# OXYSTEROLS AND METHODS OF USE THEREOF

## Related Applications

This application claims priority to U.S. Provisional Application Number 62/189,048 filed July 6, 2015, and 62/280,394 filed January 19, 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).

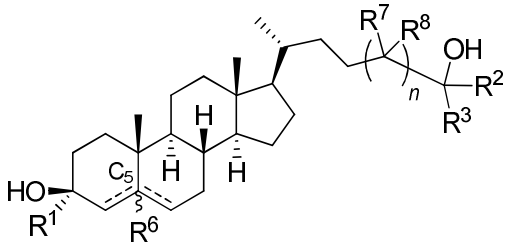
**[0002]** Oxysterols are derived from cholesterol and have been shown to potently and selectively modulate NMDA receptor function. New and improved oxysterols are needed that modulate the NMDA receptor for the prevention and treatment of conditions associated with NMDA expression and function. Compounds,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

## Summary of the Disclosure

**[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, there is provided a compound of Formula (I):




(I)

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ is $C_{1-6}$ alkyl;

each of $R^2$ and $R^3$ is independently hydrogen, halogen, $C_{1-6}$ alkyl, or carbocyclyl; or

$R^2$ and $R^3$, together with the carbon atom to which they are attached, form a 3-8 membered ring;

$R^6$ is absent or hydrogen;

each of $R^7$ and $R^8$ is independently hydrogen, halogen, $C_{1-6}$ alkyl, or carbocyclyl; or

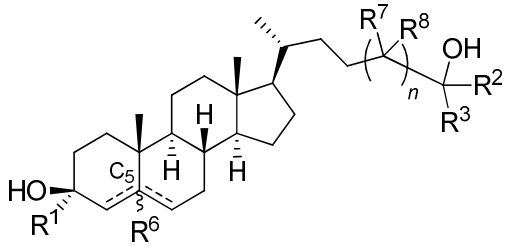
each of $R^7$ and $R^8$, together with the carbon atom to which they are attached, form a 3-8 membered ring; or

$R^2$ and $R^7$, together with the carbon atoms to which they are attached, form a 3-8 membered ring;

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

⁼⁼⁼ represents a single or double bond, wherein when one ⁼⁼⁼ is a double bond, the other ⁼⁼⁼ is a single bond; and when one of the ⁼⁼⁼ is a double bond, $R^6$ is absent

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




(I)

or a pharmaceutically acceptable salt thereof, wherein: $R^1$ is $C_{1-6}$ alkyl; each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl; or $R^2$ and $R^3$, together with the carbon atom to which they are attached, form a 3-8 membered ring; $R^6$ is absent or hydrogen; each of $R^7$ and $R^8$ is

independently hydrogen, halogen, $C_{1-6}$ alkyl, or carbocyclyl; or each of $R^7$ and $R^8$, together with the carbon atom to which they are attached, form a 3-8 membered ring; or$R^2$ and $R^7$, together with the carbon atoms to which they are attached, form a 3-8 membered ring; *n* is 1, 2, or 3; and ----- represents a single or double bond, wherein when one ----- is a double bond, the other ----- is a single bond; and when one of the ----- is a double bond, $R^6$ is absent.

**[0005]** 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., $-CHF_2$, $-CH_3$, $-CF_3$, $-CH_2OCH_3$, or $-CH_2OCH_2CH_3$), ethyl, or isopropyl. In some examples, $R^1$ is $-CH_3$. In some examples, $R^1$ is ethyl.

**[0006]** In some examples, each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl, or wherein $R^2$ and $R^3$ are taken together with the carbon atom to which they are attached form a 3-8 membered ring. In some examples, the 3-8 membered ring is a carbocyclyl ring (e.g., cyclopropyl). In some examples, each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl. In some examples, each of $R^2$ and $R^3$ is independently hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $CH_2CF_3$), propyl, isopropyl, cyclopropyl, or butyl.

**[0007]** In some examples, $R^2$ substituted $C_{1-6}$ alkyl. In some examples, $R^2$ unsubstituted $C_{1-6}$ alkyl.

**[0008]** In some examples, $R^2$ is hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), ethyl, or isopropyl-.

**[0009]** In some examples, $R^3$ substituted $C_{1-6}$ alkyl. In some examples, $R^3$ unsubstituted $C_{1-6}$ alkyl.

**[0010]** In some examples, $R^3$ is methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $CH_2CF_3$), propyl, isopropyl, cyclopropyl, or butyl.

**[0011]** In some examples, $R^2$ and $R^3$ are hydrogen. In some examples, $R^2$ is hydrogen and $R^3$ is $C_{1-6}$ alkyl (e.g., methyl (e.g., $-CH_3$, $-CF_3$), ethyl, isopropyl). In some examples, $R^2$ is $C_{1-6}$ alkyl and $R^3$ is $C_{1-6}$ alkyl. In some examples, $R^2$ and $R^3$ are $-CH_3$. In some examples, $R^2$ is $-CH_3$ and $R^3$ is $-CF_3$. In some examples, $R^2$ is $-CH_3$ and $R^3$ is ethyl. In some examples, $R^2$ is $-CH_3$ and $R^3$ is isopropyl.

**[0012]** In some examples, each of ----- is a single bond.

**[0013]** In some examples, $R^6$ is hydrogen. In some examples, $R^6$ is in the alpha position. In some examples, $R^6$ is in the beta position.

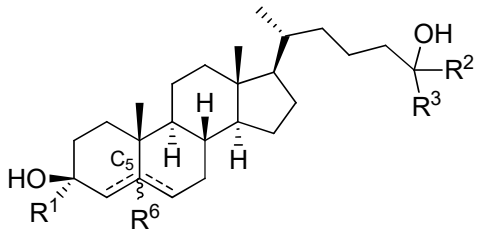
**[0014]** In some examples, $R^6$ is absent.

**[0015]** In some examples, $R^7$ and $R^8$ are hydrogen.

**[0016]** In some examples, *n* is 1. In some examples, *n* is 1 and $R^7$ and $R^8$ are hydrogen.

**[0017]** In some examples, *n* is 2. In some examples, *n* is 2 and each of $R^7$ and $R^8$ is independently hydrogen, halogen, $C_{1-6}$ alkyl, or carbocyclyl.

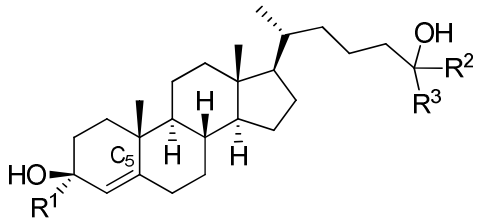
**[0018]** In some examples, the compound Formula (I) is a compound of Formula (II):



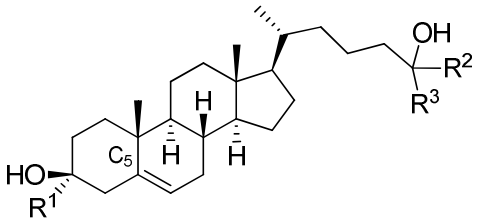

(II)

or a pharmaceutically acceptable salt thereof.

**[0019]** In some examples, the compound of Formula (II) is a compound of Formula (II-A) or Formula (II-B):



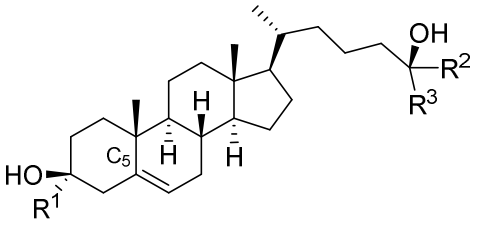

(II-A)



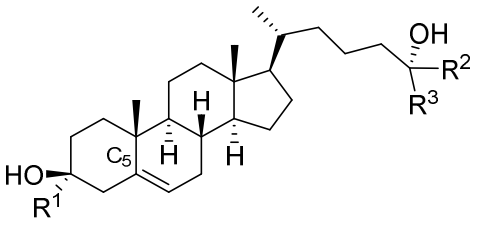

(II-B),

or a pharmaceutically acceptable salt thereof.

