FARNESOID X RECEPTOR AGONISTS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/733,004, filed on September 18, 2018, U.S. Provisional Application No. 62/733,006, filed on September 18, 2018, and U.S. Provisional Application No. 62/881,560, filed on August 1, 2019, all of which are herein incorporated by reference in their entirety.

FIELD OF THE INVENTION

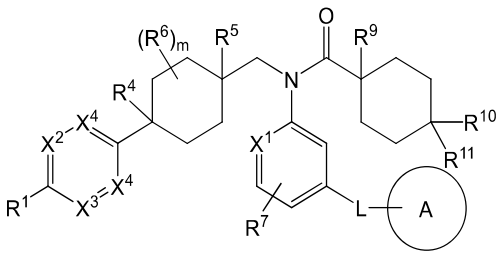
[0002] Described herein are compounds that are farnesoid X receptor agonists, methods of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds in the treatment of conditions, diseases, or disorders associated with farnesoid X receptor activity.

BACKGROUND OF THE INVENTION

[0003] Farnesoid X receptor (FXR) is a nuclear receptor highly expressed in the liver, intestine, kidney, adrenal glands, and adipose tissue. FXR regulates a wide variety of target genes involved in the control of bile acid synthesis and transport, lipid metabolism, and glucose homeostasis. FXR agonism is a treatment modality for many metabolic disorders, liver diseases or conditions, inflammatory conditions, gastrointestinal diseases, or cell proliferation diseases.

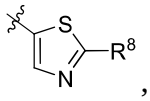
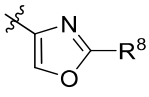
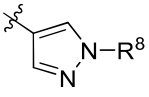
SUMMARY

[0003a] In an aspect, there is provided a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II);

wherein:

ring A is , , or ;

X^1 is CH or N;

R^1 is H, halogen, -CN, -OH, -$N(R^{17})_2$, -$NR^{17}S(=O)_2(C_1$-C_4alkyl), -$S(=O)_2N(R^{17})_2$, -$OC(=O)(C_1$-C_4alkyl), -CO_2H, -$CO_2(C_1$-C_4alkyl), -$C(=O)N(R^{17})_2$, -$NR^{17}C(=O)(C_1$-C_4alkyl), -$NR^{17}C(=O)O(C_1$-C_4alkyl), -$OC(=O)N(R^{17})_2$, -$NR^{15}C(=O)N(R^{17})_2$, -SH, -$S(C_1$-C_4alkyl), -$S(=O)(C_1$-C_4alkyl), -$S(=O)_2(C_1$-C_4alkyl), C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4heteroalkyl, or monocyclic C_2-C_5heterocycloalkyl;

X^2 is CR^2 or N;

R^2 is H, halogen, -CN, -OH, -$N(R^{17})_2$, -$NR^{17}S(=O)_2(C_1$-C_4alkyl), -$S(=O)_2N(R^{17})_2$, -$OC(=O)(C_1$-C_4alkyl), -CO_2H, -$CO_2(C_1$-C_4alkyl), -$C(=O)N(R^{17})_2$, -$NR^{17}C(=O)(C_1$-C_4alkyl), -$NR^{17}C(=O)O(C_1$-C_4alkyl), -$OC(=O)N(R^{17})_2$, -$NR^{17}C(=O)N(R^{17})_2$, -SH, -$S(C_1$-C_4alkyl), -$S(=O)(C_1$-C_4alkyl), -$S(=O)_2(C_1$-C_4alkyl), C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4heteroalkyl, or monocyclic C_2-C_5heterocycloalkyl;

or R^1 and R^2 are taken together with the intervening atoms to form a fused 5- or 6-membered ring with 0-3 N atoms and 0-2 O or S atoms in the ring, wherein the fused 5- or 6-membered ring is optionally substituted with halogen or C_1-C_4alkyl;

X^3 is CR^3 or N;

R^3 is H, halogen, -CN, -OH, -$N(R^{17})_2$, -$NR^{17}S(=O)_2(C_1$-C_4alkyl), -$OC(=O)(C_1$-C_4alkyl), -CO_2H, -$CO_2(C_1$-C_4alkyl), -$C(=O)N(R^{17})_2$, -$NR^{17}C(=O)(C_1$-C_4alkyl), C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl;

each X^4 is independently CH or N;

R^4 and R^5 are taken together to form a bridge that is -CH_2- or -CH_2CH_2-;

each R^6 is independently H, F, -OH, or -CH_3;

R^7 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl;

L is absent;

R^8 is C_4-C_8alkyl;

R^9 is H, F, or -CH_3;

R^{10} is -$OC(=O)N(R^{12})(R^{13})$, -$N(R^{16})C(=O)R^{14}$, or -$N(R^{16})C(=O)OR^{15}$;

R^{11} is H, F, or -CH_3;

R^{12} and R^{13} are taken together to form a 4-, 5-, or 6- membered heterocycloalkyl ring optionally containing an additional heteroatom selected from O, S, and N and

optionally substituted with 1, 2, or 3 groups selected from -OH, -N(C_1-C_4alkyl)$_2$, C_1-C_6alkyl, and C_1-C_6alkoxy;

R^{14} is C_1-C_6alkyl or -C_1-C_6alkyl-OR^{17};

R^{15} is C_1-C_6alkyl, -C_1-C_6alkyl-OR^{17}, or C_2-C_6heterocycloalkyl;

R^{16} is H or C_1-C_6alkyl;

each R^{17} is independently H or C_1-C_6alkyl; and

m is 0, 1, or 2.

