COMBINATION TREATMENT OF LIVER DISORDERS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of U.S. Provisional Application No. 63/024,359, 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

[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 Semicarbazide-Sensitive Amine Oxidase (SSAO) inhibitor.

[0004a] In an aspect of the present disclosure, there is provided a use of a Farnesoid X Receptor (FXR) agonist and a Semicarbazide-Sensitive Amine Oxidase (SSAO) inhibitor 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).

[0004b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising an effective amount of an FXR agonist, a therapeutically effective amount of an SSAO inhibitor, and a pharmaceutically acceptable carrier, diluent, excipient, or a combination of any of the foregoing.

[0004c] In a further aspect of the present disclosure, there is provided a dosage form comprising a therapeutically effective amount of an FXR agonist and a therapeutically effective amount of an SSAO inhibitor.

[0004d] In another aspect of the present disclosure, there is provided a kit comprising a container comprising an FXR agonist and an SSAO inhibitor.

[0004e] In a further aspect of the present disclosure, there is provided a kit comprising a first container comprising an FXR agonist and a second container comprising an SSAO inhibitor.

[0004f] In another aspect of the present disclosure, there is provided a use of a FXR agonist and a SSAO inhibitor in the manufacture of a medicament for reducing hepatic steatosis in a patient in need thereof.

[0004g] In a further aspect of the present disclosure, there is provided a use of a FXR agonist and a SSAO inhibitor in the manufacture of a medicament for treating a disease or condition characterized by steatosis of the liver in a patient in need thereof.

[0004h] In another aspect of the present disclosure, there is provided a use of a FXR agonist and a SSAO inhibitor in the manufacture of a medicament for reducing hepatic inflammation in a patient in need thereof.

[0004i] In a further aspect of the present disclosure, there is provided a use of a FXR agonist and a SSAO inhibitor in the manufacture of a medicament for reducing leukocyte activation in a patient with a disorder characterized by high leukocyte levels in the liver.

[0004j] In another aspect of the present disclosure, there is provided a use of a FXR agonist and a SSAO inhibitor in the manufacture of a medicament for treating a disease or condition characterized by fibrosis of the liver.

[0005] In one 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 SSAO inhibitor. The administration of a combination of a FXR agonist and a SSAO inhibitor 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 a reduction of leukocyte activation in the liver.

[0006] In another 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 SSAO inhibitor. The administration of a combination of a FXR agonist and a SSAO inhibitor 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.

[0007] In another example, the disclosure provides methods of treating a disease or condition characterized by hepatic steatosis, comprising administering to the patient a therapeutically effective amount of a FXR agonist and a therapeutically effective amount of a SSAO inhibitor. It has been discovered that the combination of a FXR agonist and a SSAO inhibitor reduces hepatic steatosis, in part, by regulating genes involved with lipid metabolism and fatty acid transportation. Surprisingly, the FXR agonist potentiates the effect of the SSAO inhibitor in regulating genes associated with lipid metabolism and fatty acid transportation, hence resulting in the reduction of fat (e.g., triglyceride) accumulation in the liver. Accordingly, the administration of a combination of a FXR agonist and a SSAO inhibitor reduces hepatic steatosis in a patient in need thereof to a significantly greater extent than administration of either agent alone.

[0008] As set forth herein, the synergy observed when administering the combination of a FXR agonist and a SSAO inhibitor to patients in need thereof allows for the reduction of the dose of either or both the FXR agonist and the SSAO inhibitor relative to when either agonist is administered as a monotherapy. The lower doses of the FXR agonist and the SSAO inhibitor results in an improved therapeutic index and alleviates side effects that are sometimes accompanied with FXR agonism or SSAO inhibition.

[0009] In some examples, the administration of the FXR agonist and the SSAO inhibitor does not result in pruritus in the patient at a severity of Grade 2 or more. In some examples, the administration of the FXR agonist and the SSAO inhibitor does not result in pruritus of Grade 1 or more. In some examples, the administration of the FXR agonist and the SSAO inhibitor does not result in pruritus.

