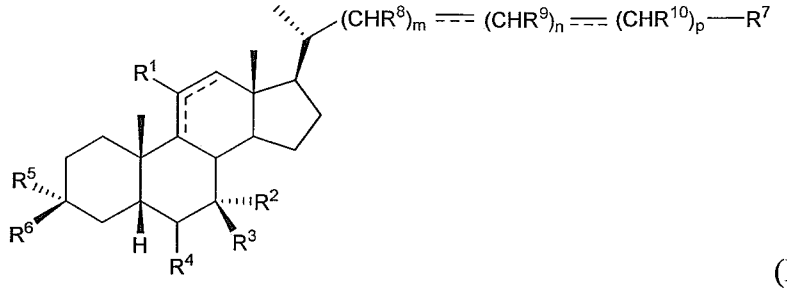
SUMMARY

An objective of the present disclosure is to provide compounds that modulate FXR. The present disclosure provides a compound of formula I:



(I),

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

R^1 is OH, alkoxy, halogen, or oxo;

R^2 and R^3 are each independently H, OH, halogen, or alkyl optionally substituted with one or more halogen or OH, or R^2 and R^3 taken together with the carbon atom to which they are attached form a carbonyl;

R^4 is H, halogen, alkyl optionally substituted with one or more halogen or OH, alkenyl, or alkynyl;

R^5 and R^6 are each independently H, OH, OSO_3H, $OCOCH_3$, OPO_3H_2, or halogen, or R^5 and R^6 taken together with the carbon atom to which they are attached form a carbonyl;

R^7 is OH, OSO_3H, SO_3H, OSO_2NH_2, SO_2NH_2, OPO_3H_2, PO_3H_2, CO_2H, C(O)NHOH, tetrazolyl, oxadiazolyl, thiadiazolyl, 5-oxo-1,2,4-oxadiazolyl, 5-oxo-1,2,4-thiadiazolyl, oxazolidine-dionyl, thiazolidine-dionyl, 3-hydroxyisoxazolyl, 3-hydroxyisothiazolyl, or 2,4-difluoro-3-hydroxyphenyl;

R^8, R^9, and R^{10} are each independently H, OH, halogen, or alkyl optionally substituted with one or more halogen or OH, or R^8 and R^9 taken together with the carbon atoms to which they are attached form a 3- to 6-membered carbocyclic or heterocyclic ring comprising 1 or 2 heteroatoms selected from N, O, and S, or R^9 and R^{10} taken together with the carbon atoms to which they are attached form a 3- to 6-membered carbocyclic or heterocyclic ring comprising 1 or 2 heteroatoms selected from N, O, and S;

m is 0, 1, or 2;

n is 0 or 1;

p is 0 or 1; and

=== is a single or double bond, provided that when each === is a single bond, the sum of m, n, and p is 2, R^1 is OH, and R^8, R^9, and R^{10} are each H, then R^7 is not CO_2H.

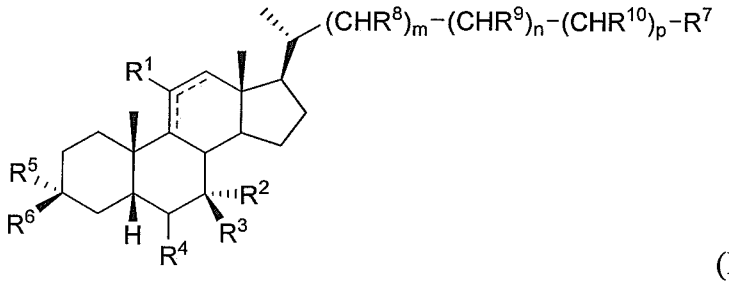
The present disclosure further provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof, and a pharmaceutically acceptable carrier or excipient.

The present disclosure also provides a method for treating or preventing a disease or condition mediated by FXR, comprising administering to a subject in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

The present disclosure also provides for the manufacture of a medicament for treating or preventing a disease or condition mediated by FXR, wherein the medicament comprises a compound of formula I or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

The present disclosure further provides compositions, including pharmaceutical compositions, for use in treating or preventing a disease or condition mediated by FXR, wherein the composition comprises a compound of formula I or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

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 OH, alkoxy, halogen, or oxo;

R^2 and R^3 are each independently H, OH, halogen, alkyl optionally substituted with one or more halogen or OH, or R^2 and R^3 taken together with the carbon atom to which they are attached form a carbonyl;

R^4 is H, halogen, alkyl optionally substituted with one or more halogen or OH, alkenyl, or alkynyl;

R^5 and R^6 are each independently H, OH, OSO_3H, $OCOCH_3$, OPO_3H_2, halogen, or R^5 and R^6 taken together with the carbon atom to which they are attached form a carbonyl;

R^7 is OH, OSO_3H, SO_3H, OSO_2NH_2, SO_2NH_2, OPO_3H_2, PO_3H_2, CO_2H, C(O)NHOH, tetrazolyl, oxadiazolyl, thiadiazolyl, 5-oxo-1,2,4-oxadiazolyl, 5-oxo-1,2,4-thiadiazolyl,

oxazolidine-dionyl, thiazolidine-dionyl, 3-hydroxyisoxazolyl, 3-hydroxyisothiazolyl, or 2,4-difluoro-3-hydroxyphenyl;

