COMPOUNDS AND METHODS FOR MODULATING FXR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Application No. 63/132,363, filed on December 30, 2020, the content of which is incorporated herein by reference in its entirety.

FIELD

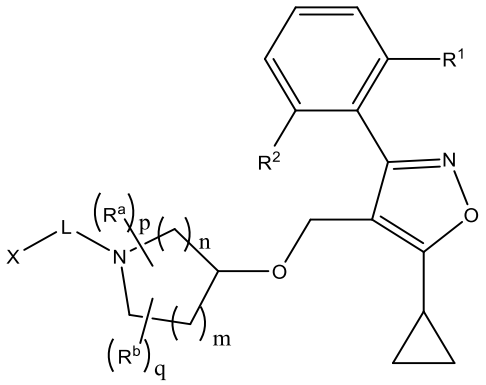
[0002] This disclosure generally relates to compounds for modulating farnesoid X receptor (FXR) and methods of use thereof.

BACKGROUND

[0003] FXR agonists are ligands for a nuclear receptor that regulates the transcription of genes that control triglyceride, cholesterol, and carbohydrate metabolism. The above efforts and others not withstanding, there remains a need to discover and develop compounds that are believed to be potent and efficacious (based on in-vitro and in-vivo models) agonists of FXR. Such compounds would be useful for remedy or improvement of the lives of patients in need of treatment of liver disorders, such as 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 SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a compound of formula (I):



(I)

or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

R^1 and R^2 are independently hydrogen, halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy are optionally substituted by one to three halogen;

m is 0, 1 or 2;

n is 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

R^a and R^b are independently halogen or C_1-C_6 alkyl,

or p and q are both 1, and R^a and R^b are taken together with the carbon atoms to which they are attached to form a C_4-C_6 bridge;

L is -C(=O)-, phenylene, or 5- or 6-membered heteroarylene, wherein the phenylene and 5- or 6-membered heteroarylene are optionally substituted by one to three substituents each independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, and cyano; and

X is 3- to 6-membered heterocyclyl or 3- to 6-membered heteroaryl each containing one to four annular heteroatoms selected from the group consisting of N, O and S, wherein the 3- to 6-membered heterocyclyl and 3- to 6-membered heteroaryl are optionally substituted by one to three substituents each independently selected from the group consisting of halogen, cyano and oxo.

[0003b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutical acceptable excipient.

[0003c] In a further aspect of the present disclosure, there is provided a use of a therapeutically effective amount of the compound disclosed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease mediated by farnesoid X receptor (FXR) in an individual in need thereof.

[0003d] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition disclosed herein, for use in therapy.

[0004] Disclosed herein are compounds that can be used as Farnesoid X Receptor (FXR) agonists, compositions containing these compounds and methods for treating diseases or conditions mediated by FXR.

[0005] In one ~~aspect~~example, provided is a compound of Formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, as detailed herein.

[0006] Further provided is a pharmaceutical composition comprising a compound of Formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient.

[0007] In another ~~aspect~~example, provided is a method of treating a disease or a condition mediated by FXR in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a stereoisomer, tautomer,

or a pharmaceutically acceptable salt of any of the foregoing. In some ~~embodiment~~examples, the disease or the condition is a liver disease. In some ~~embodiment~~examples, the disease or disorder is liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), or non-alcoholic steatohepatitis (NASH). Also provided is a compound of Formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing as detailed herein, for use in a method as disclosed herein. Also provided is use of a compound of Formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing as detailed herein, in the manufacture of a medicament for treating a disease or disorder as disclosed herein.

[0008] Further provided is a kit comprising a compound of Formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing. In some ~~embodiment~~examples, the kit comprises instructions for use according to a method described herein.

[0009] In yet another ~~aspect~~example, provided is a method of making a compound of Formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing. Also provided are compound intermediates useful in synthesis of a compound of Formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing.

DETAILED DESCRIPTION

Definitions

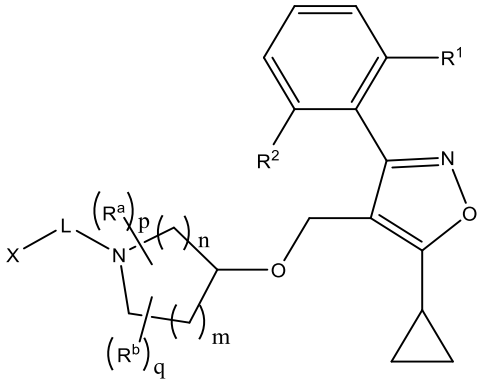
[0010] As used herein, the following definitions shall apply unless otherwise indicated. Further, if any term or symbol used herein is not defined as set forth below, it shall have its ordinary meaning in the art.