[0010] In another 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 SSAO inhibitor. In one example, the patient in need thereof is a patient that suffers from fatty liver disease

such as NAFLD. In another example, the patient in need thereof is a patient that suffers from insulin resistance syndrome.

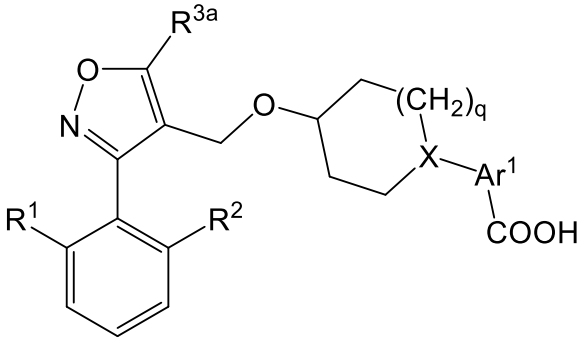
[0011] In some examples, the FXR agonist and the SSAO inhibitor are administered simultaneously. In some such examples, the FXR agonist and the SSAO inhibitor are provided as a fixed-dose composition in a single pharmaceutical composition as set forth herein. In other examples, the FXR agonist and the SSAO inhibitor are administered sequentially. In some examples, either or both of the FXR agonist and the SSAO inhibitor are administered orally.

[0012] In some examples, the patient has a liver disorder and diabetes mellitus. In some examples, the patient has a liver disorder and a cardiovascular disorder. In some examples, the treatment period is the remaining lifespan of the patient. In some examples, the method does not comprise administering an antihistamine, an immunosuppressant, a steroid, rifampicin, an opioid antagonist, or a selective serotonin reuptake inhibitor (SSRI).

[0013] In some examples, the FXR agonist is administered once daily. In some examples, the FXR agonist is administered twice daily. In some examples, the SSAO inhibitor is administered once daily. In some examples, the SSAO inhibitor is administered twice daily. In some examples, the administration comprises administering the FXR agonist daily for a treatment period of one or more weeks. In some examples, the administration comprises administering the SSAO inhibitor daily for a treatment period of one or more weeks. In some examples, the administration comprises administering the FXR agonist daily and the SSAO inhibitor daily for a treatment period of one or more weeks.

[0014] A variety of different FXR agonists and SSAO inhibitors can be used to achieve the beneficial effects observed on liver disease as discussed herein. For instance, in some examples, the FXR agonist administered to the patient in need thereof is obeticholic acid. In some examples, the FXR agonist administered to the patient in need thereof is cilofexor. In some examples, the FXR agonist administered to the patient in need thereof is tropifexor. In some examples, the FXR agonist administered to the patient in need thereof is EYP001 (Vonafexor, proposed INN). In some examples, the FXR agonist administered to the patient in need thereof is MET409 (Metacrine). In some examples, the FXR agonist administered to the patient in need thereof is MET642 (Metacrine). In some examples, the FXR agonist is EDP-305 (by Enanta). In some examples, the FXR agonist is EDP-297 (by Enanta).

[0015] In some 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;

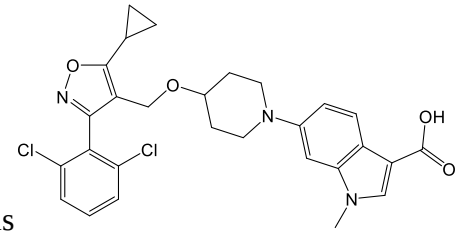
X is CH or N, provided that when X is CH, q is 1; and

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.

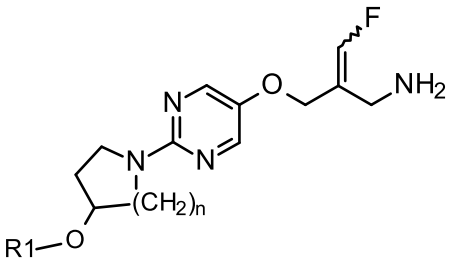
[0016] In some examples, the FXR agonist administered to the patient in need thereof is a compound of formula (I) wherein R^1 is chloro or trifluoromethoxy. In some examples, the FXR agonist is a compound of formula (I) wherein R^2 is hydrogen or chloro. In some examples, the FXR agonist is a compound of formula (I) wherein R^{3a} is cyclopropyl or isopropyl. In some 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 examples, the FXR agonist is a compound of formula (I) wherein q is 1 and X is N.

