COMBINATION TREATMENT OF LIVER DISORDERS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of U.S. Provisional Application No. 63/024,360, filed May 13, 2020, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates to methods and compositions for treating liver disorder in a patient.

BACKGROUND

[0003] Fatty liver disease (FLD) encompasses a spectrum of disease states characterized by excessive accumulation of fat in the liver often accompanied with inflammation. FLD can lead to non-alcoholic fatty liver disease (NAFLD), which may be characterized by insulin resistance. If untreated, NAFLD can progress to a persistent inflammatory response or non-alcoholic steatohepatitis (NASH), progressive liver fibrosis, and eventually to cirrhosis. In Europe and the US, NAFLD is the second most common reason for liver transplantation. Accordingly, the need for treatment is urgent, but due to the lack of obvious symptoms to the patient, patients may lack the motivation to maintain treatment regimens, particularly burdensome treatment regimens, such as injected medicines, medications that are administered many times a day, or any that produce dangerous or irritating side effects. There is currently no approved treatment of NASH.

BRIEF SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a use of a Farnesoid X Receptor (FXR) agonist and a THRβ agonist in the manufacture of a medicament for treating a liver disorder in a patient in need thereof, wherein the liver disorder is selected from the group consisting of liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

[0003b] In another aspect of the present disclosure, there is provided a use of a FXR agonist and a THRβ agonist in the manufacture of a medicament for reducing hepatic inflammation in a patient in need thereof.

[0003c] In a further aspect of the present disclosure, there is provided a use of a FXR agonist and a THRβ agonist in the manufacture of a medicament for reducing hepatic inflammation in a patient in need thereof without increasing LDL-C levels in the patient.

[0003d] In another aspect of the present disclosure, there is provided a use of a FXR agonist and a THRβ agonist in the manufacture of a medicament for reducing leukocyte activation in a patient with a disorder characterized by high leukocyte levels in the liver.

[0003e] In a further aspect of the present disclosure, there is provided a use of a FXR agonist and a THRβ agonist in the manufacture of a medicament for treating NASH in a patient in need thereof, wherein the THRβ agonist is to be administered to the patient at a dose that reduces LDL-C levels in the patient.

[0003f] In another aspect of the present disclosure, there is provided a use of a FXR agonist and a THRβ agonist in the manufacture of a medicament for treating NASH in a patient in need thereof, wherein the THRβ agonist is to be administered to the patient at a dose that prevents an increase in LDL-C levels in the patient.

[0003g] In a further aspect of the present disclosure, there is provided a use of a FXR agonist and a THRβ agonist in the manufacture of a medicament for treating a disease or condition characterized by fibrosis of the liver in a patient in need thereof.

[0003g] In a further aspect of the present disclosure, there is provided a use of a FXR agonist and a THRβ agonist in the manufacture of a medicament for inhibiting the expression of fibroblast genes responsible for the production of collagen in the extracellular matrix of the liver of a patient in need thereof.

[0004] Provided herein are methods and compositions for treating a liver disorder in a patient in need thereof. The methods comprise administering to the patient a Farnesoid X Receptor (FXR) agonist and a thyroid hormone receptor beta (THRβ) agonist.

[0005] In one ~~aspect~~example, the disclosure provides methods of reducing hepatic inflammation in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a FXR agonist and a therapeutically effective amount of a THRβ agonist. The administration of a combination of a FXR agonist and a THRβ agonist reduces hepatic inflammation in a patient in need thereof to a significantly greater extent than administration of either agonist by itself. The reduction of hepatic inflammation is characterized by reduced

expression of inflammatory genes and markers of leukocyte activation in the liver. In some ~~embodiment~~examples, hepatic inflammation is reduced without increasing the low-density lipoprotein cholesterol (LDL-C) levels in the blood of the patient.

[0006] In another ~~aspect~~example, the disclosure provides methods of treating a disease or condition characterized by fibrosis of the liver, comprising administering to the patient a therapeutically effective amount of a FXR agonist and a therapeutically effective amount of a THRβ agonist. The administration of a combination of a FXR agonist and a THRβ agonist reduces fibrosis in a patient in need thereof to a significantly greater extent than administration of either agonist alone. The reduction of fibrosis is characterized by histological improvement and reduced expression of pro-fibrotic genes in the liver. In some ~~embodiment~~examples, hepatic fibrosis is reduced without increasing the low-density lipoprotein cholesterol (LDL-C) levels in the blood of the patient. In some ~~embodiment~~examples, administration of the FXR agonist and the THRβ agonist results in reduction of liver fibrosis and hepatic inflammation.

[0007] As set forth herein, the synergy observed when administering the combination of a FXR agonist and a THRβ agonist to patients in need thereof allows for the reduction of the dose of either or both the FXR agonist and the THRβ agonist relative to when either agonist is administered as a monotherapy. The lower doses of the FXR agonist and the THRβ agonist results in an improved therapeutic index and alleviates side effects that are sometimes accompanied with FXR agonism or THRβ agonism.

[0008] In some ~~embodiment~~examples, the administration of the FXR agonist and the THRβ agonist does not result in pruritus in the patient at a severity of Grade 2 or more. In some ~~embodiment~~examples, the administration of the FXR agonist and the THRβ agonist does not result in pruritus of Grade 1 or more. In some ~~embodiment~~examples, the administration of the FXR agonist and the THRβ agonist does not result in pruritus.