[0003b] In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0003c] In another aspect, there is provide the use of a compound as defined above, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating or preventing:

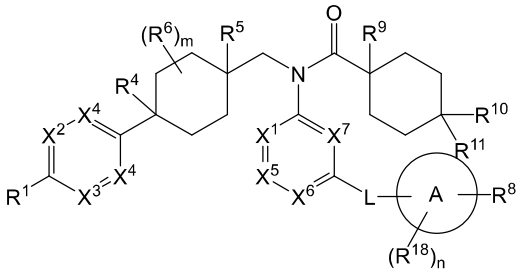
a liver disease or condition in a mammal;

a liver fibrosis in a mammal;

a liver inflammation in a mammal; or

a gastrointestinal disease or condition in a mammal.

[0004] In one example, described herein is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I');

wherein:

ring A is a 5-membered heteroaryl that is oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, or thiadiazolyl;

Y^2 is absent, -O-, -S-, -S(=O)-, -$S(=O)_2$-, -$S(=O)_2NR^{17}$-, -CH_2-, -CH=CH-, -C≡C-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^{17}-, -NR^{17}C(=O)-, -OC(=O)NR^{17}-, -NR^{17}C(=O)O-, -NR^{17}C(=O)NR^{17}-, -$NR^{17}S(=O)_2$-, or -NR^{17}-;

L^1 is absent or C_1-C_4alkylene;

each R^7 is independently selected from H, halogen, -CN, -OH, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_3-C_6cycloalkyl, and C_1-C_4heteroalkyl;

R^8 is C_4-C_8alkyl or C_4-C_8haloalkyl;

R^9 is H, F, or -CH_3;

R^{10} is -OC(=O)N(R^{12})(R^{13}), -N(R^{16})C(=O)R^{14}, or -N(R^{16})C(=O)OR^{15};

R^{11} is H, F, or -CH_3;

R^{12} is -C_1-C_6alkyl-OR^{17} or monocyclic C_2-C_5heterocycloalkyl optionally substituted with one or two oxo groups;

R^{13} is H or C_1-C_4alkyl; or R^{12} and R^{13} are taken together to form a 4-, 5-, or 6-membered heterocycloalkyl ring optionally containing an additional heteroatom selected from O, S, and N and optionally substituted with 1, 2, or 3 groups selected from -OH, -N(C_1-C_4alkyl)$_2$, C_1-C_6alkyl, C_1-C_6alkoxy, -S(C_1-C_4alkyl), -S(=O)(C_1-C_4alkyl), -$S(=O)_2$(C_1-C_4alkyl), -C_1-C_4alkyl-$S(=O)_2$(C_1-C_4alkyl), -C_1-C_6alkyl-OR^{17}, and -O-C_1-C_6alkyl-OR^{17};

R^{14} is C_1-C_6alkyl, C_3-C_6cycloalkyl, or -C_1-C_6alkyl-OR^{17};

R^{15} is C_1-C_6alkyl, -C_1-C_6alkyl-OR^{17}, C_3-C_6cycloalkyl, or C_2-C_6heterocycloalkyl;

R^{16} is H or C_1-C_6alkyl;

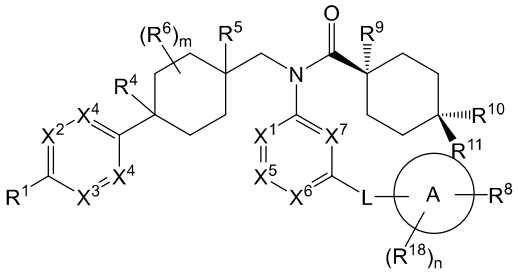
each R^{17} is independently H or C_1-C_6alkyl;

each R^{18} is independently halogen, -CN, -OH, -N(R^{17})$_2$, -$NR^{17}S(=O)_2$(C_1-C_4alkyl), -S(C_1-C_4alkyl), -S(=O)(C_1-C_4alkyl), -$S(=O)_2$(C_1-C_4alkyl), -$S(=O)_2$N(R^{17})$_2$, -C(=O)(C_1-C_4alkyl), -OC(=O)(C_1-C_4alkyl), -CO_2H, -CO_2(C_1-C_4alkyl), -NR^{17}C(=O)(C_1-C_4alkyl), -C(=O)N(R^{17})$_2$, -NR^{17}C(=O)O(C_1-C_4alkyl), -OC(=O)N(R^{17})$_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4heteroalkyl, C_3-C_6cycloalkyl, monocyclic C_2-C_6heterocycloalkyl, phenyl, or monocyclic heteroaryl;

m is 0, 1, or 2; and

n is 0, 1, or 2.

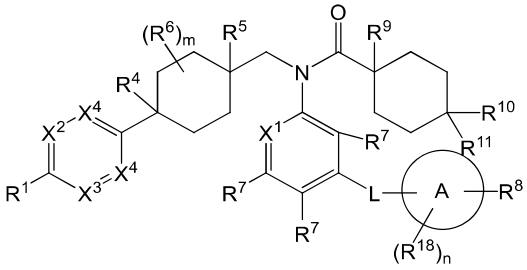
[0005] In some examples is a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (Ia'):



Formula (Ia').