**[0020]** In some examples, the compound of Formula (I) is a compound of Formula (II-B-i) or Formula (II-B-ii):

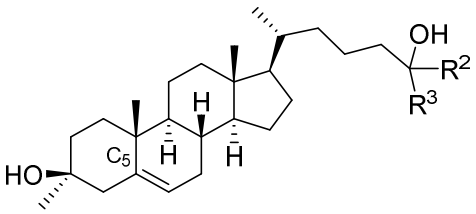



(II-B-i)



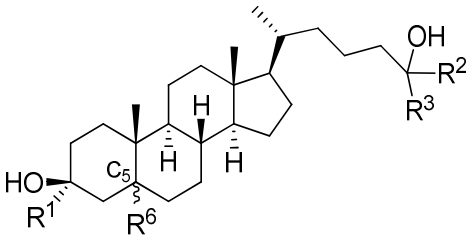

(II-B-ii), or a pharmaceutically acceptable salt thereof.

**[0021]** In some examples, the compound of Formula (I) is a compound of Formula (II-B-iii):



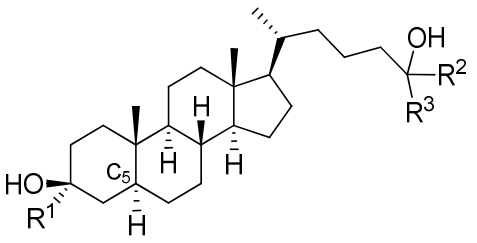

(II-B-iii), or a pharmaceutically acceptable salt thereof.

**[0022]** In some examples, the compound of Formula (I) is a compound of Formula (III):

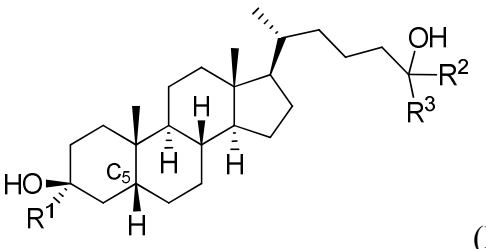



(III), or a pharmaceutically acceptable salt thereof.

**[0023]** In some examples, the compound of Formula (III) is a compound of Formula (III-A) or Formula (III-B):

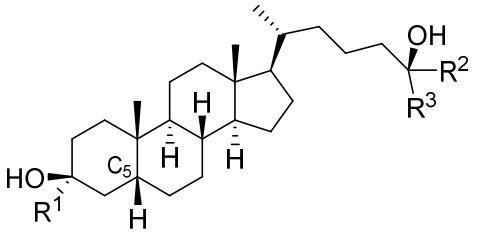



(III-A) or

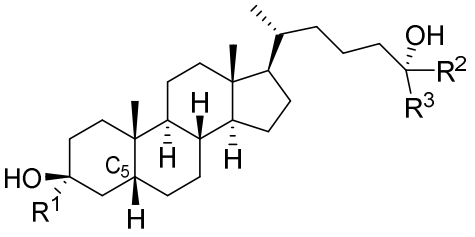



(III-B), or a pharmaceutically acceptable salt thereof.

**[0024]** In some examples, the compound of Formula (III-B) is a compound of Formula (III-C) or Formula (III-D):



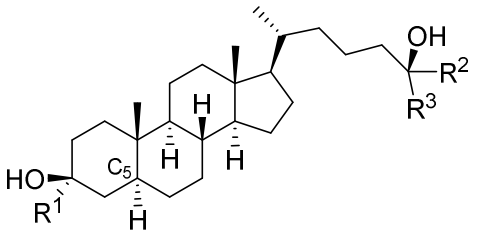

(III-C) or



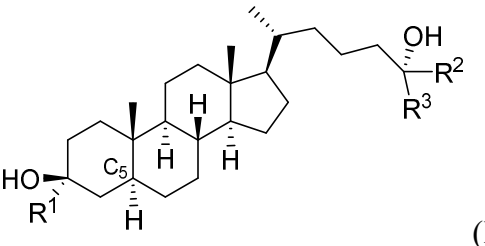

(III-D),

or a pharmaceutically acceptable salt thereof.

**[0025]** In some examples, the compound of Formula (III-A) is a compound of Formula (III-E) or Formula (III-F):



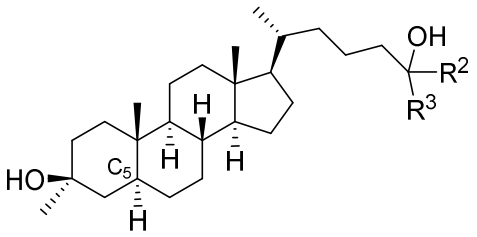

(III-E) or



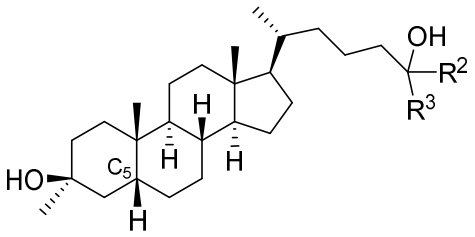

(III-F),

or a pharmaceutically acceptable salt thereof.

**[0026]** In some examples, the compound of Formula (III) is a compound of Formula (III-A-i-a) or Formula (III-B-i-a):




(III-A-i-a) or




(III-B-i-a), or a pharmaceutically acceptable salt thereof.

**[0027]** In some examples, $R^1$ is methyl (e.g., $-CHF_2$, $-CF_3$, $-CH_2OCH_3$, or $-CH_2OCH_2CH_3$), ethyl, or isopropyl.

**[0028]** In some examples, each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl, or wherein $R^2$ and $R^3$ are taken together with the carbon atom to which they are attached form a 3-8 membered ring.

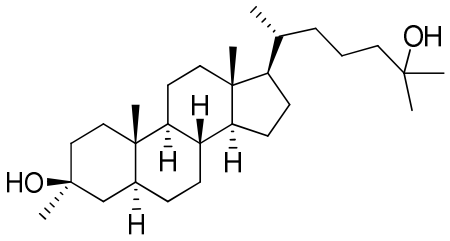
**[0029]** In some examples, each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl.

**[0030]** In some examples, each of $R^2$ and $R^3$ is independently hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $-CH_2CF_3$), propyl, isopropyl, cyclopropyl, or butyl.

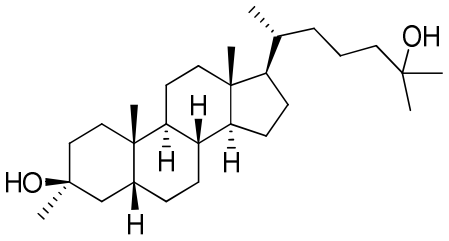
**[0031]** In some examples, $R^2$ is hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), or ethyl.

**[0032]** In some examples, $R^3$ is methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $-CH_2CF_3$), propyl, isopropyl, cyclopropyl, or butyl.

**[0033]** In some examples, the compound is selected from the group consisting of:



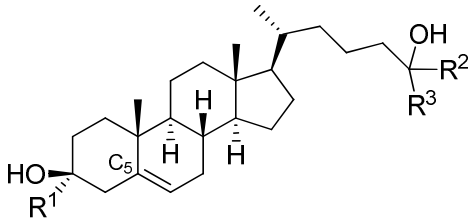

and




,

or a pharmaceutically acceptable salt thereof.

**[0034]** In some examples, the compound of Formula (I) is a compound of Formula (IV):




(IV), or a pharmaceutically acceptable salt thereof.

**[0035]** In some examples, $R^1$ is methyl (e.g., $-CHF_2$, $-CF_3$, $-CH_2OCH_3$, or $-CH_2OCH_2CH_3$), ethyl, or isopropyl.

**[0036]** In some examples, each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl, or wherein $R^2$ and $R^3$ are taken together with the carbon atom to which they are attached form a 3-8 membered ring.

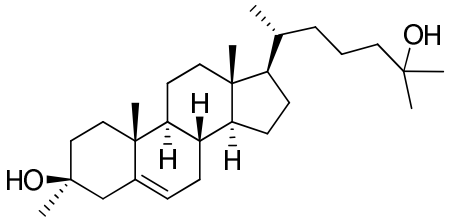
**[0037]** In some examples, each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl.

**[0038]** In some examples, each of $R^2$ and $R^3$ is independently hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $CH_2CF_3$), propyl, isopropyl, cyclopropyl, or butyl.

