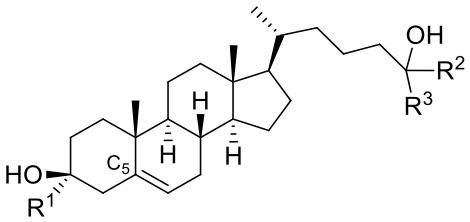
oral bioavailability, formulatability, stability, and/or safety as compared to other oxysterols. Further provided are pharmaceutical compositions comprising the compounds of the present disclosure, and methods of their use and treatment.

[0003a] In one aspect, there is provided a compound of Formula (IV):



(IV),

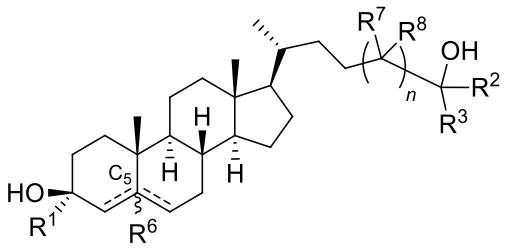
or a pharmaceutically acceptable salt thereof, wherein:

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

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

R^2 and R^3, together with the carbon atom to which they are attached, form a substituted or unsubstituted 3-8 membered ring.

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



(I)

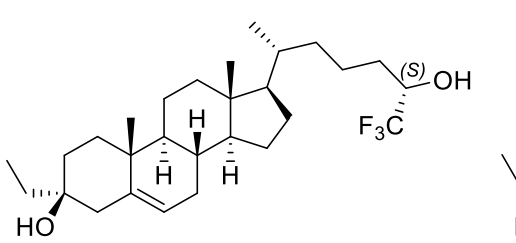
or a pharmaceutically acceptable salt thereof, wherein: R^1 is C_{1-6} alkyl; each of R^2 and R^3 is independently hydrogen, C_{1-6} alkyl, or carbocyclyl; or R^2 and R^3, together with the carbon atom to which they are attached, form a 3-8 membered ring; R^6 is absent or hydrogen; each of R^7 and R^8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



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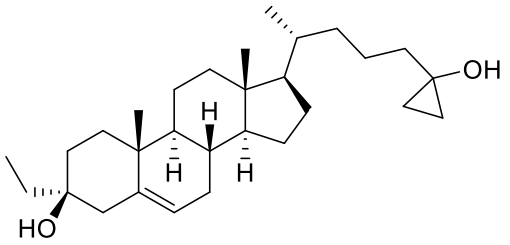

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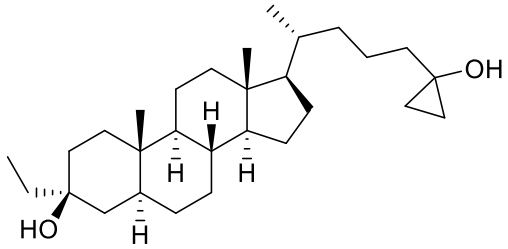

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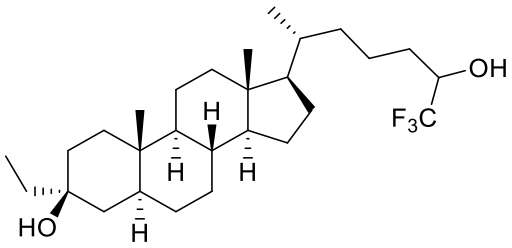

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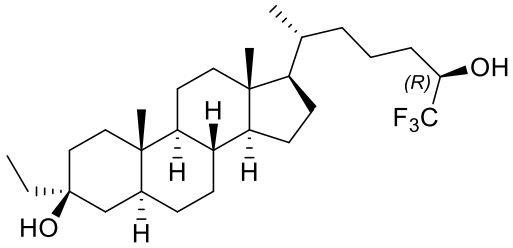

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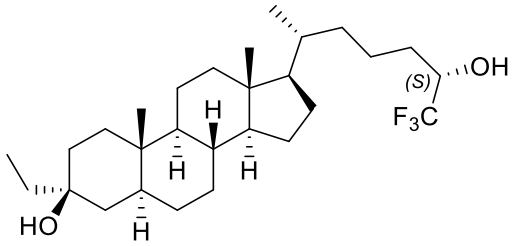


,
or a pharmaceutically acceptable salt thereof.

[0050] In another example, 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 pharmaceutical composition comprising the compound, or the pharmaceutically acceptable salt, described herein, and a pharmaceutically acceptable carrier.

[0050b] In another aspect, provided herein is a use of the compound, or pharmaceutically acceptable salt, described herein, or pharmaceutical composition described herein 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 the compound described herein, or pharmaceutically acceptable salt thereof, or pharmaceutical composition described herein in the manufacture of a medicament for treating or preventing a disorder selected from the group consisting of a gastrointestinal (GI) disorder, structural disorders affecting the GI, anal disorders,

colon polyps, cancer, diabetes, a sterol synthesis disorder, a metabolic disorder and colitis.

