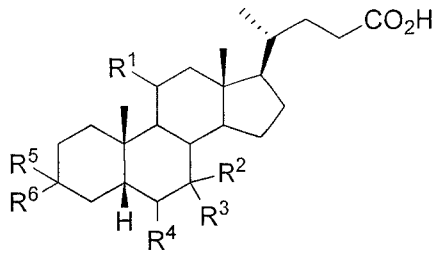
involved in bile acid and cholesterol homeostasis. Accordingly, there is a need for FXR modulators suitable for drug development. The present invention addresses this need.

SUMMARY

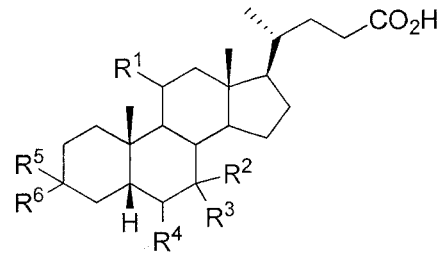
The present disclosure provides compounds and methods of preparing these compounds. Specifically, the present disclosure provides a compound of formula I:



(I),

or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof, wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as described herein. The compounds of the present disclosure are useful for treating and preventing diseases and conditions.

In one aspect of the present disclosure, there is provided a compound of formula I:



(I),

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

R^1 is hydroxyl;

R^2 is hydrogen, hydroxyl, alkyl, or halogen, wherein said alkyl is unsubstituted or substituted with one or more R^a;

R^3 is hydrogen, hydroxyl, alkyl, or halogen, wherein said alkyl is unsubstituted or substituted with one or more R^b;

R^4 is alkyl, alkenyl, alkynyl, or halogen, wherein said alkyl is unsubstituted or substituted with one or more R^c;

R^a, R^b, and R^c are each independently halogen or hydroxyl;

R^5 is hydroxyl, OSO_3H, OSO_3^-, $O(CO)CH_3$, OPO_3H_2, OPO_3^{2-}, or hydrogen; and

R^6 is hydroxyl, OSO_3H, OSO_3^-, $O(CO)CH_3$, OPO_3H_2, OPO_3^{2-}, or hydrogen;

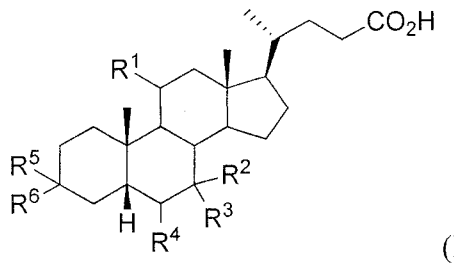
or taken together R^5 and R^6 with the carbon atom to which they are attached form a carbonyl.

In another aspect of the present disclosure, there is provided a use of the compound as described herein in the manufacture of a medicament for treating or preventing a disease or condition mediated by FXR in a subject, wherein the disease or condition mediated by FXR is selected from cardiovascular disease, chronic liver disease, lipid disorder, gastrointestinal disease, renal disease, metabolic disease, cancer, and neurological disease.

In yet another aspect of the present disclosure, there is provided a compound as described herein for use in treating or preventing a disease or condition mediated by FXR in a subject.

The present disclosure also provides a composition for use in a method for treating or preventing a disease or condition (*e.g.*, a disease or condition mediated by FXR), wherein the composition comprises a compound of the present disclosure or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this present disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those



(I),

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

R^1 is hydroxyl;

R^2 is hydrogen, hydroxyl, alkyl, or halogen, wherein said alkyl is unsubstituted or substituted with one or more R^a;

R^3 is hydrogen, hydroxyl, alkyl, or halogen, wherein said alkyl is unsubstituted or substituted with one or more R^b;

R^4 is hydrogen, alkyl, alkenyl, alkynyl, or halogen, wherein said alkyl is unsubstituted or substituted with one or more R^c;

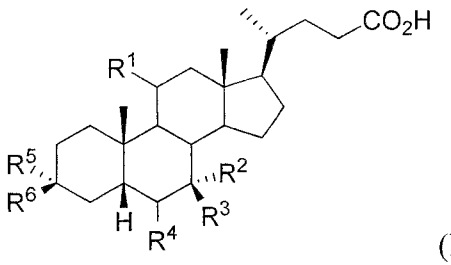
R^a, R^b, and R^c are each independently halogen or hydroxyl;

R^5 is hydroxyl, OSO_3H, OSO_3^-, $O(CO)CH_3$, OPO_3H_2, OPO_3^{2-}, or hydrogen; and

R^6 is hydroxyl, OSO_3H, OSO_3^-, $O(CO)CH_3$, OPO_3H_2, OPO_3^{2-}, or hydrogen;

or taken together R^5 and R^6 with the carbon atom to which they are attached form a carbonyl.