**[0039]** In some examples, $R^2$ is hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), or ethyl.

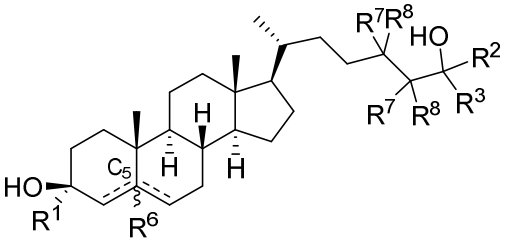
**[0040]** In some examples, $R^3$ is methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $-CH_2CF_3$), propyl, isopropyl, cyclopropyl, butyl.

**[0041]** In some examples, the compound is:



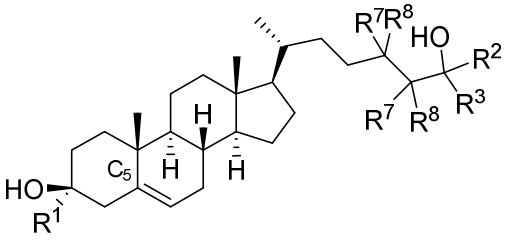
, or a pharmaceutically acceptable salt thereof.

**[0042]** In some examples, the compound Formula (I) is a compound of Formula (V):



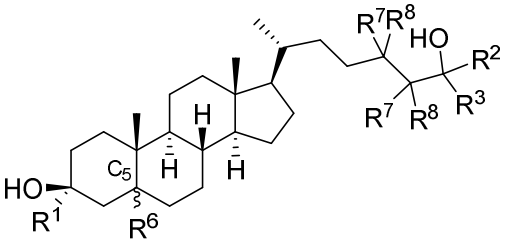
(V) or a pharmaceutically acceptable salt thereof.

**[0043]** In some examples, the compound of Formula (I) is a compound of Formula (V-A):



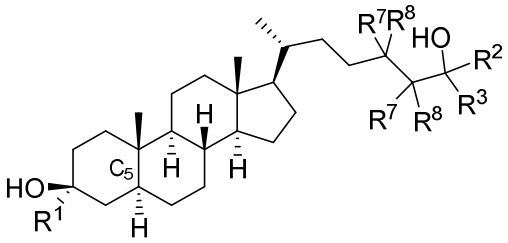
(V-A), or a pharmaceutically acceptable salt thereof.

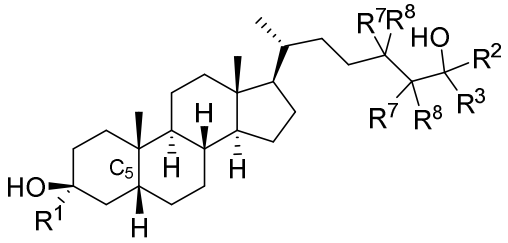
**[0044]** In some examples, the compound of Formula (I) is a compound of Formula (V-B):



(V-B), or a pharmaceutically acceptable salt thereof.

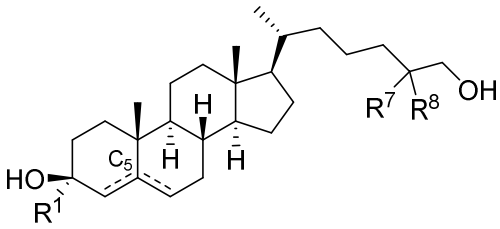
**[0045]** In some examples, the compound of Formula (III) is a compound of Formula (V-C) or Formula (V-D):



(V-C) or 

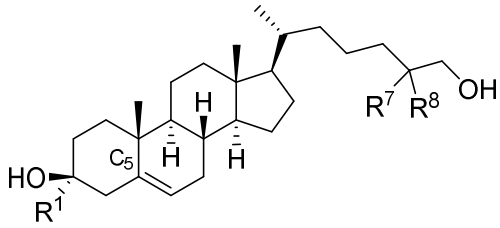
(V-D), or a pharmaceutically acceptable salt thereof.

**[0046]** In some examples, the compound of Formula (I) is a compound of Formula (V-E):



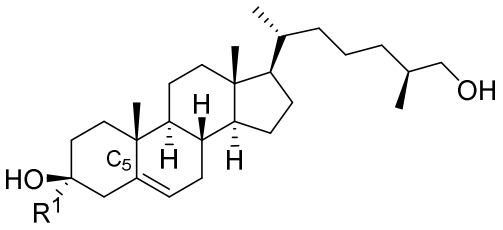
(V-E), or a pharmaceutically acceptable salt thereof.

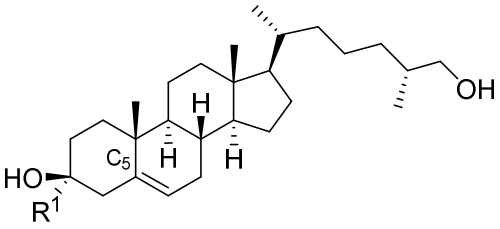
**[0047]** In some examples, the compound of Formula (V-E) is a compound of Formula (V-E-i):



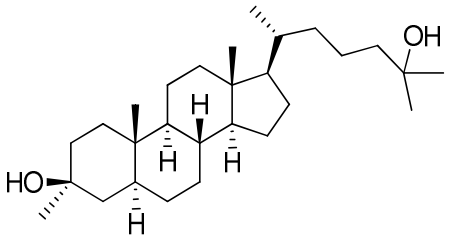
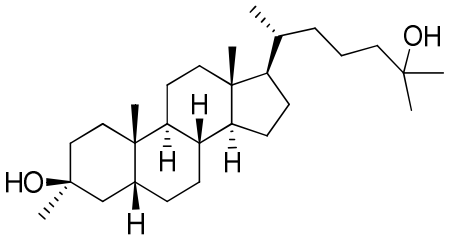
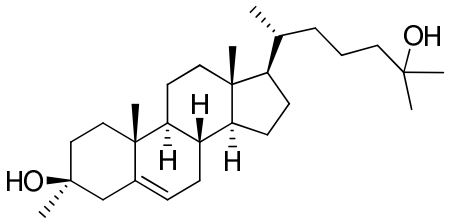
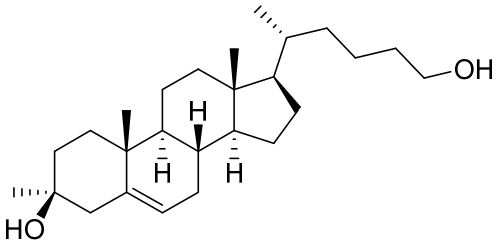
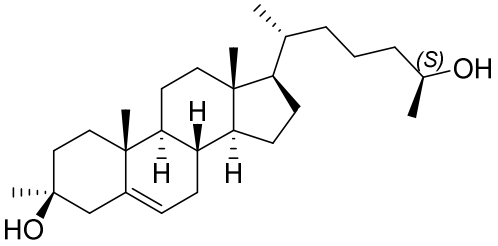
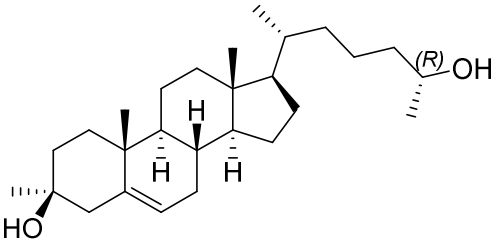
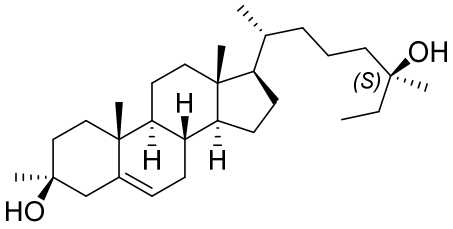
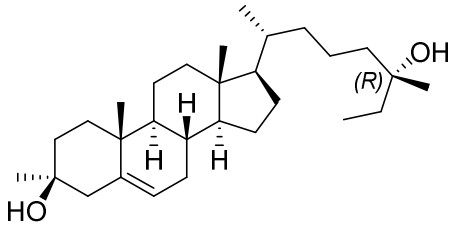
(V-E-i), or a pharmaceutically acceptable salt thereof.

