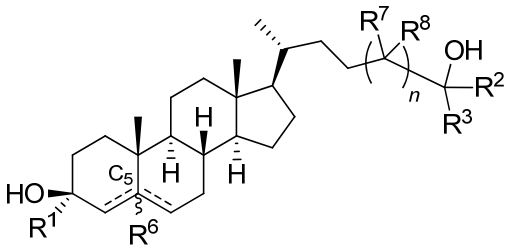
oral bioavailability, formulatability, stability, and/or safety as compared to other oxysterols. Further provided are pharmaceutical compositions comprising the compounds of the present disclosure, and methods of their use and treatment.

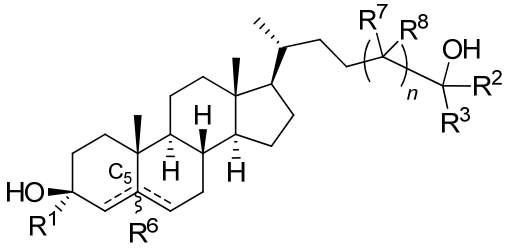
[0004] Provided herein are compounds according to Formula (I):



(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.

[0004a] In one aspect of the present disclosure, there is provided a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

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

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;

R^6 is absent or hydrogen;

each of R^7 and R^8 is independently hydrogen, halogen, substituted or unsubstituted 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 substituted or unsubstituted 3-8 membered ring; or

R^2 and R^7, together with the carbon atoms to which they are attached, form a substituted or unsubstituted 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 embodiments, R^1 is substituted C_{1-6} alkyl. In some embodiments, R^1 is unsubstituted C_{1-6} alkyl. In some embodiments, 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 embodiments, R^1 is $-CH_3$. In some embodiments, R^1 is ethyl.

[0006] In some embodiments, 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 embodiments, the 3-8 membered ring is a carbocyclyl ring (e.g., cyclopropyl). In some embodiments, each of R^2 and R^3 is independently hydrogen, C_{1-6} alkyl, or carbocyclyl. In some embodiments, 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 embodiments, R^2 substituted C_{1-6} alkyl. In some embodiments, R^2 unsubstituted C_{1-6} alkyl.

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

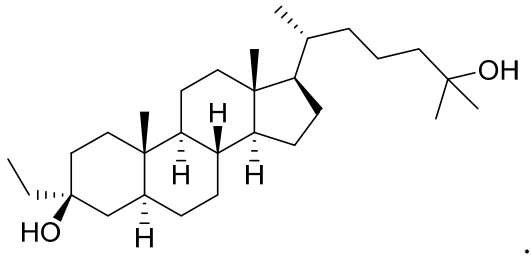
[0052a] In an aspect, provided herein is a use of a compound described herein, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, in the manufacture of a medicament for treating or preventing a disorder selected from the group consisting of a gastrointestinal (GI) disorder, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), structural disorders affecting the GI, anal disorders, colon polyps, cancer, colitis.

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

[0054] In some embodiments, 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.

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

[0060a] In another aspect, the present disclosure refers to a pharmaceutically acceptable salt of the compound of claim 1, wherein the compound is



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[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.

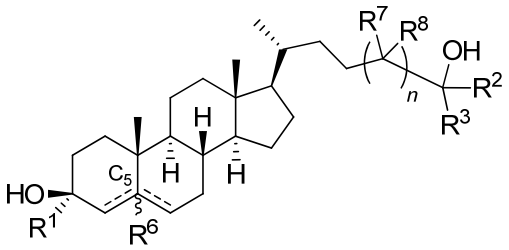
[0063] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be 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 substituted or unsubstituted C_{1-6} alkyl;

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;

R^6 is absent or hydrogen;

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

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

R^2 and R^7, together with the carbon atoms to which they are attached, form a substituted or unsubstituted 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, $-CHF_2$, $-CF_3$, $-CH_2OCH_3$, 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, 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.

6. The compound of claim 5, wherein the substituted or unsubstituted 3-8 membered ring is a substituted or unsubstituted carbocyclyl ring.

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

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

9. The compound of claim 7, wherein R^2 is hydrogen, $-CH_3$, $-CF_3$, or $-CH_2CH_3$.

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

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

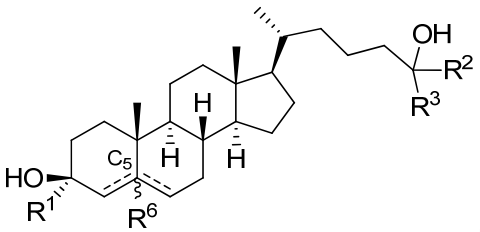
12. The compound of claim 7, wherein R^2 is substituted or unsubstituted C_{1-6} alkyl and R^3 is substituted or unsubstituted C_{1-6} alkyl.