[0009] In another ~~aspect~~example, the disclosure provide methods of treating or preventing NASH in a patient in need thereof, said method comprising administering to the patient a therapeutically effective amount of a FXR agonist and a therapeutically effective amount of a THRβ agonist. In one ~~embodiment~~example, the patient in need thereof is a patient that suffers from fatty liver disease such as NAFLD. In another ~~embodiment~~example, the patient in need thereof is a patient that suffers from metabolic syndrome.

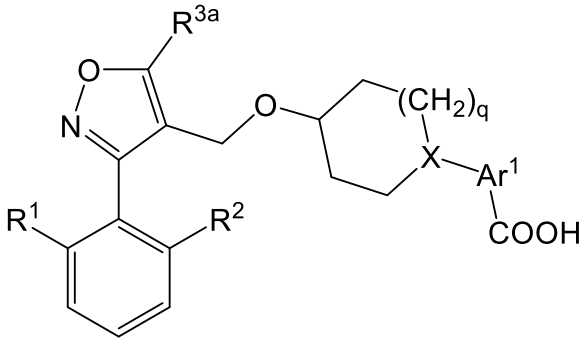
[0010] In some ~~embodiment~~examples, the FXR agonist and the THRβ agonist are administered simultaneously. In some such ~~embodiment~~examples, the FXR agonist and the THRβ agonist are provided as a fixed-dose composition in a single pharmaceutical composition as set forth herein. In other ~~embodiment~~examples, the FXR agonist and the THRβ agonist are administered sequentially. In some ~~embodiment~~examples, either or both of the FXR agonist and the THRβ agonist are administered orally.

[0011] In some ~~embodiment~~examples, the patient has a liver disorder and diabetes mellitus. In some ~~embodiment~~examples, the patient has a liver disorder and a cardiovascular disorder. In some ~~embodiment~~examples, the treatment period is the remaining lifespan of the patient. In some ~~embodiment~~examples, the method does not comprise administering an antihistamine, an immunosuppressant, a steroid, rifampicin, an opioid antagonist, or a selective serotonin reuptake inhibitor (SSRI).

[0012] In some ~~embodiment~~examples, the FXR agonist is administered once daily. In some ~~embodiment~~examples, the FXR agonist is administered twice daily. In some ~~embodiment~~examples, the THRβ agonist is administered once daily. In some ~~embodiment~~examples, the THRβ agonist is administered twice daily. In some ~~embodiment~~examples, the administration comprises administering the FXR agonist daily for a treatment period of one or more weeks. In some ~~embodiment~~examples, the administration comprises administering the THRβ agonist daily for a treatment period of one or more weeks. In some ~~embodiment~~examples, the administration comprises administering the FXR agonist daily and the THRβ agonist daily for a treatment period of one or more weeks.

[0013] A variety of different FXR agonists and THRβ agonist can be used to achieve the beneficial effects observed on liver disease as discussed herein. For instance, in some ~~embodiment~~examples, the FXR agonist administered to the patient in need thereof is obeticholic acid. In some ~~embodiment~~examples, the FXR agonist administered to the patient in need thereof is cilofexor. In some ~~embodiment~~examples, the FXR agonist administered to the patient in need thereof is tropifexor. In some ~~embodiment~~examples, the FXR agonist administered to the patient in need thereof is EYP001 (Vonafexor, proposed INN). In some ~~embodiment~~examples, the FXR agonist administered to the patient in need thereof is MET642 (Metacrine). In some ~~embodiment~~examples, the FXR agonist administered to the patient in need thereof is MET409 (Metacrine). In some ~~embodiment~~examples, the FXR agonist is EDP-305 (by Enanta). In some ~~embodiment~~examples, the FXR agonist is EDP-297 (by Enanta).

[0014] In some ~~embodiment~~examples, the FXR agonist administered to the patient in need thereof is a compound of formula (I):



(I)

wherein:

q is 1 or 2;

R^1 is chloro, fluoro, or trifluoromethoxy;

R^2 is hydrogen, chloro, fluoro, or trifluoromethoxy;

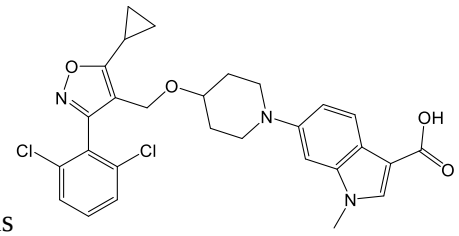
R^{3a} is trifluoromethyl, cyclopropyl, or isopropyl;

X is CH or N,
provided that when X is CH, q is 1; and

Ar^1 is indolyl, benzothienyl, naphthyl, phenyl, benzoisothiazolyl, indazolyl, or pyridinyl, each of which is optionally substituted with methyl or phenyl,

or a pharmaceutically acceptable salt thereof.

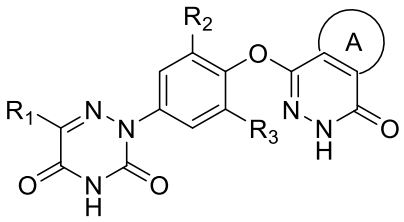
[0015] In some ~~embodiment~~examples, the FXR agonist administered to the patient in need thereof is a compound of formula (I) wherein R^1 is chloro or trifluoromethoxy. In some ~~embodiment~~examples, the FXR agonist is a compound of formula (I) wherein R^2 is hydrogen or chloro. In some ~~embodiment~~examples, the FXR agonist is a compound of formula (I) wherein R^{3a} is cyclopropyl or isopropyl. In some ~~embodiment~~examples, the FXR agonist is a compound of formula (I) wherein Ar^1 is 5-benzothienyl, 6-benzothienyl, 5-indolyl, 6-indolyl, or 4-phenyl, each of which is optionally substituted with methyl. In some ~~embodiment~~examples, the FXR agonist is a compound of formula (I) wherein q is 1 and X is N.

