OXYSTEROLS AND METHODS OF USE THEREOF

Related Applications

This application claims priority to U.S. Provisional Application Number 62/189,068 filed July 6, 2015, and 62/332,931 filed May 6, 2016, the contents of each of which are incorporated by reference in their entirety.

Background of the Invention

[0001] NMDA receptors are heteromeric complexes comprised of NR1, NR2, and/or NR3 subunits and possess distinct recognition sites for exogenous and endogenous ligands. These recognition sites include binding sites for glycine, and glutamate agonists and modulators. NMDA receptors are expressed in the peripheral tissues and the CNS, where they are involved in excitatory synaptic transmission. Activating these receptors contributes to synaptic plasticity in some circumstances and excitotoxicity in others. These receptors are ligand-gated ion channels that admit Ca2+ after binding of the glutamate and glycine, and are fundamental to excitatory neurotransmission and normal CNS function. Positive modulators may be useful as therapeutic agents with potential clinical uses as cognitive enhancers and in the treatment of psychiatric disorders in which glutamatergic transmission is reduced or defective (see, *e.g.*, Horak et al., J. of Neuroscience, 2004, 24(46), 10318-10325). In contrast, negative modulators may be useful as therapeutic agents with potential clinical uses in the treatment of psychiatric disorders in which glutamatergic transmission is pathologically increased (*e.g.*, treatment resistant depression).

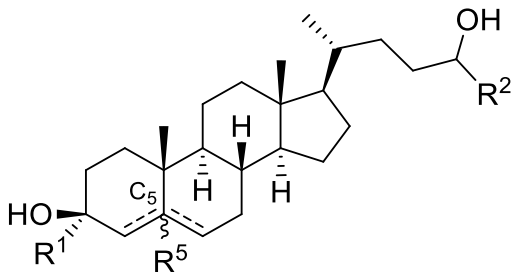
[0002] Oxysterols are derived from cholesterol and have been shown to potently and selectively modulate NMDA receptor function. New and improved oxysterols are needed that modulate the NMDA receptor for the prevention and treatment of conditions associated with NMDA expression and function. Compounds, compositions, and methods described herein are directed toward this end.

Summary

[0003] Provided herein are substituted oxysterols useful for preventing and/or treating a broad range of disorders, including, but not limited to, NMDA–mediated disorders. These compounds are expected to show improved *in vivo* potency, pharmacokinetic (PK) properties,

oral bioavailability, formulatability, stability, and/or safety as compared to other oxysterols. Further provided are pharmaceutical compositions comprising the compounds of the present disclosure, and methods of their use and treatment.

[0003a] In one aspect of the present disclosure, there is provided a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted C_{1-6} alkyl;

R^2 is substituted or unsubstituted C_{2-6} alkyl;

R^5 is absent or hydrogen; and

----- represents a single or double bond, wherein when one ----- is a double bond, the other ----- is a single bond and R^5 is absent.

[0003b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier.

[0003c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable salt of a compound disclosed herein, and a pharmaceutically acceptable carrier.

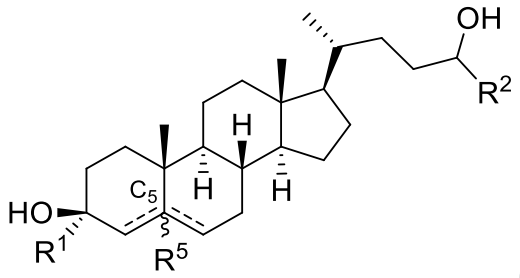
[0003d] In another aspect of the present disclosure, there is provided a use of a compound or pharmaceutically acceptable salt disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for inducing sedation or anesthesia.

[0003e] In a further aspect of the present disclosure, there is provided a use of a compound or pharmaceutically acceptable salt disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating or preventing a disorder, wherein the disorder is a gastrointestinal (GI) disorder, a structural disorder affecting the GI tract, an anal disorder, colon polyps, cancer, diabetes, a sterol synthesis disorder, or colitis.

[0003f] In another aspect of the present disclosure, there is provided a use of a compound or pharmaceutically acceptable salt disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating or preventing a CNS-related condition.

[0003g] In a further aspect of the present disclosure, there is provided a compound or pharmaceutically acceptable salt disclosed herein, or a pharmaceutical composition disclosed herein, for use in therapy.

[0004] In one example, provided herein are compounds according to Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein: R^1 is hydrogen or C_{1-6} alkyl; R^2 is C_{1-6} alkyl, carbocyclyl, or heterocyclyl; R^5 is absent or hydrogen; and ----- represents a single or double bond, wherein when one ----- is a double bond, the other ----- is a single bond and R^5 is absent.

In some examples, R^1 is hydrogen.

In some examples, R^1 is C_{1-6} alkyl. In some examples, R^1 is substituted C_{1-6} alkyl. In some examples, R^1 is unsubstituted C_{1-6} alkyl. In some examples, R^1 is methyl (e.g., $-CH_3$, $-CF_3$ or $-CH_2OCH_3$), ethyl, or isopropyl. In some examples, R^1 is methyl (e.g., $-CH_3$) or ethyl (e.g., $-CH_2CH_3$).

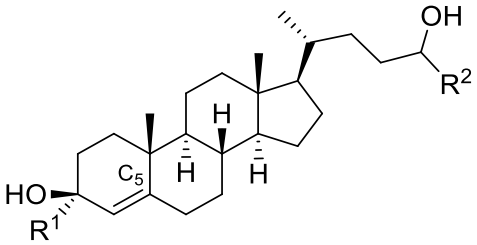
In some examples, R^2 is C_{1-6} alkyl or carbocyclyl. In some examples, R^2 is substituted C_{1-6} alkyl. In some examples, R^2 is unsubstituted C_{1-6} alkyl. In some examples, R^2 is C_{1-4} alkyl. In some examples, R^2 is substituted C_{1-4} alkyl. In some examples, R^2 is unsubstituted C_{1-4} alkyl. In some examples, R^2 is C_{1-3} alkyl. In some examples, R^2 is substituted C_{1-3} alkyl. In some examples, R^2 is unsubstituted C_{1-3} alkyl. In some examples, R^2 is methyl, ethyl (e.g., $-CH_2CH_3$, $-CH_2CF_3$, $-CH(CH_3)(CF_3)$), isopropyl, tertbutyl, or cyclopropyl. In some examples, R^2 is haloalkyl. In some examples, R^2 is $-CH_2CF_3$ or $-CH(CH_3)(CF_3)$.

In some examples, R^1 and R^2 are C_{1-6} alkyl. In some examples, R^1 is C_{1-6} alkyl and R^2 is C_{1-6} alkyl, carbocyclyl, or heterocyclyl.

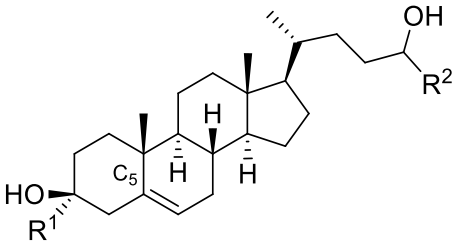
In some examples, R^1 is methyl or ethyl, and R^2 is unsubstituted or substituted C_{1-6} alkyl (*e.g.*, haloalkyl). In some examples, R^1 is methyl or ethyl, and R^2 is carbocyclyl or heterocyclyl.

In some examples, ----- represents a single bond.

In some examples, the compound of Formula (I) is a compound of Formula (I-A) or Formula (I-B):

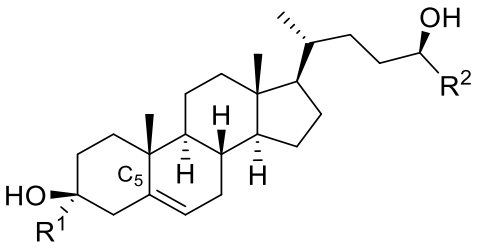


(I-A) or

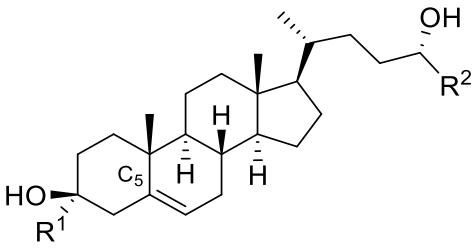


(I-B).