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

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

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

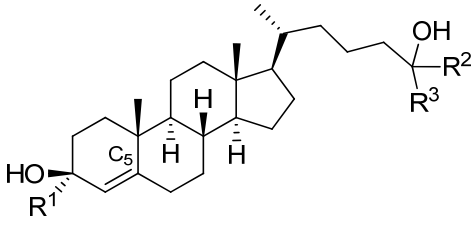
16. The compound of claim 1, wherein the compound Formula (I) is a compound of Formula (II):



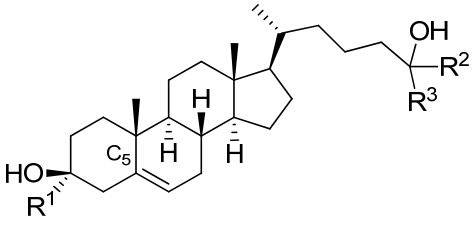
(II)

or a pharmaceutically acceptable salt thereof.

17. The compound of claim 16, wherein the compound of Formula (I) is a compound of Formula (II-A) or Formula (II-B):



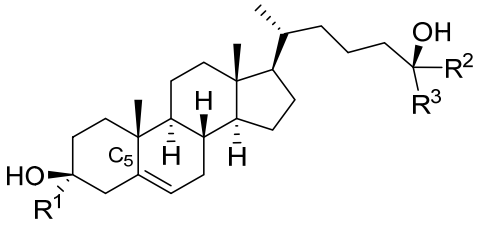
(II-A)



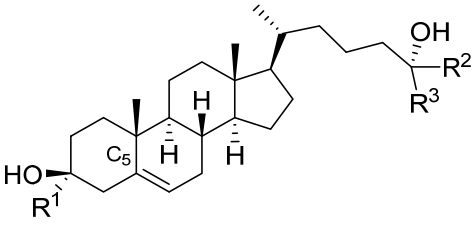
(II-B),

or a pharmaceutically acceptable salt thereof.

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



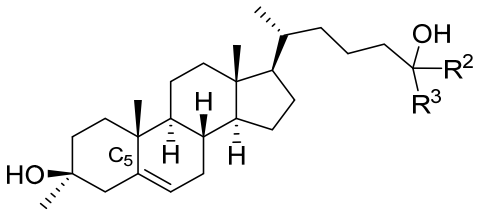
(II-B-i)



(II-B-ii),

or a pharmaceutically acceptable salt thereof.

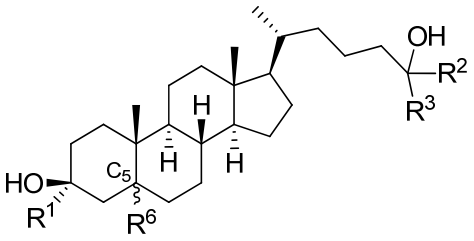
19. The compound of claim 17, wherein the compound of Formula (II-B) is a compound of Formula (II-B-iii):



(II-B-iii),

or a pharmaceutically acceptable salt thereof.

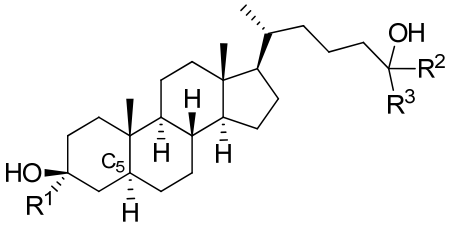
20. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (III):



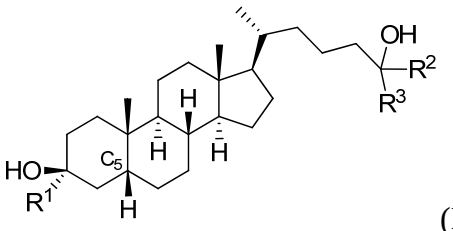
(III),

or a pharmaceutically acceptable salt thereof.

21. The compound of claim 20, wherein the compound of Formula (III) is a compound of Formula (III-A) or Formula (III-B):



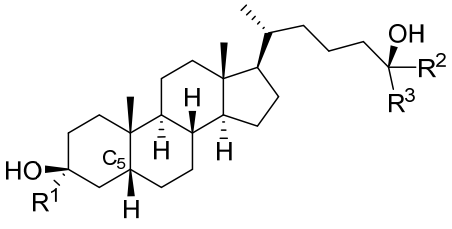
(III-A) or



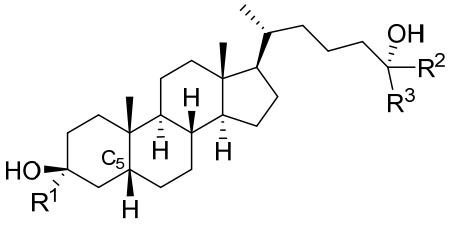
(III-B),

or a pharmaceutically acceptable salt thereof.

