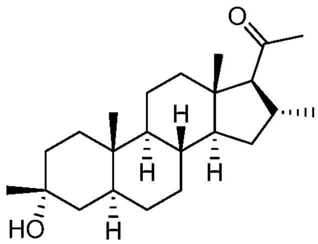

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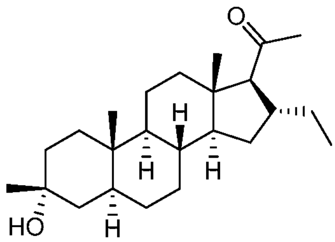

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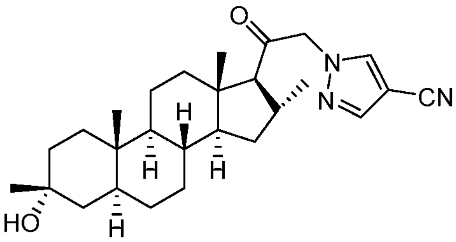

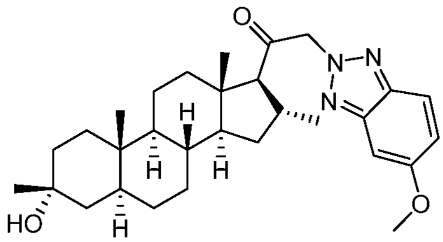

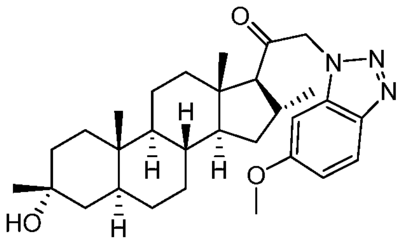

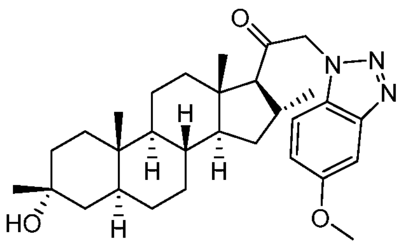

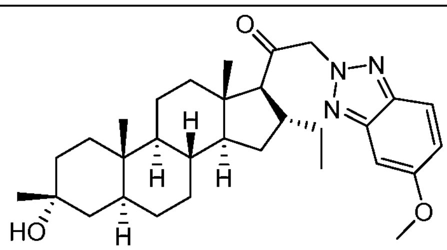

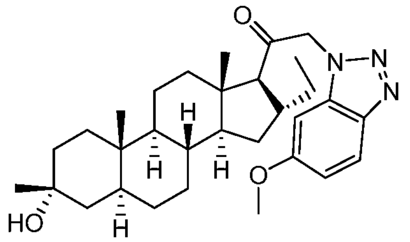

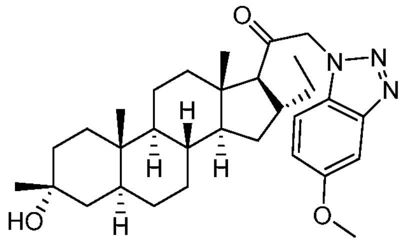

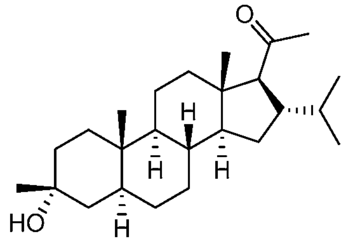

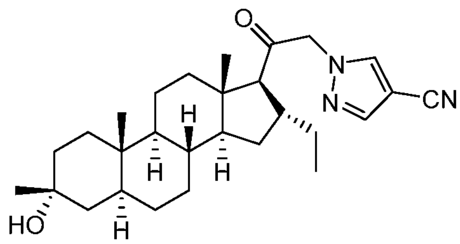

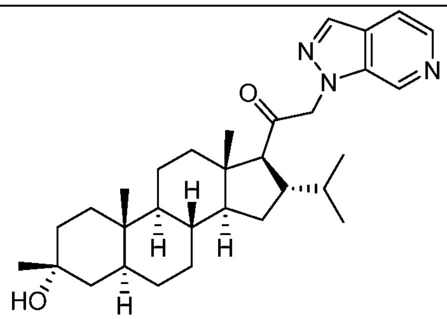

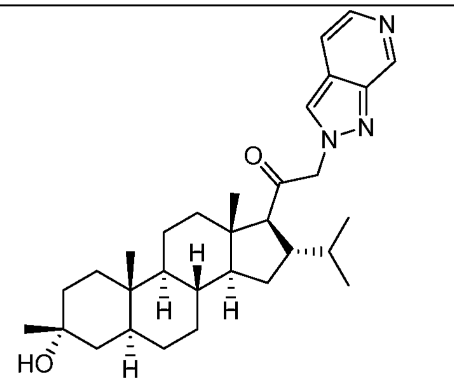
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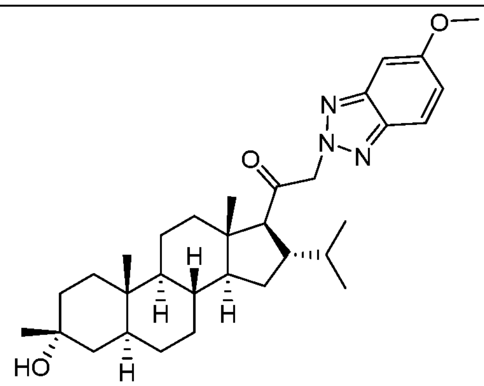