In some examples, the compound of Formula (I) is a compound of Formula (I-B-i) or Formula (I-B-ii):

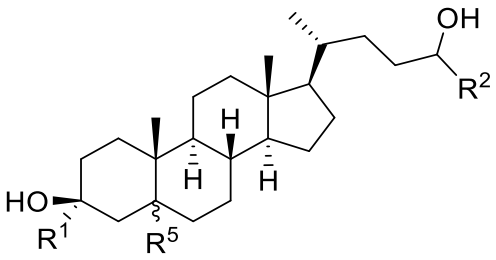


(I-B-i) or



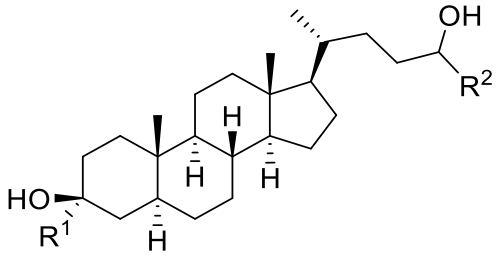
(I-B-ii).

In some examples, the compound of Formula (I) is a compound of Formula (I-C):

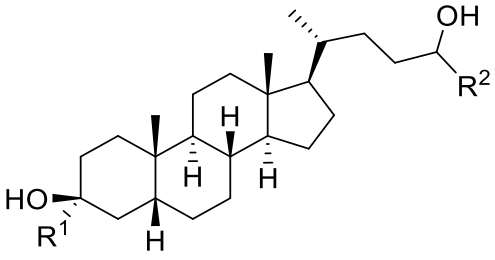


(I-C).

In some examples, the compound of Formula (I-C) is a compound of Formula (I-C-i) or (I-C-ii):

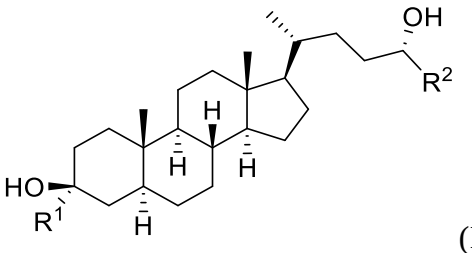


(I-C-i) or

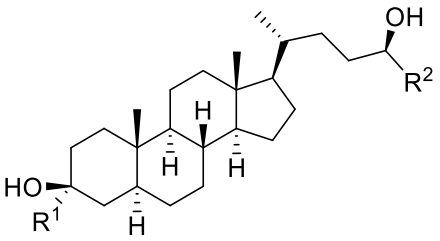


(I-C-ii).

In some examples, the compound of Formula (I-C-i) is a compound of Formula (I-C-i-a) or (I-C-i-b):



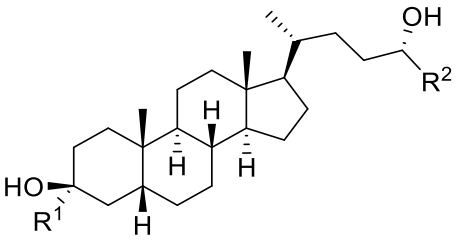
(I-C-i-a) or



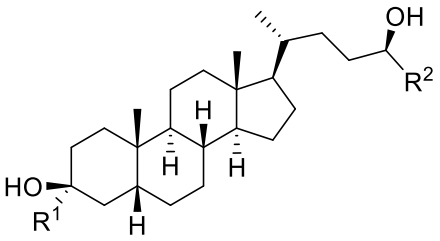
(I-C-i-b)

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In some examples, the compound of Formula (I-C-ii) is a compound of Formula (I-C-ii-a) or (I-C-ii-b):



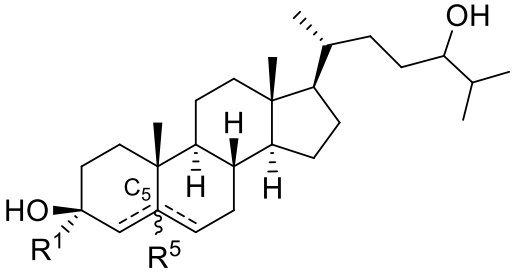
(I-C-ii-a) or



(I-C-ii-b).

In some examples, R^2 is C_{1-6} alkyl. In some examples, R^2 is substituted C_{1-6} alkyl. In some examples, R^2 is C_{1-6} haloalkyl.

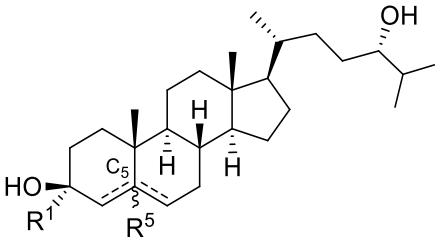
In some examples, the compound of Formula (I) is a compound of Formula (II):



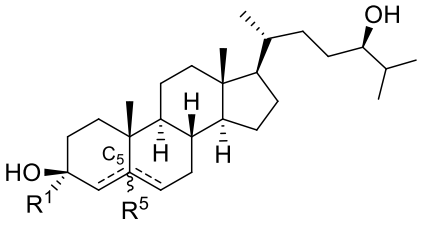
(II),

or a pharmaceutically acceptable salt thereof.

In some examples, the compound of Formula (II) is a compound of Formula (II-A) or Formula (II-B):

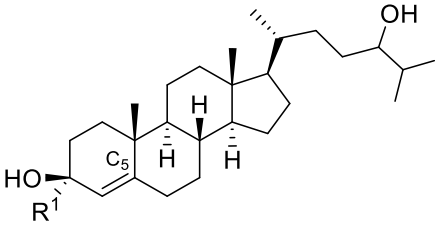


(II-A) or

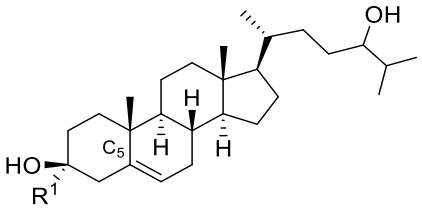


(II-B).

In some examples, the compound of Formula (II) is a compound of Formula (II-C) or Formula (II-D):

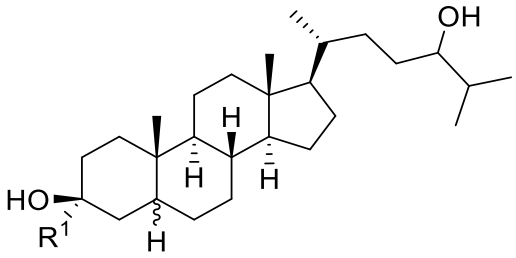


(II-C) or



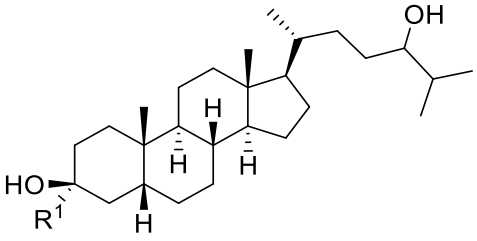
(II-D).

In some examples, the compound of Formula (II) is a compound of Formula (II-E):

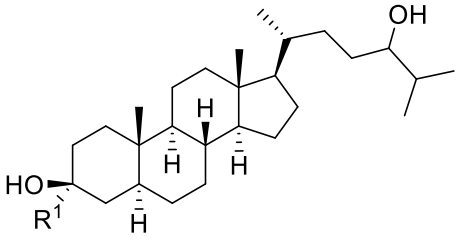


(II-E).

In some examples, the compound of Formula (II-E) is a compound of Formula (II-E-i) or Formula (II-E-ii):

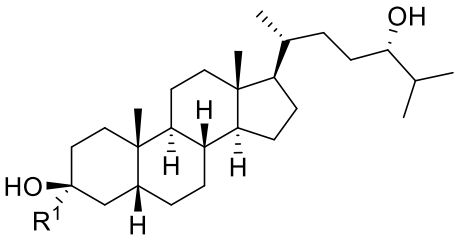


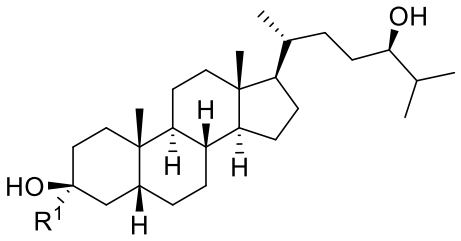
(II-E-i) or



(II-E-ii).

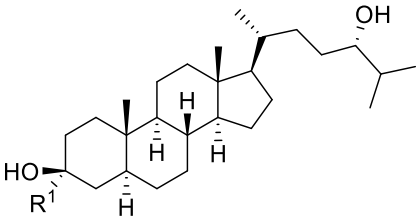
In some examples, the compound of Formula (II-E-i) is a compound of Formula (II-E-i-a) or Formula (II-E-i-b):

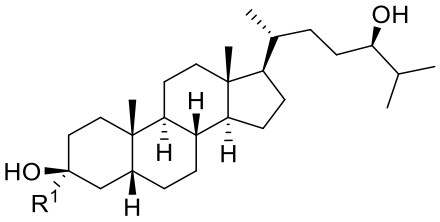


(II-E-i-a) or 

(II-E-i-b).