[0011] As used herein and in the appended claims, the singular forms “a”, “an” and “the” include plural forms, unless the context clearly dictates otherwise.

[0012] As used herein, and unless otherwise specified, the terms “about” and “approximately,” when used in connection with doses, amounts, or weight percent of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by those of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. Specifically, the terms “about” and “approximately,” when used in connection with a value, contemplate a variation within ±15%, within ±10%, within ±5%, within ±4%, within ±3%, within ±2%,

CLAIMS

1. A compound of formula (I):



(I)

or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

R^1 and R^2 are independently hydrogen, halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy are optionally substituted by one to three halogen;

m is 0, 1 or 2;

n is 1 or 2;

p is 0, 1 or 2;

q is 0, 1 or 2;

R^a and R^b are independently halogen or C_1-C_6 alkyl,

or p and q are both 1, and R^a and R^b are taken together with the carbon atoms to which they are attached to form a C_4-C_6 bridge;

L is -C(=O)-, phenylene, or 5- or 6-membered heteroarylene, wherein the phenylene and 5- or 6-membered heteroarylene are optionally substituted by one to three substituents each independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, and cyano; and

X is 3- to 6-membered heterocyclyl or 3- to 6-membered heteroaryl each containing one to four annular heteroatoms selected from the group consisting of N, O and S, wherein the 3- to 6-membered heterocyclyl and 3- to 6-membered heteroaryl are optionally substituted by

one to three substituents each independently selected from the group consisting of halogen, cyano and oxo.

2. The compound of claim 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are independently hydrogen, chloro, fluoro, methoxy, ethoxy, or trifluoromethoxy.

3. The compound of claim 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein at least one of R^1 and R^2 is not hydrogen.

4. The compound of claim 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein one of R^1 and R^2 is chloro, fluoro, methoxy or trifluoromethoxy and the other is hydrogen.

5. The compound of any one of claims 1-4, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein m is 1 and n is 2.

6. The compound of any one of claims 1-4, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein m is 2 and n is 2.

7. The compound of any one of claims 1-4, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein m is 0 and n is 1.

8. The compound of any one of claims 1-7, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^a and R^b are independently halogen.

9. The compound of any one of claims 1-7, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^a and R^b are independently chloro, fluoro, or methyl.

10. The compound of any one of claims 1-7, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein p and q are both 0.

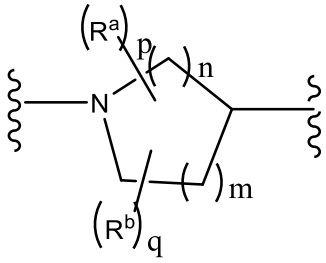
11. The compound of any one of claims 1-9, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein p and q are both 1.

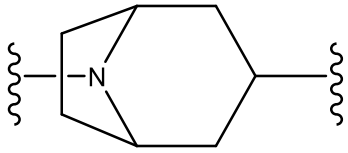
12. The compound of any one of claims 1-9, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein one of p and q is 0, and the other is 2.

13. The compound of any one of claims 1-9, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein p and q are both 2.

14. The compound of any one of claims 1-7, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein p and q are both 1, and R^a and R^b are taken together with the carbon atoms to which they are attached to form a C_4-C_6 bridge.

15. The compound of claim 14, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^a and R^b are taken together with the carbon atoms to which they are attached to form a C_4 bridge.

16. The compound of claim 15, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein the  moiety is



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17. The compound of any one of claims 1-16, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is -C(=O)-.

18. The compound of any one of claims 1-16, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is phenylene or 5- or 6-membered heteroarylene, and wherein the phenylene and 5- or 6-membered heteroarylene are optionally substituted by one to three substituents each independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, and cyano.

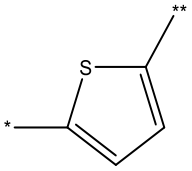
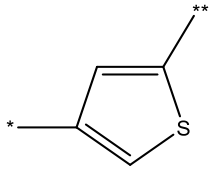
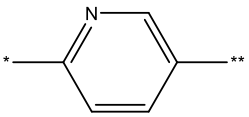
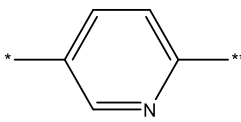
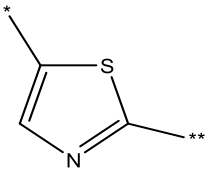
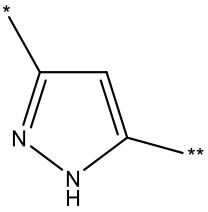
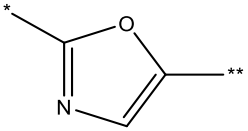
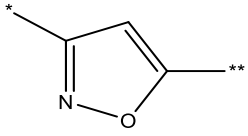
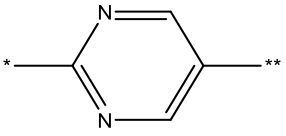
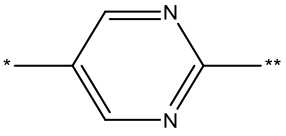
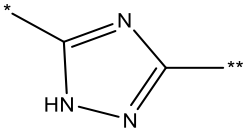
19. The compound of claim 18, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is phenylene optionally substituted by one to three substituents each independently selected from the group consisting of methyl, chloro and fluoro.