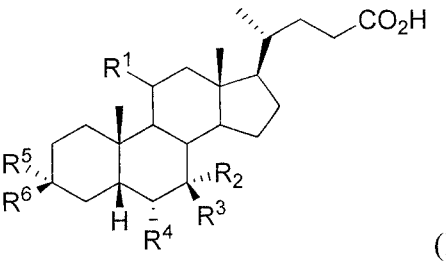
In one aspect, the present invention relates to a compound formula II:



(II),

or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

In one aspect, the present invention relates to a compound of formula III:



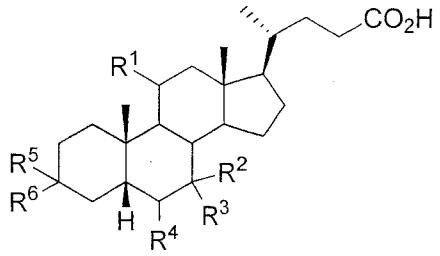
(III),

or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

In one aspect, the present invention relates to a compound of formula IV:

CLAIMS

1. A compound of formula I:



(I),

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

R^1 is hydroxyl;

R^2 is hydrogen, hydroxyl, alkyl, or halogen, wherein said alkyl is unsubstituted or substituted with one or more R^a;

R^3 is hydrogen, hydroxyl, alkyl, or halogen, wherein said alkyl is unsubstituted or substituted with one or more R^b;

R^4 is alkyl, alkenyl, alkynyl, or halogen, wherein said alkyl is unsubstituted or substituted with one or more R^c;

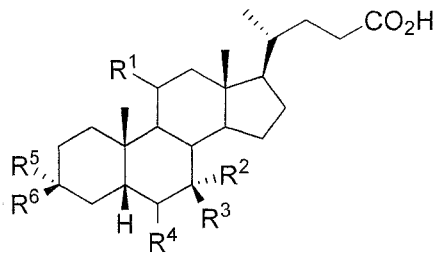
R^a, R^b, and R^c are each independently halogen or hydroxyl;

R^5 is hydroxyl, OSO_3H, OSO_3^-, $O(CO)CH_3$, OPO_3H, OPO_3^{2-}, or hydrogen; and

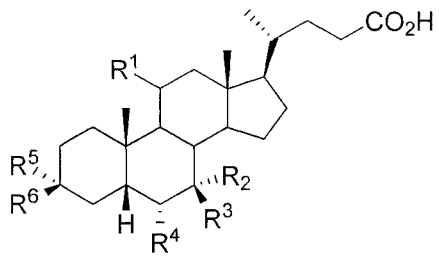
R^6 is hydroxyl, OSO_3H, OSO_3^-, $O(CO)CH_3$, OPO_3H, OPO_3^{2-}, or hydrogen;

or taken together R^5 and R^6 with the carbon atom to which they are attached form a carbonyl.

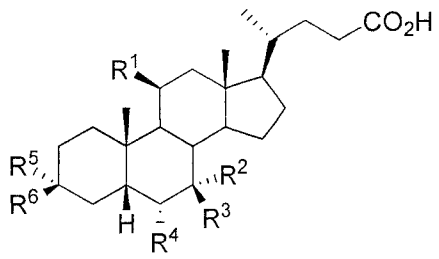
2. The compound of claim 1, wherein the compound is of a formula selected from the group consisting of:



(II),

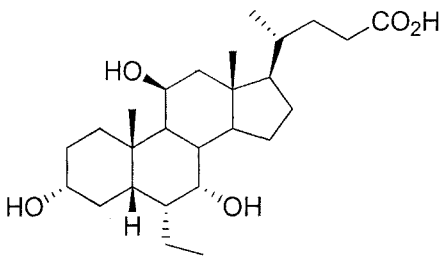


(III), and



(IV),

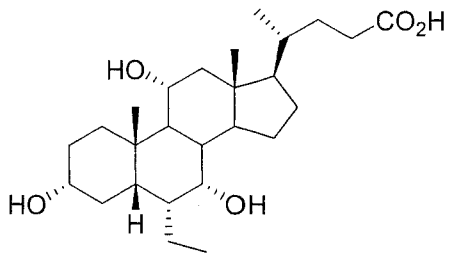
or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.



,

or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

17. A compound of the following formula:



,

or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

18. A pharmaceutical composition comprising the compound of any one of claims 1-17 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof, and a pharmaceutically acceptable excipient.

19. Use of the compound of any one of claims 1-17 in the manufacture of a medicament for treating or preventing a disease or condition mediated by FXR in a subject, wherein the disease or condition mediated by FXR is selected from cardiovascular disease, chronic liver disease, lipid disorder, gastrointestinal disease, renal disease, metabolic disease, cancer, and neurological disease.

~~20. The use of claim 19, wherein the disease or condition mediated by FXR is selected from cardiovascular disease, chronic liver disease, lipid disorder, gastrointestinal disease, renal disease, metabolic disease, cancer, and neurological disease.~~

~~21~~20. A compound of any one of claims 1-17 for use in treating or preventing a disease or condition mediated by FXR in a subject.

~~22~~21. The compound of claim ~~21~~20, wherein the disease or condition mediated by FXR is selected from cardiovascular disease, chronic liver disease, lipid disorder, gastrointestinal disease, renal disease, metabolic disease, cancer, and neurological disease.