[0017] In some examples, the FXR agonist is



or a pharmaceutically acceptable salt thereof.

[0018] In some examples, the SSAO inhibitor administered to the patient in need thereof is a compound of Formula (II)



(II)

wherein:

n is 1 or 2; and

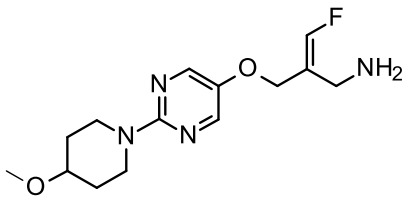
R1 is H or -CH_3,

or a pharmaceutically acceptable salt thereof.

[0019] In some examples, the SSAO inhibitor administered to the patient in need thereof is a compound of Formula (II), where n is 1, or a pharmaceutically acceptable salt thereof. In another example, the SSAO inhibitor is a compound of Formula (II), where n is 2, or a pharmaceutically acceptable salt thereof.

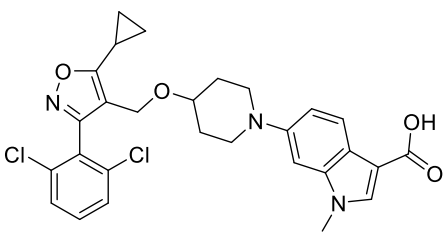
[0020] In some examples, the SSAO inhibitor administered to the patient in need thereof is a compound of Formula (II), where R1 is H, or a pharmaceutically acceptable salt thereof. In yet another example, the present disclosure provides a compound of Formula (II), where R1 is -CH_3, or a pharmaceutically acceptable salt thereof.

[0021] In some examples, the SSAO inhibitor administered to the patient in need thereof is



, or a pharmaceutically acceptable salt thereof.

[0022] In some examples, provided are methods of treating a liver disorder in a patient in need thereof with a Farnesoid X Receptor (FXR) agonist and a Semicarbazide-Sensitive Amine Oxidase (SSAO) inhibitor, comprising administering a therapeutically effective amount of the FXR agonist, wherein the FXR agonist is



, or a

CLAIMS

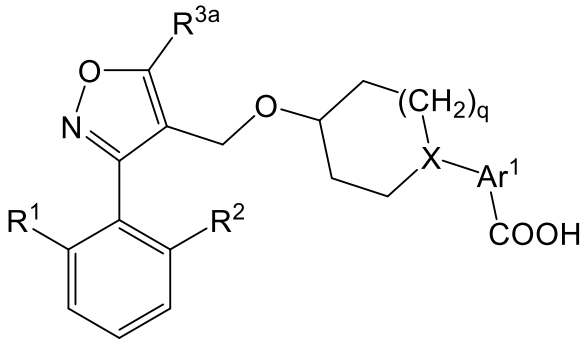
What is claimed is:

1. Use of a Farnesoid X Receptor (FXR) agonist and a Semicarbazide-Sensitive Amine Oxidase (SSAO) inhibitor 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 use of claim 1, wherein the FXR agonist is obeticholic acid, cilofexor, tropifexor, EYP001 (Vonafexor, proposed INN), MET409 (Metacrine), MET642 (Metacrine), EDP-305 (by Enanta), or EDP-297 (by Enanta).

3. The use of claim 1 or 2, wherein the SSAO inhibitor is PXS-4728A (BI-1467335).

4. The 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 use of claim 4, wherein:

R^1 is chloro or trifluoromethoxy; and

R^2 is hydrogen or chloro.

6. The use of claim 4 or 5, wherein:

R^{3a} is cyclopropyl or isopropyl.

