TREATING LIVER DISORDERS

FIELD OF THE INVENTION

[0001] This invention relates to methods and compositions for treating liver disorder in a patient.

STATE OF THE ART

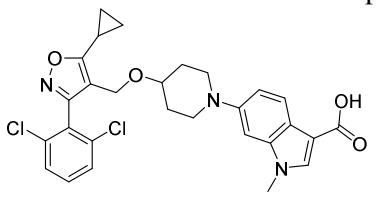
[0002] There is a need to provide alternative therapies for liver disorders such as non-alcoholic fatty liver disease (NAFLD), or non-alcoholic steatohepatitis (NASH).

SUMMARY

[0003] Provided herein are methods and compositions for treating a patient in need of treatment for a liver disorder. The method comprises administering to the patient a therapeutically effective amount of a compound of formulae I, II, or another compound utilized herein. In certain examples, liver disorders include, without limitation, liver inflammation, fibrosis, and steatohepatitis. In certain examples, the liver disorder is selected from: liver fibrosis, alcohol induced fibrosis, alcoholic steatosis, NAFLD, and NASH. In one example, the liver disorder is NASH. In another example, the liver disorder is liver inflammation. In another example, the liver disorder is liver fibrosis. In another example, the liver disorder is alcohol induced fibrosis. In another example, the liver disorder is alcoholic steatosis. In another example, the liver disorder is NAFLD. In one example, the treatment methods provided herein impedes or slows the progression of NAFLD to NASH. In one example, the treatment methods provided herein impedes or slows the progression of NASH. NASH can progress, e.g., to one or more of liver cirrhosis, hepatic cancer, etc.

[0004] As used herein, 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.

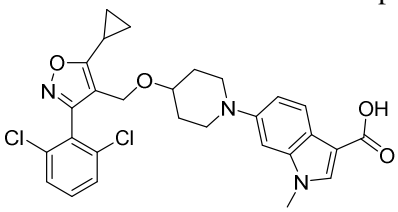
[0004a] In one aspect, the present disclosure refers to use of a compound of formula (I)



(I),

in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH) in a patient in need thereof, wherein the compound of formula (I) is to be administered as a monotherapy at a dose of from about 5 mg/day to about 600 mg/day.

[0004b] In one aspect, the present disclosure refers to use of a compound of formula (I)



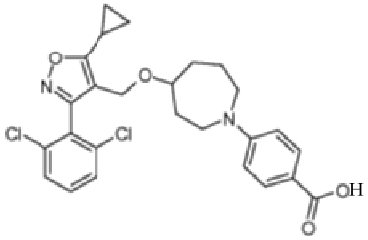
(I),

in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH) and liver fibrosis in a patient in need thereof, wherein the compound of formula (I) is to be administered at a dose of from about 5 mg/day to about 600 mg/day.

[0005] In one example provided herein is a pharmaceutically acceptable composition comprising a compound of formula (I) or (II), or a tautomer thereof, or an isotopomer of each thereof, or an enantiomer or diastereomer of the foregoing, or a pharmaceutically acceptable salt of each of the above, and at least one pharmaceutically acceptable excipient, carrier, or diluent for treating a liver disorder; impeding or slowing the progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH); or for impeding or slowing the progression of NASH, in a patient in need thereof, wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, NAFLD, and NASH.

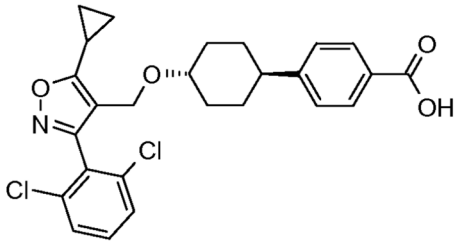
[0006] In one example, provided herein is a unit dose form of the pharmaceutically acceptable formulations provided herein. In some examples, the unit dose form comprises a therapeutically effective amount of a compound of formula (I) or (II). In one example, the unit dose form is for treating a liver disorder; of impeding or slowing the progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH); or of impeding or slowing the progression of NASH, in a patient in need thereof, wherein the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, NAFLD, and NASH.

[0007] In one example, the compound of formula (I) or (II) is the compound is: 4-{4-[5-cyclopropyl-3-(2,6-dichloro-phenyl)-isoxazol-4-ylmethoxy]-azepan-l-yl}-benzoic acid:



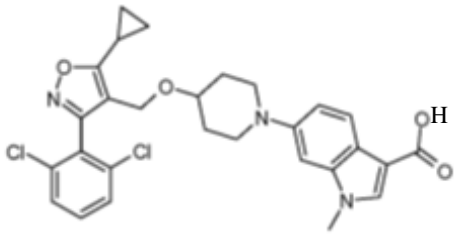
or a pharmaceutically acceptable salt or enantiomer thereof.

[0008] In one example, the compound of formula (I) or (II) is trans-4-{4-[5-cyclopropyl-3-(2,6-dichloro-phenyl)-isoxazol-4-ylmethoxy]-cyclohexyl}-benzoic acid:



or a pharmaceutically acceptable salt or enantiomer thereof.