[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 the compound, or pharmaceutically acceptable salt, described herein, or pharmaceutical composition described herein in the manufacture of a medicament for treating or preventing a CNS-related condition.

[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.

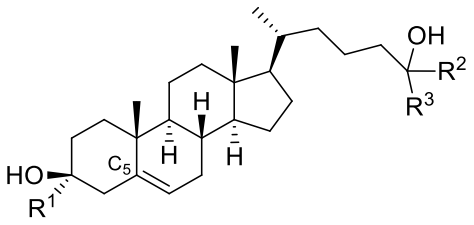
[0060] In some examples, the disorder is Smith-Lemli-Opitz Syndrome (SLOS). In some examples, the disorder is desmosterolosis. In some examples, the disorder is sitosterolemia. In some examples, the disorder is cerebrotendinous xanthomatosis (CTX). In some examples, the

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

Claims

What is claimed is:

1. A compound of Formula (IV):



(IV),

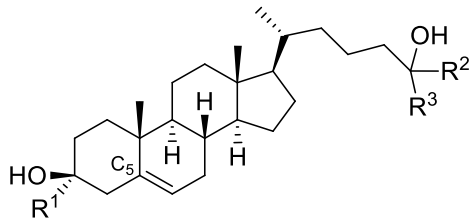
or a pharmaceutically acceptable salt thereof, wherein:

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

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

R^2 and R^3, together with the carbon atom to which they are attached, form a substituted or unsubstituted 3-8 membered ring.

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



(IV).

3. The compound, or the pharmaceutically acceptable salt, of claim 1 or 2, wherein R^1 is methyl, $-CHF_2$, $-CF_3$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, ethyl, or isopropyl.

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

5. The compound, or the pharmaceutically acceptable salt, of claim 4, wherein each of R^2 and R^3 is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted carbocyclyl.

6. The compound, or the pharmaceutically acceptable salt, of claim 5, wherein each of R^2 and R^3 is independently hydrogen, methyl, -CF_3, ethyl, CH_2CF_3, propyl, isopropyl, cyclopropyl, or butyl.

7. The compound, or the pharmaceutically acceptable salt, of claim 6, wherein R^2 is hydrogen, methyl, -CF_3, or ethyl.

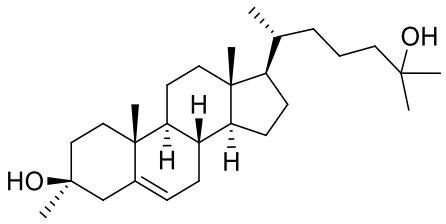
8. The compound, or the pharmaceutically acceptable salt, of claim 5, wherein R^3 is methyl, -CF_3, ethyl, -CH_2CF_3, propyl, isopropyl, cyclopropyl, butyl.

9. The compound, or the pharmaceutically acceptable salt, of claim 1 or 2, wherein R^2 is hydrogen and R^3 is methyl, -CF_3, ethyl, -CH_2CF_3, propyl, isopropyl, or butyl.

10. The compound, or the pharmaceutically acceptable salt, of claim 1 or 2, wherein each of R^2 and R^3 is independently methyl, -CF_3, ethyl, -CH_2CF_3, propyl, isopropyl, cyclopropyl, or butyl.

11. The compound, or the pharmaceutically acceptable salt, of claim 1 or 2, wherein R^2 and R^3, together with the carbon atom to which they are attached, form an unsubstituted cyclopropyl ring.