7. The use of any one of claims 4 to 6, wherein:

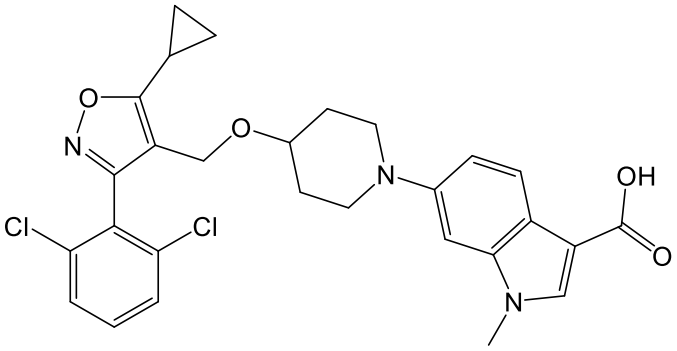
Ar^1 is 5-benzothienyl, 6-benzothienyl, 5-indolyl, 6-indolyl, or 4-phenyl, each of which is optionally substituted with methyl.

8. The use of any one of claims 4 to 7, wherein:

q is 1; and

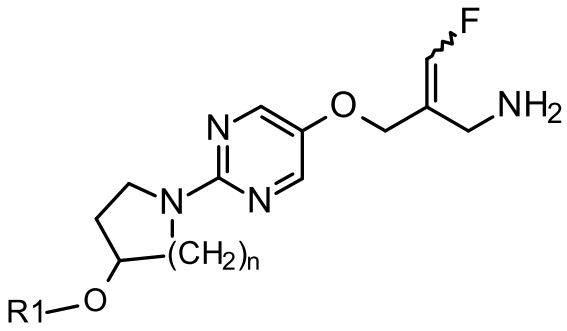
X is N.

9. The use of claim 1 or 4, wherein the FXR agonist is:



or a pharmaceutically acceptable salt thereof.

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



(II)

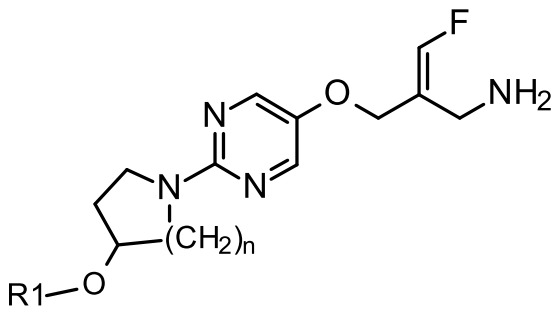
wherein:

n is 1 or 2; and

R^1 is H or -CH_3,

or a pharmaceutically acceptable salt thereof.

11. The use of claim 10, wherein the SSAO inhibitor is a compound of formula (IIa)



(IIa)

wherein:

n is 1 or 2; and

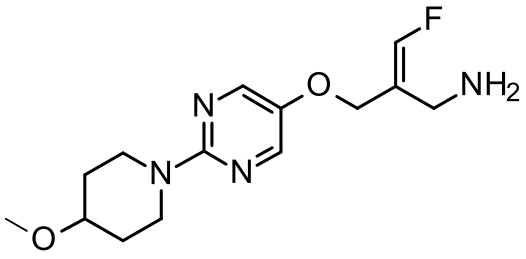
R^1 is H or -CH_3,

or a pharmaceutically acceptable salt thereof.

12. The use of claim 10 or 11, wherein n is 2.

13. The use of any one of claims 10 to 12, wherein R^1 is CH_3.

14. The use of any one of claims 1, 2, and 4 to 9, wherein the SSAO inhibitor is:



or a pharmaceutically acceptable salt thereof.

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

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

17. The use of any one of claims 1 to 16, wherein the FXR agonist and the SSAO inhibitor 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 use of any one of claims 1 to 17, wherein the FXR agonist and the SSAO inhibitor 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 use of any one of claims 1 to 18, wherein the FXR agonist and the SSAO inhibitor are to be administered to the patient in need thereof, and wherein the administration does not result in pruritus in the patient.

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

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

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

23. The 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 use of any one of claims 1 to 23, wherein the SSAO inhibitor is to be administered once daily or twice daily to the patient in need thereof.

25. The use of any one of claims 1 to 24, wherein 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 use of any one of claims 1 to 25, wherein the SSAO inhibitor is to be administered daily to the patient in need thereof, for a treatment period of one or more weeks.

27. The 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 use of any one of claims 1 to 26, wherein the liver disorder is non-alcoholic steatohepatitis.