[0016] In some ~~embodiment~~examples, the FXR agonist is 

or a pharmaceutically acceptable salt thereof.

[0017] In some ~~embodiment~~examples, the THRβ agonist administered to the patient in need thereof is resmetirom (MGL-3196). In some ~~embodiment~~examples, the THRβ agonist is administered to the patient in need thereof VK2809 (by Viking Therapeutics). In some ~~embodiment~~examples, the THRβ agonist administered to the patient in need thereof is sobetirome. In some ~~embodiment~~examples, the THRβ agonist administered to the patient in need thereof is eprotirome. In some ~~embodiment~~examples, the THRβ agonist administered to the patient in need thereof is ALG-055009 (by Aligo). In some ~~embodiment~~examples, the THRβ agonist administered to the patient in need thereof is CNPT-101101. In some ~~embodiment~~examples, the THRβ agonist administered to the patient in need thereof is CNPT-101207. In some ~~embodiment~~examples, the THRβ agonist administered to the patient in need thereof is ASC41 (by Ascletis).

[0018] In some ~~embodiment~~examples, the THRβ agonist is a compound of Formula (II)



(II)

wherein:

R_1 is selected from the group consisting of hydrogen, cyano, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{3-6} cycloalkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C_{1-6} alkoxy;

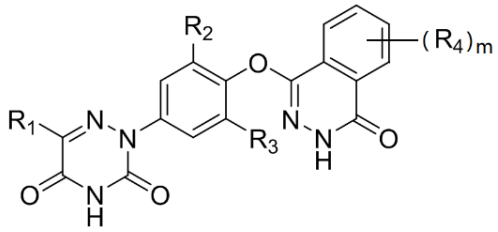
R_2 and R_3 are each independently selected from the group consisting of halogen atoms and substituted or unsubstituted C_{1-6} alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C_{1-6} alkoxy;

ring A is a substituted or unsubstituted saturated or unsaturated C_{5-10} aliphatic ring, or a substituted or unsubstituted C_{5-10} aromatic ring, the substituent being one or more substances selected from the group consisting of hydrogen, halogen atoms, hydroxy, $-OCF_3$, $-NH_2$, $-NHC_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl$)_2$, $-CONH_2$, $-CONHC_{1-4}$ alkyl, $-CON(C_{1-4}$ alkyl$)_2$, $-NHCOC_{1-4}$ alkyl, C_{1-6} alkyl, C_{1-6} alkoxy or C_{3-6} cycloalkyl, and when two substituents are contained, the two substituents can form a ring structure together with the carbon connected thereto; and

the halogen atoms are selected from the group consisting of F, Cl and Br,

or a pharmaceutically acceptable salt thereof.

[0019] In some ~~embodiment~~examples, the THRβ agonist administered to the patient in need thereof is a compound of Formula (IIa)



(IIa)

wherein:

R_1 to R_3 are defined as detailed herein for Formula (II);

R_4 is selected from the group consisting of hydrogen, halogen atoms, hydroxy, $-OCF_3$, $-NH_2$, $-NHC_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl$)_2$, $-CONH_2$, $-CONHC_{1-4}$ alkyl, $-CON(C_{1-4}$ alkyl$)_2$, $-NHCOC_{1-4}$ alkyl, C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl;

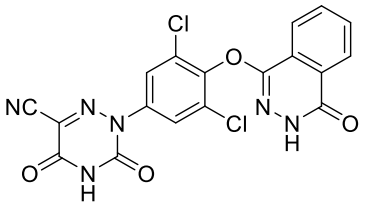
m is an integer from the range 1 to 4; and

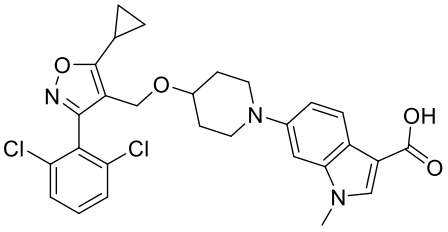
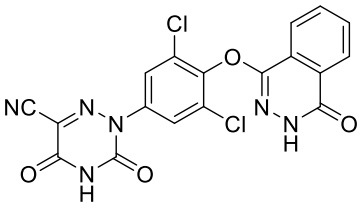
the halogen atoms are selected from the group consisting of F, Cl and Br.

or a pharmaceutically acceptable salt thereof.

[0020] In some ~~embodiment~~examples, wherein R_4 is selected from the group consisting of hydrogen, halogen atoms, hydroxy, $-OCF_3$, C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl; and m is an integer from the range 1 to 3.

[0021] In some ~~embodiment~~examples, wherein R_1 is selected from the group consisting of hydrogen, cyano, and substituted or unsubstituted C_{1-6} alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C_{1-6} alkoxy; and the halogen atoms are selected from the group consisting of F, Cl and Br.

[0022] In some ~~embodiment~~examples, the THRβ agonist is , or a pharmaceutically acceptable salt thereof.

[0023] In some ~~embodiment~~examples, provided are methods of treating a liver disorder in a patient in need thereof with a Farnesoid X Receptor (FXR) agonist and a thyroid hormone receptor beta (THRβ) agonist, comprising administering a therapeutically effective amount of the FXR agonist, wherein the FXR agonist is , or a pharmaceutically acceptable salt thereof, and administering a therapeutically effective amount of the THRβ agonist, wherein the THRβ agonist is , or a pharmaceutically acceptable salt thereof, wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

BRIEF DESCRIPTION OF THE FIGURES

[0024] FIG. 1A shows plasma concentrations of Compound 1 at various time points after intravenous (IV) administration to rats (1 mg/kg), dogs (1 mg/kg) and monkeys (0.3 mg/kg).