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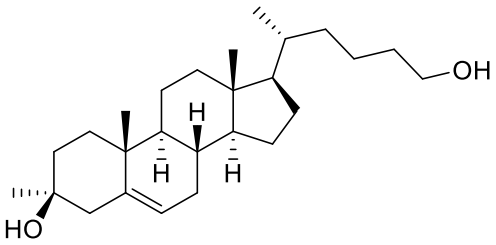
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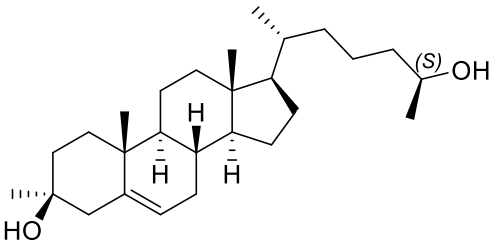
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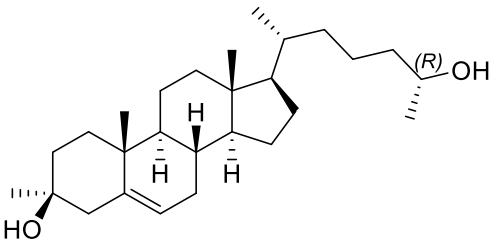
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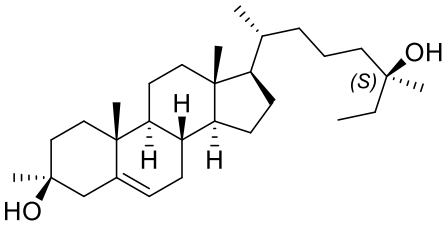
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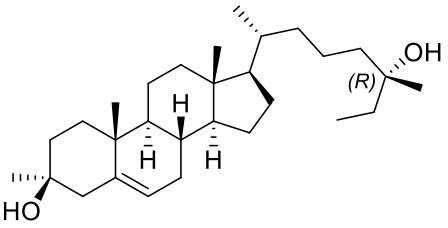
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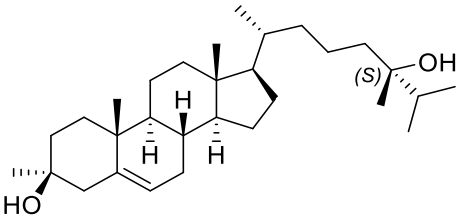
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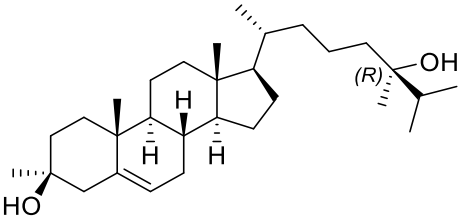
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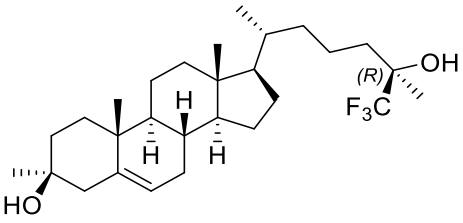
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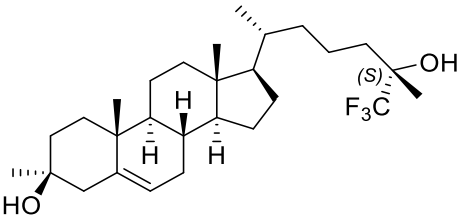
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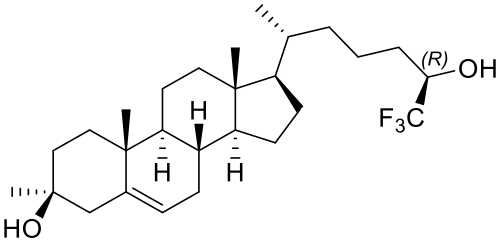
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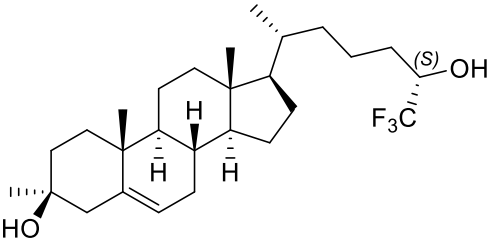
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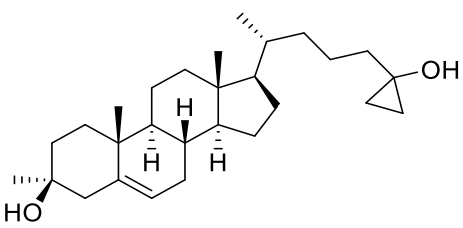
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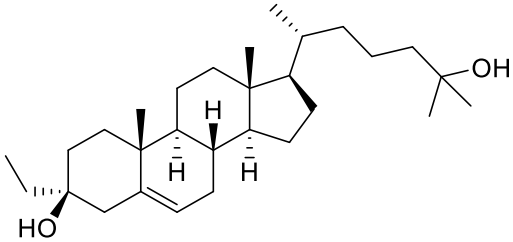
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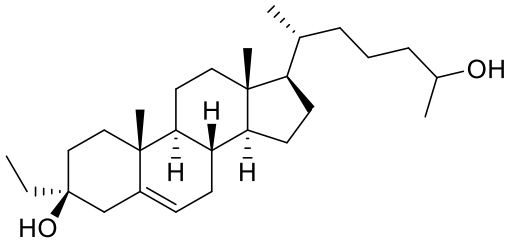

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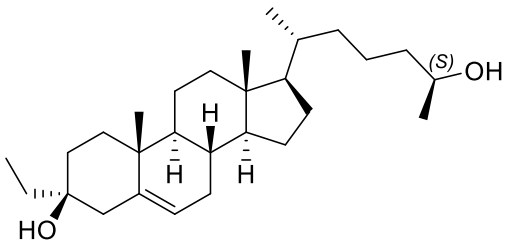

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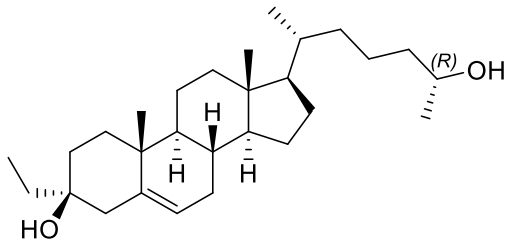

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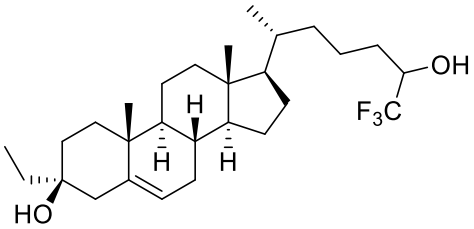

