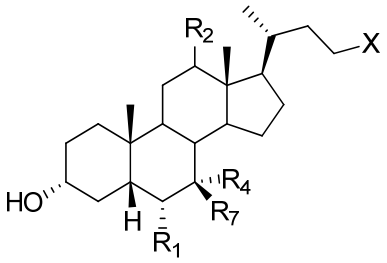
The present disclosure also relates to a pharmaceutical composition comprising (i) a first compound, (ii) at least one fibrate, (iii) at least one statin, and optionally (iv) one or more pharmaceutically acceptable carriers, wherein the first compound is an FXR agonist.

The present disclosure also relates to the therapeutic use of the pharmaceutical compositions of the present disclosure.

In one embodiment, the first compound is a compound of formula A:



(A)

or a pharmaceutically acceptable salt or amino acid conjugate thereof, wherein R_1, R_2, R_4, R_7, and X are as defined herein.

The present disclosure also relates to methods for treating or preventing an FXR mediated disease or condition or a disease or condition in which elevated concentrations of circulating lipid compounds in the blood are involved, reducing the level of a liver enzyme, or inhibiting or reversing fibrosis, comprising administering a therapeutically effective amount of a pharmaceutical composition of the present disclosure to a subject in need thereof.

The present disclosure also relates to use of a pharmaceutical composition of the present disclosure for treating or preventing an FXR mediated disease or condition or a disease or condition in which elevated concentrations of circulating lipid compounds in the blood are involved, reducing the level of a liver enzyme, or inhibiting or reversing fibrosis.

In another aspect of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating or preventing an FXR mediated disease or condition or a condition related to elevated lipid levels, wherein the disease or condition is selected from primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), portal hypertension, bile acid diarrhea, a chronic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C infection, an alcoholic liver disease, liver damage due to progressive fibrosis, liver fibrosis, a cardiovascular disease, and hyperlipidemia.

In a aspect of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating or preventing an FXR mediated disease or condition or a condition related to elevated lipid levels, wherein the condition is selected from resistant primary biliary cirrhosis; primary biliary cirrhosis where there is associated liver function test elevation and hyperlipidemia; primary sclerosing cholangitis; non-alcohol-induced steatohepatitis; chronic liver disease associated with hepatitis B, C or alcohol; hyperlipidemia where the hyperlipidemia is primary hyperlipidemia with or without a genetic component; and hyperlipidemia associated with coronary artery disease, cerebrovascular arterial disease, peripheral vascular disease, aortic aneurisms, or carotid atherosclerosis.

In yet another aspect of the present disclosure, there is provided a use of the pharmaceutical composition as described herein in the manufacture of a medicament for inhibiting or reversing fibrosis.

In a further aspect of the present disclosure, there is provided the pharmaceutical composition as described herein for use in treating or preventing an FXR mediated disease or condition or a condition related to elevated lipid levels.

In another aspect of the present disclosure, there is provided the pharmaceutical composition as described herein for use in inhibiting or reversing fibrosis.

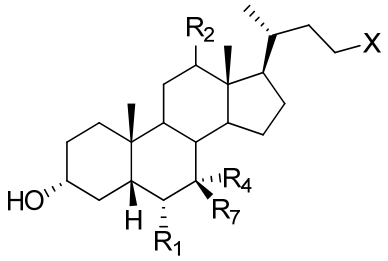
The present disclosure also relates to use of a pharmaceutical composition of the present disclosure in the manufacture of a medicament for treating or preventing an FXR mediated disease or condition or a disease or condition in which elevated concentrations of circulating lipid compounds in the blood are involved, reducing the level of a liver enzyme, or inhibiting or reversing fibrosis.

The compositions and methods of the present disclosure address unmet needs in the treatment or prevention of a disease or disorder in which elevated concentrations of circulating lipid compounds in the blood, such as cholesterol and triglycerides, are involved.

