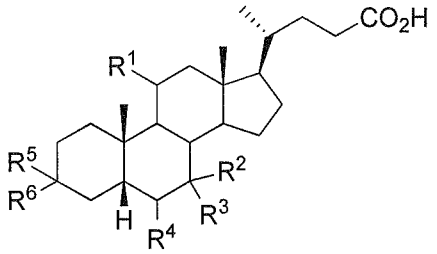
involved in bile acid and cholesterol homeostasis. Accordingly, there is a need for FXR modulators suitable for drug development. The present invention addresses this need.

SUMMARY ~~OF THE INVENTION~~

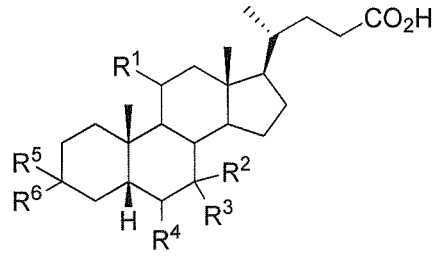
The ~~invention~~ present disclosure provides compounds and methods of preparing these compounds. Specifically, the ~~invention~~ present disclosure provides a compound of formula I:



(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 ~~invention~~ 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;

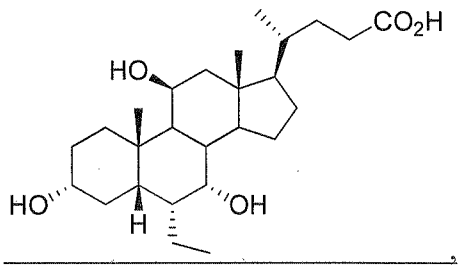
R^a, R^b, and R^c are each independently halogen or hydroxyl;

R^5 is hydroxyl, OSO_3H, OSO_3^-, $OCOCH_3$, OPO_3H, OPO_3^{2-}, or hydrogen; and

R^6 is hydroxyl, OSO_3H, OSO_3^-, $OCOCH_3$, OPO_3H, OPO_3^{2-}, or hydrogen;

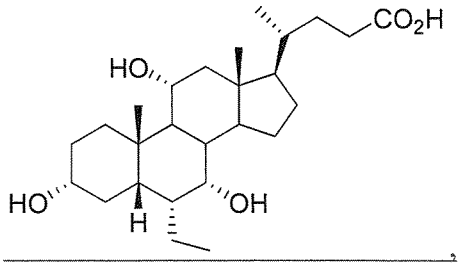
or taken together R^5 and R^6 with the carbon atom to which they are attached form a carbonyl.

In another aspect of the present disclosure, there is provided a compound of the following formula:



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

In yet another aspect of the present disclosure, there is provided a compound of the following formula:



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

In a further aspect of ~~T~~the ~~invention~~ present disclosure, there is ~~also~~ provided~~s~~ a pharmaceutical composition comprising a compound of the ~~invention~~ present disclosure or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof, and a pharmaceutically acceptable carrier or excipient.

The ~~invention~~ present disclosure also provides a method for the treatment or prevention of a disease and condition, comprising administering to the subject in need thereof an effective amount of a compound of the ~~invention~~ present disclosure or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof. In one ~~aspect~~embodiment, the disease or condition is FXR-mediated.

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

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.

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 ~~invention~~ 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 ~~invention~~ 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 ~~invention~~ 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

described herein can be used in the practice or testing of the present ~~invention~~disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the ~~claimed invention~~present disclosure. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

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

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the activity of a compound of the invention and a comparison compound in a transactivation assay in HEK293T cells

Figure 2 is a series of graphs showing the lack of TGR5 activity of a compound of the invention in human enteroendocrine cells expressing TGR5 at physiological level (A) and in human Chinese hamster ovary (CHO) cells over-expressing TGR5 (B).

Figure 3 is a series of graphs showing the activity of a compound of the invention and other comparison compounds in regulating expression of OSTα (A), OSTβ (B), BSEP (C), MRP2 (D), CYP7A1 (E), SHP (F), FGF-19 (G), and UGT2B4 (H).

Figure 4 is a series of graphs showing the activity of a compound of the invention and other comparison compounds in regulating PLTP involved in lipid metabolism (A), SREBP-1C (B), APOCII (C), and PPARγ (D).

Figure 5 is a graph showing the regulation of a compoundd of the invention and other comparison compounds on PEPCK gene.

Figure 6 is a graph showing the measurement of ATP in HepG2 cells, treated with the indicated concentrations of a compound of the invention for 4 h.