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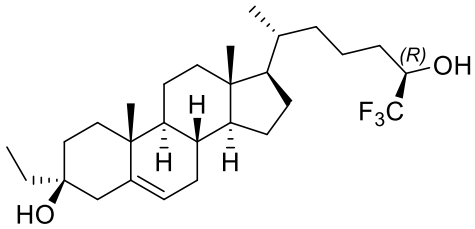

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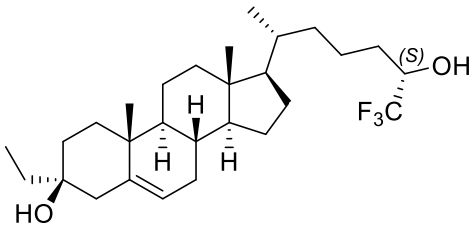

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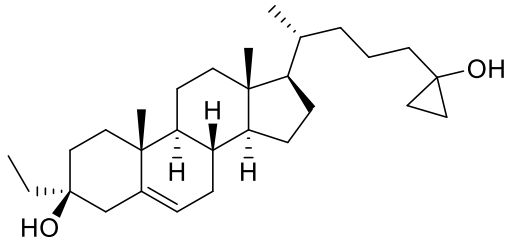

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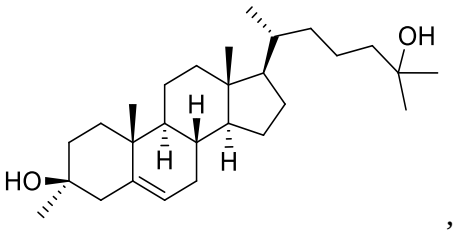
or a pharmaceutically acceptable salt thereof.