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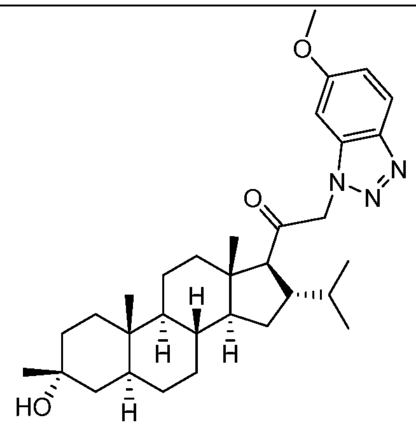
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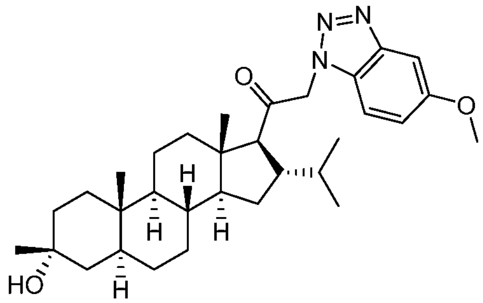
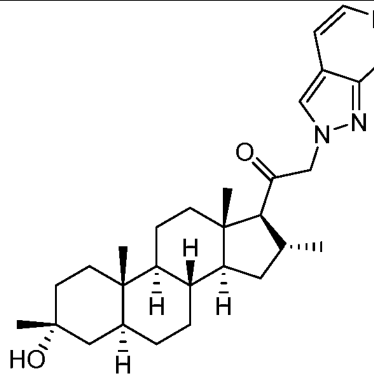
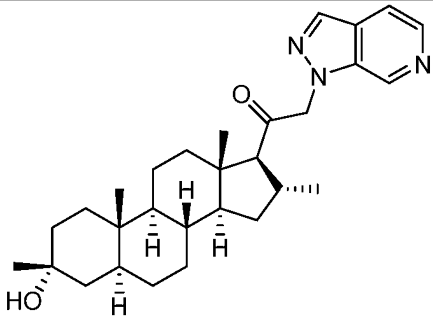
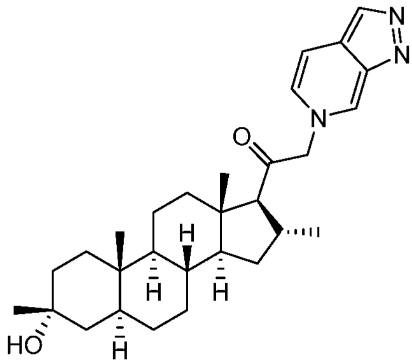
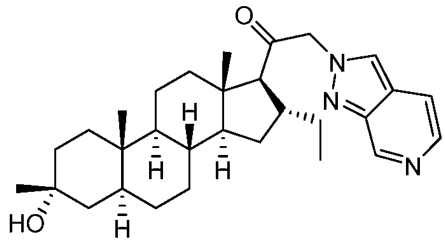
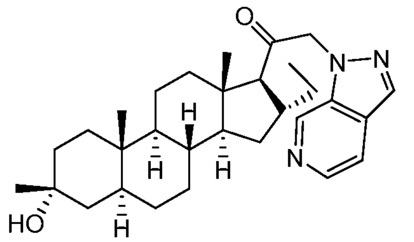
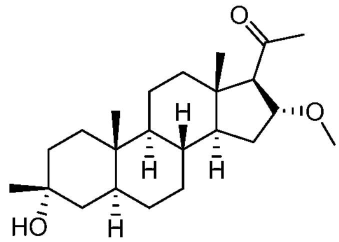
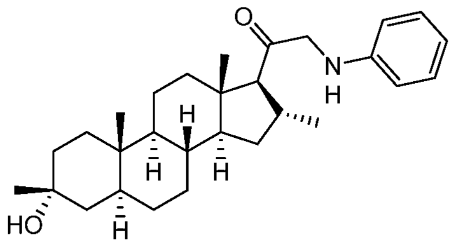
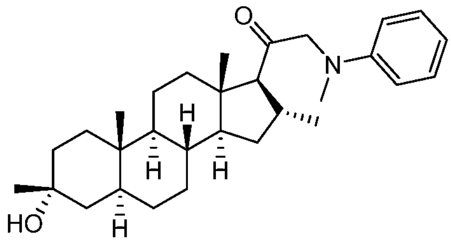
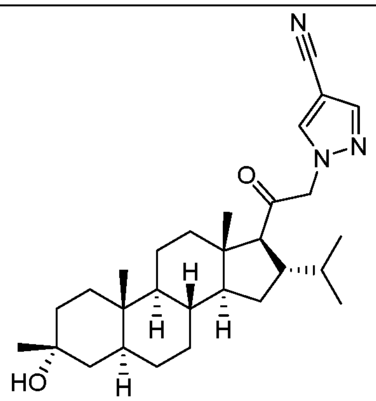
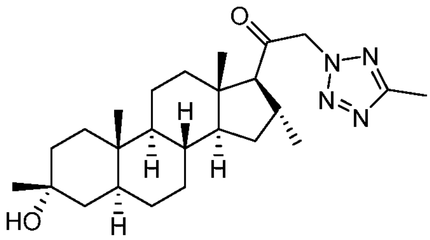
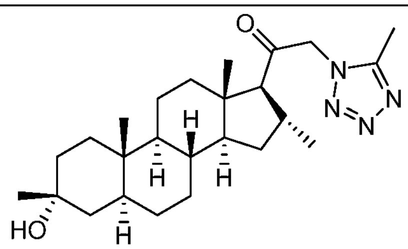
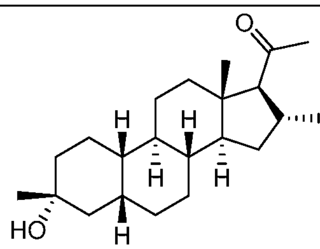
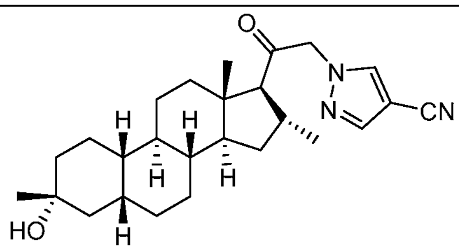