Figure 7 is a series of graphs showing the choleretic effect of Compound 100 for id and iv administration (A), the secretion of Compound 100 over time for id and iv administration (B), and the plasma concentration of Compound 100 over time (C).

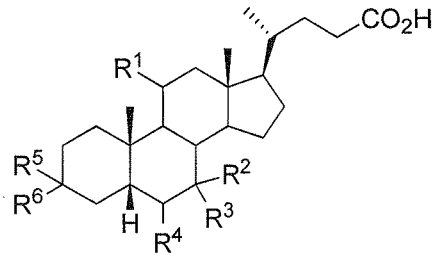
DETAILED DESCIRPTION OF THE INVENTION

Compounds of the invention

The present invention relates to a compound of formula I:

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

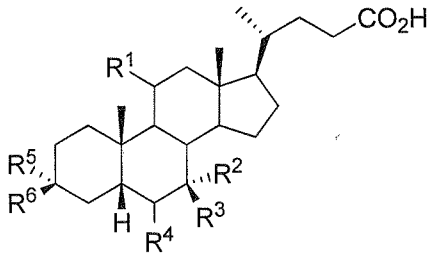
R^a, R^b, and R^c are each independently halogen or hydroxyl;

R^5 is hydroxyl, OSO_3H, OSO_3^-, $OCOCH_3$, OPO_3H, OPO_3^{2-}, or hydrogen; and

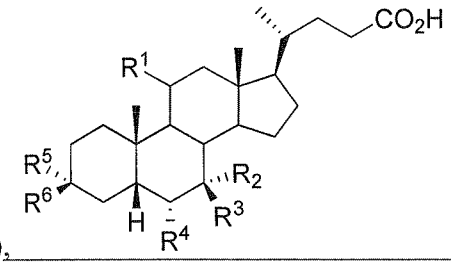
R^6 is hydroxyl, OSO_3H, OSO_3^-, $OCOCH_3$, OPO_3H, OPO_3^{2-}, or hydrogen;

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

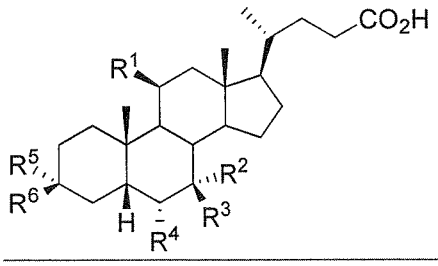
2. The compound of claim 1, wherein the compound is of a formula selected from the group consisting of: ~~having formula II:~~



(II),



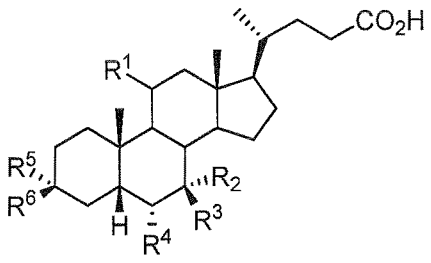
(III), and



(IV),

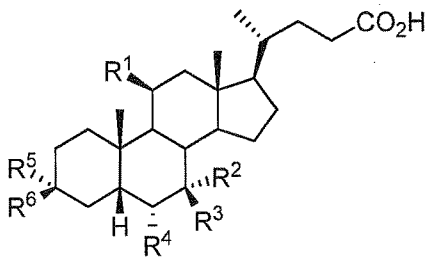
or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

~~3. The compound of claim 1, having formula III:~~



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

4. The compound of claim 1, having formula IV:



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

5. The compound of any one of claims 1-4, wherein the compound is the compound.

6. The compound of any one of claims 1-4, wherein the compound is the pharmaceutically acceptable salt.

7. The compound of any one of claims 1-4, wherein the compound is the amino acid conjugate.

8. The compound of claim 7, wherein the amino acid conjugate is a glycine conjugate.

9. The compound of claim 7, wherein the amino acid conjugate is a taurine conjugate.

10. The compound of any one of claims 1-9, wherein one of R^2 or R^3 is hydroxyl or halogen and the remaining R^2 or R^3 is hydrogen or unsubstituted alkyl.

11. The compound of claim 10, wherein one of R^2 or R^3 is hydroxyl and the remaining R^2 or R^3 is hydrogen.

12. The compound of any one of claims 1-11, wherein one of R^5 or R^6 is hydroxyl and the remaining R^5 or R^6 is hydrogen.