13. The compound of claim 12, wherein the compound is selected from the group consisting of: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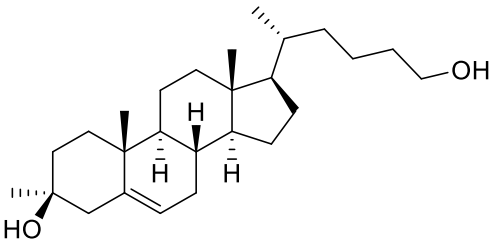
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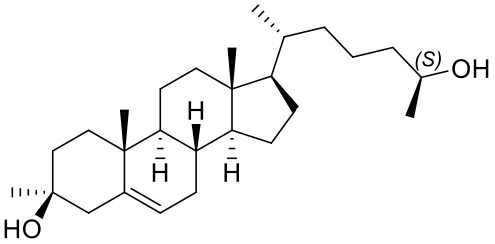
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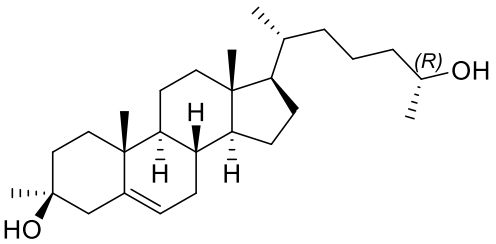
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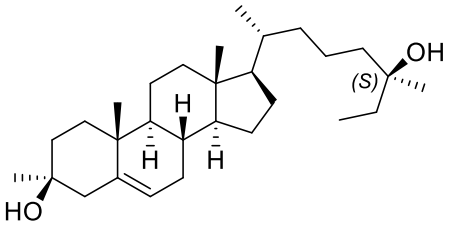
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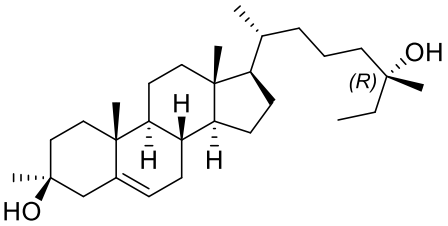
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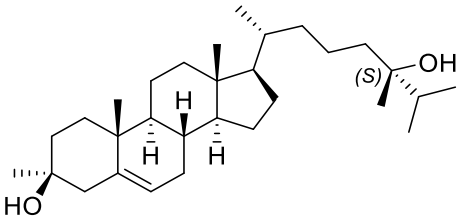
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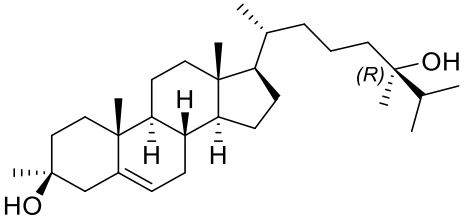
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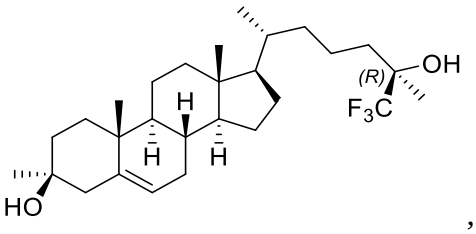
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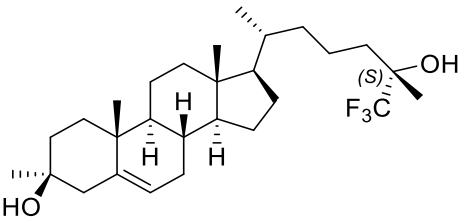
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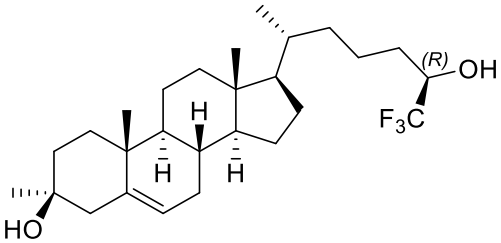
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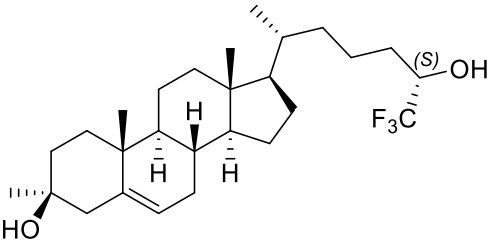
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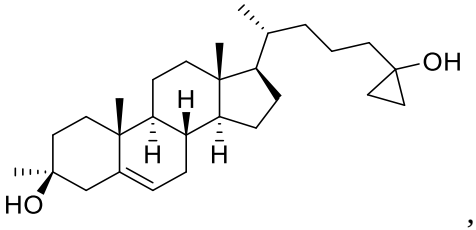
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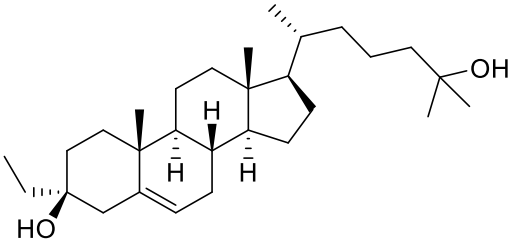
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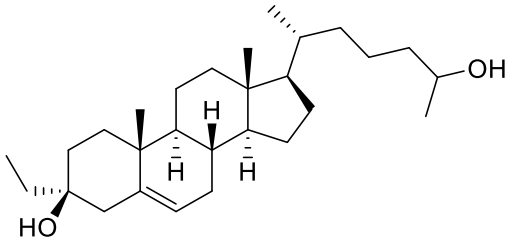
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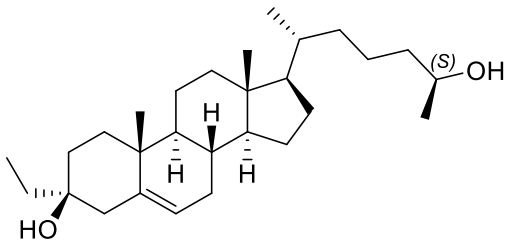
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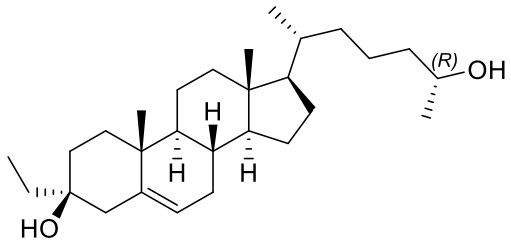
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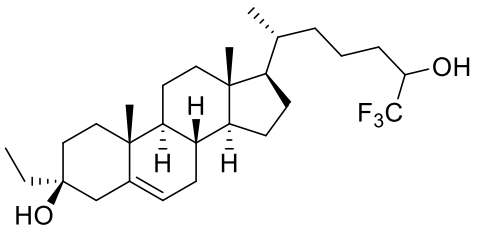
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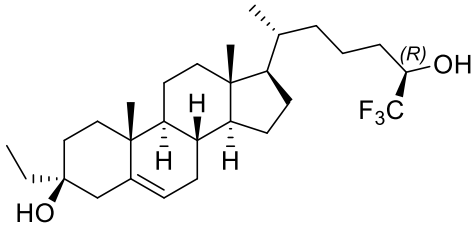
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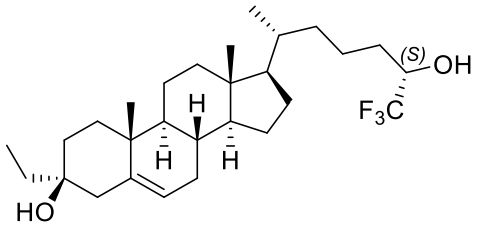
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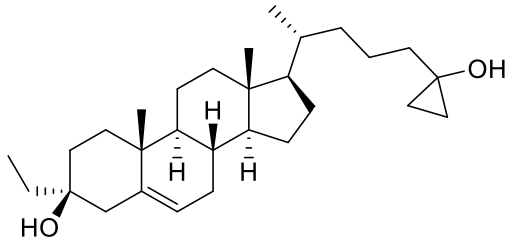
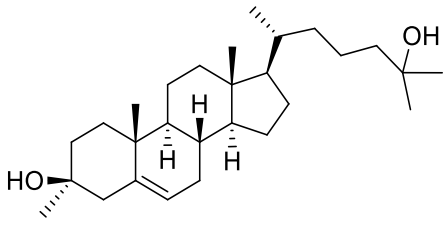

.

