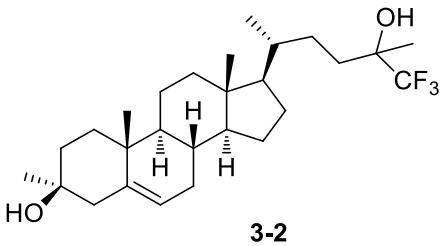
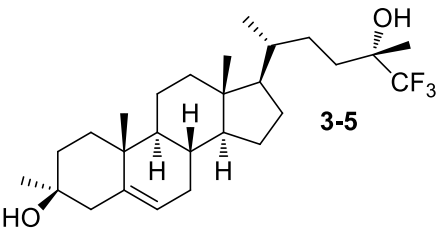
Summary of the ~~Invention~~Disclosure

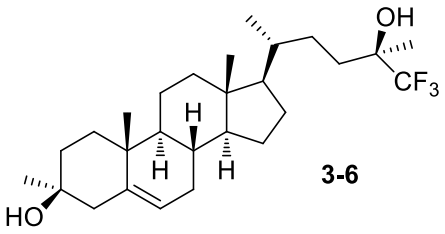
[0003a] In one aspect, there is provided a use of a compound in the manufacture of a medicament for treating Smith-Lemli-Opitz syndrome in a subject, wherein the compound is selected from the group consisting of:



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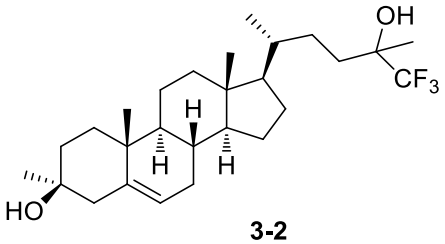
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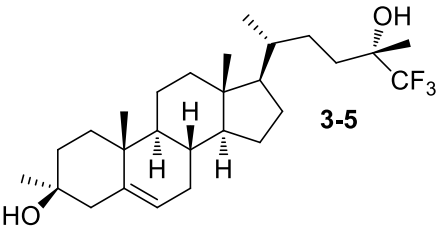
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and pharmaceutically acceptable salts thereof.

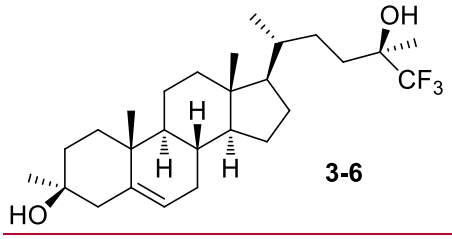
[0003b] In another aspect, there is provided a use of a compound in the manufacture of a medicament for treating a symptom of Smith-Lemli-Opitz syndrome in a subject, wherein the compound is selected from the group consisting of:



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and pharmaceutically acceptable salts thereof.

[0004] Thus, in one ~~aspect~~example, described herein are methods of treating a sterol synthesis disorder such as SLOS or a sterol deficiency disorder. The methods of treatment can include treating a subject by administering to the subject an NMD A receptor modulating compound. Exemplary compounds are described herein.

[0005] In one ~~aspect~~example, described herein is a method of treating a subject suffering from a sterol synthesis disorder (e.g., disorder of cholesterol biosynthesis; disorder characterized by a significant disruption of sterol biosynthesis) or a sterol deficiency disorder (e.g., abnormal levels of a sterol described herein; e.g., at least 1, e.g., at least 2 standard deviations below normal sterol levels), comprising administering to the subject an effective amount of an NMD A receptor modulating compound or pharmaceutically acceptable salt thereof.

[0006] As used herein, "normal sterol level" varies by age, and is defined, as described in as Bjorkhem et al., . of Lipid Res. 2001, 42: 366-371 ; for example, within 2 standard deviations of the values provided in Table 2 (e.g., within 2 standard deviations, within 1.5 standard deviations, or within 1 standard deviation). Normal and abnormal sterol levels (e.g., 24(S)-hydroxycholesterol and 27(S)-hydroxycholesterol) for example in various age groups, have been reported in e.g., Bjorkhem et al., . of Lipid Res. 2001, 42: 366-371 ; Bretillon et al., . Lipid Res. 2000, 41: 840-845; Bjorkhem et al., . Lipid Res. 1998, 39: 1594-1600; Lutjohann et al., Proc. Natl. Acad. Sci. USA 1996, 93: 9799-9804, the contents of each of which are incorporated herein by reference.