[0009] In one example, the compound of formula (I) or (II) is 6-{4-[5-cyclopropyl-3-(2,6-dichloro-phenyl)-isoxazol-4-ylmethoxy]-piperidin-l-yl}-l -methyl- 1 H-indole-3 -carboxylic acid:



or a pharmaceutically acceptable salt or enantiomer thereof.

[0010] In one example, the therapeutically effective amount is 5 mg/day/patient - 600 mg/day/patient. In another example, the therapeutically effective amount is 75 mg/day/patient-600 mg/day/patient. In another example, the therapeutically effective amount is about 25 mg/day/patient. In another example, the therapeutically effective amount is about 75 mg/day/patient. In another example, the therapeutically effective amount is about 200 mg/day/patient. In another example, the therapeutically effective amount is about 400 mg/day/patient. In another example, the therapeutically effective amount is about 600 mg/day/patient. In one example, the compound of formula (I) or (II) is administered as a monotherapy, i.e., administered in absence of another agent, which: is useful in treating or substantially treating a liver disorder, impedes or slows the progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH); or impedes or slows the progression of NASH, in a patient in need thereof

[0011] In one example, the therapeutically effective amount is administered once daily. In one example, the therapeutically effective amount of is administered twice daily. In one

example, the therapeutically effective amount is 75 mg - 200 mg twice daily per patient. In one example, the compound is administered as a pharmaceutically acceptable composition comprising at least one pharmaceutically acceptable excipient, carrier, or diluent.

DETAILED DESCRIPTION

Definitions

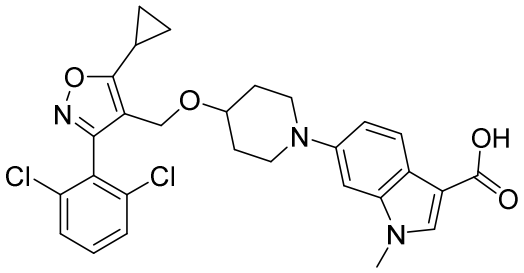
[0012] As used herein, the following definitions shall apply unless otherwise indicated. Further, if any term or symbol used herein is not defined as set forth below, it shall have its ordinary meaning in the art.

[0013] "Comprising" is intended to mean that the compositions and methods include the recited elements, but not excluding others. "Consisting essentially of" when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination. For example, a composition consisting essentially of the elements as defined herein would not exclude other elements that do not materially affect the basic and novel characteristic(s) of the claimed invention. "Consisting of" shall mean excluding more than trace amount of, e.g., other ingredients and substantial method steps recited. Embodiments defined by each of these transition terms are within the scope of this invention.

[0014] The term "excipient" as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound of the invention as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, *e.g.*, carbomers, povidone, xanthan gum, etc.; coatings include, *e.g.*, cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, *e.g.*, calcium carbonate, dextrose, fructose dc (dc = "directly compressible"), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, *e.g.*, croscarmellose sodium, gellan gum, sodium starch

CLAIMS

1. Use of a compound of formula (I)



(I),

in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH) in a patient in need thereof, wherein the compound of formula (I) is to be administered as a monotherapy at a dose of from about 5 mg/day to about 600 mg/day.

2. The use according to claim 1, wherein the compound of formula (I) is to be administered at a dose of from about 5 mg/day to about 75 mg/day.

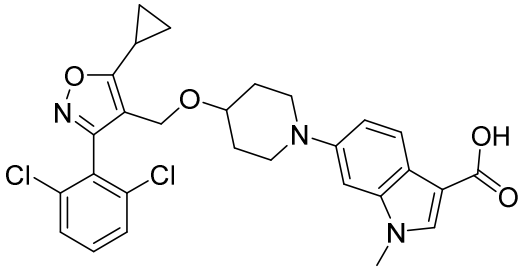
3. The use according to 1, wherein the compound of formula (I) is to be administered at a dose of from about 5 mg/day to about 25 mg/day.

4. The use according to any one of claims 1-3, wherein the compound of formula (I) is to be administered once daily to the patient.

5. The use according to any one of claims 1-4, wherein the compound of formula (I) is to be administered orally to the patient.

6. The use according to any one of claims 1-5, wherein the patient also has liver fibrosis.

7. Use of a compound of formula (I)



(I),

in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH) and liver fibrosis in a patient in need thereof, wherein the compound of formula (I) is to be administered at a dose of from about 5 mg/day to about 600 mg/day.

8. The use according to claim 7, wherein the compound of formula (I) is to be administered at a dose of from about 5 mg/day to about 75 mg/day.

9. The use according to claim 7, wherein the compound of formula (I) is to be administered at a dose of from about 5 mg/day to about 25 mg/day.

10. The use according to any one of claims 7-9, wherein the compound of formula (I) is to be administered once daily to the patient.

11. The use according to any one of claims 7-10, wherein the compound of formula (I) is to be administered as a monotherapy to the patient.

12. The use according to any one of claims 7-11, wherein the compound of formula (I) is to be administered orally to the patient.