[0006] In some examples is a compound of Formula (I') or (Ia'), or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is N, and X^5, X^6, and X^7 are CH. In some examples is a compound of Formula (I') or (Ia'), or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 and X^6 are N, and X^5 and X^7 are CH. In some examples is a compound of Formula (I') or (Ia'), or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 and X^7 are N, and X^5 and X^6 are CH. In some examples is a compound of Formula (I') or (Ia'), or a pharmaceutically acceptable salt or solvate thereof, wherein X^1, X^5, X^6, and X^7 are CH.

[0007] In another example, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I);

wherein:

ring A is a 5-membered heteroaryl that is oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, or thiadiazolyl;

or ring A is a 6-membered heteroaryl that is pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl;

X^1 is C(H), C(F), or N;

R^1 is selected from H, halogen, -CN, -OH, $-N(R^{17})_2$, $-NR^{17}S(=O)_2(C_1\text{-}C_4\text{alkyl})$, $-S(=O)_2N(R^{17})_2$, $-OC(=O)(C_1\text{-}C_4\text{alkyl})$, $-CO_2H$, $-CO_2(C_1\text{-}C_4\text{alkyl})$, $-C(=O)N(R^{17})_2$, $-NR^{17}C(=O)(C_1\text{-}C_4\text{alkyl})$, $-NR^{17}C(=O)O(C_1\text{-}C_4\text{alkyl})$, $-OC(=O)N(R^{17})_2$, $-NR^{15}C(=O)N(R^{17})_2$, -SH, $-S(C_1\text{-}C_4\text{alkyl})$, $-S(=O)(C_1\text{-}C_4\text{alkyl})$, $-S(=O)_2(C_1\text{-}$

R^{11} is H, F, or -CH_3;

R^{12} is -C_1-C_6alkyl-OR^{17} or monocyclic C_2-C_5heterocycloalkyl optionally substituted with one or two oxo groups;

R^{13} is H or C_1-C_4alkyl; or R^{12} and R^{13} are taken together to form a 4-, 5-, or 6-membered heterocycloalkyl ring optionally containing an additional heteroatom selected from O, S, and N and optionally substituted with 1, 2, or 3 groups selected from -OH, -N(C_1-C_4alkyl)$_2$, C_1-C_6alkyl, C_1-C_6alkoxy, -S(C_1-C_4alkyl), -S(=O)(C_1-C_4alkyl), -S(=O)$_2$(C_1-C_4alkyl), -C_1-C_4alkyl-S(=O)$_2$(C_1-C_4alkyl), -C_1-C_6alkyl-OR^{17}, and -O-C_1-C_6alkyl-OR^{17};

R^{14} is C_1-C_6alkyl or -C_1-C_6alkyl-OR^{17};

R^{15} is C_1-C_6alkyl, -C_1-C_6alkyl-OR^{17}, or C_2-C_6heterocycloalkyl;

R^{16} is H or C_1-C_6alkyl;

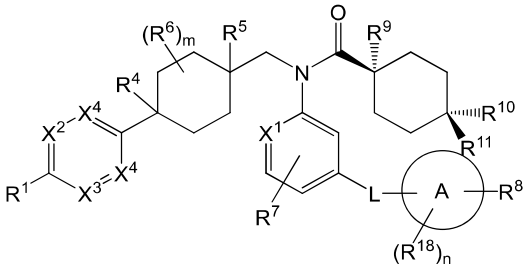
each R^{17} is independently H or C_1-C_6alkyl;

each R^{18} is independently halogen, -CN, -OH, -N(R^{17})$_2$, -NR^{17}S(=O)$_2$(C_1-C_4alkyl), -S(C_1-C_4alkyl), -S(=O)(C_1-C_4alkyl), -S(=O)$_2$(C_1-C_4alkyl), -S(=O)$_2$N(R^{17})$_2$, -C(=O)(C_1-C_4alkyl), -OC(=O)(C_1-C_4alkyl), -CO_2H, -CO_2(C_1-C_4alkyl), -NR^{17}C(=O)(C_1-C_4alkyl), -C(=O)N(R^{17})$_2$, -NR^{17}C(=O)O(C_1-C_4alkyl), -OC(=O)N(R^{17})$_2$, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, C_1-C_4heteroalkyl, C_3-C_6cycloalkyl, monocyclic C_2-C_6heterocycloalkyl, phenyl, or monocyclic heteroaryl;

m is 0, 1, or 2; and

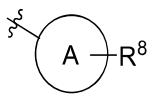
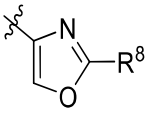
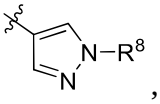
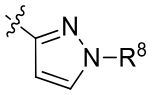
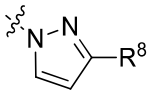
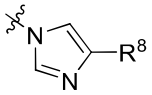
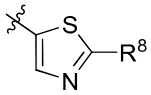
n is 0, 1, or 2.