29. The use of any one of claims 1 to 28, wherein the FXR agonist and the SSAO inhibitor are to be administered to the patient in need thereof, and wherein the administration results in differential expression of one or more genes associated with lipid metabolism or fatty-acid transportation compared to administration with a monotherapy of the FXR agonist or the SSAO inhibitor.

30. The use of claim 29, wherein the administration results in increased expression of one or more genes associated with lipid metabolism or fatty-acid transportation compared to administration with a monotherapy of the FXR agonist or the SSAO inhibitor.

31. The use of claim 30, wherein the administration results in increased expression of one or more genes associated with lipid metabolism or fatty-acid transportation compared to administration with a monotherapy of the FXR agonist, wherein the one or more genes are selected from Irs2, Irs1, Ppara, Slc27a1, Ldlrap1, Ldlr, Ppargc1a, Rxra, or Slc27a5.

32. The use of claim 30, wherein the administration results in increased expression of one or more genes associated with lipid metabolism or fatty-acid transportation compared to administration with a monotherapy of the SSAO inhibitor, wherein the one or more genes associated is selected from Lrp2, Irs2, Vegfa, Lrp1, Irs1, Ppara, Slc27a1, Ldr1, Ppargc1a, Rxra, and Slc27a5.

33. The use of claim 29, wherein the administration results in reduced expression of one or more genes associated with lipid metabolism or fatty-acid transportation compared to administration with a monotherapy of the FXR agonist or the SSAO inhibitor.

34. The use of claim 33, wherein the administration results in reduced expression of one or more genes associated with lipid metabolism or fatty-acid transportation compared to administration with a monotherapy of the FXR agonist, wherein the one or more genes associated is selected from Vldlr, Fabp2, Il1r2, and Vegfc.

35. The use of claim 33, wherein the administration results in reduced expression of one or more genes associated with lipid metabolism or fatty-acid transportation compared to administration with a monotherapy of the SSAO inhibitor, wherein the one or more genes associated is selected from Fabp2, Il1r2, and Vegfc.

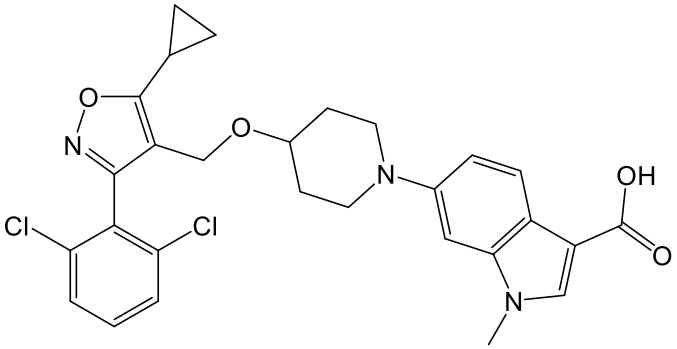
36. A pharmaceutical composition comprising an effective amount of an FXR agonist, a therapeutically effective amount of an SSAO inhibitor, and a pharmaceutically acceptable carrier, diluent, excipient, or a combination of any of the foregoing.

37. A dosage form comprising a therapeutically effective amount of an FXR agonist and a therapeutically effective amount of an SSAO inhibitor.

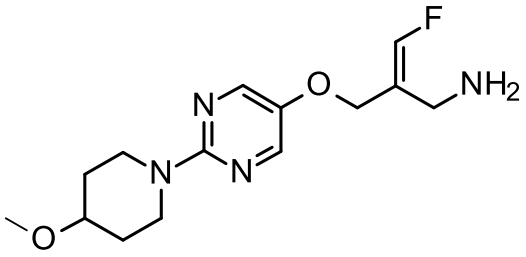
38. A kit comprising a container comprising an FXR agonist and an SSAO inhibitor.

39. A kit comprising a first container comprising an FXR agonist and a second container comprising an SSAO inhibitor.

40. The pharmaceutical composition of claim 36, the dosage form of claim 37, or the kit of claim 38 or 39, wherein the FXR agonist is



or a pharmaceutically acceptable salt thereof, and the SSAO inhibitor is:



or a pharmaceutically acceptable salt thereof.