[0007] In some ~~embodiments~~examples, the subject suffers from a sterol synthesis disorder and a 24(S)-hydroxycholesterol deficiency disorder.

[0008] In some ~~embodiments~~examples, the sterol deficiency disorder is characterized by the presence of 24(S)-hydroxycholesterol in the plasma of the subject at significantly reduced levels (e.g., at least 1 or 2 standard deviations below) compared with the plasma of a subject not suffering from a sterol deficiency disorder).

[0009] In some ~~embodiments~~examples, the metabolic processing of 24(S)-hydroxycholesterol is low as compared with a subject not suffering from the disorder.

[0010] In some ~~embodiments~~examples, the compound is 24(S)-hydroxycholesterol. In some ~~embodiments~~examples, the compound is not a product of nature. In some ~~embodiments~~examples, the sterol is 24(S)-hydroxycholesterol, 25-hydroxycholesterol, or 27(S)-hydroxycholesterol.

[0011] In some ~~embodiments~~examples, the sterol disorder is selected from: Smith-Lemli-Opitz syndrome; Conradi-Hunermann syndrome; Greenberg dysplasia; Desmosterolosis; Cerebrotendinous Xanthomatosis (CTX); Mevalonate Kinase Deficiency Syndromes (MKD); SC4MOL gene mutation (SMO Deficiency); lathosterolosis; X-linked dominant chondrodysplasia puncata; CHILD syndrome or CK-syndrome; autism spectrum disorder; Niemann-Pick disease; and disorders of dolichol synthesis or metabolism. In some ~~embodiments~~examples, the sterol disorder is Smith-Lemli-Opitz syndrome.

[0012] In some ~~embodiments~~examples, the compound has an EC_{50} of 10 μM or less (e.g., 5 μM, 1 μM, 500 nM, 350 nM, 250 nM, 100 nM, 50 nM, 10 nM or less).

[0013] In some ~~embodiments~~examples, the compound is present at an effective plasma concentration of 10 to 800 ng/mL of plasma (e.g., 10 to 600 ng/mL, 10 to 500 ng/mL, 25 to 500 ng/mL, 40 to 500 ng/mL, 25 to 350 ng/mL). In some ~~embodiments~~examples, the compound is present at an effective plasma concentration of at least 10 ng/mL of plasma (e.g., at least 15 ng/mL, 20 ng/mL, 25 ng/mL, 30 ng/mL, 30 ng/mL, 35 ng/mL, 40 ng/mL, 45 ng/mL, 50 ng/mL, 55 ng/mL).

[0014] In some ~~embodiments~~examples, the compound is a NMDA receptor modulator (e.g., positive modulator, negative modulator).

[0015] In some ~~embodiments~~examples, the compound is a compound of Formula (I), (Il-a), (II-b), (III), (IV), (V), (VI), (VII), (VIII), (IX-A), (IX-B), (X), (XI-A), or (XI-B) In some ~~embodiments~~examples, the compound is a compound of Formula (I).

[0016] In some examples~~embodiments~~, the administration to the subject normalizes concentrations of oxysterols in circulation relative to a subject not administered with the compound or administered with a placebo.

[0017] In some examples~~embodiments~~, the administration to the subject elevates levels of cholesterol in tissues and plasma relative to a subject not administered with the compound or administered with a placebo.

[0018] In some examples~~embodiments~~, the subject is an infant. In some ~~embodiments~~examples, the subject is less than 21 years old (e.g., less than 18, 15, 13, 12, 10, 8, 6, 4, 3, 2, or 1 year old).

[0019] In some examples~~embodiments~~, the method further comprises administration of an additional therapy. In some examples~~embodiments~~, the additional therapy is dietary cholesterol therapy (e.g., cholesterol supplementation, statin treatment (e.g., 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (e.g., HMG CoA reductase inhibitors), e.g., simvastatin), bile acid supplementation or downstream hormone supplementation, medical therapies, or surgical interventions; antioxidants; gene therapy.

[0020] In one example~~aspect~~, described herein is a dosage form comprising a compound of Formula (I), (Il-a), (II-b), (III), (IV), (V), (VI), (VII), (VIII), (IX-A), (IX-B), (X), (XI-A), or (XI-B) configured for administration in a subject, wherein the subject is a child. In some examples~~embodiments~~, the dosage form is a

liquid suspension, sprinkle, meltaway, sublingual, or injectable. In some ~~embodiments~~examples, the dosage form is a solid dosage form. In some examples~~embodiments~~, the solid dosage form is a tablet, capsule, or pill.