R^8, R^9, and R^{10} are each independently H, OH, halogen, alkyl optionally substituted with one or more halogen or OH, or when R^8 and R^9 are alkyl and taken together with the carbons to which they are attached form a ring of size 3, 4, 5, or 6 atoms, or when R^9 and R^{10} are alkyl and taken together with the carbons to which they are attached form a ring of size 3, 4, 5, or 6 atoms;

m is 0, 1, or 2;

n is 0 or 1;

p is 0 or 1; and

≡ is a single or double bond, provided that when each ≡ is a single bond, then R^7 is not CO_2H when the sum of m, n, and p is 2, R^1 is OH, and R^8, R^9, and R^{10} are each H.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound as defined herein and a pharmaceutically acceptable carrier or excipient.

In yet another aspect of the present disclosure, there is provided a compound as defined herein or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof for use in treating or preventing a disease or condition in a subject in need thereof, wherein the disease or condition is mediated by FXR.

In a further aspect of the present disclosure, there is provided a use of a compound as defined herein or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof in the manufacture of a medicament for treating or preventing a disease or condition in a subject in need thereof, wherein the disease or condition is mediated by FXR.

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 the present disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. The materials, methods, and examples are illustrative only and are not intended to be limiting.

Other features and advantages of the present disclosure will be apparent from the following detailed description.

DETAILED DESCRIPTION

Definitions

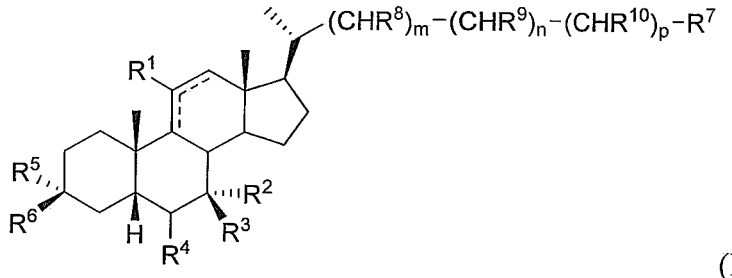
Certain terms used in the specification and claims are collected here.

As used herein, the phrase "a compound of the invention" refers to a compound of any one of formula I, II, III, IV, V, VI, VII, Ia, Ib, Ic, Id, Ie, Id, or any compound explicitly disclosed herein.

As used herein, the term "alkyl" refers to a straight-chain or branched saturated hydrocarbon moiety. The term "C_1-C_6 alkyl" refers to a straight-chain or branched hydrocarbon moiety having 1, 2, 3, 4, 5, or 6 carbon atoms. "C_1-C_4 alkyl" refers to a

CLAIMS

1. A compound of formula I:



(I),

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

R^1 is OH, alkoxy, halogen, or oxo;

R^2 and R^3 are each independently H, OH, halogen, alkyl optionally substituted with one or more halogen or OH, or R^2 and R^3 taken together with the carbon atom to which they are attached form a carbonyl;

R^4 is H, halogen, alkyl optionally substituted with one or more halogen or OH, alkenyl, or alkynyl;

R^5 and R^6 are each independently H, OH, OSO_3H, $OCOCH_3$, OPO_3H_2, halogen, or R^5 and R^6 taken together with the carbon atom to which they are attached form a carbonyl;

R^7 is OH, OSO_3H, SO_3H, OSO_2NH_2, SO_2NH_2, OPO_3H_2, PO_3H_2, CO_2H, C(O)NHOH, tetrazolyl, oxadiazolyl, thiadiazolyl, 5-oxo-1,2,4-oxadiazolyl, 5-oxo-1,2,4-thiadiazolyl, oxazolidine-dionyl, thiazolidine-dionyl, 3-hydroxyisoxazolyl, 3-hydroxyisothiazolyl, or 2,4-difluoro-3-hydroxyphenyl;

R^8, R^9, and R^{10} are each independently H, OH, halogen, alkyl optionally substituted with one or more halogen or OH, or when R^8 and R^9 are alkyl and taken together with the carbons to which they are attached form a ring of size 3, 4, 5, or 6 atoms, or when R^9 and R^{10} are alkyl and taken together with the carbons to which they are attached form a ring of size 3, 4, 5, or 6 atoms;

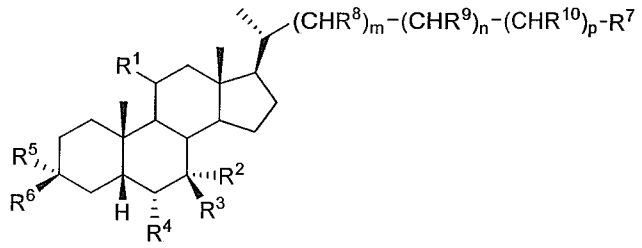
m is 0, 1, or 2;

n is 0 or 1;

p is 0 or 1; and

=== is a single or double bond, provided that when each === is a single bond, then R^7 is not CO_2H when the sum of m, n, and p is 2, R^1 is OH, and R^8, R^9, and R^{10} are each H.