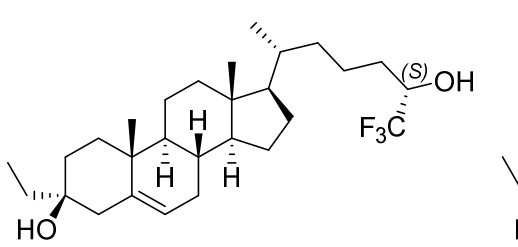
**[0048]** In some examples, the compound of Formula (I) is a compound of Formula (V-E-ii) or (V-E-iii):

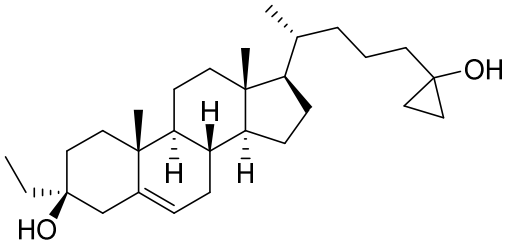
**[0049]**  (V-E-ii) or

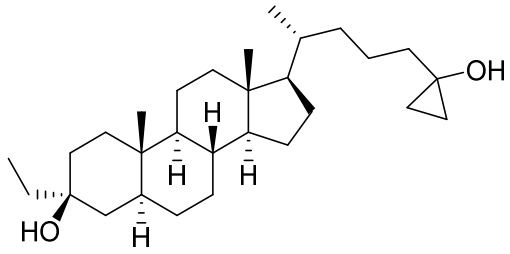
 (V-E-iii), or a pharmaceutically acceptable salt thereof.

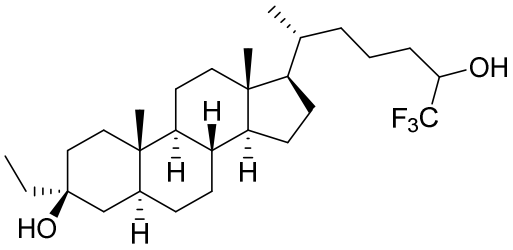
In some examples, the compound is selected from:

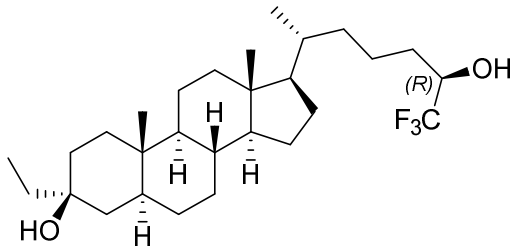
, , , , , , , ,

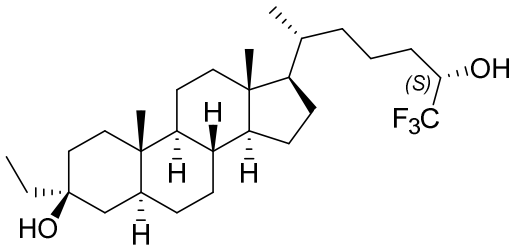


,


,


,


,


,


,

or a pharmaceutically acceptable salt thereof.

**[0050]** In another aspect, provided herein is a pharmaceutical composition comprising a compound described herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

**[0050a]** In another aspect, provided herein is a use of a compound described herein, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof in the manufacture of a medicament for inducing sedation or anesthesia.

**[0051]** 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, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

**[0051a]** In another aspect, there is provided herein a use of a compound described herein, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof in the manufacture of a medicament for treating or preventing a disorder described herein.

**[0052]** 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, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

**[0053]** In some examples, the disorder is a metabolic disorder.

**[0054]** 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.

**[0055]** `In some examples, the disorder is inflammatory bowel disease.

**[0056]** In some examples, the disorder is cancer, diabetes, or a sterol synthesis disorder.

**[0056a]** In another aspect, provided herein is a use of a compound as described herein, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof in the manufacture of a medicament for treating or preventing a CNS-related condition.

**[0056b]** In another aspect, provided herein is a compound as described herein, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof for use in therapy.

**[0057]** 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, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof. In some embodiments, 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 (e.g., frontotemporal 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; headaches, e.g., migraine headaches), 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.

**[0058]** In some examples, the disorder is Huntington's disease. In some examples, the disorder is Parkinson's disease. In some examples, the disorder is an inflammatory disease (e.g., lupus).

**[0059]** In some examples, the disorder is sterol synthesis disorder.

**[0060]** In some examples, the disorder is Smith-Lemli-Opitz Syndrome (SLOS). In some examples, the disorder is desmosterolosis. In some examples, the

disorder is sitosterolemia. In some examples, the disorder is cerebrotendinous xanthomatosis (CTX). In some examples, the disorder is Mevalonate Kinase Deficiency (MKD). In some examples, the disorder is SC4MOL gene mutation (SMO Deficiency). In some examples, the disorder is Niemann-Pick disease. In some examples, the disorder is

autism spectrum disorder (ASD). In some examples, the disorder is associated with phenylketomuria.

**[0061]** 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*

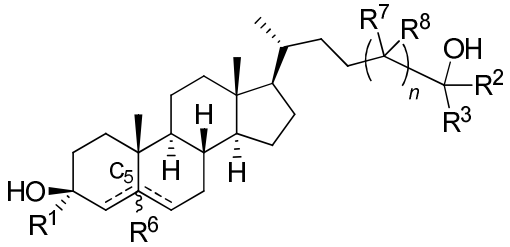
**[0062]** Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups 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.

**[0063]** 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, 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.

## Claims

What is claimed is:

1. A compound of Formula (I):




(I)

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ is $C_{1-6}$ alkyl;

each of $R^2$ and $R^3$ is independently hydrogen, halogen, $C_{1-6}$ alkyl, or carbocyclyl; or

$R^2$ and $R^3$, together with the carbon atom to which they are attached, form a 3-8 membered ring;

$R^6$ is absent or hydrogen;

each of $R^7$ and $R^8$ is independently hydrogen, halogen, $C_{1-6}$ alkyl, or carbocyclyl; or

each of $R^7$ and $R^8$, together with the carbon atom to which they are attached, form a 3-8 membered ring; or

$R^2$ and $R^7$, together with the carbon atoms to which they are attached, form a 3-8 membered ring;

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

⋯ represents a single or double bond, wherein when one ⋯ is a double bond, the other ⋯ is a single bond; and when one of the ⋯ is a double bond, $R^6$ is absent.

2. The compound of claim 1, each ⋯ is a single bond.

3. The compound of claim 1, wherein $R^1$ is methyl (e.g., $-CHF_2$, $-CF_3$, $-CH_2OCH_3$, or $-CH_2OCH_2CH_3$), ethyl, or isopropyl.

4. The compound of claim 3, wherein $R^1$ is methyl or ethyl.

5. The compound of claim 1, wherein each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl, or wherein $R^2$ and $R^3$ are taken together with the carbon atom to which they are attached form a 3-8 membered ring.

6. The compound of claim 5, wherein the 3-8 membered ring is a carbocyclyl ring (e.g., cyclopropyl).

7. The compound of claim 5, wherein each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl.

8. The compound of claim 7, wherein each of $R^2$ and $R^3$ is independently hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $CH_2CF_3$), propyl, isopropyl, cyclopropyl, or butyl.

9. The compound of claim 7, wherein $R^2$ is hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), or ethyl.

10. The compound of claim 7, wherein $R^3$ is methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $CH_2CF_3$), propyl, isopropyl, cyclopropyl, or butyl.

11. The compound of claim 7, wherein $R^2$ is hydrogen and $R^3$ is $C_{1-6}$ alkyl.

12. The compound of claim 7, wherein $R^2$ is $C_{1-6}$ alkyl and $R^3$ is $C_{1-6}$ alkyl.

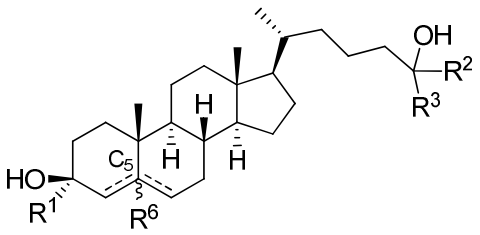
13. The compound of claim 1, wherein each of ----- is a single bond.