14. The compound of claim 12, wherein the compound is selected from the group consisting of: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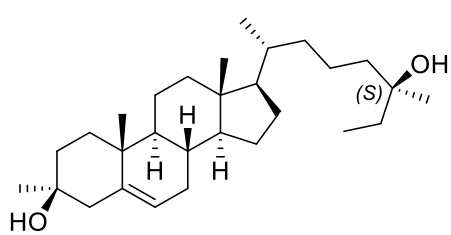
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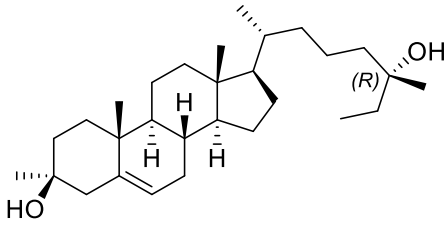
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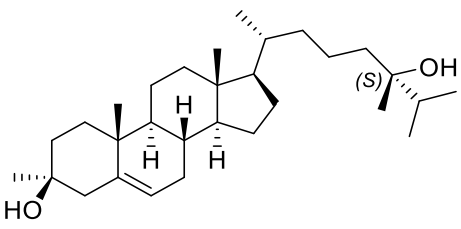
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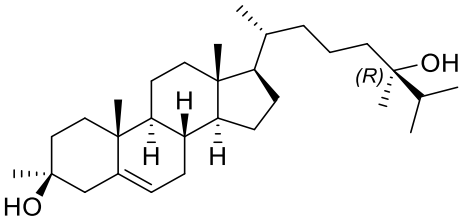

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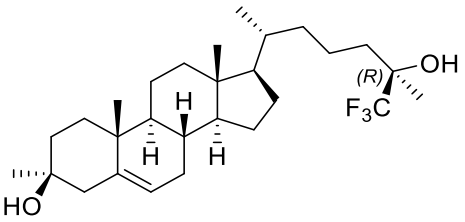

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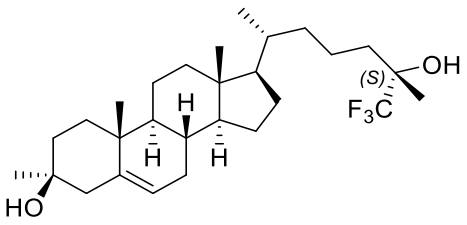

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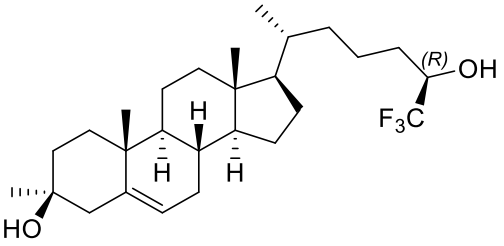

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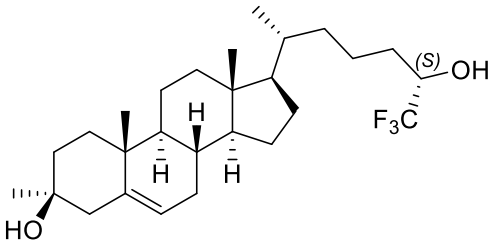

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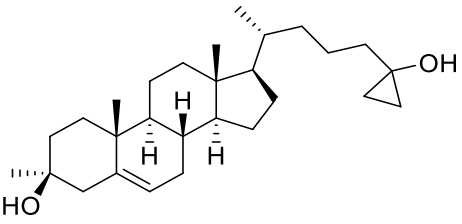
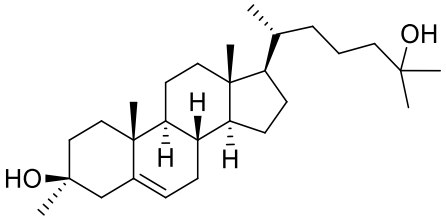


, or a pharmaceutically acceptable salt thereof.