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



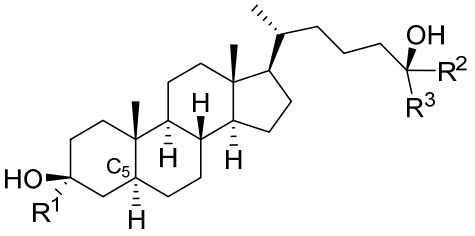
(III-C) or



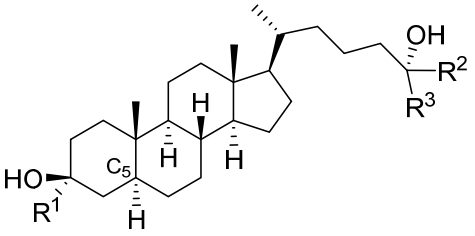
(III-D),

or a pharmaceutically acceptable salt thereof.

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



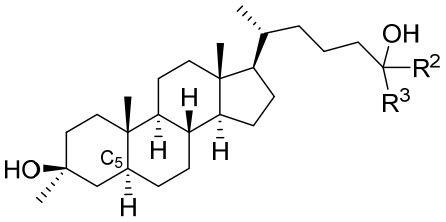
(III-E) or



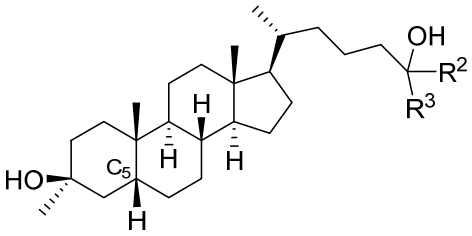
(III-F),

or a pharmaceutically acceptable salt thereof.

24. The compound of claim 20, 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.

25. The compound of claim 23, wherein R^1 is methyl, -CHF_2, -CF_3, -CH_2OCH_3, -$CH_2OCH_2CH_3$, ethyl, or isopropyl.

26. The compound of claim 20, 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 3-8 membered ring.

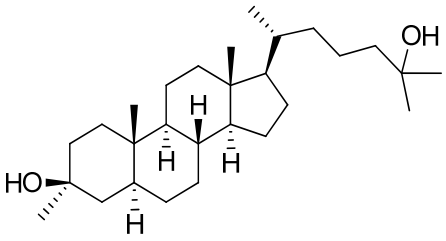
27. The compound of claim 26, wherein each of R^2 and R^3 is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted carbocyclyl.

28. The compound of claim 27, wherein each of R^2 and R^3 is independently hydrogen, -CH_3, -CF_3, -CH_2CH_3, CH_2CF_3, propyl, isopropyl, cyclopropyl, or butyl.

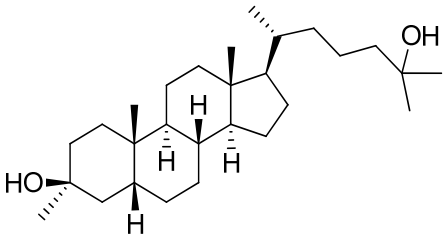
29. The compound of claim 28, wherein R^2 is hydrogen, -CH_3, -CF_3, or -CH_2CH_3.

30. The compound of claim 26, wherein R^3 is -CH_3, -CF_3, -CH_2CH_3, -CH_2CF_3, propyl, isopropyl, cyclopropyl, or butyl.

31. The compound of claim 20, wherein the compound is selected from the group consisting of:



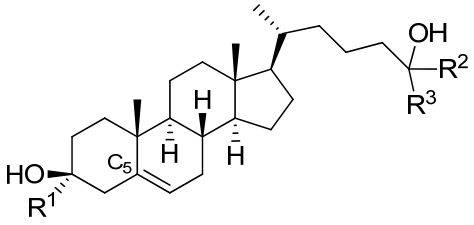
and



,

or a pharmaceutically acceptable salt thereof.

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



(IV),

or a pharmaceutically acceptable salt thereof.