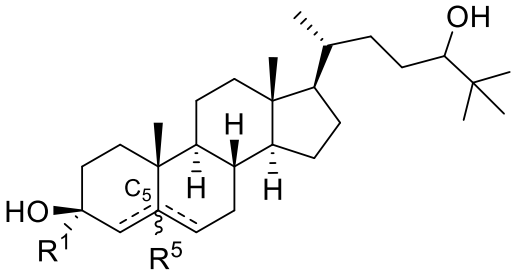
In some examples, the compound of Formula (II-E-ii) is a compound of Formula (II-E-ii-a) or Formula (II-E-ii-b):



(II-E-ii-a) or 

(II-E-ii-b).

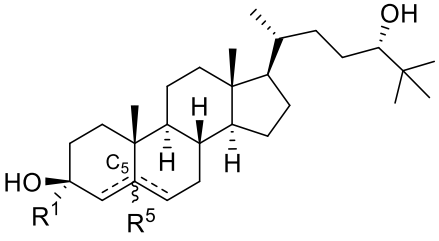
In some examples, the compound of Formula (I) is a compound of Formula (VII):

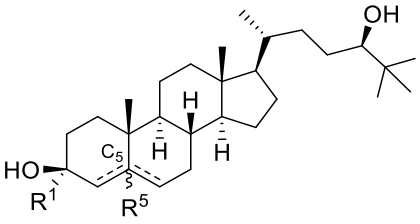


(VII),

or a pharmaceutically acceptable salt thereof.

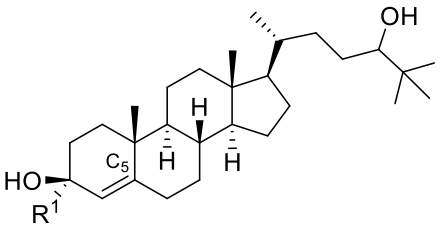
In some examples, the compound of Formula (VII) is a compound of Formula (VII-A) or Formula (VII-B):



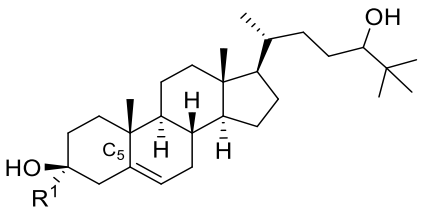
(VII-A) or 

(VII-B).

In some examples, the compound of Formula (VII) is a compound of Formula (VII-C) or Formula (VII-D):

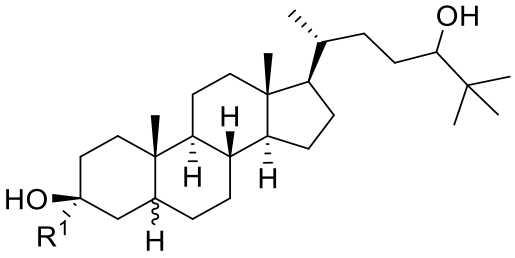


(VII-C) or



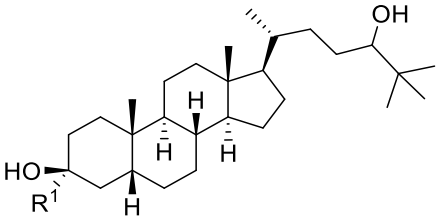
(VII-D).

In some examples, the compound of Formula (VII) is a compound of Formula (VII-E):

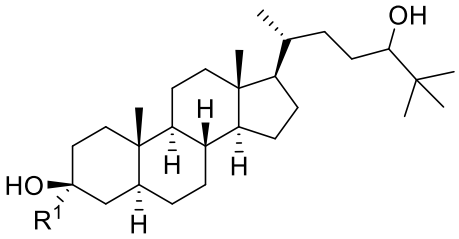


(VII-E).

In some examples, the compound of Formula (VII-E) is a compound of Formula (VII-E-i) or Formula (VII-E-ii):

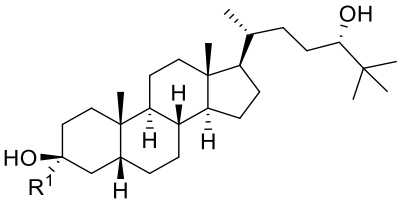


(VII-E-i) or

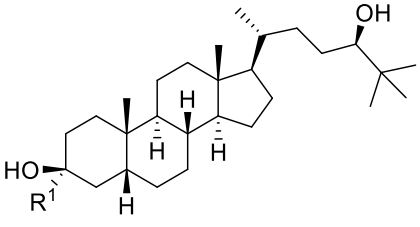


(VII-E-ii).

In some examples, the compound of Formula (VII-E-i) is a compound of Formula (VII-E-i-a) or Formula (VII-E-i-b):

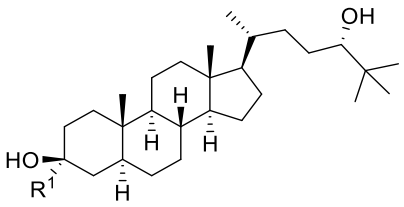


(VII-E-i-a) or

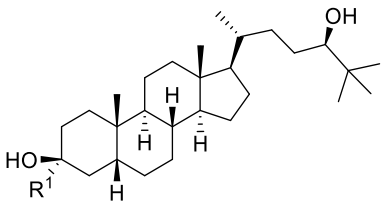


(VII-E-i-b).

In some examples, the compound of Formula (VII-E-ii) is a compound of Formula (VII-E-ii-a) or Formula (VII-E-ii-b):

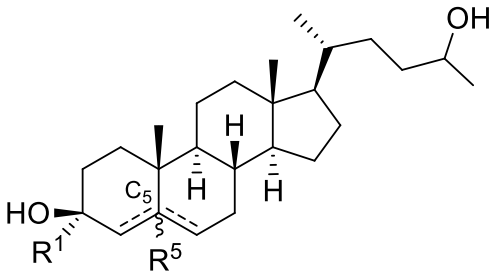


(VII-E-ii-a) or



(VII-E-ii-b).

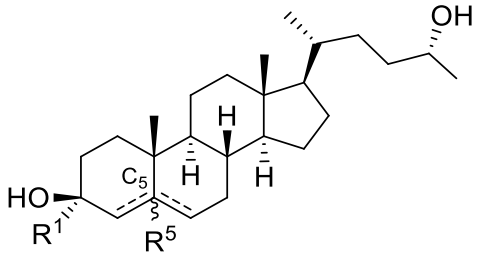
In some examples, the compound of Formula (I) is a compound of Formula (III):



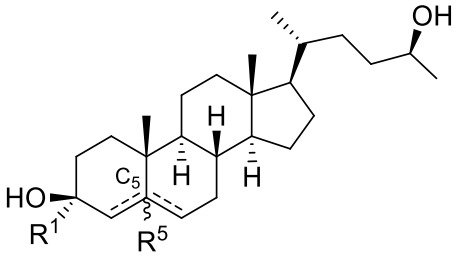
(III),

or a pharmaceutically acceptable salt thereof.

In some examples, the compound of Formula (III) is a compound of Formula (III-A) or Formula (III-B):

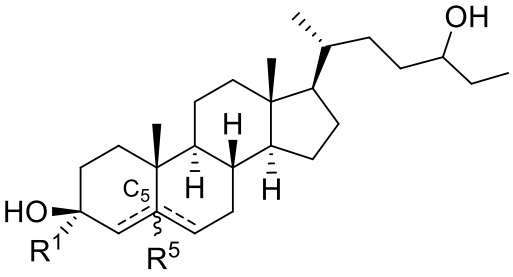


(III-A) or



(III-B).

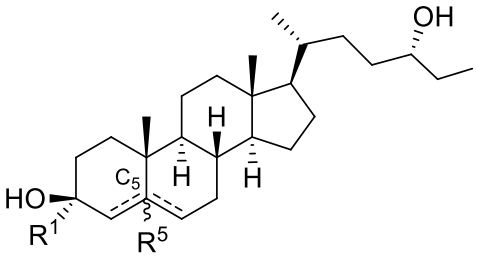
In some examples, the compound of Formula (I) is a compound of Formula (IV):



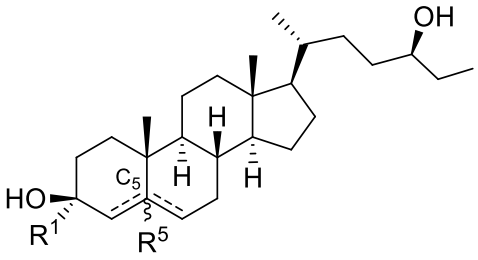
(IV),

or a pharmaceutically acceptable salt thereof.