Detailed Description of Certain Embodiments of the Invention

Diseases and disorders

Described herein are methods of treating a sterol synthesis disorder. Exemplary disorders are described herein. The methods include administering to a subject, e.g., a subject suffering from a sterol synthesis disorder such as SLOS, a NMDA receptor modulating compound. Exemplary compounds are described herein. In some embodiments the compounds is 24(S) hydroxyl cholesterol. In some embodiments, the compound is a compound of a formula described herein such as a compound of Formula (I), (Il-a), (Il-b), (III), (IV), (V), (VI), (VII), (VIII), (IX-A), (IX-B), (X), (XI-A), or (XI-B).

Sterol Synthesis Disorders

In one aspect, described herein are methods for treating a sterol synthesis disorder. Cholesterol has an essential rule in growth and development. It is a membrance lipid and a precursor to many molecules that play important roles in cellular growth and diffierentiation, protein glycosylation, and signaling pathways. Biosynthesis of cholesterol involves a number of enzymes and intermediates.

Disorders resulting from a deficiency in any of the enzymes involved in cholesterol biosynthesis lead to the accumulation of intermediates and imbalance in biomolecules, resulting in disorders including congenital skeletal malformations, dysmorphic facial features, psychomotor retardation, and failure to thrive. In an embodiment, a sterol synthesis disorder or symptom of a sterol synthesis disorder can be treated by administering to a subject suffering from a sterol synthesis disorder a compound described herein, such as a NMDA receptor modulating compound as described herein. Additional disorders are described below.

Smith- Lemli-Opitz Syndrome

In one aspect, described herein are methods for treating Smith-Lemli-Opitz Syndrome (or SLOS, or 7-dehydrocholesterol reductase deficiency). SLOS is an inborn error of cholesterol synthesis. In addition to microcephaly, moderate to severe intellectual disability, sensory hypersensitivity, stereotyped

Claims

1. A method of treating a subject suffering from a sterol synthesis disorder (e.g., disorder of cholesterol biosynthesis; disorder characterized by a significant disruption of sterol biosynthesis) or a sterol deficiency disorder (e.g., abnormal levels (e.g., abnormally low) of a sterol described herein; e.g., 2 standard deviations below normal sterol levels as described herein), comprising administering to the subject an effective amount of an NMD A receptor modulating compound or pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein the subject suffers from a sterol synthesis disorder and a 24(S) hydroxycholesterol deficiency disorder.

3. The method of claim 1, wherein the sterol deficiency disorder is characterized by the presence of 24(S) hydroxycholesterol in the plasma of the subject at significantly reduced levels (e.g., at least 1 or 2 standard deviations below) compared with the plasma of a subject not suffering from a sterol deficiency disorder).

4. The method of claim 1, wherein the metabolic processing of 24(S) hydroxycholesterol is low as compared with a subject not suffering from the disorder.

5. The method of claim 1, wherein the compound is 24(S) hydroxycholesterol.

6. The method of claim 1, wherein the compound is 24(S) hydroxycholesterol 3 sulfate.

7. The method of claim 1, wherein the sterol is 24(S) hydroxycholesterol, 25 hydroxycholesterol, or 27(S) hydroxycholesterol.

8. The method of claim 1, wherein the sterol disorder is selected from: Smith -Lemli-Opitz syndrome; Conradi-Hunermann syndrome; Greenberg dysplasia; Desmosterolosis; Cerebrotendinous Xanthomatosis (CTX); Mevalonate Kinase Deficiency Syndromes (MKD); SC4MOL gene mutation (SMO Deficiency); lathosterolosis; X-linked dominant chondrodysplasia puncata; CHILD syndrome or CK-syndrome; autism spectrum disorder; Niemann-Pick disease; and disorders of dolichol synthesis or metabolism.

9. The method of claim 8, wherein the sterol disorder is selected from: Smith-Lemli-Opitz syndrome.

10. The method of claim 1, wherein the compound has an EC_{50} of 10 μM or less (e.g., 5 μM, 1 μM, 500 nM, 350 nM, 250 nM, 100 nM, 50 nM, 10 nM or less).