[0008] In some examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (Ia):

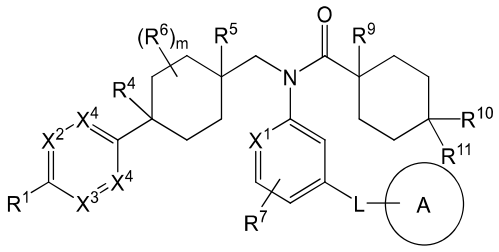


Formula (Ia).

[0009] In some examples is a compound of Formula (I'), (I), (Ia'), or (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein ring A is a 5-membered heteroaryl that is oxazolyl, thiazolyl, imidazolyl, or pyrazolyl; or ring A is a 6-membered

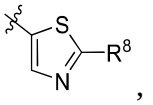
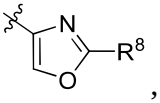
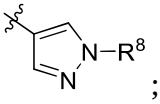
heteroaryl that is pyridinyl or pyrimidinyl. In some examples is a compound of Formula (I'), (I), (Ia'), or (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein ring n is 0. In some examples is a compound of Formula (I'), (I), (Ia'), or (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein ring  is , , , ,  or . In some examples is a compound of Formula (I'), (I), (Ia'), or (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is -OC(=O)N(R^{12})(R^{13}). In some examples is a compound of Formula (I'), (I), (Ia'), or (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{12} is -C_1-C_6alkyl-OR^{17}. In some examples is a compound of Formula (I'), (I), (Ia'), or (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{12} is -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, or -$CH_2CH_2C(CH_3)_2OH$. In some examples is a compound of Formula (I'), (I), (Ia'), or (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{13} is H. In some examples is a compound of Formula (I'), (I), (Ia'), or (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{12} and R^{13} are taken together to form a 4-, 5-, or 6- membered heterocycloalkyl ring optionally containing an additional heteroatom selected from O, S, and N and optionally substituted with 1, 2, or 3 groups selected from -OH, -N(C_1-C_4alkyl)$_2$, C_1-C_6alkyl, C_1-C_6alkoxy, -S(=O)$_2$(C_1-C_4alkyl), -C_1-C_4alkyl-S(=O)$_2$(C_1-C_4alkyl), -C_1-C_6alkyl-OR^{17}, and -O-C_1-C_6alkyl-OR^{17}.

[0010] In another example, described herein is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II);

wherein:

ring A is , , or ;

X^1 is CH or N;

R^8 is C_4-C_8alkyl;

R^9 is H, F, or -CH_3;

R^{10} is -OC(=O)N(R^{12})(R^{13}), -N(R^{16})C(=O)R^{14}, or -N(R^{16})C(=O)OR^{15};

R^{11} is H, F, or -CH_3;

R^{12} and R^{13} are taken together to form a 4-, 5-, or 6- membered heterocycloalkyl ring optionally containing an additional heteroatom selected from O, S, and N and optionally substituted with 1, 2, or 3 groups selected from -OH, -N(C_1-C_4alkyl)$_2$, C_1-C_6alkyl, and C_1-C_6alkoxy;

R^{14} is C_1-C_6alkyl or -C_1-C_6alkyl-OR^{17};

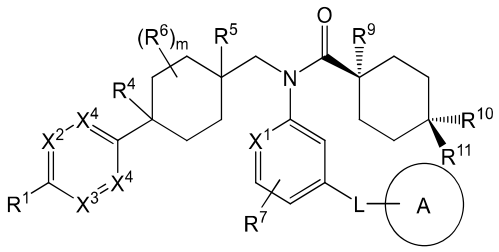
R^{15} is C_1-C_6alkyl, -C_1-C_6alkyl-OR^{17}, or C_2-C_6heterocycloalkyl;

R^{16} is H or C_1-C_6alkyl;

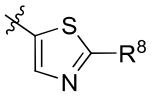
each R^{17} is independently H or C_1-C_6alkyl; and

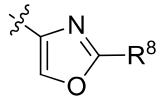
m is 0, 1, or 2.

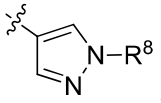
[0011] In some examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (IIa):



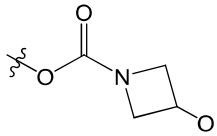
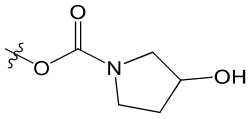
Formula (IIa).

[0012] In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein ring A is 

. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein ring A is 

. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein ring A is 

. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^8 is -$C(CH_3)_3$. In some examples is a compound of Formula (I), (Ia), (II), or (IIa), or a pharmaceutically

acceptable salt or solvate thereof, wherein X^1 is N. In some examples is a compound of Formula (I), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CH. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^4 is H and R^5 is H. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^4 and R^5 are taken together to form a bridge that is $-CH_2-$ or $-CH_2CH_2-$. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^4 and R^5 are taken together to form a bridge that is $-CH_2CH_2-$. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is $-OC(=O)N(R^{12})(R^{13})$. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II) or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{12} and R^{13} are taken together to form a 4-membered or 5-membered heterocycloalkyl ring optionally containing an additional heteroatom selected from O, S, and N and optionally substituted with 1 or 2 groups selected from -OH, $-N(C_1\text{-}C_4\text{alkyl})_2$, $C_1\text{-}C_6$alkyl, and $C_1\text{-}C_6$alkoxy. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II) or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is . In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II) or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is . In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is $-N(R^{16})C(=O)R^{14}$. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{14} is $C_1\text{-}C_6$alkyl. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{14} is $-C_1\text{-}C_6\text{alkyl-}OR^{17}$. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is $-N(R^{16})C(=O)OR^{15}$. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{15} is $C_1\text{-}C_6$alkyl. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a