CLAIMS

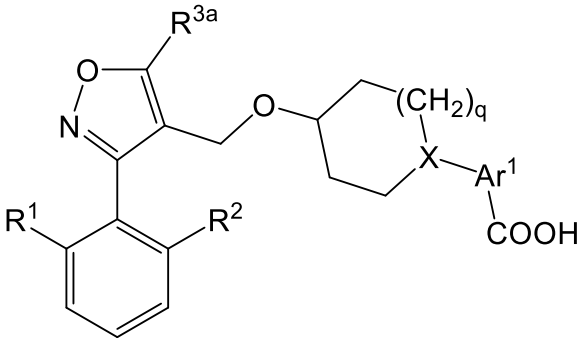
What is claimed is:

1. ~~A method of treating a liver disorder in a patient in need thereof, comprising administering to the patient~~ Use of a Farnesoid X Receptor (FXR) agonist and a THRβ agonist in the manufacture of a medicament for treating a liver disorder in a patient in need thereof, wherein the liver disorder is selected from the group consisting of liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

2. The ~~method~~use of claim 1, wherein the FXR agonist is obeticholic acid, cilofexor, tropifexor, EYP001 (Vonafexor, proposed INN), MET409 (Metacrine), or EDP-305 (by Enanta).

3. The ~~method~~use of claim 1 or 2, wherein the THRβ agonist is resmetirom (MGL-3196), VK2809 (by Viking Therapeutics), sobetirome, eprotirome, CNPT-101101, CNPT-101207, or ALG-055009 (by Aligo).

4. The ~~method~~use of claim 1, wherein the FXR agonist is a compound of formula (I)



(I)

wherein:

q is 1 or 2;

R^1 is chloro, fluoro, or trifluoromethoxy;

R^2 is hydrogen, chloro, fluoro, or trifluoromethoxy;

R^{3a} is trifluoromethyl, cyclopropyl, or isopropyl;

X is CH or N,

provided that when X is CH, q is 1; and

Ar^1 is indolyl, benzothienyl, naphthyl, phenyl, benzoisothiazolyl, indazolyl, or pyridinyl, each of which is optionally substituted with methyl or phenyl,
or a pharmaceutically acceptable salt thereof.

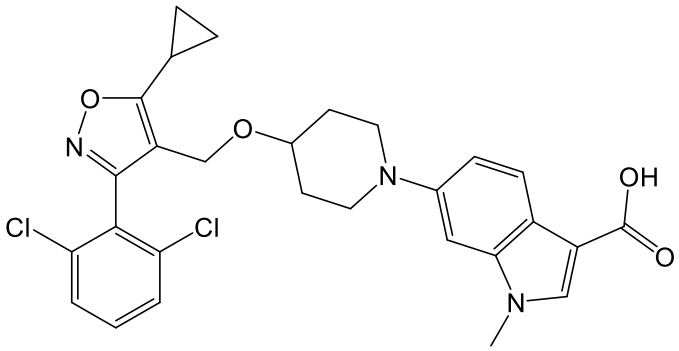
5. The ~~method~~use of claim 4, wherein:
R^1 is chloro or trifluoromethoxy; and
R^2 is hydrogen or chloro.

6. The ~~method~~use of claim 4 or 5, wherein:
R^{3a} is cyclopropyl or isopropyl.

7. The ~~method~~use of any one of claims 4 to 6, wherein:
Ar^1 is 5-benzothienyl, 6-benzothienyl, 5-indolyl, 6-indolyl, or 4-phenyl, each of which is optionally substituted with methyl.

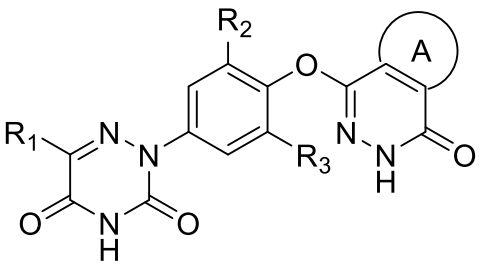
8. The ~~method~~use of any one of claims 4 to 7, wherein:
q is 1; and
X is N.

9. The ~~method~~use of any one of claims 1 and 4 to 8, wherein the FXR agonist is:



or a pharmaceutically acceptable salt thereof.

10. The ~~method~~use of any one of claims 1, 2, and 4 to 9, wherein the THRβ agonist is a compound of formula (II)



(II)

wherein:

R_1 is selected from the group consisting of hydrogen, cyano, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{3-6} cycloalkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C_{1-6} alkoxy;

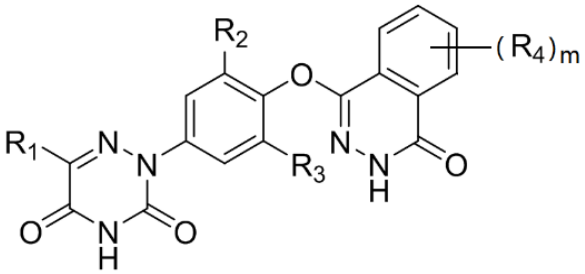
R_2 and R_3 are each independently selected from the group consisting of halogen atoms and substituted or unsubstituted C_{1-6} alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C_{1-6} alkoxy;

ring A is a substituted or unsubstituted saturated or unsaturated C_{5-10} aliphatic ring, or a substituted or unsubstituted C_{5-10} aromatic ring, the substituent being one or more substances selected from the group consisting of hydrogen, halogen atoms, hydroxy, $-OCF_3$, $-NH_2$, $-NHC_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl$)_2$, $-CONH_2$, $-CONHC_{1-4}$ alkyl, $-CON(C_{1-4}$ alkyl$)_2$, $-NHCOC_{1-4}$ alkyl, C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl, and when two substituents are contained, the two substituents can form a ring structure together with the carbon connected thereto; and

the halogen atoms are selected from the group consisting of F, Cl and Br,

or a pharmaceutically acceptable salt thereof.