15. The compound of claim 14, wherein the compound is selected from the group consisting of:



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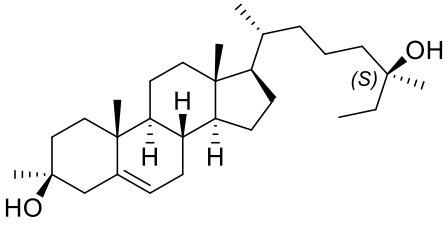

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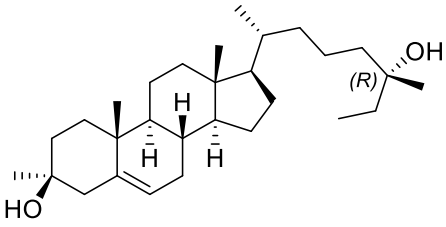

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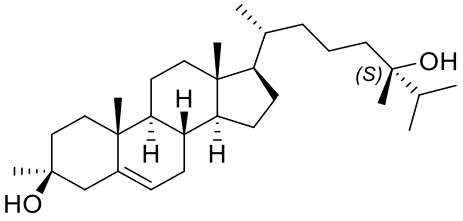

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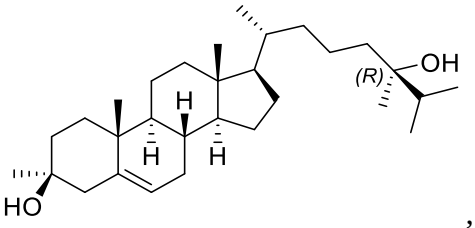

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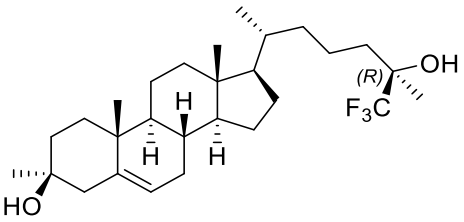

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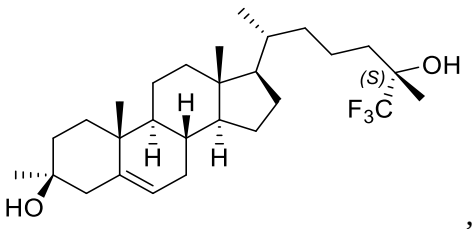

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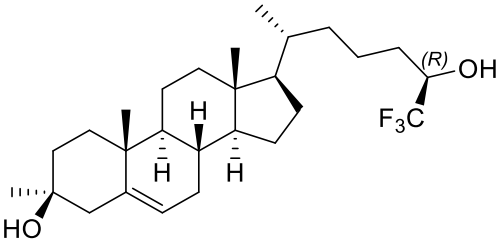

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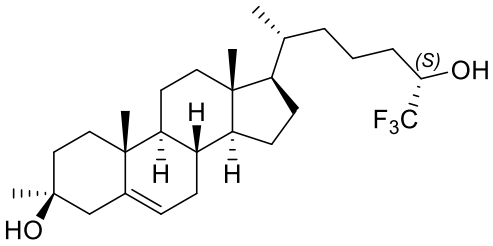

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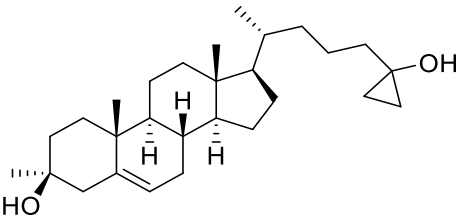
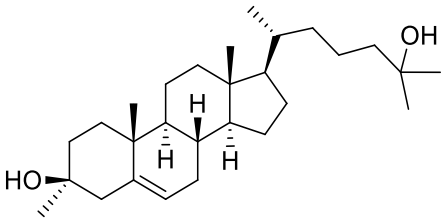


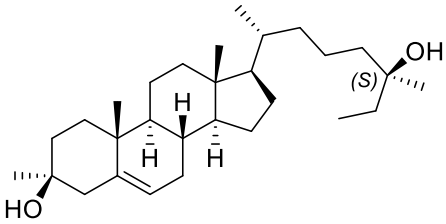
.

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



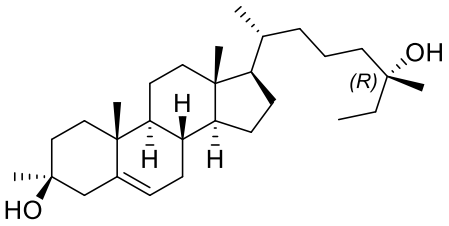
.

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



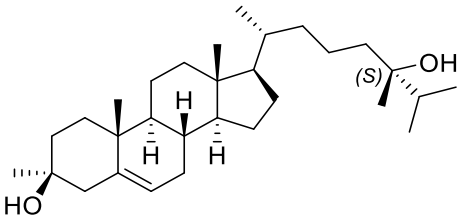
.

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



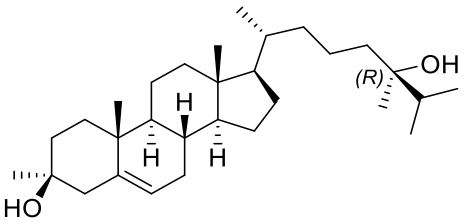
.

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



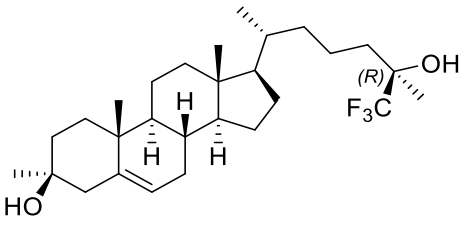
.