pharmaceutically acceptable salt or solvate thereof, wherein R^{15} is -C_1-C_6alkyl-OR^{17}. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{15} is C_2-C_6heterocycloalkyl. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{16} is H. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein one X^4 is CH and one X^4 is N. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each X^4 is CH. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein X^3 is CH. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein X^2 is CR^2. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is halogen, -CN, or C_1-C_4alkyl. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is C_1-C_4alkyl. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is C_1-C_4alkyl or C_1-C_4alkoxy. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is C_1-C_4alkoxy. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is -OCH_3. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein L is absent. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein m is 0. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^9 is H. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{11} is H. In some examples is a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^7 is H.

[0013] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0014] In one example, described herein is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient. In some examples, the pharmaceutical composition is formulated for administration to a mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration. In some examples, the pharmaceutical composition is formulated for administration to a mammal by intravenous administration, subcutaneous administration, or oral administration. In some examples, the pharmaceutical composition is formulated for administration to a mammal by oral administration. In some examples, the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion. In some examples, the pharmaceutical composition is in the form of a tablet, a pill, or a capsule.

[0015] In another example, described herein is a method of treating a disease or condition in a mammal that would benefit from FXR agonism comprising administering a compound as described herein, or pharmaceutically acceptable salt or solvate thereof, to the mammal in need thereof. In some examples, the disease or condition is a metabolic condition. In some examples, the disease or condition is a liver condition.

[0016] In some examples, the compound is administered to the mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration.

[0017] In one example, described herein is a method of treating or preventing any one of the diseases or conditions described herein comprising administering a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, to a mammal in need thereof.

[0018] In one example, described herein is a method for the treatment or prevention of a metabolic or liver condition in a mammal comprising administering a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, to the mammal in need thereof. In other examples, the metabolic or liver condition is amenable to treatment with an FXR agonist. In some examples, the method further comprises administering a second therapeutic agent to the mammal in addition to the compound described herein, or a pharmaceutically acceptable salt or solvate thereof.

[0019] In one example, described herein is a method of treating or preventing a liver disease or condition in a mammal, comprising administering to the mammal a compound of Formula

(I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof. In some examples, the liver disease or condition is an alcoholic or non-alcoholic liver disease. In some examples, the liver disease or condition is primary biliary cirrhosis, primary sclerosing cholangitis, cholestasis, nonalcoholic steatohepatitis (NASH), or nonalcoholic fatty liver disease (NAFLD). In some examples, the alcoholic liver disease or condition is fatty liver (steatosis), cirrhosis, or alcoholic hepatitis. In some examples, the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH), or nonalcoholic fatty liver disease (NAFLD). In some examples, the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH). In some examples, the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH) and is accompanied by liver fibrosis. In some examples, the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH) without liver fibrosis. In some examples, the non-alcoholic liver disease or condition is intrahepatic cholestasis or extrahepatic cholestasis.

[0020] In one example, described herein is a method of treating or preventing a liver fibrosis in a mammal, comprising administering to the mammal a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof. In some examples, the mammal is diagnosed with hepatitis C virus (HCV), nonalcoholic steatohepatitis (NASH), primary sclerosing cholangitis (PSC), cirrhosis, Wilson's disease, hepatitis B virus (HBV), HIV associated steatohepatitis and cirrhosis, chronic viral hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic steatohepatitis (ASH), nonalcoholic steatohepatitis (NASH), primary biliary cirrhosis (PBC), or biliary cirrhosis. In some examples, the mammal is diagnosed with nonalcoholic steatohepatitis (NASH).

[0021] In one example, described herein is a method of treating or preventing a liver inflammation in a mammal, comprising administering to the mammal a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof. In some examples, the mammal is diagnosed with hepatitis C virus (HCV), nonalcoholic steatohepatitis (NASH), primary sclerosing cholangitis (PSC), cirrhosis, Wilson's disease, hepatitis B virus (HBV), HIV associated steatohepatitis and cirrhosis, chronic viral hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic steatohepatitis (ASH), nonalcoholic steatohepatitis (NASH), primary biliary cirrhosis (PBC), or biliary cirrhosis. In some examples, the mammal is diagnosed with nonalcoholic steatohepatitis (NASH). In some examples, the liver inflammation is associated with inflammation in

the gastrointestinal tract. In some examples, the mammal is diagnosed with inflammatory bowel disease.

[0022] In one example, described herein is a method of treating or preventing a gastrointestinal disease or condition in a mammal, comprising administering to the mammal a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof. In some examples, the gastrointestinal disease or condition is necrotizing enterocolitis, gastritis, ulcerative colitis, Crohn's disease, inflammatory bowel disease, irritable bowel syndrome, gastroenteritis, radiation induced enteritis, pseudomembranous colitis, chemotherapy induced enteritis, gastro-esophageal reflux disease (GERD), peptic ulcer, non-ulcer dyspepsia (NUD), celiac disease, intestinal celiac disease, post-surgical inflammation, gastric carcinogenesis, graft versus host disease, or any combination thereof. In some examples, the gastrointestinal disease is irritable bowel syndrome (IBS), irritable bowel syndrome with diarrhea (IBS-D), irritable bowel syndrome with constipation (IBS-C), mixed IBS (IBS-M), unsubtyped IBS (IBS-U), or bile acid diarrhea (BAD).