 and
 .

84. A pharmaceutical composition comprising a compound of any one of the preceding claims and a pharmaceutically acceptable excipient.

85. A method of inducing sedation and/or anesthesia in a subject, comprising administering to the subject an effective amount of a compound of of any one claims 1-83.

86. A method of administering an effective amount of a compound of any one of claims 1-83 or pharmaceutical composition of claim 84, to a subject in need thereof, wherein the subject experiences sedation and/or anesthesia within two hours of administration.

87. The method of claim 85, wherein the subject experiences sedation and/or anesthesia within one hour of administration.

88. The composition of claim 85, wherein the subject experiences sedation and/or anesthesia instantaneously.

89. The composition of any one of claims 85-88, wherein the compound is administered by intravenous administration.

90. The composition of any one of claims 85-89, wherein the compound is administered chronically.

91. The composition of any one of claims 85-90, wherein the subject is a mammal.

92. The composition of any one of claims 85-91, wherein the subject is a human.

93. The composition of any one of claims 85-92, wherein the compound is administered in combination with another therapeutic agent.

94. A composition for use in treating seizure in a subject, comprising administering to the subject an effective amount of a compound of any one of claims 1-83.

95. A composition for use in treating epilepsy or status epilepticus in a subject, comprising an effective amount of a compound of any one of claims 1-83.

96. A composition for use in treating a neuroendocrine disorder or dysfunction in a subject, comprising an effective amount of a compound of any one of claims 1-83.

97. A composition for use in treating a neurodegenerative disease or disorder in a subject, comprising an effective amount of a compound of any one of claims 1-83.

98. A composition for use in treating a movement disorder or tremor in a subject, comprising an effective amount of a compound of any one of claims 1-83.

99. A composition for use in treating a mood disorder or anxiety disorder in a subject, comprising an effective amount of a compound of any one of claims 1-83.

100. A composition for use in treating disorders related to GABA function in a subject in need thereof, comprising a therapeutically effective amount of a compound of a compound of any one of claims 1-83.

101. A composition for use in treating a CNS-related disorder in a subject in need thereof, comprising an effective amount of a compound of any one of claims 1-83.

102. The method of claim 101, wherein the CNS-related disorder is a sleep disorder, a mood disorder, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, or tinnitus.

103. The method of claim 101, wherein the subject is a subject with Rett syndrome, Fragile X syndrome, or Angelman syndrome.

104. A kit comprising a solid composition comprising a compound of any one of claims 1-83 and a sterile diluent.