11. The method of claim 1, wherein the compound is present at an effective plasma concentration of 10 to 800 ng/mL of plasma (e.g., 10 to 600 ng/mL, 10 to 500 ng/mL, 25 to 500 ng/mL, 40 to 500 ng/mL, 25 to 350 ng/mL).

12. The method of claim 1, wherein the compound is present at an effective plasma concentration of at least 10 ng/mL of plasma (e.g., at least 15 ng/mL, 20 ng/mL, 25 ng/mL, 30 ng/mL, 30 ng/mL, 35 ng/mL, 40 ng/mL, 45 ng/mL, 50 ng/mL, 55 ng/mL).

13. The method of claim 1, wherein the compound is a NMD A receptor modulator (e.g., positive modulator, negative modulator).

14. The method of claim 1, wherein the compound is a compound of Formula (I), (Il-a), (II-b), (III), (IV), (V), (VI), (VII), (VIII), (IX-A), (IX-B), (X), (XI-A), or (XI-B).

15. The method of claim 1, wherein the compound is a compound of Formula (I).

16. The method of claim 1, wherein the administration to the subject normalizes concentrations of oxysterols in circulation relative to a subject not administered with the compound or administered with a placebo.

17. The method of claim 1, wherein the administration to the subject elevates levels of cholesterol in tissues and plasma relative to a subject not administered with the compound or administered with a placebo.

18. The method of claim 1, wherein the subject is an infant.

19. The method of claim 1, wherein the subject is less than 21, 18, 15, 13, 12, 10, 8, 6, 4, 3, 2, 1 year old.

20. The method of claim 1, further comprising administration of an additional therapy.

21. The method of claim 1, within the additional therapy is dietary cholesterol therapy (e.g., cholesterol supplementation, statin treatment (e.g., 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (e.g., HMG-Co-A reductase inhibitors), e.g., simvastatin), bile acid supplementation or downstream hormone supplementation, medical therapies, or surgical interventions; antioxidants; gene therapy.

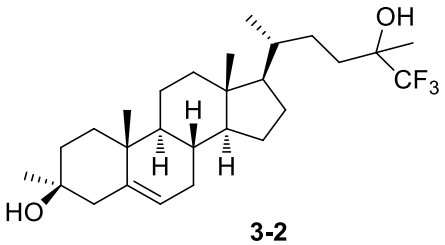
22. A dosage form comprising a compound of Formula (I), (Il-a), (II-b), (III), (IV), (V), (VI), (VII), (VIII), (IX-A), (IX-B), (X), (XI-A), or (XI-B) configured for administration in a subject, wherein the subject is a child.

~~23. The dosage form of claim 22, wherein the dosage form is a liquid suspension, sprinkle, meltaway, sublingual, or injectable.~~

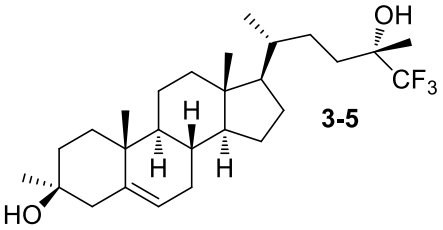
~~24. The dosage form of claim 23, wherein the dosage form is a solid dosage form.~~

~~25. The dosage form of claim 24, wherein the solid dosage form is a tablet, capsule, or pill.~~

1. Use of a compound in the manufacture of a medicament for treating Smith-Lemli-Opitz syndrome in a subject, wherein the compound is selected from the group consisting of:

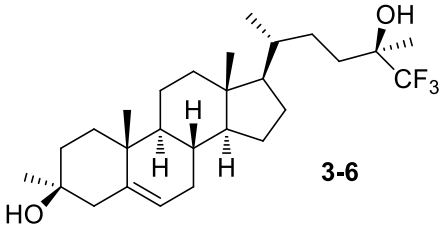


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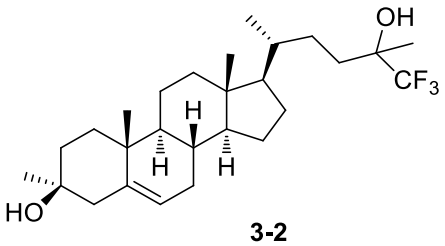
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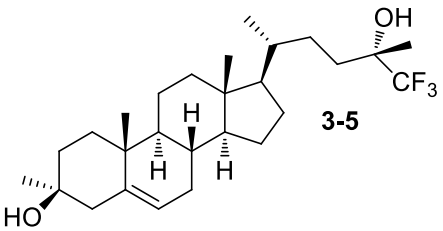
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and pharmaceutically acceptable salts thereof.

