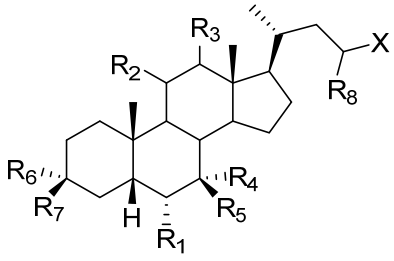
small intestine. Furthermore, the gut microbiota has the unique ability to biochemically alter the structure of bile acids. In turn, bile acids can have a significant effect on the biology of bacteria where they have been shown to help shape the composition of the gut microbiota. Thus, there is a need for novel compositions comprising a bile acid or a derivative thereof and one or more gut microbes as a therapeutic agent, and methods of using a bile acid or a derivative thereof in combination with one or more gut microbes for treating or preventing diseases or disorders. The present application addresses the need.

SUMMARY

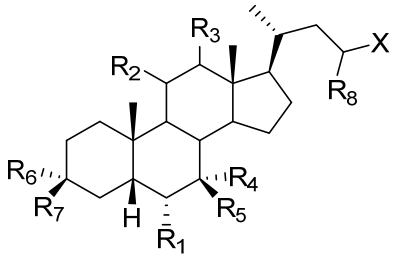
[0003] The present application relates to a pharmaceutical composition comprising a compound of formula I:



(I),

or a pharmaceutically acceptable salt or amino acid conjugate thereof, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, X, m, and n are each as defined herein, and one or more gut microbiome species, and a pharmaceutically acceptable carrier.

[0003a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound of formula I:



(I),

or a pharmaceutically acceptable salt or amino acid conjugate thereof, wherein:

R_1 is unsubstituted C_1-C_6 alkyl;

R_2 is H or hydroxyl;

R_3 is H or hydroxyl;

R_4, R_5, R_6, and R_7 are each independently H or hydroxyl;

R_8 is H or unsubstituted C_1-C_6 alkyl;

X is $C(O)OH$, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

m is 1, 2, or 3; and

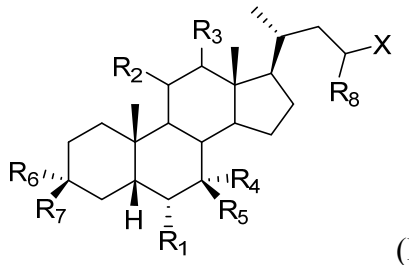
n is 1, 2, or 3,

and one or more gut microbiome species, and a pharmaceutically acceptable carrier.

[0003b] In another aspect, the present disclosure refers to a use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating or preventing an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved.

[0003c] In a further aspect, the present disclosure refers to a pharmaceutical composition disclosed herein for use in treating or preventing an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved.

[0003d] In another aspect, the present disclosure refers to a compound of formula I:



(I),

or a pharmaceutically acceptable salt or amino acid conjugate thereof, wherein:

R_1 is unsubstituted C_1-C_6 alkyl;

R_2 is H or hydroxyl;

R_3 is H or hydroxyl;

R_4, R_5, R_6, and R_7 are each independently H or hydroxyl;

R_8 is H or unsubstituted C_1-C_6 alkyl;

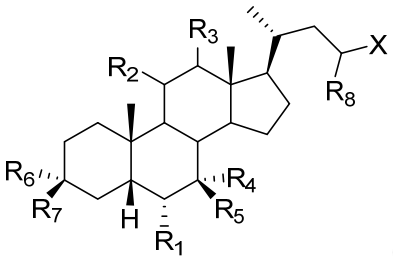
X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

m is 1, 2, or 3; and

n is 1, 2, or 3,

for use in combination with one or more gut microbiome species in treating or preventing an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved.

[0003e] In a further aspect, the present disclosure refers to a use of a compound of formula I:



(I),

or a pharmaceutically acceptable salt or amino acid conjugate thereof, wherein:

R_1 is unsubstituted C_1-C_6 alkyl;

R_2 is H or hydroxyl;

R_3 is H or hydroxyl;

R_4, R_5, R_6, and R_7 are each independently H or hydroxyl;

R_8 is H or unsubstituted C_1-C_6 alkyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

m is 1, 2, or 3; and

n is 1, 2, or 3,

in the manufacture of a medicament for a combinational therapy with one or more gut microbiome species for the treatment or prevention of an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved.

[0003f] In another aspect, the present disclosure refers to one or more gut microbiome species, for use in enhancing the efficacy of an FXR ligand in treating or preventing a disease or condition.