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



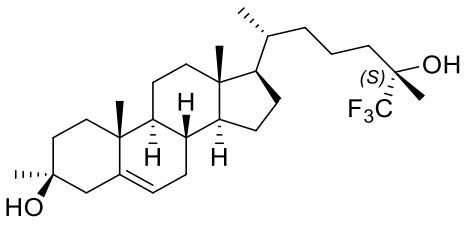
.

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



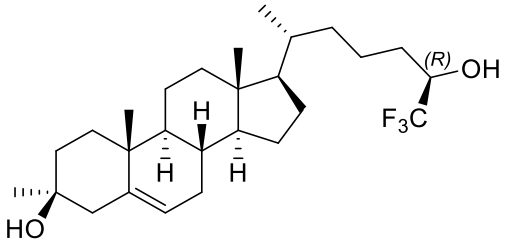
.

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



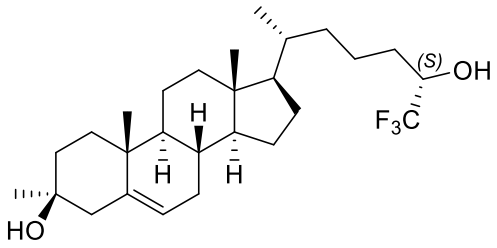
.

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



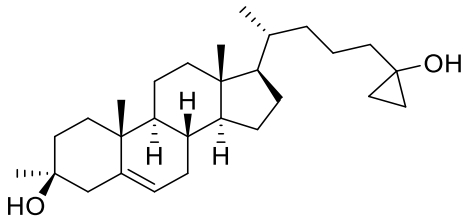
.

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



.

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



.

26. A pharmaceutical composition comprising the compound, or the pharmaceutically acceptable salt, of any one of claims 1-25, and a pharmaceutically acceptable carrier.

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

28. Use of the compound of any one of claims 1-25, or pharmaceutically acceptable salt thereof, or pharmaceutical composition of claim 26 in the manufacture of a medicament for treating or preventing a disorder selected from the group consisting of a gastrointestinal (GI)

disorder, structural disorders affecting the GI, anal disorders, colon polyps, cancer, diabetes, a sterol synthesis disorder, a metabolic disorder and colitis.

29. The use according to claim 28, wherein the GI disorder is selcected from the group consisting of constipation, irritable blowel syndrome (IBS), and inflammatory bowel disease (IBD).

30. The use according to claim 29, wherein the GI disorder is inflammatory bowel disease.

31. The use according to claim 28, wherein the anal disorder is selected from the group consisting of hemorrhoids, internal hemorrhoids, external hemorrhoids, anal fissures, perianal abscesses, and anal fistula.

32. The use according to claim 28, wherein the disorder is cancer, diabetes, or a sterol synthesis disorder.

33. The use according to claim 28, wherein the disorder is a metabolic disorder.

34. Use of the compound, or the pharmaceutically acceptable salt, of any one of claim 1-25, or pharmaceutical composition of claim 26 in the manufacture of a medicament for treating or preventing a CNS-related condition.

35. The use according to claim 34, wherein the CNS-related condition is an adjustment disorder, anxiety disorder, cognitive disorder, dissociative disorder, eating disorder, mood disorder, schizophrenia or other psychotic disorder, sleep disorder, substance-related disorder, personality disorder, autism spectrum disorders, a neurodevelopmental disorder, multiple sclerosis, a sterol synthesis disorder, pain, an encephalopathy secondary to a medical condition, seizure disorder, stroke, traumatic brain injury, movement disorder, vision impairment, hearing loss, and tinnitus.

36. The use according to claim 35, wherein the CNS-related condition is sterol synthesis disorder.

37. The use according to claim 35, wherein the CNS-related condition is a psychotic disorder, wherein the psychotic disorder is schizophrenia.

38. The use according to claim 35, wherein the CNS-related condition is an autism spectrum disorder.

39. The use according to claim 35, wherein the CNS-related condition is Huntington's disease or Parkinson's disease.

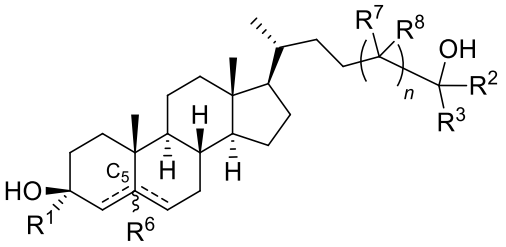
40. The use according to claim 35, wherein the CNS-related condition is Alzheimer's disease.

41. The use according to claim 35, wherein the CNS-related condition is an encephalopathy secondary to a medical condition, wherein the encephalopathy secondary to a medical condition is anti-NMDA receptor encephalitis.

OXYSTEROLS AND METHODS OF USE THEREOF

Abstract

Compounds are provided according to Formula (I):



(I)

and pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof; wherein R^1, R^2, R^3, R^6, R^7, R^8, and *n* are as defined herein. Compounds of the present invention are contemplated useful for the prevention and treatment of a variety of conditions.

[No Suitable Figure]