14. The compound of claim 1, wherein $R^7$ and $R^8$ are hydrogen.

15. The compound of claim 1, wherein *n* is 1.

16. The compound of claim 1, wherein *n* is 1 and $R^7$ and $R^8$ are hydrogen.

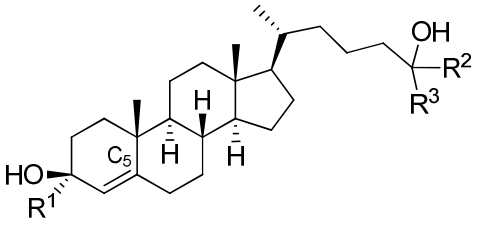
17. The compound of claim 1, wherein the compound Formula (I) is a compound of Formula (II):



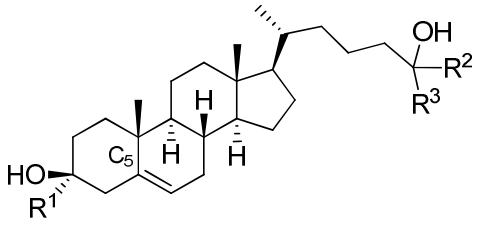

(II)

or a pharmaceutically acceptable salt thereof.

18. The compound of claim 17, wherein the compound of Formula (I) is a compound of Formula (II-A) or Formula (II-B):



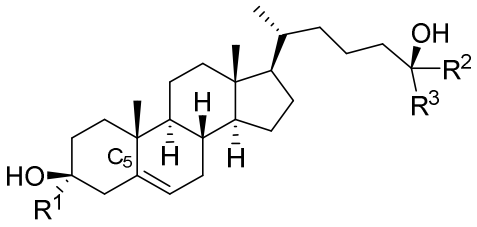

(II-A)



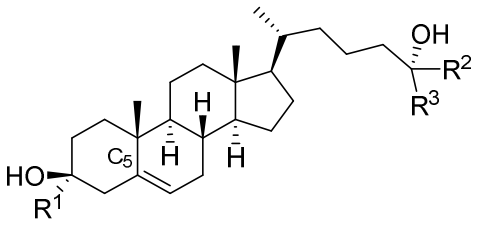

(II-B),

or a pharmaceutically acceptable salt thereof.

19. The compound of claim 17, wherein the compound of Formula (I) is a compound of Formula (II-B-i) or Formula (II-B-ii):



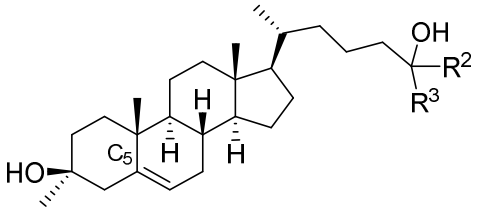

(II-B-i)




(II-B-ii),

or a pharmaceutically acceptable salt thereof.

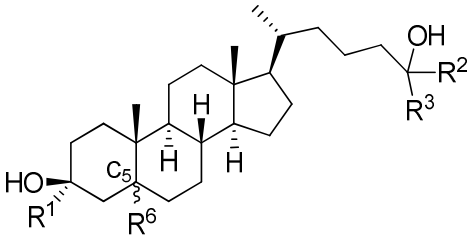
20. The compound of claim 17, wherein the compound of Formula (I) is a compound of Formula (II-B-iii):



(II-B-iii),

or a pharmaceutically acceptable salt thereof.

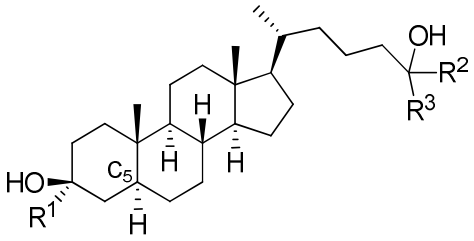
21. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (III):



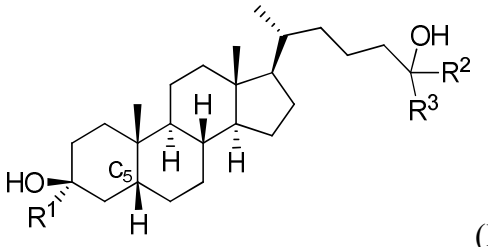
(III),

or a pharmaceutically acceptable salt thereof.

22. The compound of claim 21, wherein the compound of Formula (III) is a compound of Formula (III-A) or Formula (III-B):



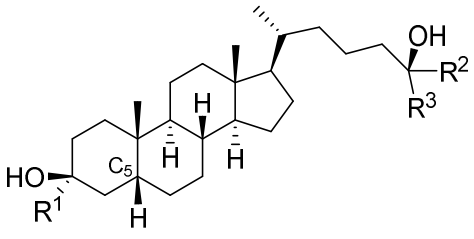
(III-A) or



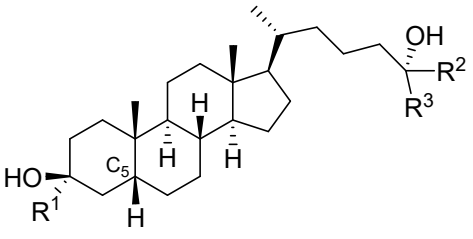
(III-B),

or a pharmaceutically acceptable salt thereof.

23. The compound of claim 21, wherein the compound of Formula (III-B) is a compound of Formula (III-C) or Formula (III-D):



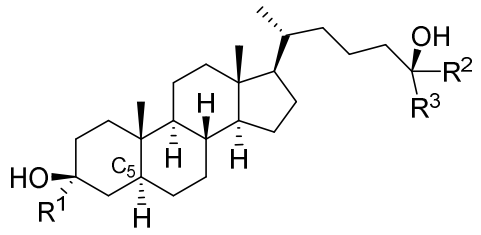
(III-C) or



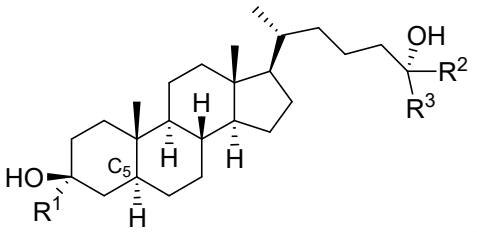
(III-D),

or a pharmaceutically acceptable salt thereof.

24. The compound of claim 21, wherein the compound of Formula (III-A) is a compound of Formula (III-E) or Formula (III-F):



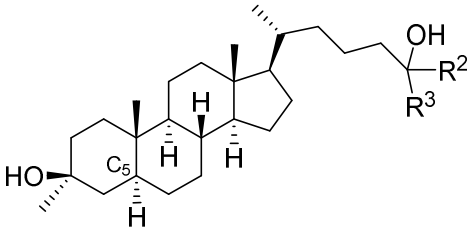

(III-E) or



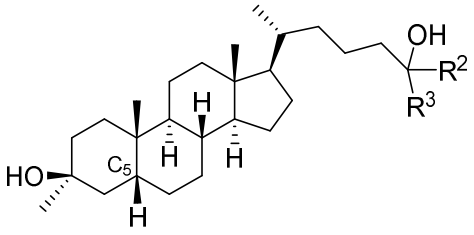

(III-F),

or a pharmaceutically acceptable salt thereof.

25. The compound of claim 21, wherein the compound of Formula (III) is a compound of Formula (III-A-i-a) or Formula (III-B-i-a):




(III-A-i-a) or




(III-B-i-a),

or a pharmaceutically acceptable salt thereof.

26. The compound of claim 25, wherein $R^1$ is methyl (e.g., $-CHF_2$, $-CF_3$, $-CH_2OCH_3$, or $-CH_2OCH_2CH_3$), ethyl, or isopropyl.

27. The compound of claim 21, wherein each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl, or wherein $R^2$ and $R^3$ are taken together with the carbon atom to which they are attached form a 3-8 membered ring.

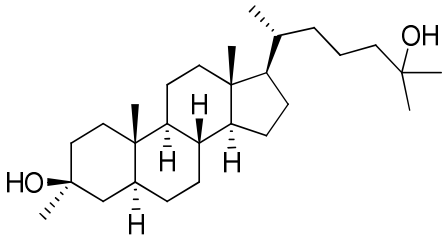
28. The compound of claim 27, wherein each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl.