[0004] The present application also relates to a method of treating or preventing an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved, comprising administering to a subject in need thereof a compound of the present application, or a pharmaceutically acceptable amino acid conjugate or salt thereof, and one or more gut microbiome species. In one example, the present application relates to a method of treating. In one example, the present application relates to a method of preventing.

[0005] The present application also relates to a compound of the present application, or a pharmaceutically acceptable amino acid conjugate or salt thereof, for use in combination with one or more gut microbiome species in treating or preventing an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved. In one example, the present application relates to treating. In one example, the present application relates to preventing.

[0006] The present application also relates to use of a compound of the present application, or a pharmaceutically acceptable amino acid conjugate or salt thereof, in the manufacture of a medicament for a combinational therapy with one or more gut microbiome species for the treatment or prevention of an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved. In one example, the present application relates to treatment. In one example, the present application relates to prevention.

[0007] The present application also relates to use of a compound of the present application, or a pharmaceutically acceptable amino acid conjugate or salt thereof, in combination with one or more gut microbiome species, in treating or preventing an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved. In one example, the present application relates to treating. In one example, the present application relates to preventing.

[0008] The present application also relates to a method of enhancing the efficacy of an FXR ligand in treating or preventing a disease or condition, comprising administering to a subject in need thereof one or more gut microbiome species. In one example, the present application relates to a method of treating. In one example, the present application relates to a method of preventing.

[0009] The present application also relates to one or more gut microbiome species, for use in enhancing the efficacy of an FXR ligand in treating or preventing a disease or condition. In one example, the present application relates to treating. In one example, the present application relates to preventing.

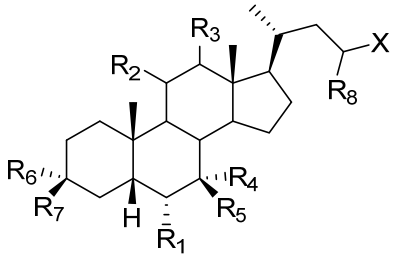
[0010] The present application also relates to use of one or more gut microbiome species in the manufacture of a medicament for enhancing the efficacy of an FXR ligand in the treatment or prevention of a disease or condition. In one example, the present application relates to treatment. In one example, the present application relates to prevention.

[0011] The present application also relates to use of one or more gut microbiome species in enhancing the efficacy of an FXR ligand in treating or preventing a disease or condition. In one example, the present application relates to treating. In one example, the present application relates to preventing.

[0012] The details of the application are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present application, illustrative methods and materials are now described. In the case of conflict, the present specification, including definitions,

CLAIMS

1. A pharmaceutical composition comprising a compound of formula I:



(I),

or a pharmaceutically acceptable salt or amino acid conjugate thereof, wherein:

R_1 is unsubstituted C_1-C_6 alkyl;

R_2 is H or hydroxyl;

R_3 is H or hydroxyl;

R_4, R_5, R_6, and R_7 are each independently H or hydroxyl;

R_8 is H or unsubstituted C_1-C_6 alkyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

m is 1, 2, or 3; and

n is 1, 2, or 3,

and one or more gut microbiome species, and a pharmaceutically acceptable carrier.

2. The pharmaceutical composition of claim 1, wherein R_1 is methyl or ethyl.

3. The pharmaceutical composition of claim 1 or 2, wherein R_1 is ethyl.

4. The pharmaceutical composition of any one of claims 1-3, wherein R_2 is H.

5. The pharmaceutical composition of any one of claims 1-3, wherein R_2 is hydroxyl.

6. The pharmaceutical composition of any one of claims 1-5, wherein R_3 is H.

7. The pharmaceutical composition of any one of claims 1-5, wherein R_3 is hydroxyl.

8. The pharmaceutical composition of any one of claims 1-7, wherein R_4 is hydroxyl and R_5 is H.

9. The pharmaceutical composition of any one of claims 1-7, wherein R_4 is H and R_5 is hydroxyl.

10. The pharmaceutical composition of any one of claims 1-9, wherein R_6 is hydroxyl and R_7 is H.

11. The pharmaceutical composition of any one of claims 1-9, wherein R_6 is H and R_7 is hydroxyl.

12. The pharmaceutical composition of any one of claims 1-11, wherein R_8 is H.

13. The pharmaceutical composition of any one of claims 1-11, wherein R_8 is methyl or ethyl.

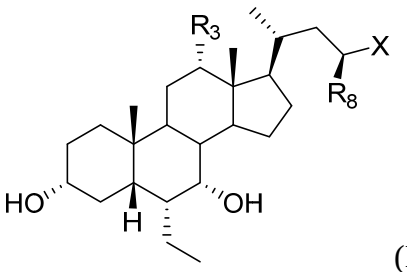
14. The pharmaceutical composition of any one of claims 1-13, wherein R_8 is methyl.