CLAIMS

1. A pharmaceutical composition comprising an FXR agonist, at least one PPAR-alpha agonist, and/or at least one PPAR-delta agonist, and/or at least one PPAR-alpha and delta dual agonist, and optionally one or more pharmaceutically acceptable carriers, wherein:

the FXR agonist is a compound of formula A:



(A),

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

R_1 is hydrogen or unsubstituted C_1-C_6 alkyl;

R_2 is hydrogen or α-hydroxyl;

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

R_4 is hydroxyl or hydrogen;

R_7 is hydroxyl or hydrogen;

m is 1 , 2, or 3; and

n is 1 , 2, or 3;

the at least one PPAR-alpha agonist is a fibrate;

the at least one PPAR-delta agonist is {4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]-2-methylphenoxy}acetic acid, {2-methyl-4-[5-methyl-2-(4-trifluoromethyl-phenyl)-2H-[1,2,3]triazol-4-ylmethylsylfanyl]-phenoxy}-acetic acid, or [4-[[[2-[3-fluoro-4-(trifluoromethyl)phenyl] -4-methyl-5 -thiazolyl] methyl] thio]-2 -methyl phenoxy]-acetic acid, or a pharmaceutically acceptable salt thereof; and

the at least one PPAR-alpha and delta dual agonist is 2-[2,6 dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl]phenoxyl]-2-methylpropanoic acid, (2S)-2-methoxy-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-7-benzothiophenyl]propanoic acid, N-[(4-methoxyphenoxy)carbonyl]-N-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}glycine, (2S)-2-ethoxy-3-[4-[2-(4-methylsulfonyloxyphenyl)ethoxy]phenyl]propanoic acid, or (2S)-2-ethoxy-3-[4-(2-{2-methyl-5-[4-(methylsulfanyl)phenyl]-1H-pyrrol-1-yl}ethoxy)phenyl]propanoic acid, or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition of claim 1, wherein the fibrate is selected from bezafibrate, ciprofibrate, clofibrate, fenofibrate, gemfibrozil, binifibrate, clinofibrate, clofibric acid, nicofibrate, pirifibrate, plafibride, ronifibrate, theofibrate, and tocofibrate, or a pharmaceutically acceptable salt or ester thereof, and a derivative of 2-phenoxy-2-methylpropanoic acid in which the phenoxy moiety is substituted with an optionally substituted piperidine, 4-hydroxypiperidine, piperid-3-ene or piperazine.

3. The pharmaceutical composition of claim 2, wherein the fibrate is bezafibrate.

4. The pharmaceutical composition of claim 2, wherein the fibrate is 2-[3-[1-(4-fluorobenzoyl)-piperidin-4-yl]phenoxyl-2-methylpropanoic acid.

5. The pharmaceutical composition of any one of claims 1-4, further comprising a statin.

6. The pharmaceutical composition of claim 5, wherein the statin is selected from simvastatin, fluvastatin, pravastatin, rivastatin, mevastatin, atorvastatin, cerivastatin, lovastatin, pitavastatin, fluindostatin, velostatin, dalvastatin, rosuvastatin, dihydrocompactin, and compactin.

7. The pharmaceutical composition of any one of claims 1-6, wherein R_1 is unsubstituted C_1-C_6 alkyl.

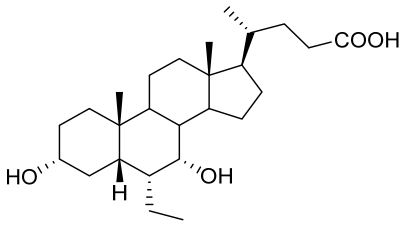
8. The pharmaceutical composition of claim 7, wherein R_1 is methyl, ethyl, or propyl.

9. The pharmaceutical composition of claim 8, wherein R_1 is ethyl.

10. The pharmaceutical composition of any one of claims 1 to 9, wherein X is selected from C(O)OH, $C(O)NH(CH_2)SO_3H$, $C(O)NH(CH_2)CO_2H$, $C(O)NH(CH_2)_2SO_3H$, and $C(O)NH(CH_2)_2CO_2H$.

11. The pharmaceutical composition of any one of claims 1 to 9, wherein X is C(O)OH.

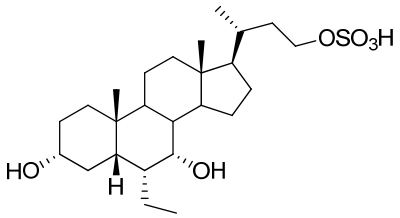
12. The pharmaceutical composition of claim 1, wherein the FXR agonist is a compound of formula (1):



(1)

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

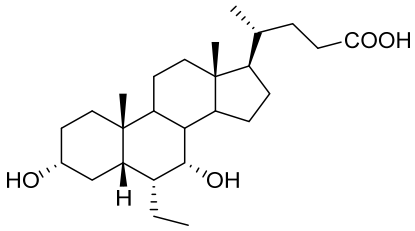
a compound of formula (2):



(2)

or a pharmaceutically acceptable salt thereof.