11. The ~~method~~use of claim 10, wherein the THRβ agonist is a compound of formula (IIa)



(IIa)

wherein:

R_1 to R_3 are defined as described in claim 10;

R_4 is selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF_3, -NH_2, -NHC_{1-4} alkyl, -$N(C_{1-4}$ alkyl$)_2$, -$CONH_2$, -$CONHC_{1-4}$ alkyl, -$CON(C_{1-4}$ alkyl$)_2$, -$NHCOC_{1-4}$ alkyl, C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl;

m is an integer from the range 1 to 4; and

the halogen atoms are selected from the group consisting of F, Cl and Br.

or a pharmaceutically acceptable salt thereof.

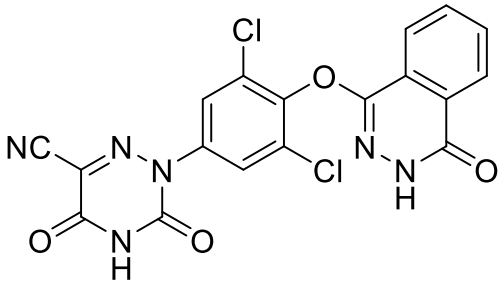
12. The ~~method~~use of claim 10 or 11, wherein R_4 is selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF_3, C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl; and

m is an integer from the range 1 to 3.

13. The ~~method~~use of any one of claims 10 to 12, wherein R_1 is selected from the group consisting of hydrogen, cyano, and substituted or unsubstituted C_{1-6} alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C_{1-6} alkoxy; and

the halogen atoms are selected from the group consisting of F, Cl and Br.

14. The ~~method~~use of any one of claims 1, 2 and 4 to 13, wherein the THRβ agonist is:



or a pharmaceutically acceptable salt thereof.

15. The ~~method~~use of any one of claims 1 to 14, wherein the FXR agonist and the THRβ agonist are to be administered simultaneously to the patient in need thereof.

16. The ~~method~~use of any one of claims 1 to 14, wherein the FXR agonist and the THRβ agonist are to be administered sequentially to the patient in need thereof.

17. The ~~method~~use of any one of claims 1 to 16, wherein the FXR agonist and the THRβ agonist are to be administered to the patient in need thereof, and wherein the administration does not result in pruritus in the patient at a severity of Grade 2 or more.

18. The ~~method~~use of any one of claims 1 to 17, wherein the FXR agonist and the THRβ agonist are to be administered to the patient in need thereof, and wherein the administration does not result in pruritus in the patient at a severity of Grade 1 or more.

19. The ~~method~~use of any one of claims 1 to 18, wherein the FXR agonist and the THRβ agonist are to be administered to the patient in need thereof, and wherein the administration does not result in pruritus in the patient.

20. The ~~method~~use of any one of claims 1 to 19, wherein the patient also has diabetes mellitus and/or a cardiovascular disorder.

21. The ~~method~~use of any one of claims 1 to 20, wherein the treatment period is the remaining lifespan of the patient.

22. The ~~method~~use of any one of claims 1 to 21, wherein ~~the method does not comprise administering~~ an antihistamine, an immunosuppressant, a steroid, rifampicin, an opioid antagonist, or a selective serotonin reuptake inhibitor (SSRI) are not to be administered.

23. The ~~method~~use of any one of claims 1 to 22, wherein the FXR agonist is to be administered once daily or twice daily to the patient in need thereof.

24. The ~~method~~use of any one of claims 1 to 23, wherein the THRβ agonist is to be administered once daily or twice daily to the patient in need thereof.

25. The ~~method~~use of any one of claims 1 to 24, wherein ~~the administration comprises administering~~ the FXR agonist is to be administered daily to the patient in need thereof, for a treatment period of one or more weeks.

26. The ~~method~~use of any one of claims 1 to 25, wherein ~~the administration comprises administering~~ the THRβ agonist is to be administered daily to the patient in need thereof, for a treatment period of one or more weeks.

27. The ~~method~~use of any one of claims 1 to 26, wherein the liver disorder is selected from the group consisting of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

28. The ~~method~~use of any one of claims 1-26, wherein the liver disorder is non-alcoholic steatohepatitis.

29. The ~~method~~use of any one of claims 1 to 28, wherein the FXR agonist and the THRβ agonist are to be administered to the patient in need thereof, and wherein the administration results in differential expression of immune-related genes or leukocyte-associated genes compared to administration with a monotherapy of the FXR agonist or the THRβ agonist.

30. The ~~method~~use of claim 29, wherein the administration results in differential expression of immune-related genes compared to administration with a monotherapy of the FXR agonist or the THRβ agonist.

31. The ~~method~~use of claim 29, wherein the administration results in differential expression of leukocyte-associated genes compared to administration with a monotherapy of the FXR agonist or the THRβ agonist.