In some examples, the compound of Formula (IV) is a compound of Formula (IV-A) or Formula (IV-B):



(IV-A) or



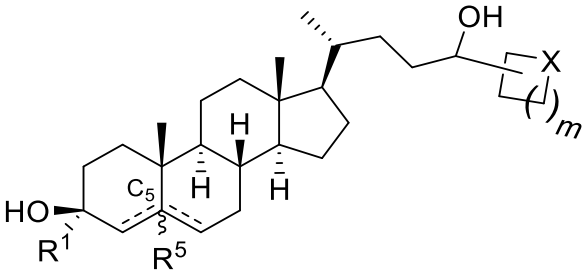
(IV-B),

or a pharmaceutically acceptable salt thereof.

In some examples, R^2 is carbocyclyl or heterocyclyl. In some examples, R^2 is carbocyclyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl).

In some examples, R^2 is heterocyclyl. In some examples, R^2 is an oxygen-containing heterocycle (e.g., tetrahydropyran).

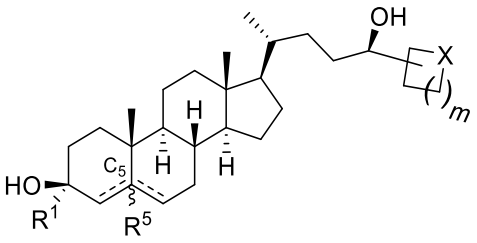
In some examples, the compound of Formula (I) is a compound of Formula (V):



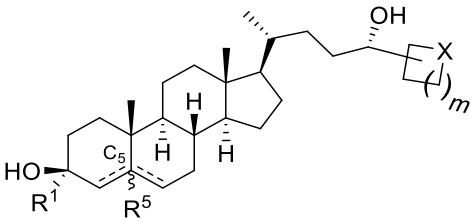
(V),

or a pharmaceutically acceptable salt thereof, wherein X is $–CH_2–$, –O–, –S–, or $–NR^A–$, and *m* is an integer selected from 0, 1, 2, 3, 4, or 5; wherein R^A is hydrogen, alkyl, $-C(O)R^C$, $-C(O)N(R^C)_2$, or $-SO_2N(R^C)_2$; and each R^C is independently hydrogen, alkyl, aryl, or heteroaryl. In some examples, X is $–CH_2–$, –O–, –S–, or –NH–.

In some examples, the compound of Formula (V) is a compound of Formula (V-A-i) or Formula (V-A-ii):

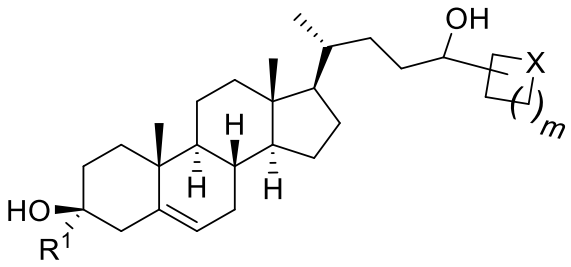


(V-A-i)



(V-A-ii).

In some examples, the compound of Formula (V) is a compound of Formula (V-B):



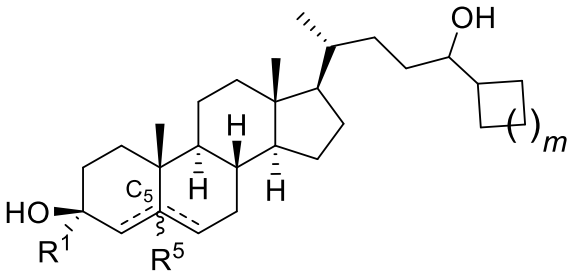
(V-B).

In some examples, X is $–CH_2–$.

In some examples, X is –O–.

In some examples, *m* is 0, 1, 2, or 3.

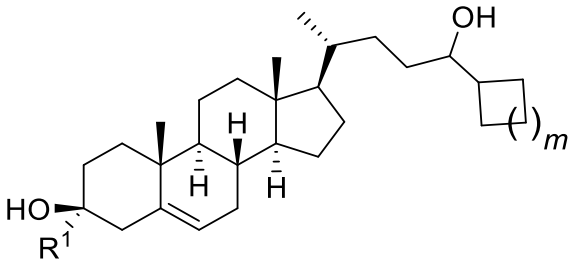
In some examples, the compound of Formula (V) is a compound of Formula (V-B-i):



(V-B-i),

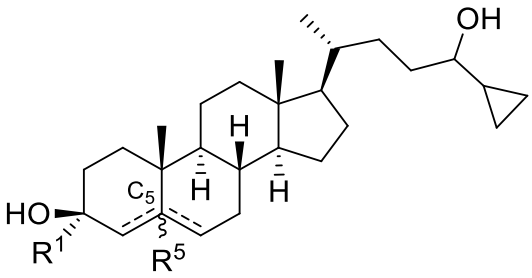
or a pharmaceutically acceptable salt thereof.

In some examples, the compound of Formula (V) is a compound of Formula (V-C):



(V-C).

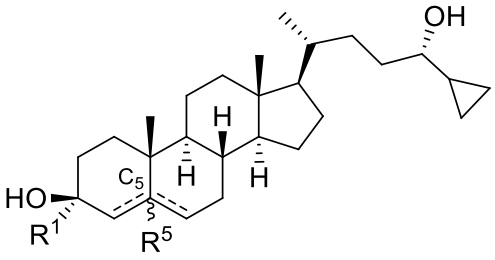
In some examples, the compound of Formula (I) is a compound of Formula (VI):



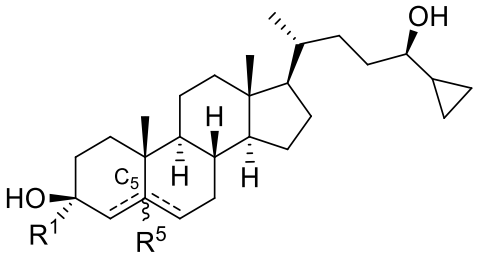
(VI),

or a pharmaceutically acceptable salt thereof.

In some examples, the compound of Formula (I) is a compound of Formula (VI-A) or Formula (VI-B):



(VI-A) or



(VI-B),

or a pharmaceutically acceptable salt thereof.

In some examples, R^1 is $C_{1\text{-}6}$ alkyl. In some examples, R^1 is methyl (e.g., $-CH_3$, $-CF_3$ or $-CH_2OCH_3$), ethyl, or isopropyl. In some examples, R^1 is methyl, ethyl or isopropyl. In some examples, R^1 is methyl (e.g., $-CH_3$). In some examples, R^1 is ethyl (e.g., $-CH_2CH_3$).

In some examples, the compound of Formula (I) is selected from:

[0005] In an example, provided herein is a pharmaceutical composition comprising a compound described herein (*e.g.*, a compound of Formula (I), or pharmaceutically acceptable salt thereof), and a pharmaceutically acceptable carrier.

[0006] In an example, provided herein is a method of inducing sedation or anesthesia comprising administering to a subject an effective amount of a compound described herein (*e.g.*, a compound of Formula (I), or pharmaceutically acceptable salt thereof), or pharmaceutical composition thereof.

[0007] In an example, provided herein is a method for treating or preventing a disorder described herein, comprising administering to a subject in need thereof an effective amount of a compound described herein (*e.g.*, a compound of Formula (I), or pharmaceutically acceptable salt thereof), or pharmaceutical composition thereof.

[0008] In some examples, the disorder is a gastrointestinal (GI) disorder *e.g.*, constipation, irritable blowel syndrome (IBS), inflammatory bowel disease (IBD) (e.g., ulcerative colitis, Crohn's disease), structural disorders affecting the GI, anal disorders (*e.g.*, hemorrhoids, internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, anal fistula), colon polyps, cancer, colitis.

[0009] In some examples, the disorder is inflammatory bowel disease.

[0010] In some examples, the disorder is cancer, diabetes, or a sterol synthesis disorder.