13. The compound of any one of claims 1-12, wherein R^2 is hydroxyl or halogen.

14. The compound of claim 13, wherein R^2 is hydroxyl.

15. The compound of claim 13, wherein R^2 is halogen.

16. The compound of any one of claims 1-12, wherein R^3 is hydrogen or unsubstituted alkyl.

17. The compound of claim 16, wherein R^3 is hydrogen.

18. The compound of claim 16, wherein R^3 is methyl.

19. The compound of any one of claims 1-12, wherein R^2 is hydroxyl and R^3 is hydrogen.

20. The compound of any one of claims 1-19, wherein R^5 is hydroxyl.

21. The compound of claim 20, wherein R^6 is hydrogen.

22. The compound of any one of claims 1-14 and 16-21, wherein R^2 and R^5 are each hydroxyl and R^3 and R^6 are each hydrogen.

23. The compound of any one of claims 1-22, wherein R^4 is alkyl or hydrogen.

24. The compound of claim 23, wherein R^4 is unsubstituted alkyl.

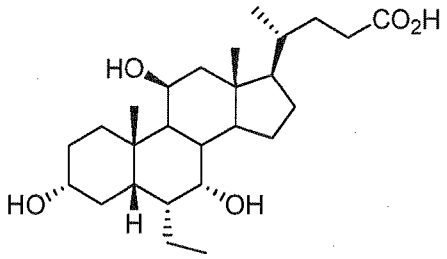
25. The compound of claim 24, wherein R^4 is methyl, ethyl, propyl, or butyl.

26. The compound of claim 25, wherein R^4 is methyl or ethyl.

27. The compound of claim 26, wherein R^4 is methyl.

28. The compound of claim 26, wherein R^4 is ethyl.

29. The compound of claim 1, having the following formula:



(100),

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

30. The compound of any one of claims 1-29, wherein the compound is an FXR agonist.

31. The compound of any one of claims 1-30, wherein the compound is not active against other nuclear receptors.

32. The compound of any one of claims 1-29, wherein the compound does not activate TGR5.

33. The compound of any one of claims 1-32, wherein the compound induces apoptosis.

34. The compound of any one of claims 1-33, wherein the compound shows no cytotoxic effect on human HepG2 liver cells.

35. The compound of any one of claims 1-34, wherein the compound does not inhibit one or more CYP450 isoforms selected from CYP1A2, CYP3A4 (green substrate), CYP3A4 (blue substrate), CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

36. The compound of any one of claims 1-35, wherein the compound does not inhibit the human ERG potassium channel.

37. A method of synthesizing a compound according to any one of claims 1-29 or a pharmaceutically acceptable salt, solvate or amino acid conjugate thereof.

38. A kit containing one or more compounds according to any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjutate thereof.

39. The kit of claim 38 further containing a pharmaceutically acceptable ingredient.

40. A pharmaceutical composition comprising a compound of any one of claims 1-29 and a pharmaceutically acceptable excipient.

41. A method of treating or preventing a disease or condition in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjutate thereof.

42. The method of claim 41, wherein the disease or condition is an FXR-mediated disease or condition.

43. The method of claim 42, wherein the disease or condition is mediated by decreased FXR activity.

44. The method of any one of claims 41-43, wherein said disease is selected from cardiovascular disease, chronic liver disease, lipid disorder, gastrointestinal disease, renal disease, metabolic disease, cancer, and neurological disease.

45. The method of claim 44, wherein the disease is cardiovascular disease selected from atherosclerosis, arteriosclerosis, dyslipidemia, hypercholesteremia, hyperlipidemia, hyperlipoproteinemia, and hypertriglyceridemia.

46. The method of claim 44, 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.

47. The method of claim 44, 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.

48. The method of claim 47, wherein the inflammatory bowel disease is selected from Crohn's disease and ulcerative colitis.

49. The method of claim 44, 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.

50. The method of claim 44, wherein the disease is metabolic disease selected from insulin resistance, hyperglycemia, diabetes mellitus, diabesity, and obesity.

51. The method of claim 50, wherein the diabetes mellitus is type I diabetes.

52. The method of claim 50, wherein the diabetes mellitus is type II diabetes.

53. The method of claim 44, wherein the disease is cancer.

54. The method of claim 53, wherein the cancer is colorectal cancer.

55. A method of reducing cholesterol levels and/or modulating cholesterol metabolism, catabolism, absorption of dietary cholesterol, and reverse cholesterol transport in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

56. A method of treating or preventing a disease affecting cholesterol, triglyceride, or bile acid levels in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

57. A method of treating or preventing one or more symptoms of disease affecting lipid metabolism in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or a amino acid conjugate thereof.