32. The ~~method~~use of any one of claims 1 to 31, wherein the FXR agonist and the THRβ agonist are to be administered to the patient in need thereof, and wherein the administration reduces at least one of steatosis, liver inflammation, or liver fibrosis compared to administration with a monotherapy of the FXR agonist or the THRβ agonist.

33. The ~~method~~use of claim 32, wherein the administration reduces steatosis compared to administration with a monotherapy of the FXR agonist or the THRβ agonist.

34. The ~~method~~use of claim 32, wherein the administration reduces liver inflammation compared to administration with a monotherapy of the FXR agonist or the THRβ agonist.

35. The ~~method~~use of claim 32, wherein the administration reduces liver fibrosis compared to administration with a monotherapy of the FXR agonist or the THRβ agonist.

36. The ~~method~~use of any one of claims 1-35, wherein the FXR agonist and the THRβ agonist are to be administered to the patient in need thereof, and wherein the administration reduces expression of at least one of Col1a1, Col3a1, Mmp2, Lgals3, Cd68, or Ccr2 compared to administration with a monotherapy of the FXR agonist or the THRβ agonist.

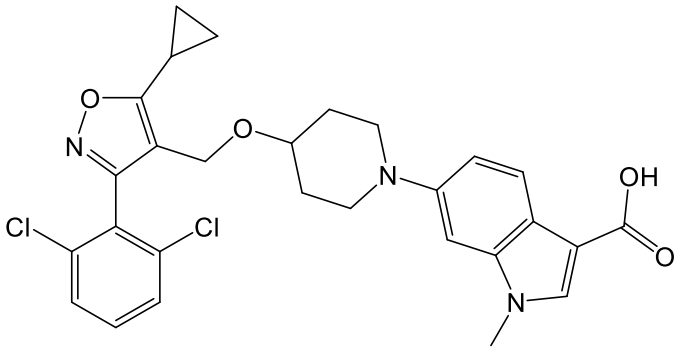
37. A pharmaceutical composition comprising a~~n~~ therapeutically effective amount of an FXR agonist, a therapeutically effective amount of a THRβ agonist, and a pharmaceutically acceptable carrier, diluent, excipient, or a combination of any of the foregoing.

38. A dosage form comprising a therapeutically effective amount of an FXR agonist and a therapeutically effective amount of a THRβ agonist.

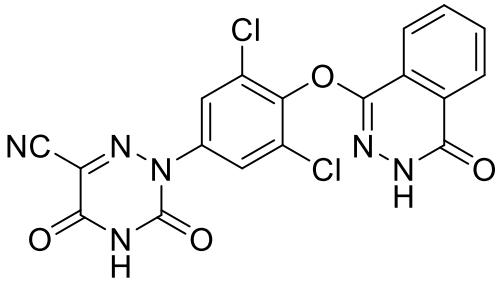
39. A kit comprising a container comprising an FXR agonist and a THRβ agonist.

40. A kit comprising a first container comprising an FXR agonist and a second container comprising a THRβ agonist.

41. The pharmaceutical composition of claim 37, the dosage form of claim 38, or the kit of claim 39 or 40, wherein the FXR agonist is



or a pharmaceutically acceptable salt thereof, and the THRβ agonist is:



or a pharmaceutically acceptable salt thereof.

42. ~~A method of reducing hepatic inflammation in a patient in need thereof, comprising administering to the patient a therapeutically effective amount~~ Use of a FXR agonist and a ~~therapeutically effective amount of a~~ THRβ agonist in the manufacture of a medicament for reducing hepatic inflammation in a patient in need thereof.

43. ~~A method of reducing hepatic inflammation in a patient in need thereof without increasing LDL-C levels in the patient, said method comprising administering to the patient a therapeutically effective amount~~ Use of a FXR agonist and a ~~therapeutically effective amount~~ THRβ agonist in the manufacture of a medicament for reducing hepatic inflammation in a patient in need thereof without increasing LDL-C levels in the patient.

44. ~~A method of reducing leukocyte activation in a patient with a disorder characterized by high leukocyte levels in the liver, said method comprising administering to the patient a therapeutically effective amount~~ Use of a FXR agonist and a ~~therapeutically effective amount~~ THRβ agonist in the manufacture of a medicament for reducing leukocyte activation in a patient with a disorder characterized by high leukocyte levels in the liver.

45. The ~~method~~use of any one of claims 42 to 44, wherein the FXR agonist is to be administered orally to the patient in need thereof.

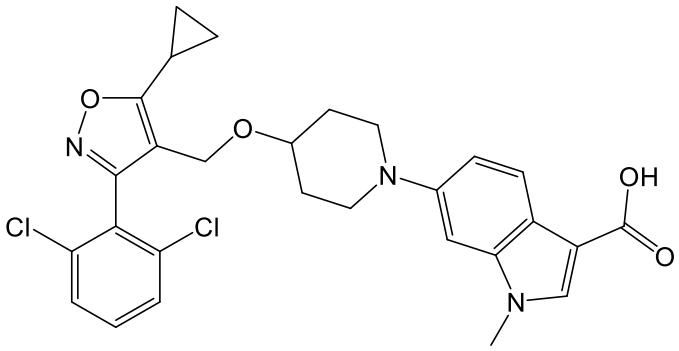
46. The ~~method~~use of any one of claims 42 to 45, wherein the THRβ agonist is to be administered orally to the patient in need thereof.

47. The ~~method~~use of any one of claims 42 to 46, wherein the patient has NASH.

48. The ~~method~~use of any one of claims 42 to 47, wherein the patient has liver fibrosis.

49. The ~~method~~use of any one of claims 42 to 48, wherein the FXR agonist is obeticholic acid, cilofexor, tropifexor, EYP001 (Vonafexor, proposed INN), MET409 (Metacrine), or EDP-305 (by Enanta).