15. The pharmaceutical composition of any one of claims 1-14, wherein X is C(O)OH, $C(O)NH(CH_2)SO_3H$, $C(O)NH(CH_2)CO_2H$, $C(O)NH(CH_2)_2SO_3H$, or $C(O)NH(CH_2)_2CO_2H$.

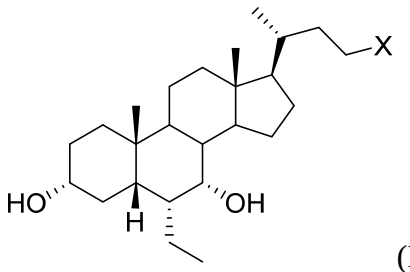
16. The pharmaceutical composition of any one of claims 1-15, wherein X is C(O)OH.

17. The pharmaceutical composition of any one of claims 1-14, wherein X is OSO_3H.

18. The pharmaceutical composition of claim 1, wherein the compound is of formula Ib-1 or Ib-2:



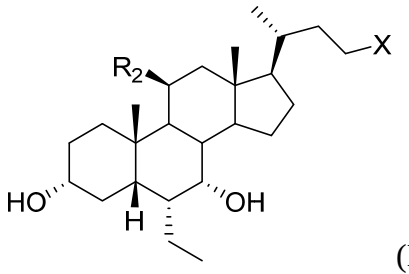
(Ib-1) or



(Ib-2),

or a pharmaceutically acceptable salt or amino acid conjugate thereof.

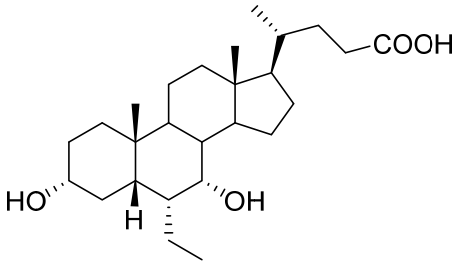
19. The pharmaceutical composition of claim 1, wherein the compound is of formula Ic:



(Ic),

or a pharmaceutically acceptable salt or amino acid conjugate thereof.

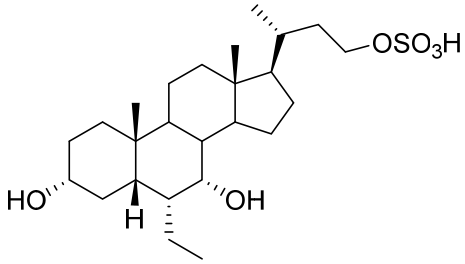
20. The pharmaceutical composition of claim 1, wherein the compound is:



(OCA),

or a pharmaceutically acceptable salt or amino acid conjugate thereof.

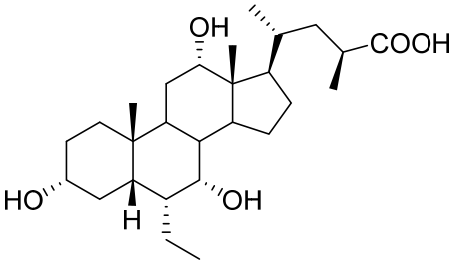
21. The pharmaceutical composition of claim 1, wherein the compound is:



(Compound 1),

or a pharmaceutically acceptable salt or amino acid conjugate thereof.

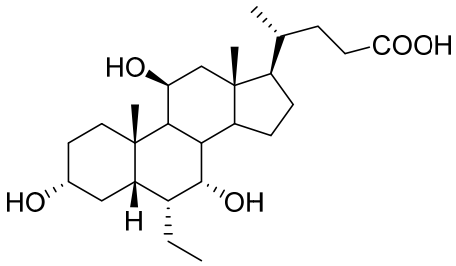
22. The pharmaceutical composition of claim 1, wherein the compound is:



(Compound 2),

or a pharmaceutically acceptable salt or amino acid conjugate thereof.

23. The pharmaceutical composition of claim 1, wherein the compound is:



(Compound 3),

or a pharmaceutically acceptable salt or amino acid conjugate thereof.