41. Use of a FXR agonist and a SSAO inhibitor in the manufacture of a medicament for reducing hepatic steatosis in a patient in need thereof.

42. Use of a FXR agonist and a SSAO inhibitor in the manufacture of a medicament for treating a disease or condition characterized by steatosis of the liver in a patient in need thereof.

43. The use of claim 41 or 42, wherein the use increases expression of one or more genes associated with lipid metabolism or fatty-acid transportation compared to administration with a monotherapy of the SSAO inhibitor, wherein the one or more genes associated is selected from Lrp2, Irs2, Vegfa, Lrp1, Irs1, Ppara, Slc27a1, Ldr1, Ppargc1a, Rxra, and Slc27a5.

44. The use of any one of claims 41 to 43, wherein the use reduces expression of one or more genes associated with lipid metabolism or fatty-acid transportation compared to administration with a monotherapy of the FXR agonist, wherein the one or more genes associated is selected from Vldlr, Fabp2, Il1r2, and Vegfc,

45. The use of any one of claims 41 to 44, wherein the FXR agonist is to be administered orally to the patient in need thereof.

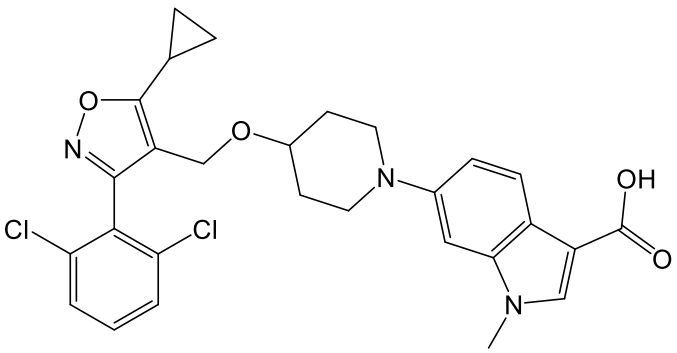
46. The use of any one of claims 41 to 45, wherein the SSAO inhibitor is to be administered orally to the patient in need thereof.

47. The use of any one of claims 41 to 46, wherein the patient has NASH.

48. The use of any one of claims 41 to 47, wherein the patient has liver fibrosis.

49. The use of any one of claims 41 to 48, wherein the FXR agonist is obeticholic acid, cilofexor, tropifexor, EYP001 (Vonafexor, proposed INN), MET409 (Metacrine), MET642 (Metacrine), EDP-305 (by Enanta), or EDP-297 (by Enanta).

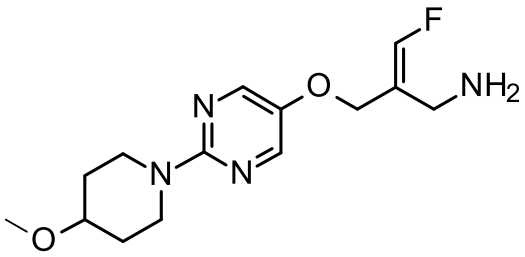
50. The use of any one of claims 41 to 48, wherein the FXR agonist is:



or a pharmaceutically acceptable salt thereof.

51. The use of any one of claims 41 to 50, wherein the SSAO inhibitor is PXS-4728A.

52. The use of any one of claims 41 to 50, wherein the SSAO inhibitor is:



or a pharmaceutically acceptable salt thereof.

53. Use of a FXR agonist and a SSAO inhibitor in the manufacture of a medicament for reducing hepatic inflammation in a patient in need thereof.

54. Use of a FXR agonist and a SSAO inhibitor in the manufacture of a medicament for reducing leukocyte activation in a patient with a disorder characterized by high leukocyte levels in the liver.