2. Use of a compound in the manufacture of a medicament for treating a symptom of Smith-Lemli-Opitz syndrome in a subject, wherein the compound is selected from the group consisting of:

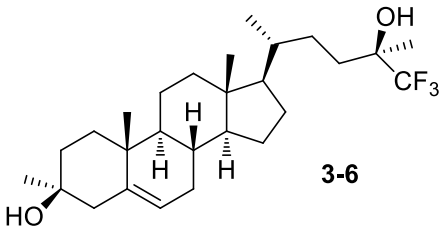


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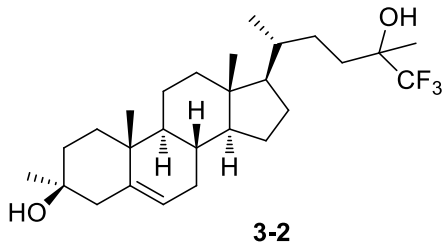


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and pharmaceutically acceptable salts thereof.

3. The use according to claim 2, wherein the symptom of Smith-Lemli-Opitz syndrome is selected from microcephaly, moderate to severe intellectual disability, sensory hypersensitivity, stereotyped behaviors, dysmorphic facial features, syndactyly of the second/third toes, and reduced cerebrosterol levels.

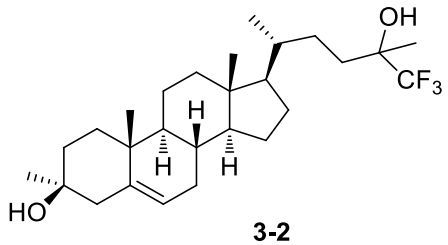
4. The use according to any one of claims 1-3, wherein the compound is:



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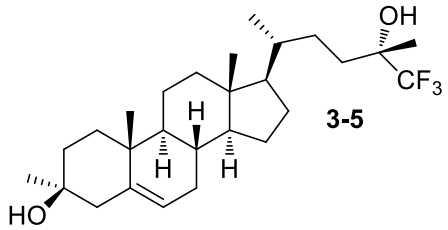
5. The use according to any one of claims 1-3, wherein the compound is a pharmaceutically acceptable salt of:



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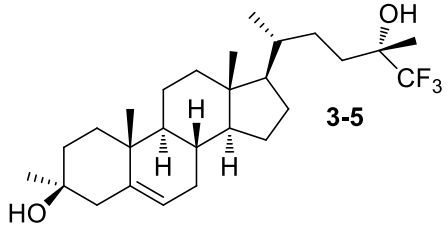
6. The use according to any one of claims 1-3, wherein the compound is:



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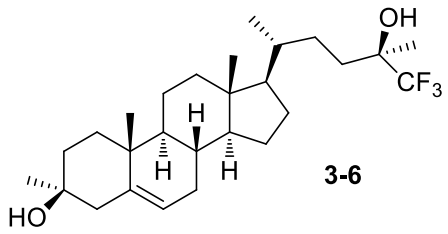
7. The use according to any one of claims 1-3, wherein the compound is a pharmaceutically acceptable salt of:



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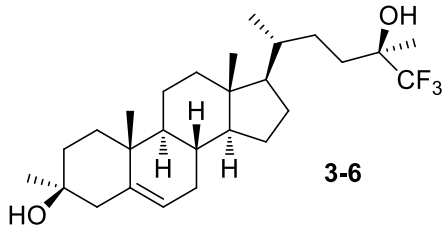
8. The use according to any one of claims 1-3, wherein the compound is:



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9. The use according to any one of claims 1-3, wherein the compound is a pharmaceutically acceptable salt of:



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10. The use according to any one of claims 1-9, wherein the subject is an infant.

11. The use according to any one of claims 1-9, wherein the subject is less than 21, 18, 15, 13, 12, 10, 8, 6, 4, 3, 2, 1 year old.

12. The use according to any one of claims 1-11, wherein the medicament is a liquid suspension, sprinkle, meltaway, sublingual, or injectable.

13. The use according to any one of claims 1-11, wherein the medicament is a solid dosage form.

14. The use according to claim 13, wherein the solid dosage form is a tablet, capsule, or pill.