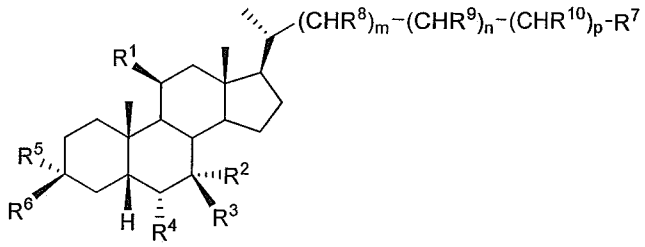
2. The compound of claim 1, wherein the compound is of formula VI:



(VI),

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

3. The compound of claim 1, wherein the compound is of formula VII:



(VII),

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

4. The compound of any one of claims 1-3, wherein R^1 is OH.

5. The compound of any one of claims 1-4, wherein R^1 is C_1-C_6 alkoxy.

6. The compound of any one of claims 1-5, wherein R^2 is OH.

7. The compound of any one of claims 1-6, wherein R^3 is H.

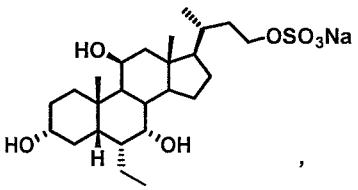
8. The compound of any one of claims 1-7, wherein R^4 is methyl, ethyl, or propyl.

9. The compound of any one of claims 1-8, wherein R^5 is OH, OSO_3H, $OCOCH_3$, or OPO_3H_2.

10. The compound of any one of claims 1-9, wherein R^7 is OH, OSO_3H, SO_3H, OSO_2NH_2, SO_2NH_2, OPO_3H_2, PO_3H_2, CO_2H, or C(O)NHOH.

11. The compound of any one of claims 1-9, wherein R^7 is tetrazolyl, oxadiazolyl, thiadiazolyl, 5-oxo-1,2,4-oxadiazolyl, 5-oxo-1,2,4-thiadiazolyl, oxazolidine-dionyl, thiazolidine-dionyl, 3-hydroxyisoxazolyl, 3-hydroxyisothiazolyl, or 2,4-difluoro-3-hydroxyphenyl.

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



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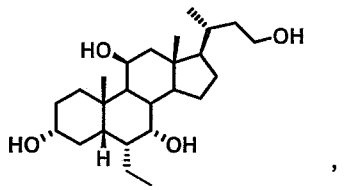

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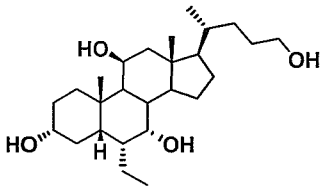
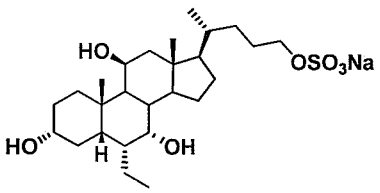


and


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13. A pharmaceutical composition comprising the compound of any one of claims 1-12 and a pharmaceutically acceptable carrier or excipient.

14. A compound of any one of claims 1-12 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof for use in treating or preventing a disease or condition in a subject in need thereof, wherein the disease or condition is mediated by FXR.

15. Use of a compound of any one of claims 1-12 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof in the manufacture of a medicament for treating or preventing a disease or condition in a subject in need thereof, wherein the disease or condition is mediated by FXR.

16. The compound or use of claim 14 or 15, wherein the disease is selected from cardiovascular disease, chronic liver disease, lipid disorder, gastrointestinal disease, renal disease, metabolic disease, cancer, and neurological disease.

17. The compound or use of claim 16, wherein the disease is cardiovascular disease selected from atherosclerosis, arteriosclerosis, dyslipidemia, hypercholesteremia, hyperlipidemia, hyperlipoproteinemia, and hypertriglyceridemia.

18. The compound or use of claim 16, wherein the disease is chronic liver disease selected from primary biliary cirrhosis (PBC), cerebrotendinous xanthomatosis (CTX), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, chronic viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver transplant associated graft versus host disease, living donor transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, Sarcoidosis, Wilson's disease, Gaucher' s disease, hemochromatosis, and alpha 1-antitrypsin deficiency.

19. The compound or use of claim 16, wherein the disease is gastrointestinal disease selected from inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), bacterial overgrowth, malabsorption, post-radiation colitis, and microscopic colitis.

20. The compound or use of claim 19, wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.

21. The compound or use of claim 16, wherein the disease is renal disease selected from diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant glomerulopathy, chronic interstitial nephritis, and polycystic kidney disease.

22. The compound or use of claim 16, wherein the disease is metabolic disease selected from insulin resistance, hyperglycemia, diabetes mellitus, diabesity, and obesity.

23. The compound or use of claim 16, wherein the disease is cancer selected from hepatocellular carcinoma, colorectal cancer, gastric cancer, renal cancer, prostate cancer, adrenal cancer, pancreatic cancer, breast cancer, bladder cancer, salivary gland cancer, ovarian cancer, uterine body cancer, and lung cancer.