33. The compound of claim 32, wherein R^1 is methyl, -CHF_2, -CF_3, -CH_2OCH_3, -$CH_2OCH_2CH_3$, ethyl, or isopropyl.

34. The compound of claim 32, 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.

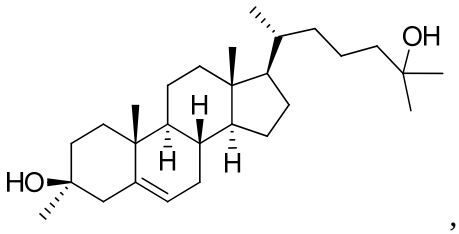
35. The compound of claim 34, wherein each of R^2 and R^3 is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted carbocyclyl.

36. The compound of claim 35, wherein each of R^2 and R^3 is independently hydrogen, $-CH_3$, $-CF_3$, $-CH_2CH_3$, CH_2CF_3, propyl, isopropyl, cyclopropyl, or butyl.

37. The compound of claim 36, wherein R^2 is hydrogen, $-CH_3$, $-CF_3$, or $-CH_2CH_3$.

38. The compound of claim 35, wherein R^3 is $-CH_3$, $-CF_3$, $-CH_2CH_3$, $-CH_2CF_3$, propyl, isopropyl, cyclopropyl, or butyl.

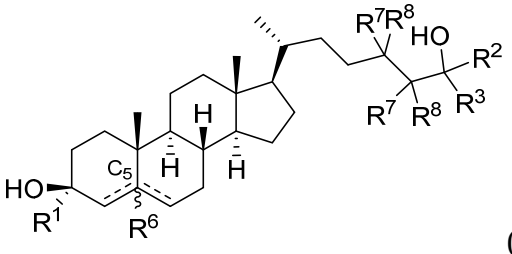
39. The compound of claim 32, wherein the compound is:



,

or a pharmaceutically acceptable salt thereof.

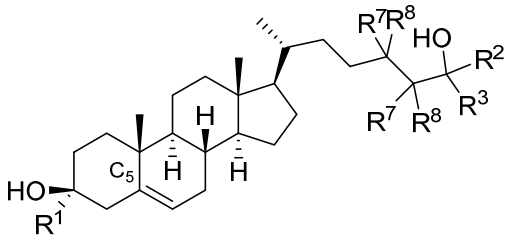
40. The compound of claim 1, wherein the compound Formula (I) is a compound of Formula (V):



(V),

or a pharmaceutically acceptable salt thereof.

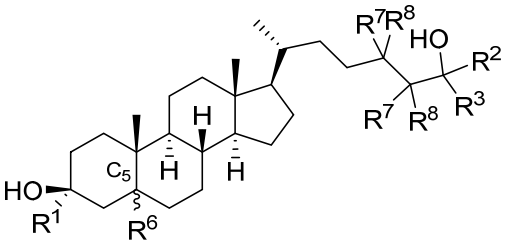
41. The compound of claim 40, wherein the compound of Formula (V) is a compound of Formula (V-A):



(V-A),

or a pharmaceutically acceptable salt thereof.

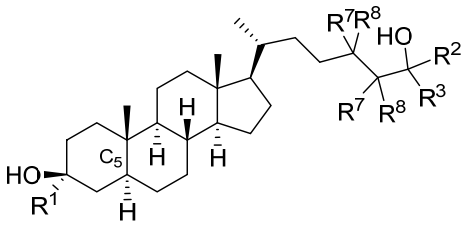
42. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (V-B):



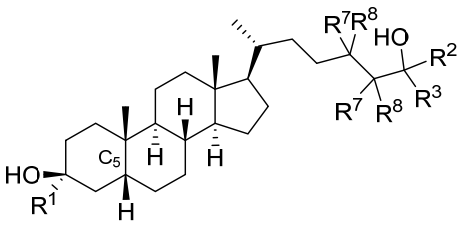
(V-B),

or a pharmaceutically acceptable salt thereof.

43. The compound of claim 42, wherein the compound of Formula (V-B) is a compound of Formula (V-C) or Formula (V-D):



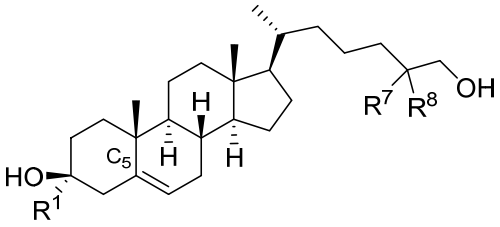
(V-C) or



(V-D),

or a pharmaceutically acceptable salt thereof.