58. A method of treating or preventing a disease state associated with an elevated cholesterol level in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

59. The method of claim 58, wherein the disease state is selected from coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma.

60. A method of treating or preventing one or more symptoms of cholestasis in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

61. A method of treating or preventing gallstones in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

62. A method of lowering triglycerides in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

63. A method of treating or preventing metabolic syndrome in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

64. A method of treating or preventing cholesterol gallstone disease in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

65. A method of decreasing lipid accumulation in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

66. A method of enhancing liver regeneration in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

67. The method of claim 66, wherein the method is enhancing liver regeneration for liver transplantation.

68. A method of treating or preventing fibrosis in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

69. A method of treating or preventing organ fibrosis in a subject comprising administering to the subject in need thereof an effective amount of a compound of any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

70. The method of claim 69, wherein the fibrosis is liver fibrosis.

71. The method of claim 44, wherein the disease is neurological disease.

72. The method of claim 71, wherein the neurological diease is stroke.

73. The method of any one of claims 41-72, wherein the compound or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof is administered by a route selected from oral, parenteral, intramuscular, intranasal, sublingual, intratracheal, inhalation, ocular, vaginal, rectal, and intracerebroventricular.

74. The method of claim 73, wherein the route is oral.

75. The method of any one of claims 41-74, wherein the compound is an FXR agonist.

76. The method of claim 75, wherein the compound is a selective FXR agonist.

77. The method of any one of claims 41-76, wherein the compound does not activate TGR5.

78. The method of any one of claims 41-77, wherein the compound induces apoptosis.

79. A method of regulating the expression level of one or more genes in a cell, wherein said genes are involved in bile acid homeostasis by administereing to the cell a compound according to any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

80. A method of down regulating the expression level of one or more genes selected from CYP7α1 and SREBP-1C in a cell by administering to the cell a compound according to any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

81. A method of up regulating the expression level of one or more genes selected from OSTα, OSTb, BSEP, SHP, UGT2B4, MRP2, FGF-19, PPARγ, PLTP, APOCII, and PEPCK in a cell by administering to the cell a compound according to any one of claims 1-29 or a pharmaceutically acceptable salt, solvate, or amino acid conjugate thereof.

3. The compound of claim 1 or 2, wherein one of R^2 or R^3 is hydroxyl or halogen and the remaining R^2 or R^3 is hydrogen or unsubstituted alkyl.

4. The compound of any one of claims 1-3, wherein one of R^2 or R^3 is hydroxyl and the remaining R^2 or R^3 is hydrogen.

5. The compound of any one of claims 1-4, wherein one of R^5 or R^6 is hydroxyl and the remaining R^5 or R^6 is hydrogen.

6. The compound of any one of claims 1-3, wherein R^2 is hydroxyl or halogen.

7. The compound of claim 1 or 2, wherein R^3 is hydrogen or unsubstituted alkyl.

8. The compound of claim 7, wherein R^3 is methyl.

9. The compound of any one of claims 1-7, wherein R^2 is hydroxyl and R^3 is hydrogen.

10. The compound of any one of claims 1-9, wherein R^5 is hydroxyl.

11. The compound of any one of claims 1-10, wherein R^6 is hydrogen.

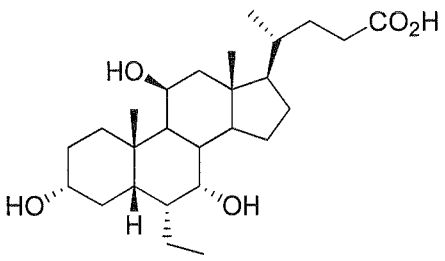
12. The compound of any one of claims 1-7 and 9-11, wherein R^2 and R^5 are each hydroxyl and R^3 and R^6 are each hydrogen.

13. The compound of any one of claims 1-12, wherein R^4 is alkyl.

14. The compound of any one of claims 1-13, wherein R^4 is unsubstituted alkyl.

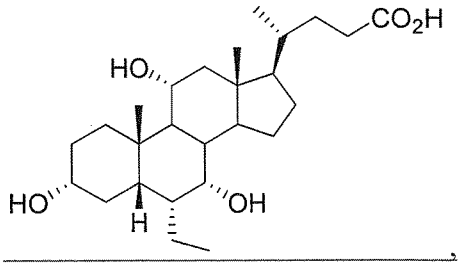
15. The compound of any one of claims 1-14, wherein R^4 is ethyl.

16. A compound of the following formula:



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.

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. 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. The compound of claim 21, 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.