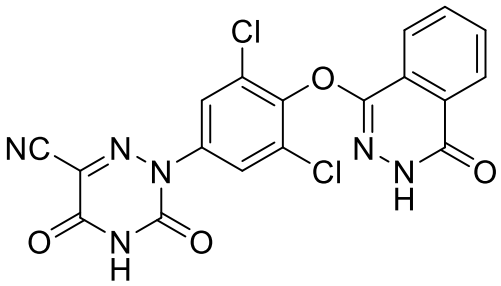
50. The ~~method~~use of any one of claims 42 to 48, wherein the FXR agonist is:



or a pharmaceutically acceptable salt thereof.

51. The ~~method~~use of any one of claims 42 to 50, wherein the THRβ agonist is resmetirom (MGL-3196), VK2809 (by Viking Therapeutics), sobetirome, eprotirome, CNPT-101101, CNPT-101207, ASC41 (Ascletis), or ALG-055009 (by Aligo).

52. The ~~method~~use of any one of claims 42 to 50, wherein the THRβ agonist is:



or a pharmaceutically acceptable salt thereof.

53. ~~A method of treating NASH in a patient in need thereof, said method comprising administering to the patient a therapeutically effective amount~~ Use of a FXR agonist and a ~~therapeutically effective amount of a~~ THRβ agonist in the manufacture of a medicament for treating NASH in a patient in need thereof, wherein the THRβ agonist is to be administered to the patient at a dose that reduces LDL-C levels in the patient.

54. ~~A method of treating NASH in a patient in need thereof, said method comprising administering to the patient a therapeutically effective amount~~ Use of a FXR agonist and a ~~therapeutically effective amount of a~~ THRβ agonist in the manufacture of a medicament for treating NASH in a patient in need thereof, wherein the THRβ agonist is to be administered to the patient at a dose that prevents an increase in LDL-C levels in the patient.

55. The ~~method~~use of claim 53 or 54, wherein the FXR agonist is to be administered orally to the patient in need thereof.

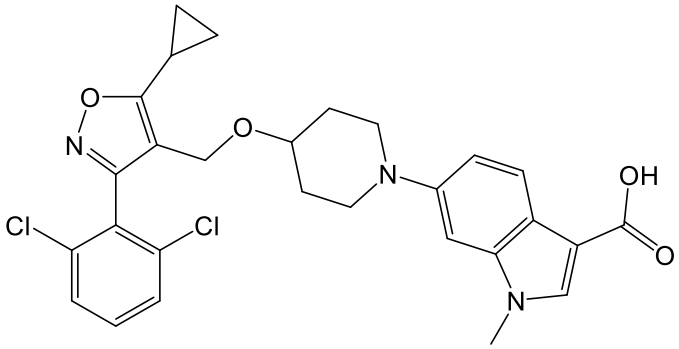
56. The ~~method~~use of any one of claims 53 to 55, wherein the THRβ agonist is to be administered orally to the patient in need thereof.

57. The ~~method~~use of any one of claims 53 to 56, wherein the patient has NASH.

58. The ~~method~~use of any one of claims 53 to 57, wherein the patient has liver fibrosis.

59. The ~~method~~use of any one of claims 53 to 58, wherein the FXR agonist is obeticholic acid, cilofexor, tropifexor, EYP001 (Vonafexor, proposed INN), MET409 (Metacrine), or EDP-305 (by Enanta).

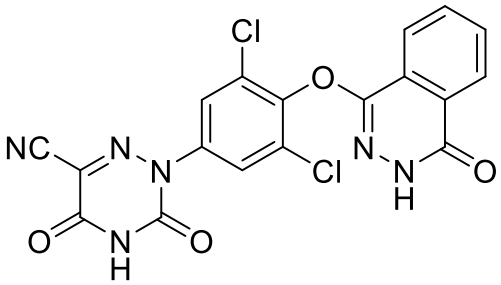
60. The ~~method~~use of any one of claims 53 to 58, wherein the FXR agonist is:



or a pharmaceutically acceptable salt thereof.

61. The ~~method~~use of any one of claims 53 to 60, wherein the THRβ agonist is resmetirom (MGL-3196), VK2809 (by Viking Therapeutics), sobetirome, eprotirome, CNPT-101101, CNPT-101207, ASC41 (Ascletis), or ALG-055009 (by Aligo).

62. The ~~method~~use of any one of claims 53 to 60, wherein the THRβ agonist is:



or a pharmaceutically acceptable salt thereof.

63. ~~A method of treating a disease or condition characterized by fibrosis of the liver, said method comprising administering to a patient in need of treatment a therapeutically effective amount~~ Use of a FXR agonist and a ~~therapeutically effective amount of a~~ THRβ agonist in the manufacture of a medicament for treating a disease or condition characterized by fibrosis of the liver in a patient in need thereof.

64. The ~~method~~use of claim 63, wherein the disease or condition is associated with hepatic inflammation.

65. The ~~method~~use of claim 63 or 64, wherein the FXR agonist and the THRβ agonist are to be administered to the patient in need thereof, and the administration ~~administering~~ reduces expression of at least one of Col1a1, Col3a1, Mmp2, Lgals3, Cd68, or Ccr2 compared to administration with a monotherapy of the FXR agonist or the THRβ agonist.

66. The ~~method~~use of any one of claims 63 to 65, wherein the FXR agonist is to be administered orally to the patient in need thereof.