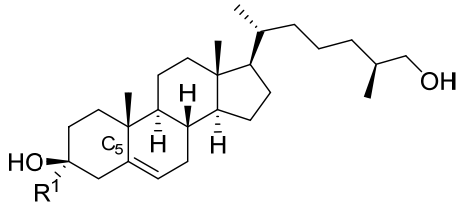
44. The compound of claim 1, wherein the compound of Formula (I) is a compound of Formula (V-E-i):



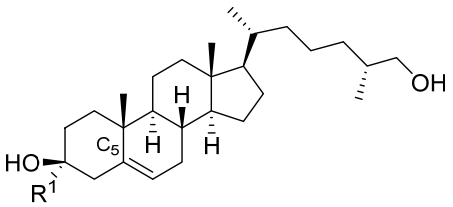
(V-E-i),

or a pharmaceutically acceptable salt thereof.

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



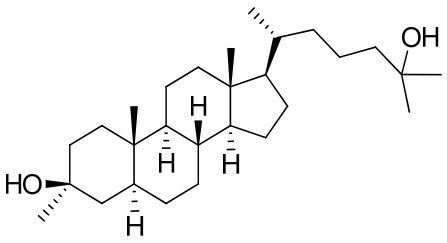
(V-E-ii) or



(V-E-iii)

or a pharmaceutically acceptable salt thereof.

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



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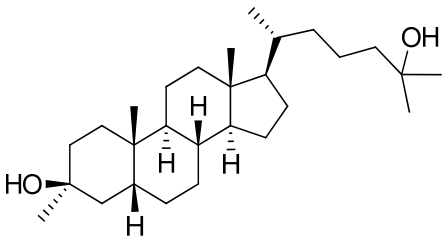

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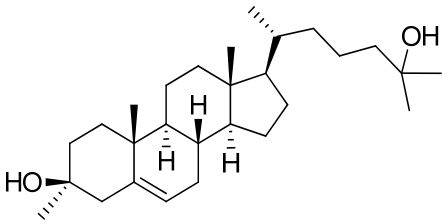

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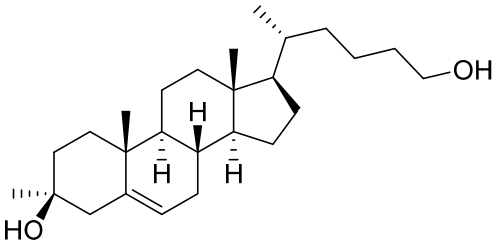

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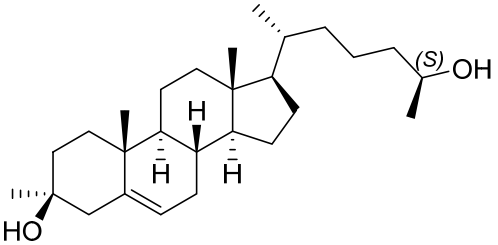

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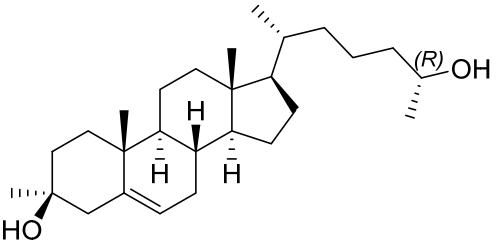