[0011] In an example, provided herein is a method for treating or preventing a CNS-related condition comprising administering to a subject in need thereof an effective amount of a compound described herein (*e.g.*, a compound of Formula (I), or pharmaceutically acceptable salt thereof), or pharmaceutical composition thereof. In some examples, the CNS-related condition is an adjustment disorder, anxiety disorder (including obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia), cognitive disorder (including Alzheimer's disease and other forms of dementia), dissociative disorder, eating disorder, mood disorder (including depression (*e.g.*, postpartum depression), bipolar disorder, dysthymic disorder, suicidality), schizophrenia or other psychotic disorder (including schizoaffective disorder), sleep disorder (including insomnia), substance-related disorder, personality disorder (including obsessive-compulsive personality disorder), autism spectrum disorders (including those involving mutations to the Shank group of proteins (*e.g.*, Shank3)), neurodevelopmental disorder (including Rett syndrome, Tuberous Sclerosis complex), multiple sclerosis, sterol synthesis

disorders, pain (including acute and chronic pain), encephalopathy secondary to a medical condition (including hepatic encephalopathy and anti-NMDA receptor encephalitis), seizure disorder (including status epilepticus and monogenic forms of epilepsy such as Dravet's disease), stroke, traumatic brain injury, movement disorder (including Huntington's disease and Parkinson's disease), vision impairment, hearing loss, and tinnitus.

[0012] In some examples, the disorder is sterol synthesis disorder.

[0013] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Detailed Description**, **Examples**, and **Claims**.

Definitions

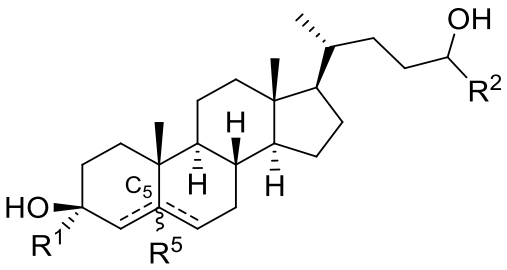
Chemical Definitions

[0014] 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.

[0015] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY,

What is claimed is:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted C_{1-6} alkyl;

R^2 is substituted or unsubstituted C_{2-6} alkyl;

R^5 is absent or hydrogen; and

----- represents a single or double bond, wherein when one ----- is a double bond, the other ----- is a single bond and R^5 is absent.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is substituted C_{1-6} alkyl.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted C_{1-6} alkyl.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl, -CF_3 -CH_2OCH_3, –$CH(CH_3)(CF_3)$, ethyl, or isopropyl.

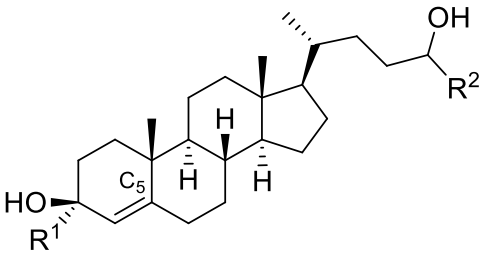
5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl or ethyl.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is unsubstituted C_{2-6} alkyl.

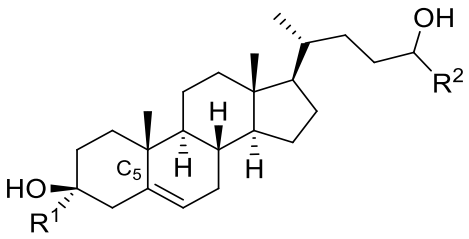
7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is ethyl or isopropyl.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ----- represents a single bond.

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is a compound of Formula (I-A) or Formula (I-B):

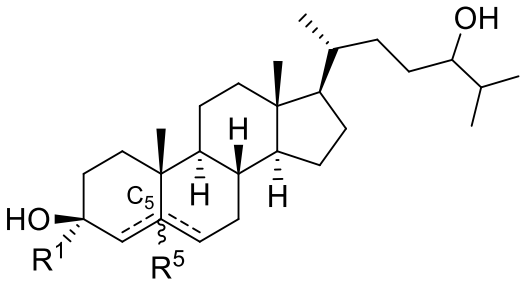


(I-A) or



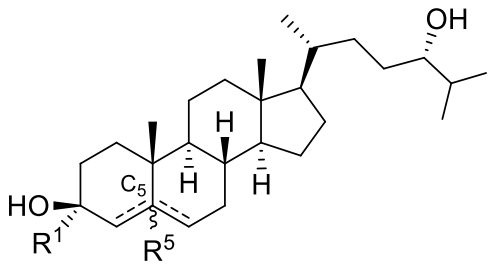
(I-B).

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof wherein the compound of Formula (I) is a compound of Formula (II):

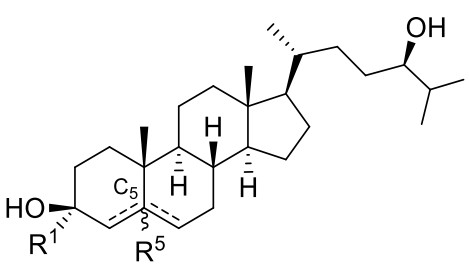


(II).

11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (II) is a compound of Formula (II-A) or Formula (II-B):

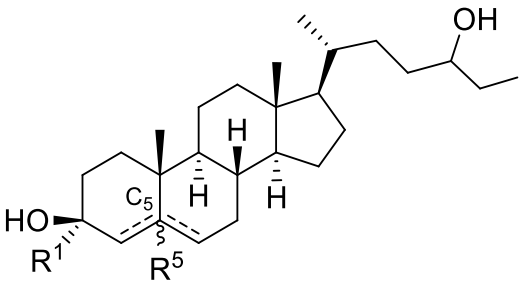


(II-A) or



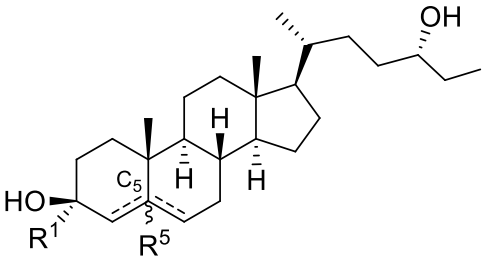
(II-B).

12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is a compound of Formula (IV):

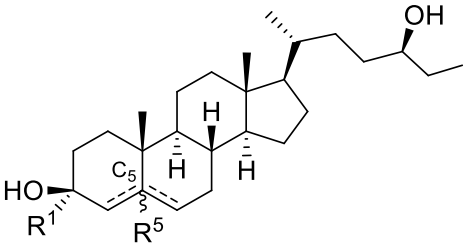


(IV).

13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (IV) is a compound of Formula (IV-A) or Formula (IV-B):

