Summary

[0004] 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] 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.

[0005a] In one aspect of the present disclosure, there is provided a use of an NMD A receptor modulating compound or pharmaceutically acceptable salt thereof in the manufacture of a medicament for 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.

[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, the subject suffers from a sterol synthesis disorder and a 24(S)-hydroxycholesterol deficiency disorder.

[0008] In some embodiments, 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, the metabolic processing of 24(S)-hydroxycholesterol is low as compared with a subject not suffering from the disorder.

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

[0011] In some embodiments, 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 punctata; CHILD syndrome or CK-syndrome; autism spectrum disorder; Niemann-Pick disease; and disorders of dolichol synthesis or metabolism. In some embodiments, the sterol disorder is Smith-Lemli-Opitz syndrome.

[0012] In some embodiments, 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, 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, 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, the compound is a NMDA receptor modulator (e.g., positive modulator, negative modulator).

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

[0016] In some 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 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 embodiments, the subject is an infant. In some embodiments, 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 embodiments, the method further comprises administration of an additional therapy. In some 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 another aspect, described herein is a dosage form comprising a compound of Formula (I), (II-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 embodiments, the dosage form is a

Claims

1. Use of an NMD A receptor modulating compound or pharmaceutically acceptable salt thereof in the manufacture of a medicament for 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.

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

3. The use 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 use 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 use of claim 1, wherein the compound is 24(S)-hydroxycholesterol.

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

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

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

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

14. The use 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 use of claim 1, wherein the compound is a compound of Formula (*I*).

16. The use of claim 1, wherein the medicament is to be administered to the subject, 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 use of claim 1, wherein the medicament is to be administered to the subject, 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 use of claim 1, wherein the subject is an infant.

19. The use 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 use of claim 1, wherein the medicament is to be administered to the subject, and an additional therapy is to be further administered.

21. The use of claim 20, 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.