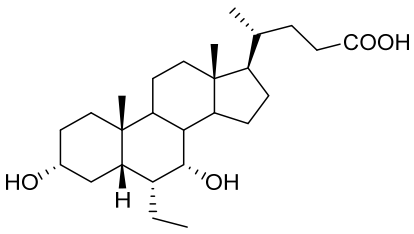
13. The pharmaceutical composition of claim 12, wherein the FXR agonist is a compound of formula (1):



(1)

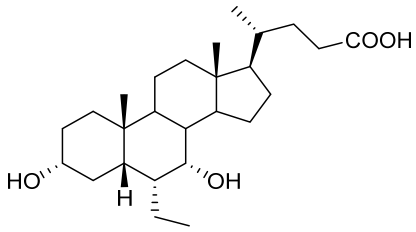
or a pharmaceutically acceptable salt or amino acid conjugate thereof.

14. The pharmaceutical composition of claim 12, wherein the FXR agonist is a compound of formula (1):



(1).

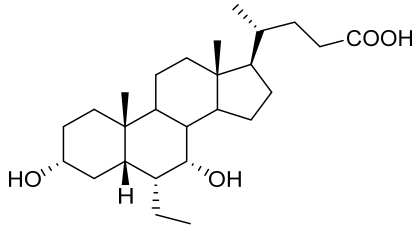
15. The pharmaceutical composition of claim 1, comprising an FXR agonist and bezafibrate, wherein the FXR agonist is a compound of formula (1):



(1)

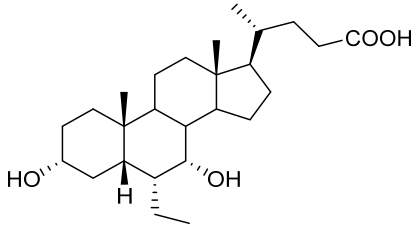
or a pharmaceutically acceptable salt or amino acid conjugate thereof.

16. The pharmaceutical composition of claim 15, wherein the FXR agonist is a compound of formula (1):



(1).

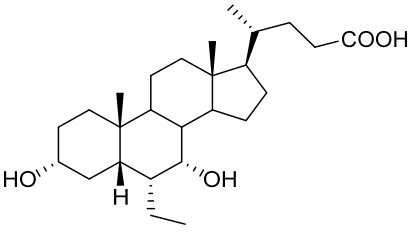
17. The pharmaceutical composition of claim 12, comprising a two-way combination of an FXR agonist and bezafibrate, wherein the FXR agonist is a compound of formula (1):



(1)

or a pharmaceutically acceptable salt or amino acid conjugate thereof.

18. The pharmaceutical composition of claim 17, wherein the FXR agonist is a compound of formula (1):



(1).

19. Use of the pharmaceutical composition of any one of claims 1-18 in the manufacture of a medicament for treating or preventing an FXR mediated disease or condition or a condition related to elevated lipid levels, wherein the disease or condition is selected from primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), portal hypertension, bile acid diarrhea, a chronic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C infection, an alcoholic liver disease, liver damage due to progressive fibrosis, liver fibrosis, a cardiovascular disease, and hyperlipidemia.

20.Use of the pharmaceutical composition of any one of claims 1-18 in the manufacture of a medicament for treating or preventing an FXR mediated disease or condition or a condition related to elevated lipid levels, wherein the condition is selected from resistant primary biliary cirrhosis; primary biliary cirrhosis where there is associated liver function test elevation and hyperlipidemia; primary sclerosing cholangitis; non-alcohol-induced steatohepatitis; chronic liver disease associated with hepatitis B, C or alcohol; hyperlipidemia where the hyperlipidemia is primary hyperlipidemia with or without a genetic component; and hyperlipidemia associated with coronary artery disease, cerebrovascular arterial disease, peripheral vascular disease, aortic aneurisms, or carotid atherosclerosis.

21. Use of the pharmaceutical composition of any one of claims 1-18 in the manufacture of a medicament for inhibiting or reversing fibrosis.

22. The use of claim 21, wherein the fibrosis is selected from liver fibrosis, kidney fibrosis, and intestinal fibrosis.

23. The pharmaceutical composition of any one of claims 1-18 for use in treating or preventing an FXR mediated disease or condition or a condition related to elevated lipid levels.

24. The pharmaceutical composition of any one of claims 1-18 for use in inhibiting or reversing fibrosis.