24. The pharmaceutical composition of any one of claims 1-23, wherein the one or more gut microbiome species is a member in a family selected from: *Actinomycetaceae, Bogoriellaceae, Brevibacteriaceae, Cellulomonadaceae, Acholeplasmataceae, Acidithiobacillaceae, Alcanivoracaceae, Alteromonadaceae, Blattabacteriaceae, Cardiobacteriaceae, Chlamydiaceae, Chromatiaceae, Clostridiales Family XIII. Incertae Sedis, Cyclobacteriaceae, Dehalococcoidaceae, Desulfobacteraceae, Desulfobulbaceae, Ectothiorhodospiraceae, Elusimicrobiaceae, Entomoplasmataceae, Erythrobacteraceae, Gallionellaceae, Halanaerobiaceae, Jonesiaceae, Kofleriaceae, Leptospiraceae, Methanobacteriaceae, Methylococcaceae, Methylophilaceae, Myxococcaceae, Nitrosomonadaceae, Nitrospiraceae, Oceanospirillaceae, Oscillospiraceae, Piscirickettsiaceae, Propionibacteriaceae, Pseudoalteromonadaceae, Puniceicoccaceae, Rickettsiaceae, Rubrobacteraceae, Shewanellaceae, Spirochaetaceae, Spiroplasmataceae, Sutterellaceae, Syntrophomonadaceae, Thermaceae, Corynebacteriaceae, Dermabacteraceae, Dietziaceae, Geodermatophilaceae, Gordoniaceae, Intrasporangiaceae, Microbacteriaceae, Micrococcaceae, Micromonosporaceae, Mycobacteriaceae, Nocardiaceae, Promicromonosporaceae, Propionibacterineae, Streptomycetaceae, Micrococcineae, Bifidobacteriaceae, Coriobacteriaceae, Deinococcaceae, Halobacteroidaceae, Alicyclobacillaceae, Bacillaceae, Bacillales Incertae Sedis XI, Listeriaceae, Paenibacillaceae, Planococcaceae, Staphylococcaceae, Aerococcaceae, Carnobacteriaceae, Enterococcaceae, Lactobacillaceae, Leuconostocaceae, Streptococcaceae, Christensenellaceae, Clostridiaceae, Ruminococcaceae, Family XIII Incertae Sedis, Peptostreptococcaceae, Family XI Incertae Sedis, Lachnospiraceae, Eubacteriaceae, Erysipelotrichaceae, Erysipelotrichaceae XVI, Erysipelotrichaceae XVII, Erysipelotrichaceae XVIII, Acidiaminococcaceae, Peptococcaceae, Veillonellaceae, Bacteroidaceae, Porphyromonadaceae, Prevotellaceae, Rikenellaceae, Cytophagaceae, Flavobacteriaceae, Chitinophagaceae, Sphingobacteriaceae, Fusobacteriaceae,*

Leptotrichiaceae, Victivallaceae, Planctomycetaceae, Caulobacteraceae, Aurantimonadaceae, Bradyrhizobiaceae, Brucellaceae, Hyphomicrobiaceae, Methylobacteriaceae, Phyllobacteriaceae, Rhizobiaceae, Xanthobacteraceae, Rhodobacteraceae, Acetobacteraceae, Rhodospirillaceae, Sphingomonadaceae, Alcaligenaceae, Burkholderiaceae, Comamonadaceae, Oxalobacteraceae, Suterellaceae, Neisseriaceae, Rhodocyclaceae, Desulfovibrionaceae, Campylobacteraceae, Helicobacteraceae, Aeromonadaceae, Succinivibrionaceae, Enterobacteriaceae, Pasteurellaceae, Moraxellaceae, Pseudomonadaceae, Vibrionaceae, Sinobacteraceae, Xanthomonadaceae, Brachyspiraceae, Synergistaceae, Mycoplasmataceae, and *Verrucomicrobiaceae*.

25. The pharmaceutical composition of any one of claims 1-24, wherein the one or more gut microbiome species is gram positive.

26. The pharmaceutical composition of any one of claims 1-25, wherein the one or more gut microbiome species is selected from *Bifidobacterium breve, Bifidobacterium longum, Lactobacillus casei, Lactobacillus paracasei, Pediococcus pentosaceus, Lactococcus lactis, Streptococcus parasanguinis, Streptococcus salivarius, Streptococcus thermophilus, Ruminococcus bromii, Ruminococcus torques, Anaerotruncus unclassified, Subdoligranulum unclassified, Clostridium difficile, Blautia (Ruminococcus) obeum, Dorea longicatena, Eubacterium ramulus, Ruminococcus gnavus, Ruminococcus torques, Lachnospiracea bacterium* 5_1_63FAA, *Lachnospiraceae bacterium* 3_1_57FAA_CT1, *and Lachnospiraceae bacterium* 8_1_57FAA, *Coprobacillus* unclassified, *Clostridium spiroforme, Clostridium symbiosum, Veillonella parvula, and Veillonella* unclassified.