29. The compound of claim 28, wherein each of $R^2$ and $R^3$ is independently hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $CH_2CF_3$), propyl, isopropyl, cyclopropyl, or butyl.

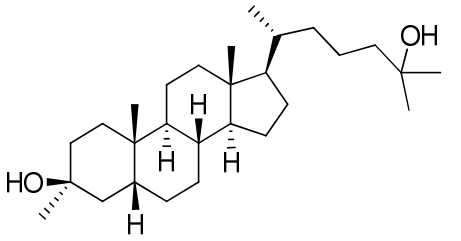
30. The compound of claim 29, wherein $R^2$ is hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), or ethyl.

31. The compound of claim 27, wherein $R^3$ is methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $-CH_2CF_3$), propyl, isopropyl, cyclopropyl, or butyl.

32. The compound of claim 21, wherein the compound is selected from the group consisting of:



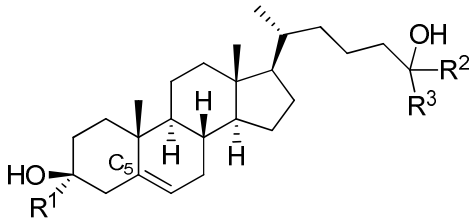

and




,

or a pharmaceutically acceptable salt thereof.

33. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (IV):




(IV),

or a pharmaceutically acceptable salt thereof.

34. The compound of claim 33, wherein $R^1$ is methyl (e.g., $-CHF_2$, $-CF_3$, $-CH_2OCH_3$, or $-CH_2OCH_2CH_3$), ethyl, or isopropyl.

35. The compound of claim 33, wherein each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl, or wherein $R^2$ and $R^3$ are taken together with the carbon atom to which they are attached form a 3-8 membered ring.

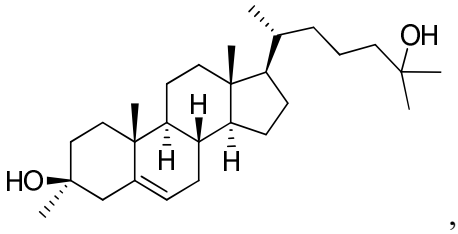
36. The compound of claim 35, wherein each of $R^2$ and $R^3$ is independently hydrogen, $C_{1-6}$ alkyl, or carbocyclyl.

37. The compound of claim 36, wherein each of $R^2$ and $R^3$ is independently hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $CH_2CF_3$), propyl, isopropyl, cyclopropyl, or butyl.

38. The compound of claim 37, wherein $R^2$ is hydrogen, methyl (e.g., $-CH_3$, $-CF_3$), or ethyl.

39. The compound of claim 36, wherein $R^3$ is methyl (e.g., $-CH_3$, $-CF_3$), ethyl (e.g., $-CH_2CH_3$, $-CH_2CF_3$), propyl, isopropyl, cyclopropyl, butyl.

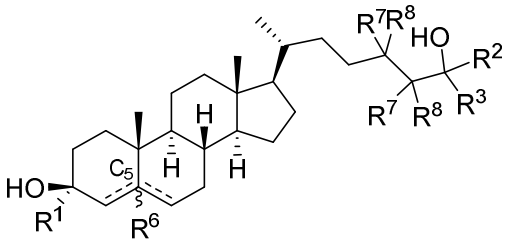
40. The compound of claim 33, wherein the compound is:




,

or a pharmaceutically acceptable salt thereof.

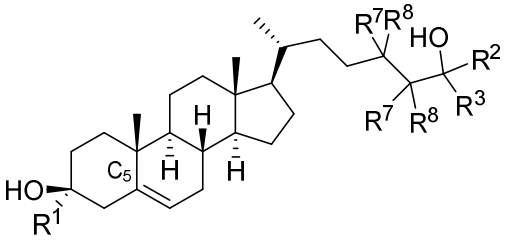
41. The compound of claim 1, wherein the compound Formula (I) is a compound of Formula (V):




(V)

or a pharmaceutically acceptable salt thereof.

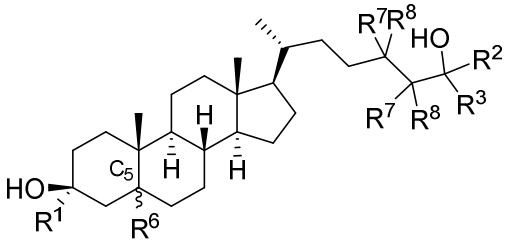
42. The compound of claim 17, wherein the compound of Formula (I) is a compound of Formula (V-A):



(V-A),

or a pharmaceutically acceptable salt thereof.

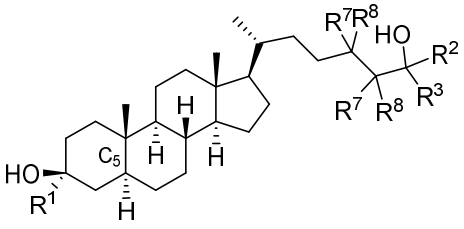
43. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (V-B):



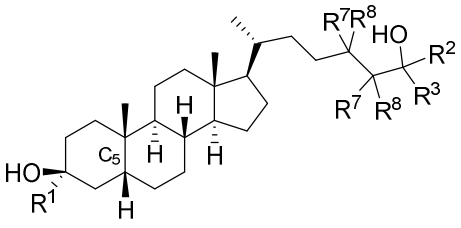
(V-B),

or a pharmaceutically acceptable salt thereof.

44. The compound of claim 21, wherein the compound of Formula (III) is a compound of Formula (V-C) or Formula (V-D):



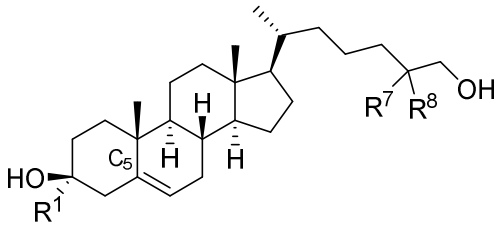
(V-C) or



(V-D),

or a pharmaceutically acceptable salt thereof.

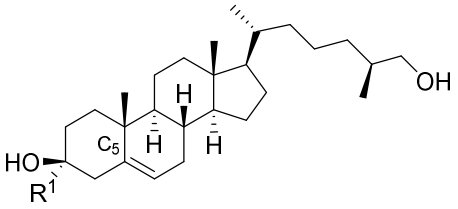
45. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (V-E-i):

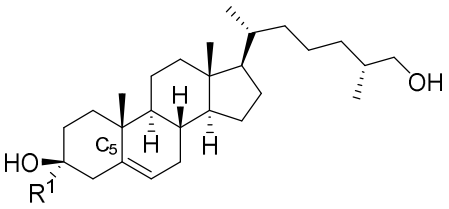


(V-E-i),

or a pharmaceutically acceptable salt thereof.

46. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (V-E-ii) or (V-E-iii):

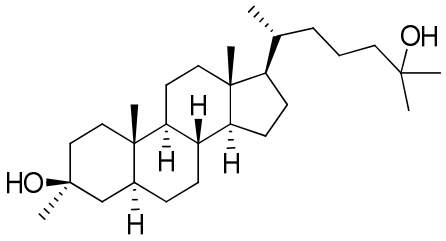


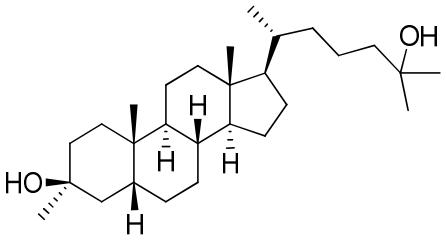
(V-E-ii) or


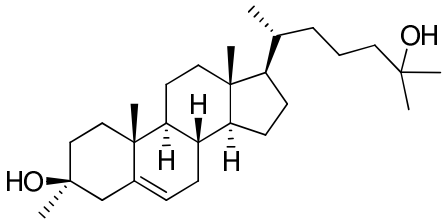
(V-E-iii)

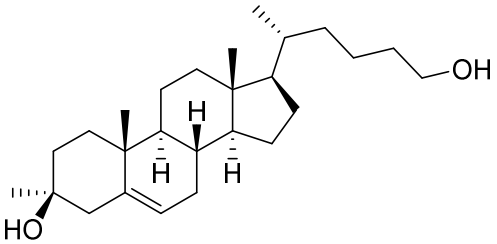
or a pharmaceutically acceptable salt thereof.