[0023] In one example, described herein is a method of treating or preventing a disease or condition in a mammal that would benefit from treatment with an FXR agonist, comprising administering to the mammal a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof. In some examples, the methods described herein further comprise administering at least one additional therapeutic agent in addition to the compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa), or a pharmaceutically acceptable salt or solvate thereof.

[0024] In any of the aforementioned examples are further exampleexamples in which the effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by inhalation; and/or (e) administered by nasal administration; or and/or (f) administered by injection to the mammal; and/or (g) administered topically to the mammal; and/or (h) administered by ophthalmic administration; and/or (i) administered rectally to the mammal; and/or (j) administered non-systemically or locally to the mammal.

[0025] In any of the aforementioned examples are further exampleexamples comprising single administrations of the effective amount of the compound, including further examples in which the compound is administered once a day to the mammal or the compound is administered to the mammal multiple times over the span of one day. In some examples,

the compound is administered on a continuous dosing schedule. In some examples, the compound is administered on a continuous daily dosing schedule.

[0026] In any of the aforementioned examples involving the treatment of a disease or condition are further examples comprising administering at least one additional agent in addition to the administration of a compound of Formula (I'), (I), (Ia'), (Ia), (II), or (IIa) described herein, or a pharmaceutically acceptable salt thereof. In various examples, each agent is administered in any order, including simultaneously.

[0027] In any of the examples disclosed herein, the mammal or subject is a human.

[0028] In some examples, compounds provided herein are administered to a human.

[0029] In some examples, compounds provided herein are orally administered.

[0030] In some examples, described herein is a method of treating or preventing a metabolic disorder in a subject, comprising: administering to a gastrointestinal tract of the subject a therapeutically effective amount of one or more of the compounds described herein, or a pharmaceutically acceptable salt or solvate thereof, thereby activating farnesoid X receptors (FXR) in the intestines, and treating or preventing a metabolic disorder in the subject. In some examples, the compound's absorption is preferentially restricted to within the intestines. In some examples, the method substantially enhances FXR target gene expression in the intestines while not substantially enhancing FXR target gene expression in the liver or kidney. In some examples, the method substantially enhances FXR target gene expression in the intestines while minimizing systemic plasma levels of the delivered compound. In some examples, the method substantially enhances FXR target gene expression in the intestines and the liver while minimizing systemic plasma levels of the delivered compound. In some examples, the method substantially enhances FXR target gene expression in the intestines while not substantially enhancing FXR target gene expression in the liver or kidney, and while minimizing systemic plasma levels. In some examples, the method substantially enhances FXR target gene expression in the intestines and the liver and provides sustained systemic plasma levels of the delivered compound. In some examples, the method reduces or prevents diet-induced weight gain. In some examples, the method increases a metabolic rate in the subject. In some examples, the increasing the metabolic rate comprises enhancing oxidative phosphorylation in the subject. In some examples, the method further comprises improving glucose and/or lipid homeostasis in the subject. In some examples, the method results in no substantial change in food intake and/or fat consumption in the subject. In some examples, the method results in no substantial change in appetite in the subject. In some examples, the

metabolic disorder is selected from obesity, diabetes, insulin resistance, dyslipidemia or any combination thereof. In some examples, the metabolic disorder is non-insulin dependent diabetes mellitus. In some examples, the method protects against diet-induced weight gain, reduces inflammation, enhances thermogenesis, enhances insulin sensitivity in the liver, reduces hepatic steatosis, promotes activation of BAT, decreases blood glucose, increases weight loss, or any combination thereof. In some examples, the method enhances insulin sensitivity in the liver and promotes brown adipose tissue (BAT) activation. In some examples, the method further comprises administering to the subject an insulin sensitizing drug, an insulin secretagogue, an alpha-glucosidase inhibitor, a glucagon-like peptide (GLP) agonist, a dipeptidyl peptidase-4 (DPP-4) inhibitor, nicotinamide ribonucleoside, an analog of nicotinamide ribonucleoside, or combinations thereof.

[0031] In some examples, described herein is a method of treating or preventing inflammation in an intestinal region of a subject, comprising: administering to a gastrointestinal tract of the subject a therapeutically effective amount of one or more of the compounds described herein, or a pharmaceutically acceptable salt or solvate thereof, thereby activating FXR receptors in the intestines, and thereby treating or preventing inflammation in the intestinal region of the subject. In some examples, the compound's absorption is preferentially restricted to within the intestines. In some examples, the method substantially enhances FXR target gene expression in the intestines while not substantially enhancing FXR target gene expression in the liver or kidney. In some examples, the inflammation is associated with a clinical condition selected from necrotizing enterocolitis, gastritis, ulcerative colitis, Crohn's disease, inflammatory bowel disease, irritable bowel syndrome, gastroenteritis, radiation induced enteritis, pseudomembranous colitis, chemotherapy induced enteritis, gastro-esophageal reflux disease (GERD), peptic ulcer, non-ulcer dyspepsia (NUD), celiac disease, intestinal celiac disease, post-surgical inflammation, gastric carcinogenesis or any combination thereof. In some examples, the one or more FXR target genes comprises IBABP, OSTα, Per1, FGF15, FGF19, SHP or combinations thereof. In some examples, the method further comprises administering a therapeutically effective amount of an antibiotic therapy to the subject, wherein the method treats or prevents inflammation associated with pseudomembranous colitis in the subject. In some examples, the method further comprises administering to the subject a therapeutically effective amount of an oral corticosteroid, other anti-inflammatory or immunomodulatory therapy, nicotinamide ribonucleoside, an analog of nicotinamide ribonucleoside, or