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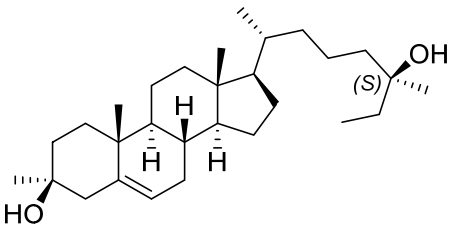
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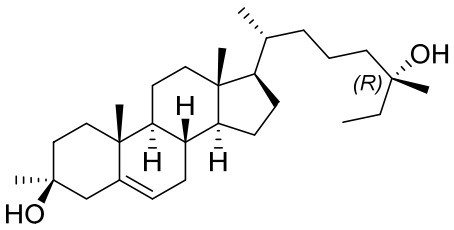
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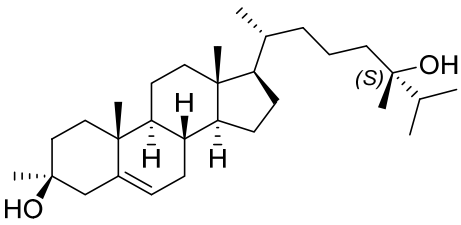
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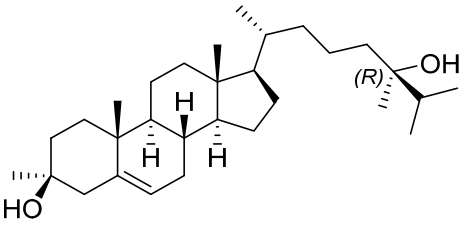
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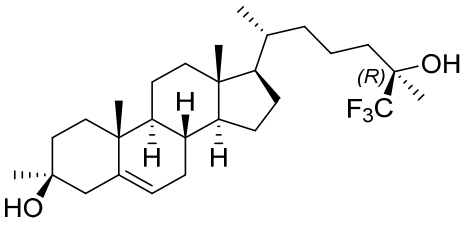
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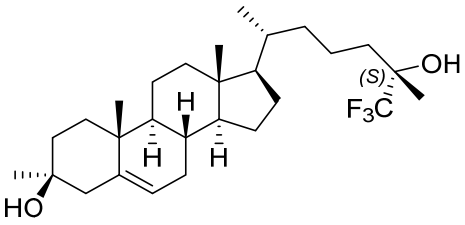
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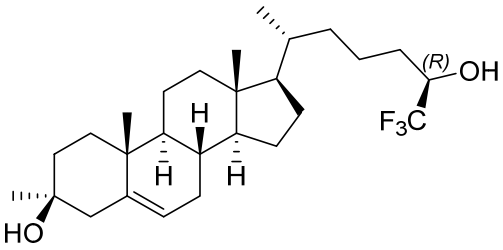
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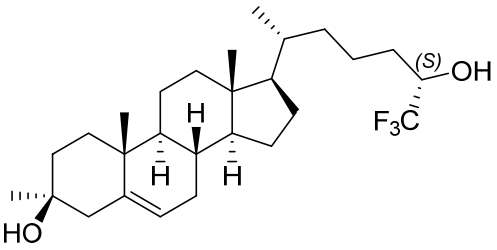
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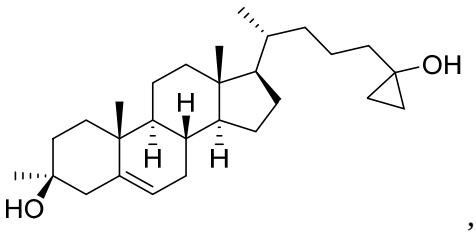
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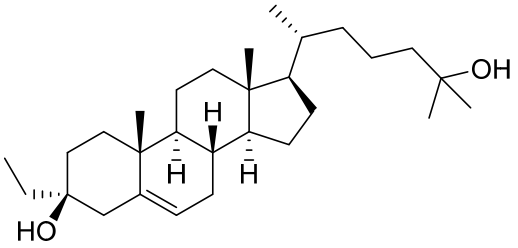
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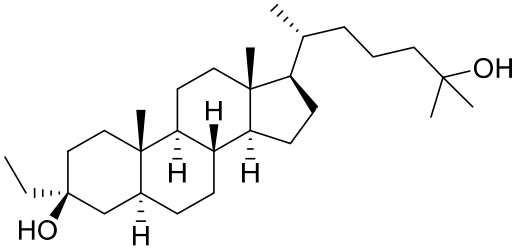
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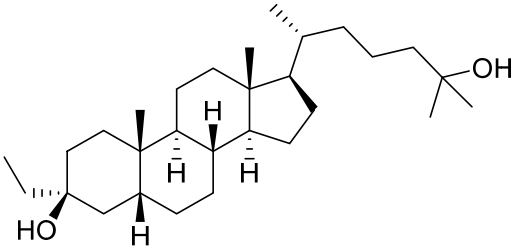
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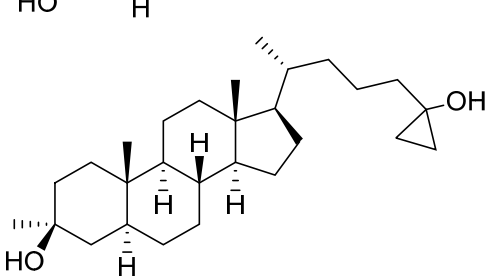
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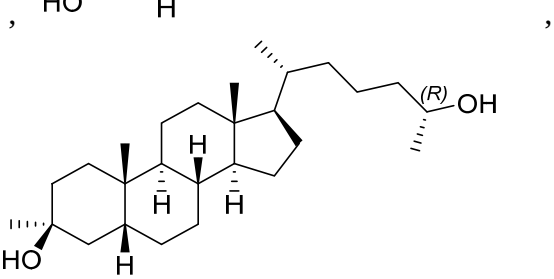