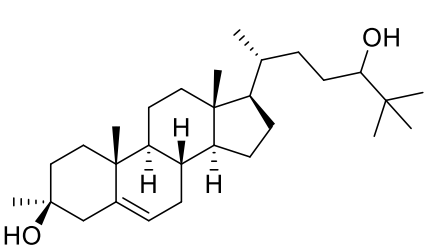
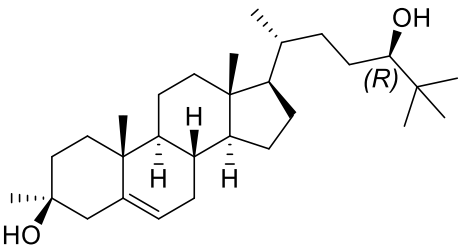
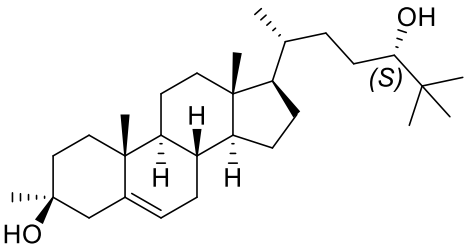
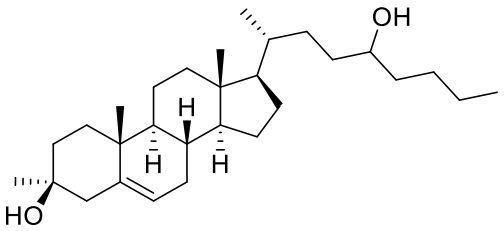
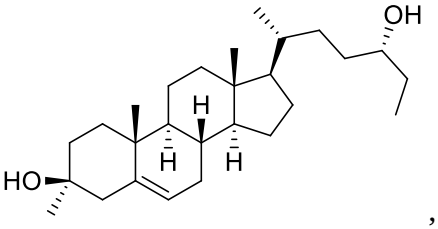
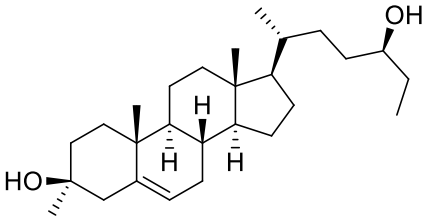
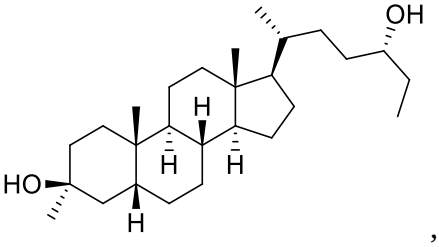
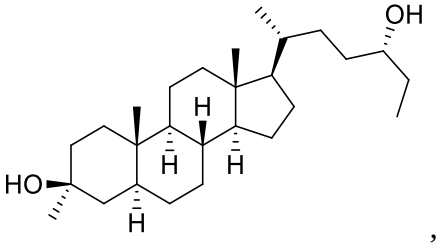
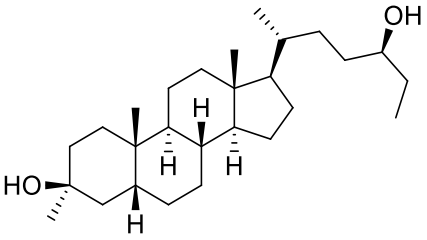
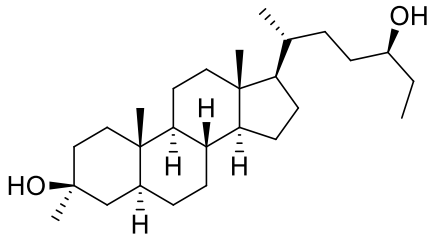
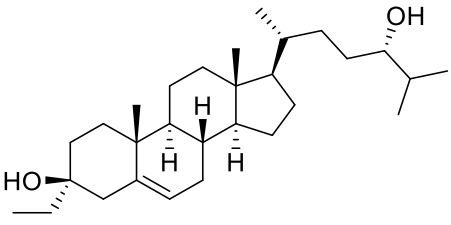
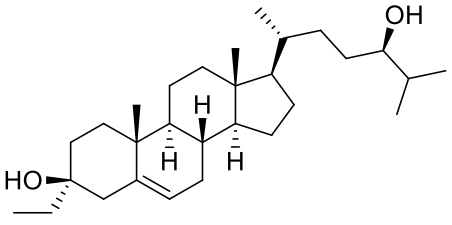
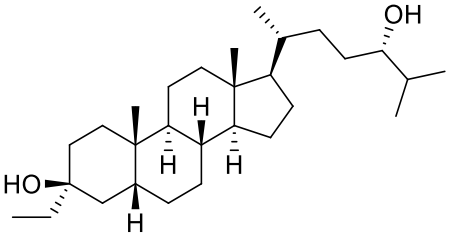
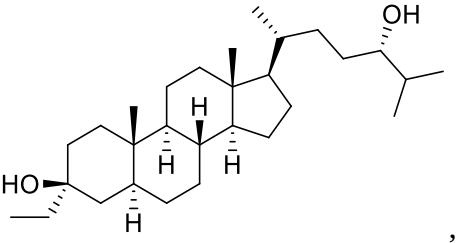


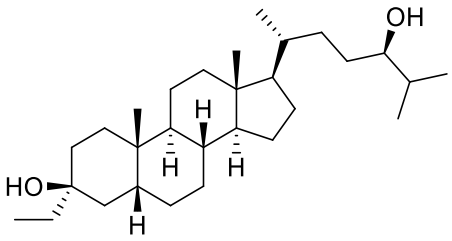
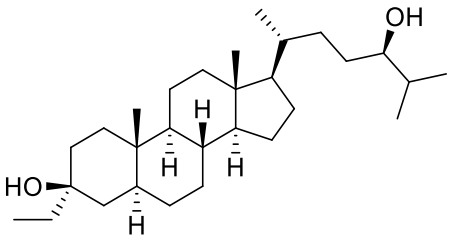
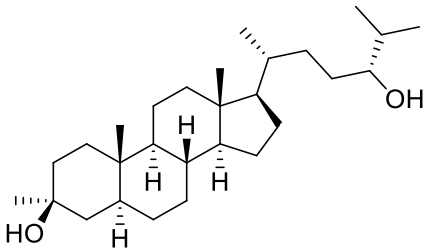
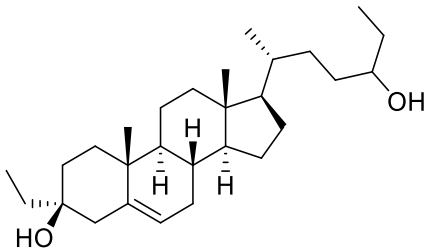
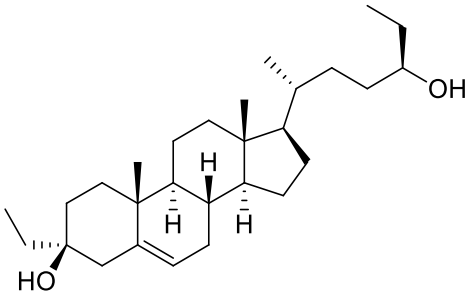
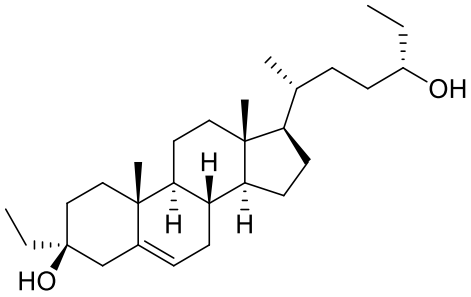
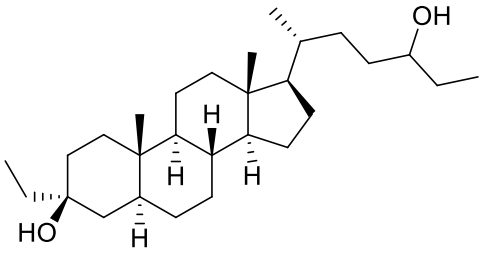
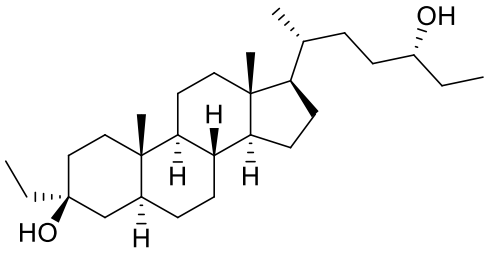
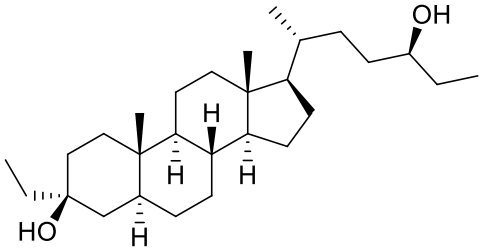
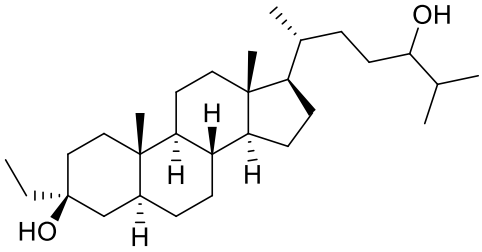
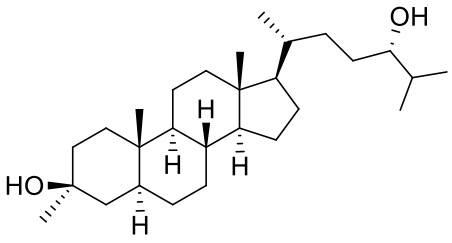
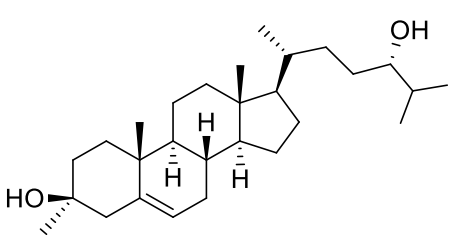
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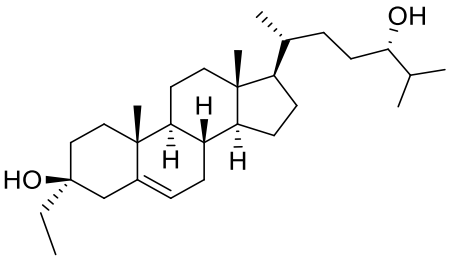
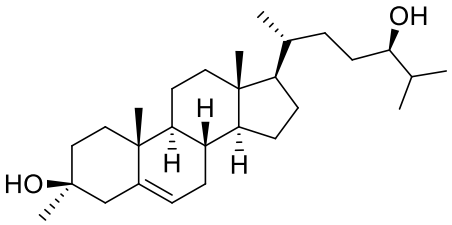
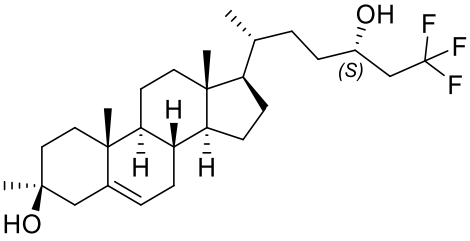
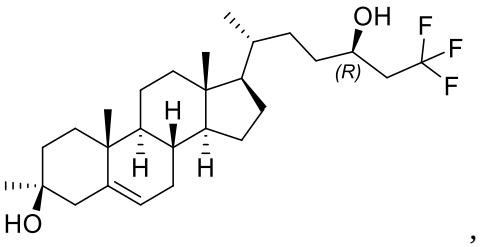
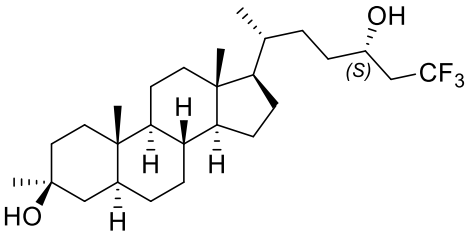
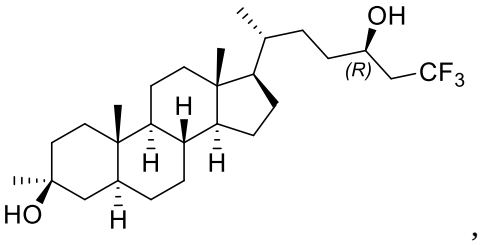
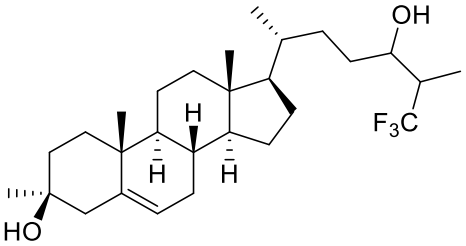
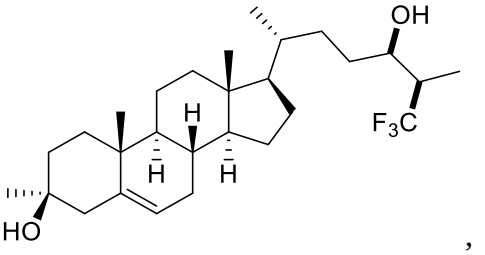
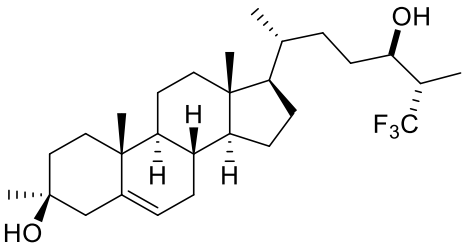
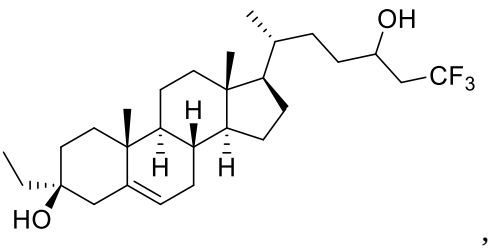
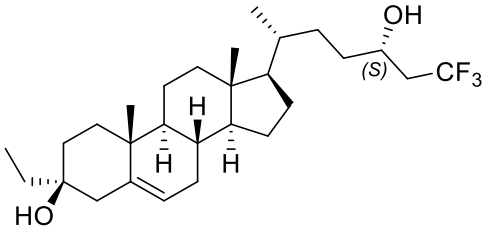
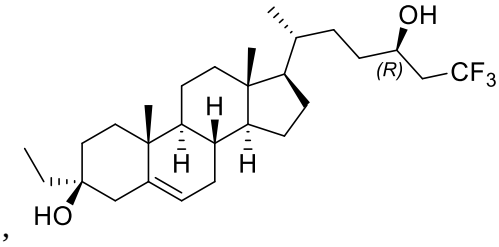