20. The compound of claim 19, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is phenylene.

21. The compound of claim 18, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is 5- or 6-membered heteroarylene optionally substituted by one to three substituents each independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, and cyano.

22. The compound of claim 21, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is 5-membered heteroarylene optionally substituted by one to three substituents each independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, and cyano.

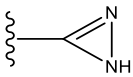
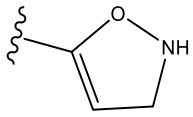
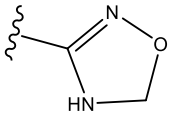
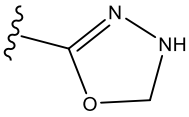
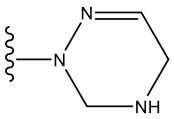
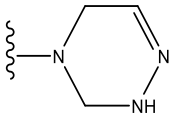
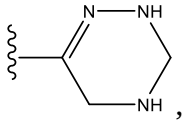
23. The compound of claim 21, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is 6-membered heteroarylene optionally substituted by one to three substituents each independently selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, and cyano.

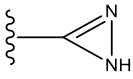
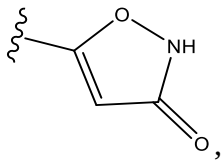
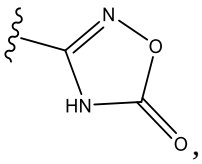
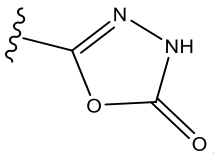
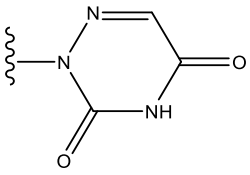
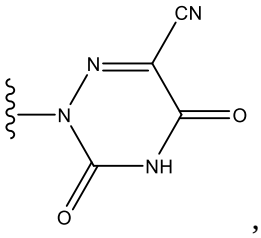
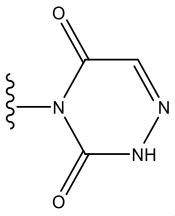
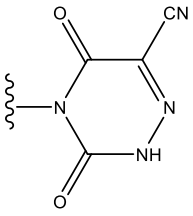
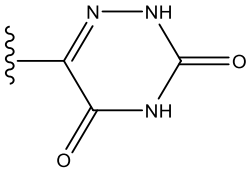
24. The compound of claim 21, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is 5- or 6-membered heteroarylene selected from the group consisting of , , , , , , , , , , and , wherein

* represents the point of attachment to the remainder of the molecule via the nitrogen,

** represents the point of attachment to the X moiety, and

each of which is optionally substituted by methyl, chloro or fluoro.

25. The compound of any one of claims 1-24, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is , , , , , , or , each of which is optionally substituted by one to three substituents each independently selected from the group consisting of cyano and oxo.

26. The compound of any one of claims 1-24, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is , , , , , , , , or .

27. The compound of claim 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is selected from the group consisting of the compounds in Table 1.

28. A pharmaceutical composition comprising the compound of any one of claims 1-27, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutical acceptable excipient.

29. ~~A method of treating a disease mediated by farnesoid X receptor (FXR) in an individual in need thereof, comprising administering to the individual~~Use of a therapeutically effective amount of the compound of any one of claims 1-27, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 28, in the manufacture of a medicament for treating a disease mediated by farnesoid X receptor (FXR) in an individual in need thereof.

30. The use~~method~~ of claim 29, wherein the disease is a liver disease.

31. The use~~method~~ of claim 30, wherein the liver disease is primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), graft versus host disease, transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, or oti-antitrypsin deficiency.

32. The use~~method~~ of claim 31, wherein the liver disease is NASH.

33. The use~~method~~ of claim 29, wherein the disease is dyslipidemia or a related disease.

34. A compound of any one of claims 1-27, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 28, for use in therapy.

~~34. A compound of any one of claims 1-27, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, for use in the treatment of a disease mediated by FXR.~~

~~35. Use of a compound of any one of claims 1-27, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for the treatment of a disease mediated by FXR.~~