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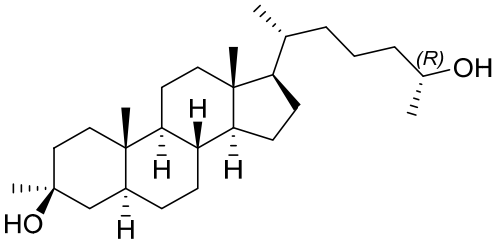
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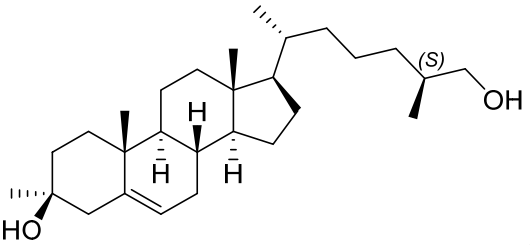
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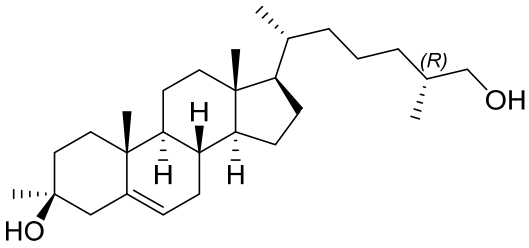
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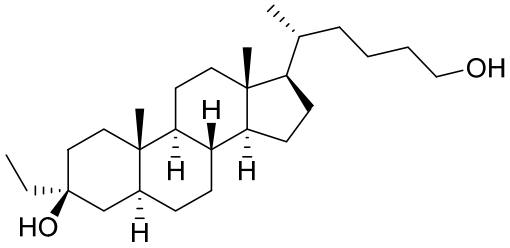
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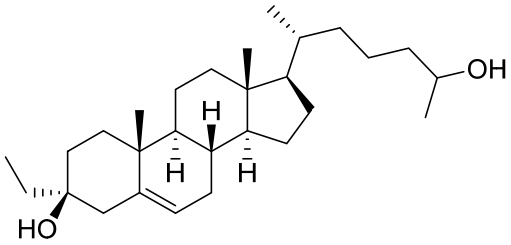
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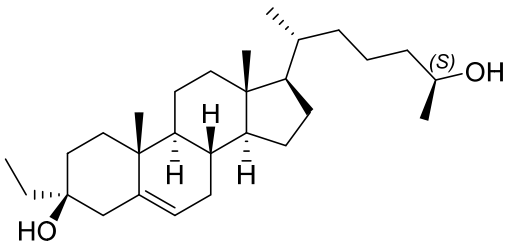
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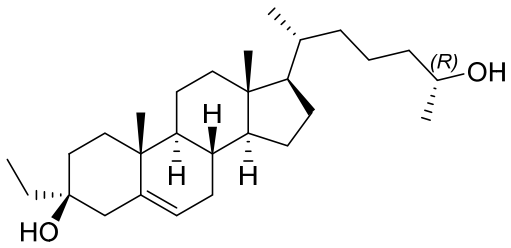
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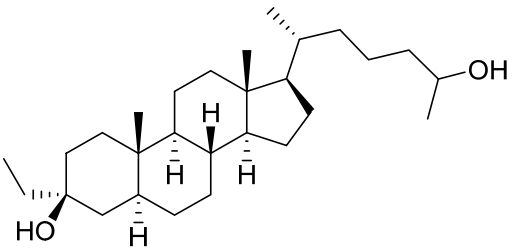
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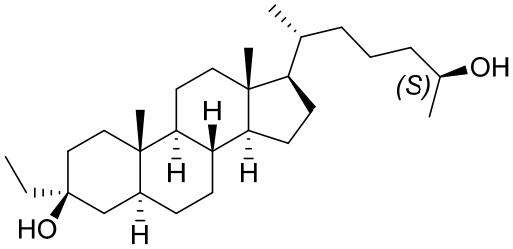
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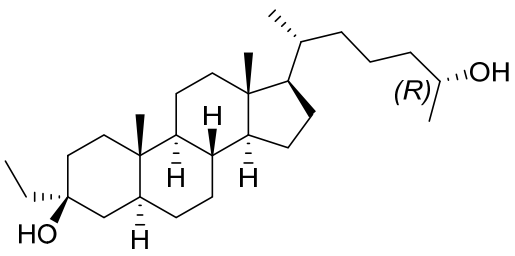
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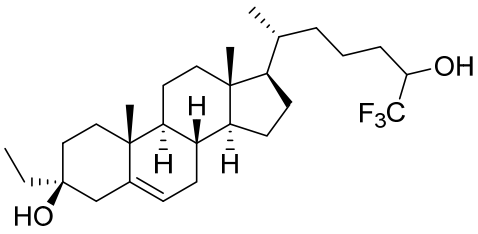
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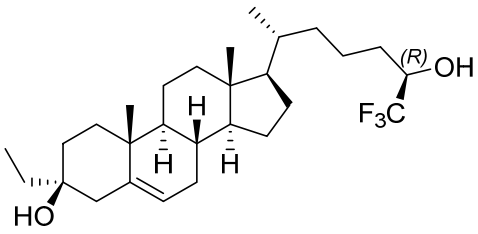
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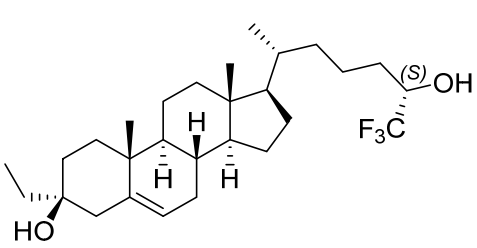