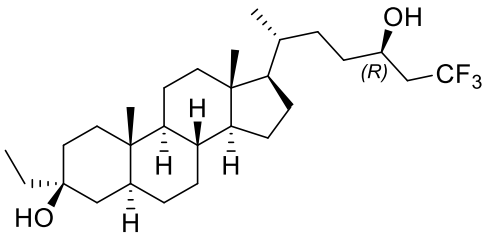
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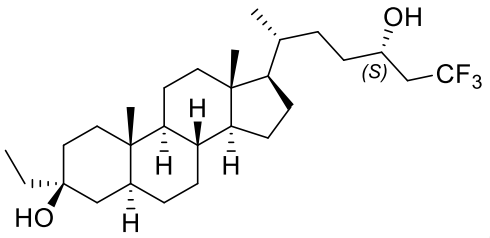
14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is selected from the group consisting of:

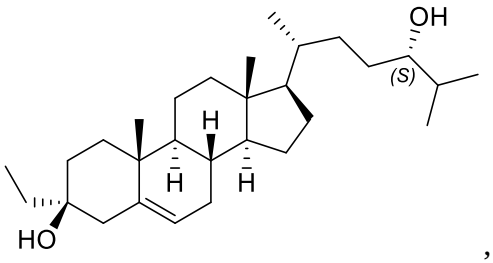















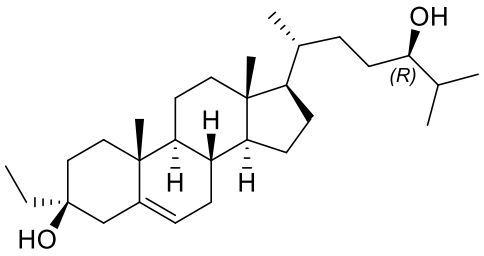

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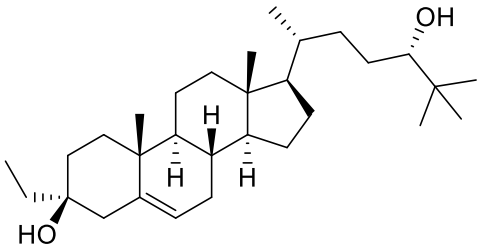













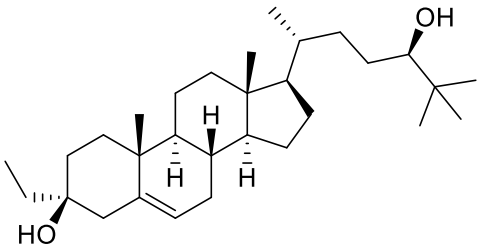


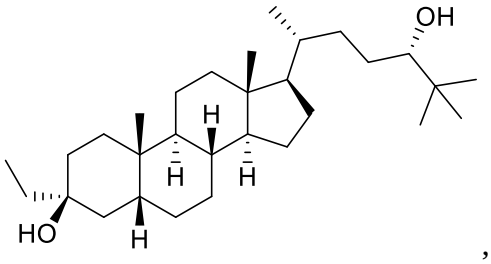
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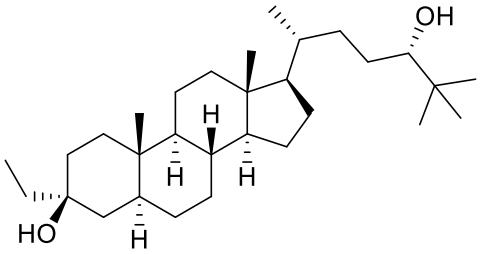
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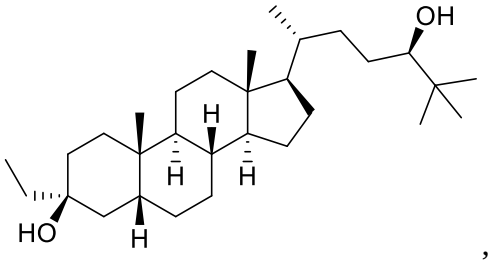
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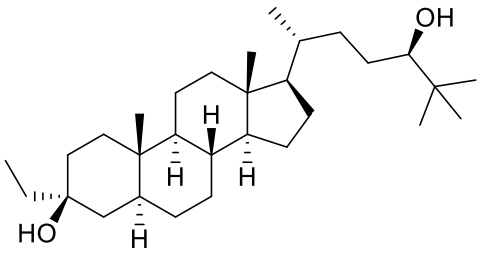
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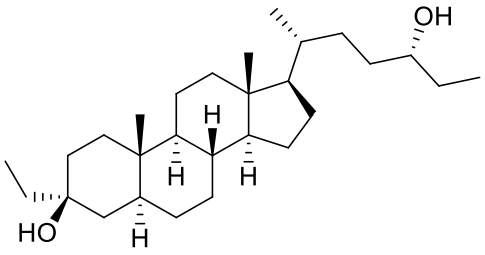
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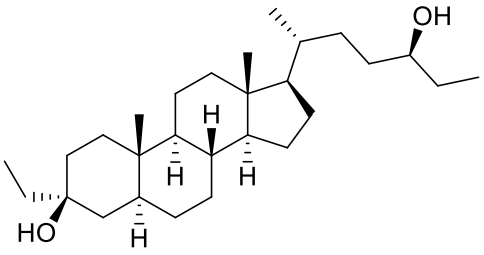
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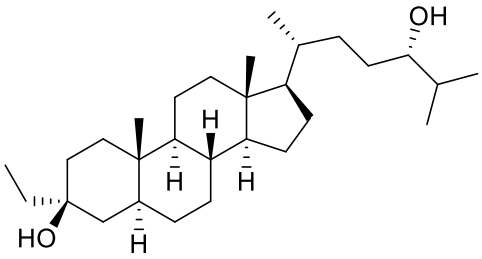
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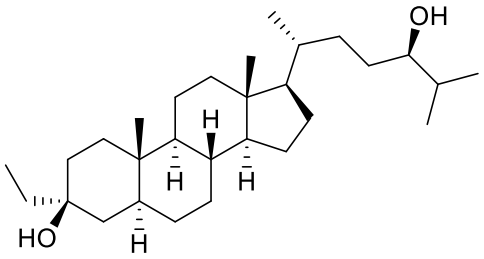
.