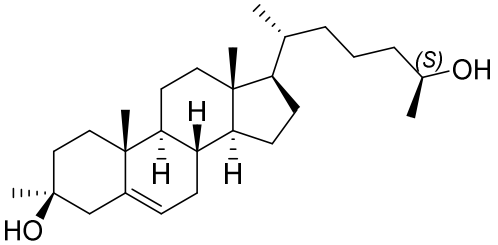
47. The compound of claim 1, wherein the compound is selected from:

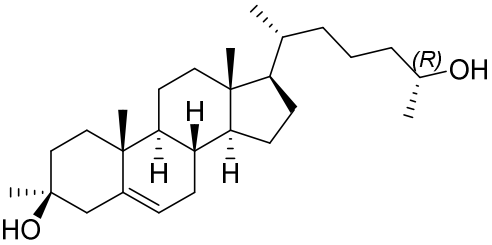


,


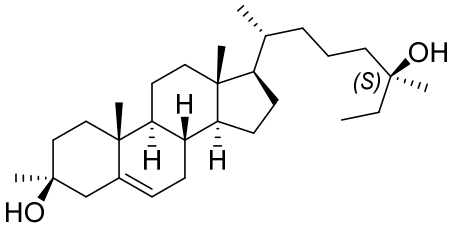
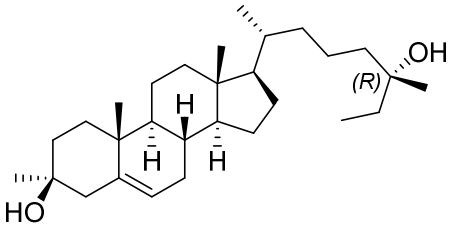
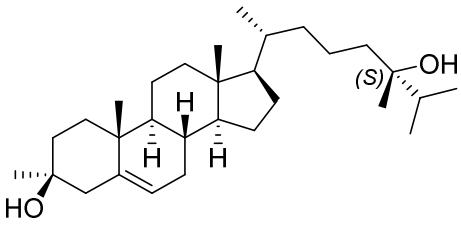
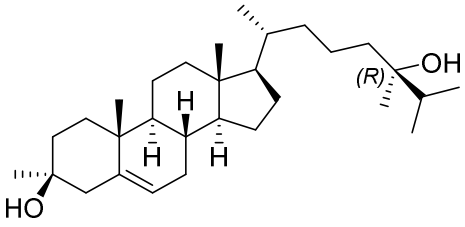
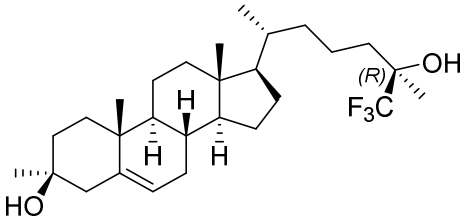
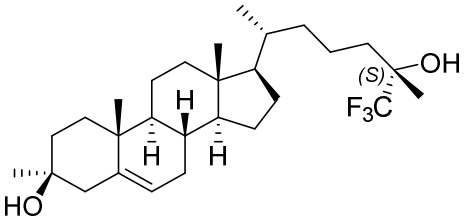
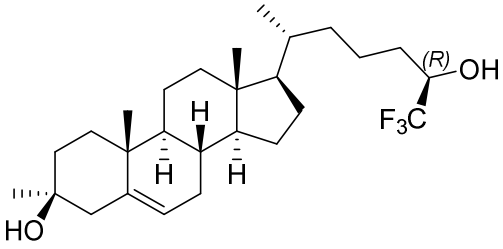
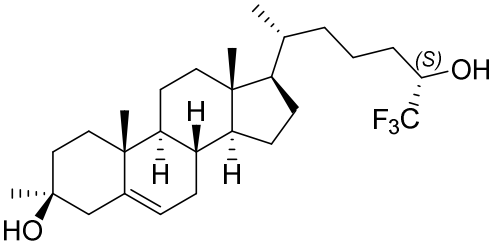
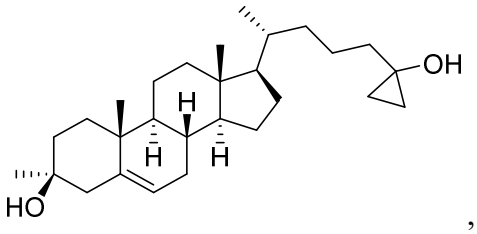
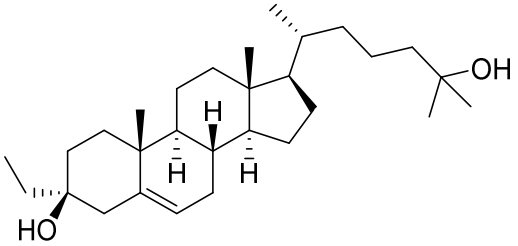
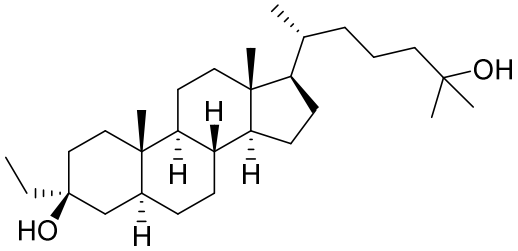
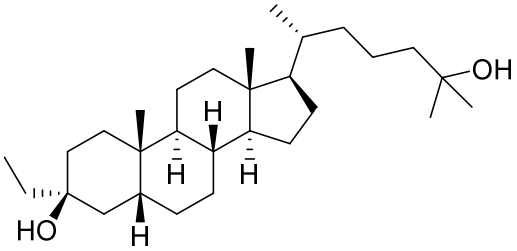
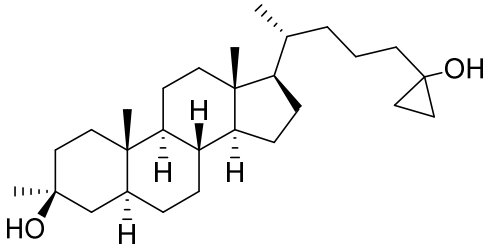
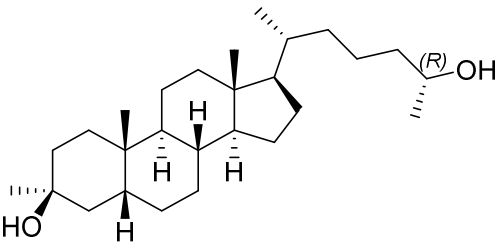
,