55. The use of any one of claims 53 or 54, wherein the FXR agonist is to be administered orally to the patient.

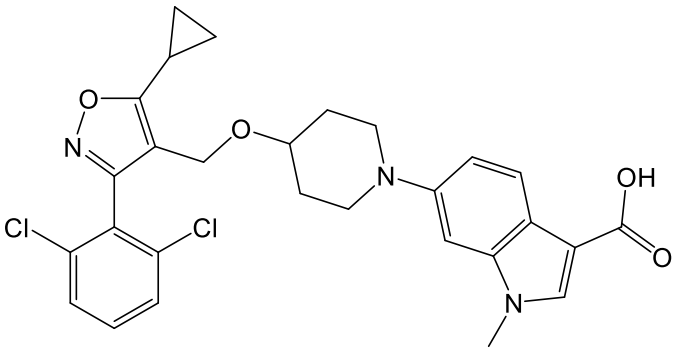
56. The use of any one of claims 53 to 55, wherein the SSAO inhibitor is to be administered orally to the patient.

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

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

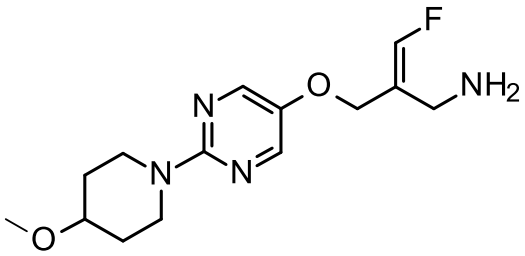
59. The use of any one of claims 53 to 58, wherein the FXR agonist is obeticholic acid, cilofexor, tropifexor, EYP001 (Vonafexor, proposed INN), MET409 (Metacrine), MET642 (Metacrine), EDP-305 (by Enanta), or EDP-297 (by Enanta).

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



or a pharmaceutically acceptable salt thereof.

61. The use of any one of claims 53 to 60, wherein the SSAO inhibitor is:



or a pharmaceutically acceptable salt thereof.

62. Use of a FXR agonist and a SSAO inhibitor in the manufacture of a medicament for treating a disease or condition characterized by fibrosis of the liver.

63. The use of claim 62, wherein the disease or condition is associated with hepatic inflammation.

64. The use of claim 62 or 63, wherein the FXR agonist and the SSAO inhibitor are to be administered to the patient, and 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 SSAO inhibitor.

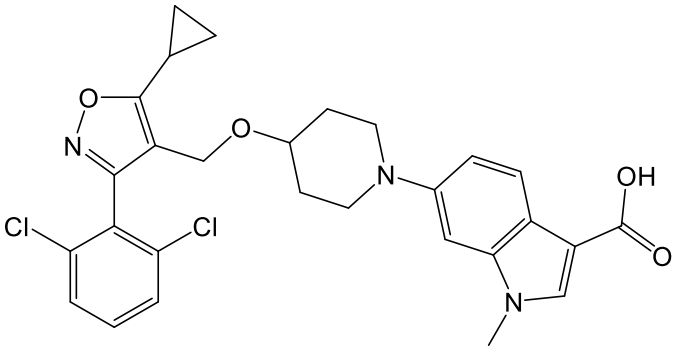
65. The use of any one of claims 62 to 64, wherein the FXR agonist is to be administered orally to a patient in need thereof.

66. The use of any one of claims 62 to 65, wherein the SSAO inhibitor is to be administered orally to a patient in need thereof.

67. The use of any one of claims 62 to 66, wherein the patient has NASH.

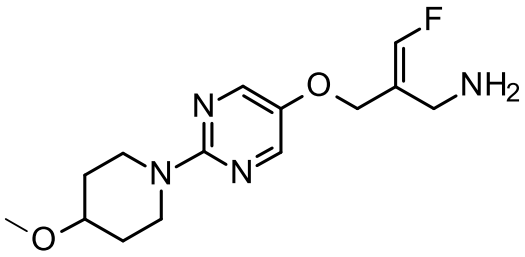
68. The use of any one of claims 62 to 67, wherein the FXR agonist is obeticholic acid, cilofexor, tropifexor, EYP001 (Vonafexor, proposed INN), MET409 (Metacrine), MET642 (Metacrine), EDP-305 (by Enanta), or EDP-297 (by Enanta).

69. The use of any one of claims 62 to 67, wherein the FXR agonist is:



or a pharmaceutically acceptable salt thereof.

70. The use of any one of claims 62 to 69, wherein the SSAO inhibitor is:



or a pharmaceutically acceptable salt thereof.