27. The pharmaceutical composition of any one of claims 1-24, wherein the one or more gut microbiome species is gram negative.

28. The pharmaceutical composition of any one of claims 1-27, wherein the one or more gut microbiome species is selected from *Bacteroides ovatus, Bacteroides plebeius, Bacteroides uniformis, Bacteroidales ph8, Odoribacter splanchnicus, Paraprevotella clara, Paraprevotella* unclassified, *Alistipes putredinis, Alistipes shahii, Escherichia coli,* and *Akkermansia muciniphila*.

29. The pharmaceutical composition of any one of claims 1-23, wherein the one or more gut microbiome species is sensitive to growth inhibition by an endogenous bile acid.

30. The pharmaceutical composition of any one of claims 1-23, wherein the one or more gut microbiome species is a human gut microbiome species.

31. The pharmaceutical composition of any one of claims 1-30, wherein the compound or a pharmaceutically acceptable amino acid conjugate or salt thereof is present in the amount of 5-25 mg in the pharmaceutical composition.

32. The pharmaceutical composition of any one of claims 1-31, wherein the pharmaceutical composition comprises the one or more gut microbiome species in the amount of 100-10^{12} colony forming unit.

33. The pharmaceutical composition of any one of claims 1-32, wherein the compound or a pharmaceutically acceptable amino acid conjugate or salt thereof is formulated for oral, parenteral, or topical administration.

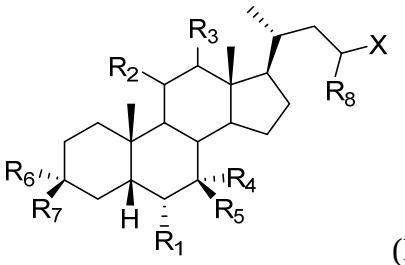
34. The pharmaceutical composition of any one of claims 1-33, wherein the compound or a pharmaceutically acceptable amino acid conjugate or salt thereof is formulated for oral administration.

35. The pharmaceutical composition of any one of claims 1-34, wherein the one or more gut microbiome species is formulated for oral administration.

36. Use of a pharmaceutical composition of any one of claims 1-35 in the manufacture of a medicament for treating or preventing an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved.

37. A pharmaceutical composition of any one of claims 1-35 for use in treating or preventing an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved.

38. A compound of formula I:



(I),

or a pharmaceutically acceptable salt or amino acid conjugate thereof, wherein:

R_1 is unsubstituted C_1-C_6 alkyl;

R_2 is H or hydroxyl;

R_3 is H or hydroxyl;

R_4, R_5, R_6, and R_7 are each independently H or hydroxyl;

R_8 is H or unsubstituted C_1-C_6 alkyl;

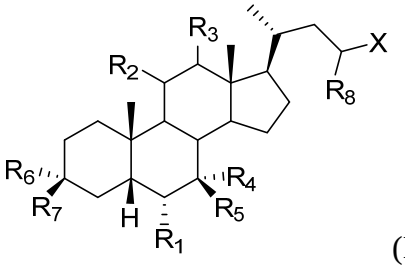
X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

m is 1, 2, or 3; and

n is 1, 2, or 3,

for use in combination with one or more gut microbiome species in treating or preventing an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved.

39. Use of a compound of formula I:



(I),

or a pharmaceutically acceptable salt or amino acid conjugate thereof, wherein:

R_1 is unsubstituted C_1-C_6 alkyl;

R_2 is H or hydroxyl;

R_3 is H or hydroxyl;

R_4, R_5, R_6, and R_7 are each independently H or hydroxyl;

R_8 is H or unsubstituted C_1-C_6 alkyl;

X is C(O)OH, $C(O)NH(CH_2)_mSO_3H$, $C(O)NH(CH_2)_nCO_2H$, or OSO_3H;

m is 1, 2, or 3; and

n is 1, 2, or 3,

in the manufacture of a medicament for a combinational therapy with one or more gut microbiome species for the treatment or prevention of an FXR mediated disease or condition or a disease or condition in which an abnormal composition of the gut microbiome is involved.

40. One or more gut microbiome species, for use in enhancing the efficacy of an FXR ligand in treating or preventing a disease or condition.

41. Use of one or more gut microbiome species in the manufacture of a medicament for enhancing the efficacy of an FXR ligand in the treatment or prevention of a disease or condition.