combinations thereof. In some examples, the method increases HSL phosphorylation and β3-adrenergic receptor expression. In some examples, a serum concentration of the compound in the subject remains below its EC_{50} following administration of the compound.

[0032] In some examples, described herein is a method of treating or preventing a cell proliferation disease in a subject, comprising administering to a gastrointestinal tract of the subject a therapeutically effective amount of one or more of the compounds described herein or a pharmaceutically acceptable salt or solvate thereof. In some examples, the cell proliferation disease is an adenocarcinoma. In some examples, the adenocarcinoma is a colon cancer. In some examples, the treating the adenocarcinoma reduces the size of the adenocarcinoma, the volume of the adenocarcinoma, the number of adenocarcinomas, cachexia due to the adenocarcinoma, delays progression of the adenocarcinoma, increases survival of the subject, or combinations thereof. In some examples, the method further comprises administering to the subject an additional therapeutic compound selected from the group consisting of a chemotherapeutic, a biologic, a radiotherapeutic, or combinations thereof.

[0033] In some examples, described herein is a method of treating or preventing a liver disease or condition in a subject, comprising administering to the subject a therapeutically effective amount of one or more of the compounds described herein, or a pharmaceutically acceptable salt or solvate thereof. In some examples, the liver disease or condition is an alcoholic or non-alcoholic liver disease. In some examples, the liver disease or condition is primary biliary cirrhosis, primary sclerosing cholangitis, cholestasis, nonalcoholic steatohepatitis (NASH), or nonalcoholic fatty liver disease (NAFLD). In some examples, the alcoholic liver disease or condition is fatty liver (steatosis), cirrhosis, or alcoholic hepatitis. In some examples, the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH), or nonalcoholic fatty liver disease (NAFLD). In some examples, the non-alcoholic liver disease or condition is intrahepatic cholestasis or extrahepatic cholestasis.

[0034] Articles of manufacture, which include packaging material, a compound described herein, or a pharmaceutically acceptable salt thereof, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from FXR agonism, are provided.

[0035] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

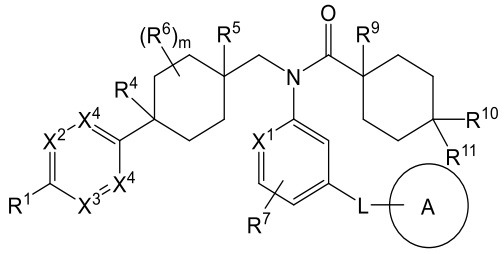
DETAILED DESCRIPTION OF THE INVENTION

[0036] The nuclear hormone receptor farnesoid X receptor (also known as FXR or nuclear receptor subfamily 1, group H, member 4 (NR1H4)) (OMIM: 603826) functions as a regulator for bile acid metabolism. FXR is a ligand-activated transcriptional receptor expressed in diverse tissues including the adrenal gland, kidney, stomach, duodenum, jejunum, ileum, colon, gall bladder, liver, macrophages, and white and brown adipose tissue. FXRs are highly expressed in tissues that participate in bile acid metabolism such as the liver, intestines, and kidneys. Bile acids function as endogenous ligands for FXR such that enteric and systemic release of bile acids induces FXR-directed changes in gene expression networks. Bile acids are the primary oxidation product of cholesterol, and in some cases, upon secretion into the intestines, are regulators of cholesterol absorption. The rate-limiting step for conversion of cholesterol into bile acids is catalyzed by cytochrome p450 enzyme cholesterol 7-α-hydroxylase (CYP7A1) and occurs in the liver. The cytochrome p450 enzyme sterol 12-α-hydroxylase (CYP8B1) mediates production of cholic acid and determines the relative amounts of the two primary bile acids, cholic acid and chenodeoxycholic acid. Activation of FXR can represses the transcription of CYP7A1 and CYP8B1 by increasing the expression level of the hepatic small heterodimer partner (SHP) (also known as nuclear receptor subfamily 0, group B, member 2; or NR0B2) and intestinal expression of fibroblast growth factor 15 (FGF15) in mice and fibroblast growth factor 19 (FGF19) in human. SHP represses the liver receptor homolog (LRH-1) and hepatocyte nuclear factor 4 alpha (HNFa4), transcription factors that regulate CYP7A1 and CYP8B1 gene expression. CYP8B1 repression by FXR can be species-specific and FXR activation may in some cases increase CYP8B1 expression in humans (Sanyal et al *PNAS*, **2007**, 104, 15665). In some cases, FGF15/19 released from the intestine then activates the fibroblast growth factor receptor 4 in the liver, leading to activation of the mitogen-activated protein kinase (MAPK) signaling pathway which suppress CYP7A1 and CYP8B1.