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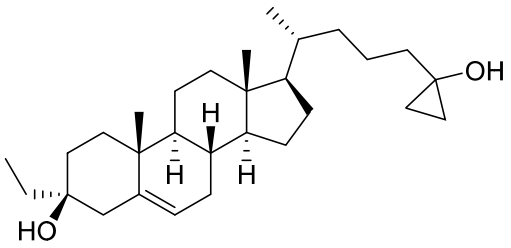

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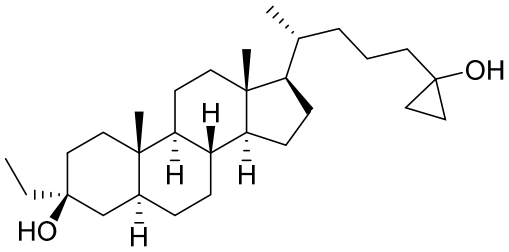

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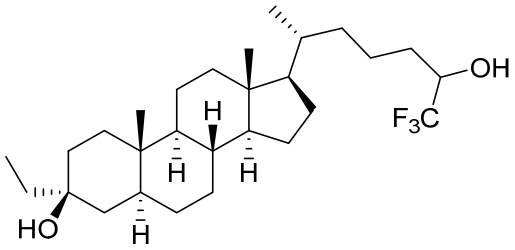

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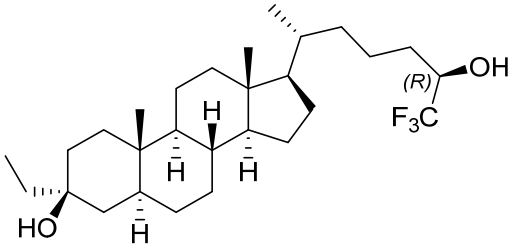

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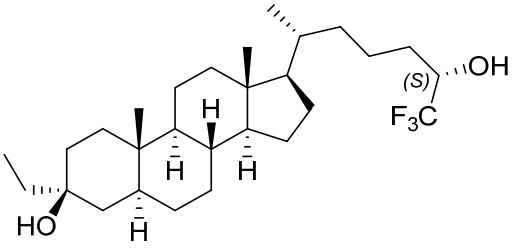

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or a pharmaceutically acceptable salt thereof.

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

48. 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.

49. 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 selected from the group consisting of a gastrointestinal (GI) disorder, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), structural disorders affecting the GI, anal disorders,

colon polyps, cancer, colitis.

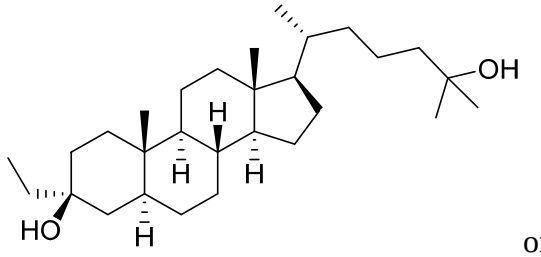
50. The use according to claim 49, wherein the disorder is inflammatory bowel disease.

51. 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.

52. The use according to claim 51, 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, 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.

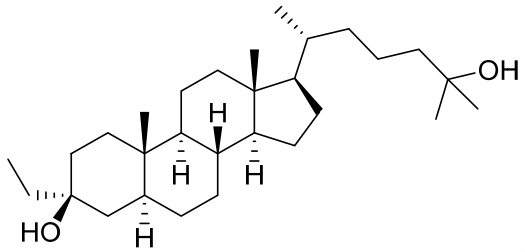
53. A compound of claim 1, or pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, for use in therapy.

54. The compound of claim 1, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

55. A pharmaceutically acceptable salt of the compound of claim 1, wherein the compound is



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