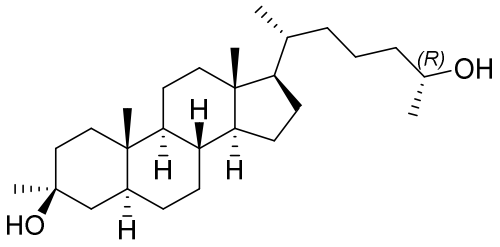
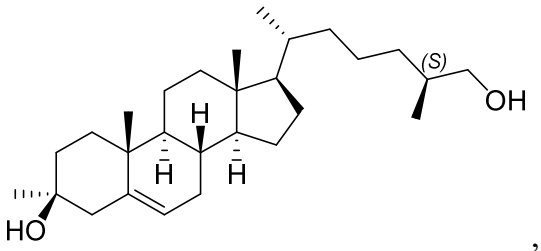
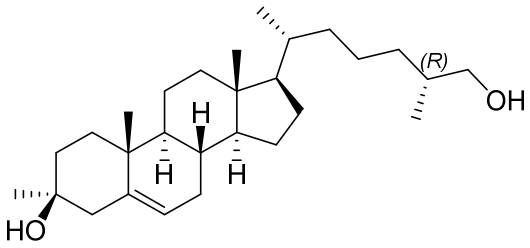
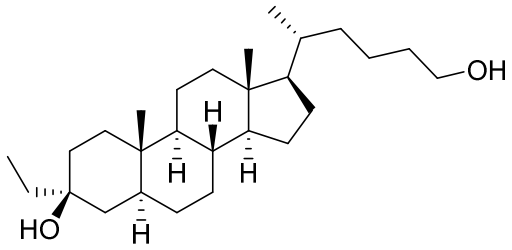
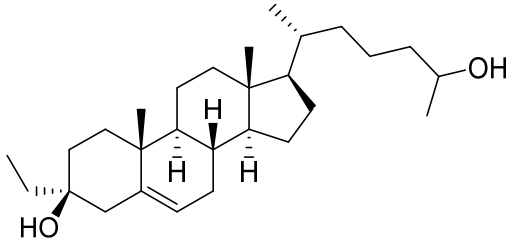
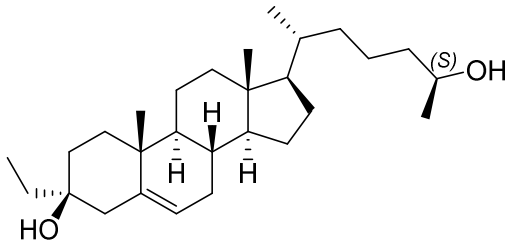
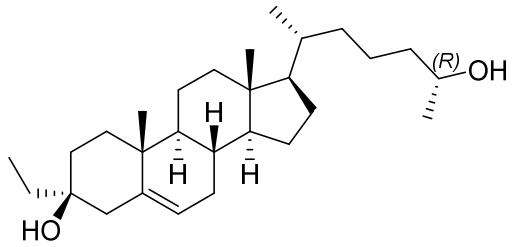
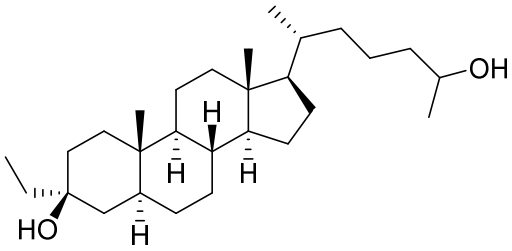
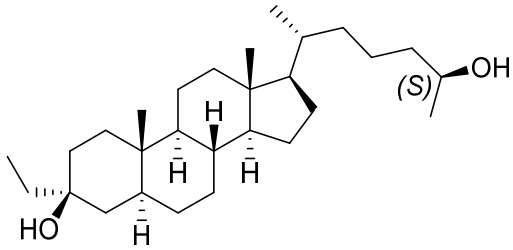
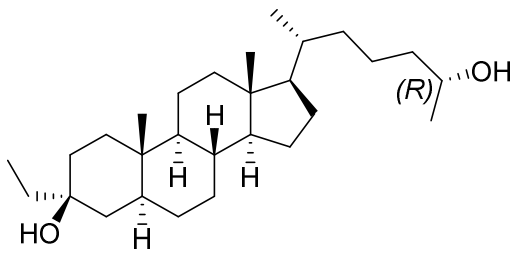
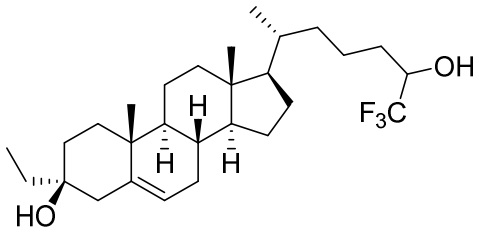
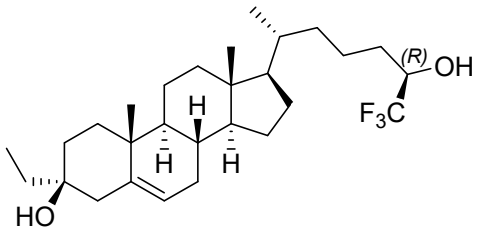
,


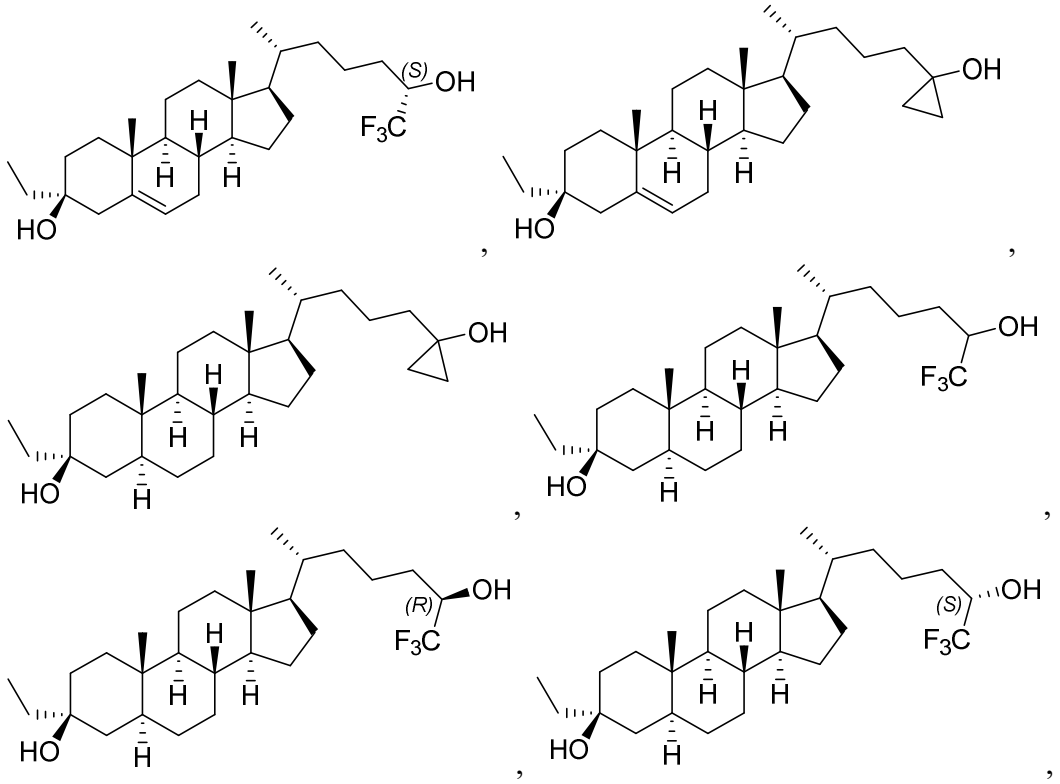
,


,


,


OH
(S)
H
H
H
HO
,

OH
(R)
H
H
H
HO
,

OH
(S)
H
H
H
HO
,

OH
(R)
H
H
H
HO
,

OH
(R)
F3C
H
H
H
HO
,

OH
(S)
F3C
H
H
H
HO
,

OH
(R)
F3C
H
H
H
HO
,

OH
(S)
F3C
H
H
H
HO
,

OH
H
H
H
HO
,

OH
H
H
H
HO
,

OH
H
H
H
HO
,

OH
H
H
H
HO
,

OH
H
H
H
HO
,

(R)
OH
H
H
H
HO
,


(R)
OH
H
H
H
HO
H
,

(S)
OH
H
H
H
HO
,

(R)
OH
H
H
H
HO
,

OH
H
H
H
HO
H
,

OH
H
H
H
HO
,

(S)
OH
H
H
H
HO
,

(R)
OH
H
H
H
HO
,

OH
H
H
H
HO
H
,

(S)
OH
H
H
H
HO
H
,

(R)
OH
H
H
H
HO
H
,

OH
F3C
H
H
H
HO
,

(R)
OH
F3C
H
H
H
HO
,



or a pharmaceutically acceptable salt thereof.

48. A pharmaceutical composition comprising a compound of claim 1, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

49. Use of a compound of claim 1, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof in the manufacture of a medicament for inducing sedation or anesthesia.

50. Use of a compound of claim 1, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof in the manufacture of a medicament for treating or preventing a disorder described herein.

51. The use according to claim 50, wherein 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.

52. The use according to claim 50, wherein the disorder is inflammatory bowel disease.

53. The use according to claim 50, wherein the disorder is cancer, diabetes, or a sterol synthesis disorder.

54. The use according to claim 50, wherein the disorder is a metabolic disorder.

55. Use of a compound of claim 1, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof in the manufacture of a medicament for treating or preventing a CNS-related condition.

56. The use according to claim 55, wherein 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.

57. The use according to claim 55, wherein the disorder is sterol synthesis disorder.

58. A compound of claim 1, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof for use in therapy.