15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is selected from the group consisting of:



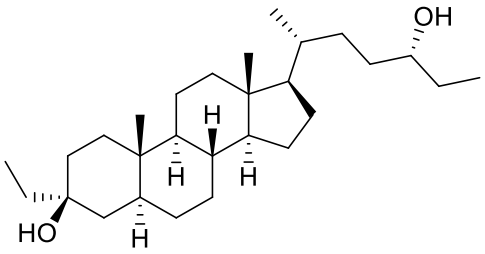
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, and


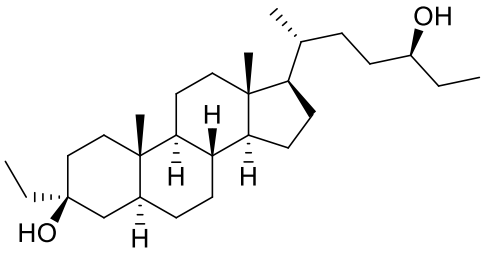
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16. The compound of claim 15, wherein the compound is:



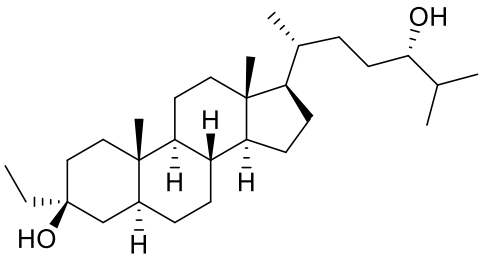
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17. The compound of claim 15, wherein the compound is:



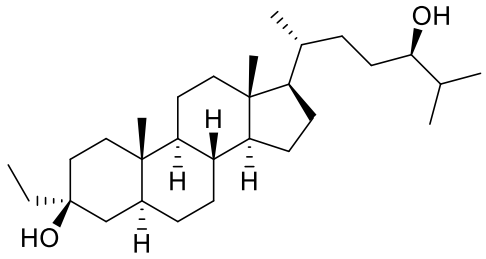
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18. The compound of claim 15, wherein the compound is:



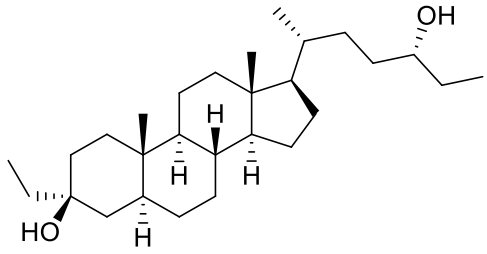
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19. The compound of claim 15, wherein the compound is:



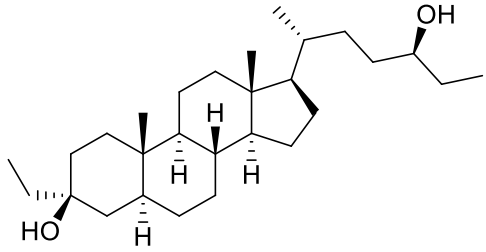
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20. The compound of claim 15, wherein the compound is a pharmaceutically acceptable salt of:



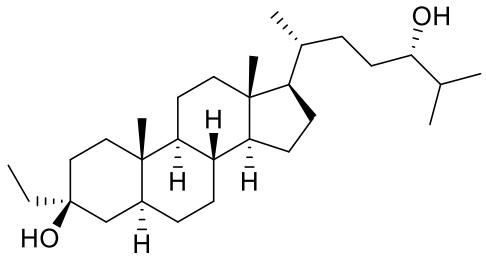
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21. The compound of claim 15, wherein the compound is a pharmaceutically acceptable salt of:



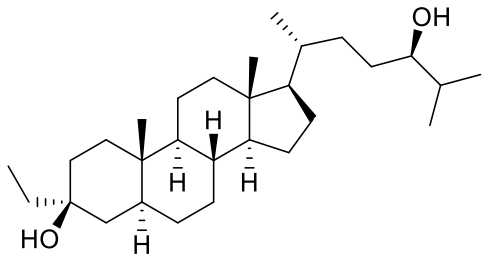
.

22. The compound of claim 15, wherein the compound is a pharmaceutically acceptable salt of:



.

23. The compound of claim 15, wherein the compound is a pharmaceutically acceptable salt of:



.

24. A pharmaceutical composition comprising a compound of any one of claims 1-19, and a pharmaceutically acceptable carrier.

25. A pharmaceutical composition comprising a pharmaceutically acceptable salt of a compound of any one of claims 1-15 and 20-23, and a pharmaceutically acceptable carrier.

26. Use of a compound or pharmaceutically acceptable salt of any one of claims 1-23, or a pharmaceutical composition of claim 24 or 25, in the manufacture of a medicament for inducing sedation or anesthesia.

27. Use of a compound or pharmaceutically acceptable salt of any one of claims 1-23, or a pharmaceutical composition of claim 24 or 25, in the manufacture of a medicament for treating or preventing a disorder, wherein the disorder is a gastrointestinal (GI) disorder, a structural disorder affecting the GI tract, an anal disorder, colon polyps, cancer, diabetes, a sterol synthesis disorder, or colitis.

28. The use of claim 27, wherein the disorder is a GI disorder, wherein the GI disorder is inflammatory bowel disease.

29. The use of claim 27, wherein the disorder is cancer, diabetes, or a sterol synthesis disorder.

30. Use of a compound or pharmaceutically acceptable salt of any one of claims 1-23, or a pharmaceutical composition of claim 24 or 25, in the manufacture of a medicament for treating or preventing a CNS-related condition.

31. The use of claim 30, wherein the CNS-related condition is an adjustment disorder, an anxiety disorder, a cognitive disorder, a dissociative disorder, an eating disorder, a mood disorder, schizophrenia or another psychotic disorder, a sleep disorder, a substance-related disorder, a personality disorder, an autism spectrum disorder, a neurodevelopmental disorder, multiple sclerosis, a sterol synthesis disorder, pain, encephalopathy secondary to a medical condition, a seizure disorder, stroke, traumatic brain injury, a movement disorder, vision impairment, hearing loss, or tinnitus.

32. The use of claim 31, wherein the CNS-related condition is a sterol synthesis disorder.

33. The use according to claim 31, wherein the CNS-related condition is obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia, Alzheimer's disease and other forms of dementia, depression, bipolar disorder, dysthymic disorder, suicidality, schizoaffective disorder, insomnia, obsessive-compulsive personality disorder, autism spectrum disorders involving mutations to the Shank group of proteins, Rett syndrome, Tuberous Sclerosis complex, acute pain, chronic pain, hepatic encephalopathy, anti-NMDA receptor encephalitis, status epilepticus, monogenic forms of epilepsy, Huntington's disease or Parkinson's disease.

34. The use of claim 31, wherein the CNS-related condition is schizophrenia.

35. The use of claim 31, wherein the CNS-related condition is an autism spectrum disorder.

36. The use of claim 31, wherein the CNS-related condition is a movement disorder, wherein the movement disorder is Huntington's disease or Parkinson's disease.

37. The use of claim 31, wherein the CNS-related condition is a cognitive disorder, wherein the cognitive disorder is Alzheimer's disease.

38. The compound or pharmaceutically acceptable salt of any one of claims 1-23, or a pharmaceutical composition of claim 24 or 25, for use in therapy.