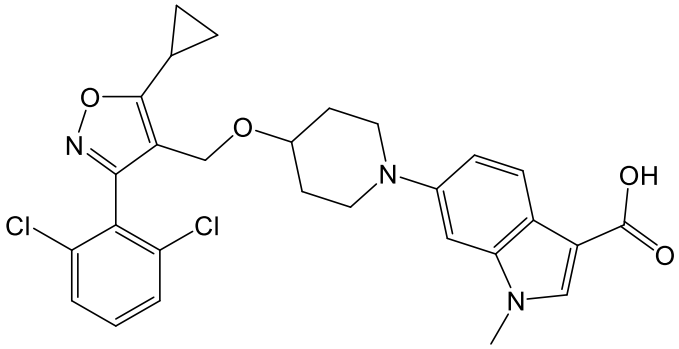
67. The ~~method~~use of any one of claims 63 to 66, wherein the THRβ agonist is to be administered orally to the patient in need thereof.

68. The ~~method~~use of any one of claims 63 to 67, wherein the patient has NASH.

69. The ~~method~~use of any one of claims 63 to 68, wherein the patient has liver fibrosis.

70. The ~~method~~use of any one of claims 63 to 69, wherein the FXR agonist is obeticholic acid, cilofexor, tropifexor, EYP001 (Vonafexor, proposed INN), MET409 (Metacrine), or EDP-305 (by Enanta).

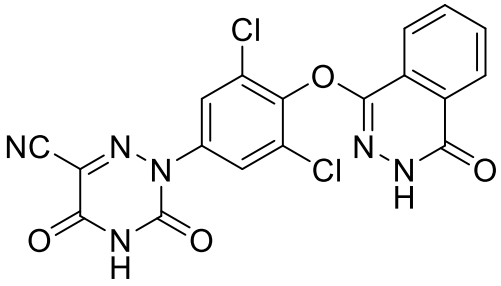
71. The ~~method~~use of any one of claims 63 to 69, wherein the FXR agonist is:



or a pharmaceutically acceptable salt thereof.

72. The ~~method~~use of any one of claims 63 to 71, wherein the THRβ agonist is resmetirom (MGL-3196), VK2809 (by Viking Therapeutics), sobetirome, eprotirome, CNPT-101101, CNPT-101207, or ALG-055009 (by Aligo).

73. The ~~method~~use of any one of claims 63 to 71, wherein the THRβ agonist is:



or a pharmaceutically acceptable salt thereof.

74. ~~A method of inhibiting the expression of fibroblast genes responsible for the production of collagen in the extracellular matrix of the liver, said method comprising administering to a patient in need of treatment a therapeutically effective amount~~ Use of a FXR agonist and a ~~therapeutically effective amount of a~~ THRβ agonist in the manufacture of a medicament for inhibiting the expression of fibroblast genes responsible for the production of collagen in the extracellular matrix of the liver of a patient in need thereof.

75. The ~~method~~use of claim 74, wherein the genes responsible for the production of collagen are selected from Col1a1, Col3a1, and Lgals3.

76. The ~~method~~use of any one of claims 74 to 75, wherein the FXR agonist is to be administered orally to the patient in need thereof.

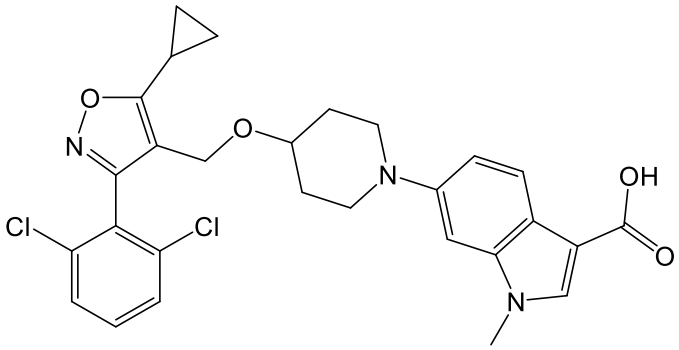
77. The ~~method~~use of any one of claims 74 to 76, wherein the THRβ agonist is to be administered orally to the patient in need thereof.

78. The ~~method~~use of any one of claims 74 to 77, wherein the patient has NASH.

79. The ~~method~~use of any one of claims 74 to 78, wherein the patient has liver fibrosis.

80. The ~~method~~use of any one of claims 74 to 79, wherein the FXR agonist is obeticholic acid, cilofexor, tropifexor, EYP001 (Vonafexor, proposed INN), MET409 (Metacrine), or EDP-305 (by Enanta).

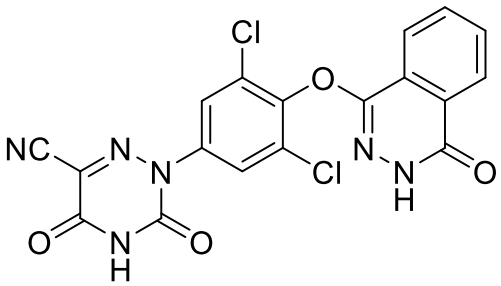
81. The ~~method~~use of any one of claims 74 to 79, wherein the FXR agonist is:



or a pharmaceutically acceptable salt thereof.

82. The ~~method~~use of any one of claims 74 to 81, wherein the THRβ agonist is resmetirom (MGL-3196), VK2809 (by Viking Therapeutics), sobetirome, eprotirome, CNPT-101101, CNPT-101207, ASC41 (Ascletis), ALG-055009 (by Aligo).

83. The ~~method~~use of any one of claims 74 to 81, wherein the THRβ agonist is:



or a pharmaceutically acceptable salt thereof.