CLAIMS

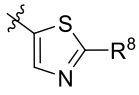
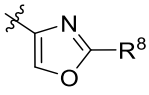
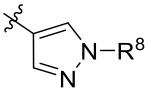
WHAT IS CLAIMED IS:

1. A compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II);

wherein:

ring A is  ,  , or  ;

X^1 is CH or N;

R^1 is H, halogen, -CN, -OH, $-N(R^{17})_2$, $-NR^{17}S(=O)_2(C_1\text{-}C_4\text{alkyl})$, $-S(=O)_2N(R^{17})_2$, $-OC(=O)(C_1\text{-}C_4\text{alkyl})$, $-CO_2H$, $-CO_2(C_1\text{-}C_4\text{alkyl})$, $-C(=O)N(R^{17})_2$, $-NR^{17}C(=O)(C_1\text{-}C_4\text{alkyl})$, $-NR^{17}C(=O)O(C_1\text{-}C_4\text{alkyl})$, $-OC(=O)N(R^{17})_2$, $-NR^{15}C(=O)N(R^{17})_2$, -SH, $-S(C_1\text{-}C_4\text{alkyl})$, $-S(=O)(C_1\text{-}C_4\text{alkyl})$, $-S(=O)_2(C_1\text{-}C_4\text{alkyl})$, $C_1\text{-}C_4$alkyl, $C_2\text{-}C_4$alkenyl, $C_2\text{-}C_4$alkynyl, $C_1\text{-}C_4$alkoxy, $C_1\text{-}C_4$fluoroalkyl, $C_1\text{-}C_4$fluoroalkoxy, $C_1\text{-}C_4$heteroalkyl, or monocyclic $C_2\text{-}C_5$heterocycloalkyl;

X^2 is CR^2 or N;

R^2 is H, halogen, -CN, -OH, $-N(R^{17})_2$, $-NR^{17}S(=O)_2(C_1\text{-}C_4\text{alkyl})$, $-S(=O)_2N(R^{17})_2$, $-OC(=O)(C_1\text{-}C_4\text{alkyl})$, $-CO_2H$, $-CO_2(C_1\text{-}C_4\text{alkyl})$, $-C(=O)N(R^{17})_2$, $-NR^{17}C(=O)(C_1\text{-}C_4\text{alkyl})$, $-NR^{17}C(=O)O(C_1\text{-}C_4\text{alkyl})$, $-OC(=O)N(R^{17})_2$, $-NR^{17}C(=O)N(R^{17})_2$, -SH, $-S(C_1\text{-}C_4\text{alkyl})$, $-S(=O)(C_1\text{-}C_4\text{alkyl})$, $-S(=O)_2(C_1\text{-}C_4\text{alkyl})$, $C_1\text{-}C_4$alkyl, $C_2\text{-}C_4$alkenyl, $C_2\text{-}C_4$alkynyl, $C_1\text{-}C_4$alkoxy, $C_1\text{-}C_4$fluoroalkyl, $C_1\text{-}C_4$fluoroalkoxy, $C_1\text{-}C_4$heteroalkyl, or monocyclic $C_2\text{-}C_5$heterocycloalkyl;

or R^1 and R^2 are taken together with the intervening atoms to form a fused 5- or 6-membered ring with 0-3 N atoms and 0-2 O or S atoms in the ring, wherein the fused 5- or 6-membered ring is optionally substituted with halogen or $C_1\text{-}C_4$alkyl;

X^3 is CR^3 or N;

R^3 is H, halogen, -CN, -OH, $-N(R^{17})_2$, $-NR^{17}S(=O)_2(C_1\text{-}C_4\text{alkyl})$, $-OC(=O)(C_1\text{-}C_4\text{alkyl})$, $-CO_2H$, $-CO_2(C_1\text{-}C_4\text{alkyl})$, $-C(=O)N(R^{17})_2$, $-NR^{17}C(=O)(C_1\text{-}C_4\text{alkyl})$, $C_1\text{-}C_4$alkyl, $C_2\text{-}C_4$alkenyl, $C_2\text{-}C_4$alkynyl, $C_1\text{-}C_4$alkoxy, $C_1\text{-}C_4$fluoroalkyl, $C_1\text{-}C_4$fluoroalkoxy, or $C_1\text{-}C_4$heteroalkyl;

each X^4 is independently CH or N;

R^4 and R^5 are taken together to form a bridge that is $-CH_2-$ or $-CH_2CH_2-$;

each R^6 is independently H, F, -OH, or $-CH_3$;

R^7 is H, halogen, -CN, -OH, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, or C_1-C_4heteroalkyl;

L is absent;

R^8 is C_4-C_8alkyl;

R^9 is H, F, or $-CH_3$;

R^{10} is $-OC(=O)N(R^{12})(R^{13})$, $-N(R^{16})C(=O)R^{14}$, or $-N(R^{16})C(=O)OR^{15}$;

R^{11} is H, F, or $-CH_3$;

R^{12} and R^{13} are taken together to form a 4-, 5-, or 6- membered heterocycloalkyl ring optionally containing an additional heteroatom selected from O, S, and N and optionally substituted with 1, 2, or 3 groups selected from -OH, $-N(C_1$-C_4alkyl$)_2$, C_1-C_6alkyl, and C_1-C_6alkoxy;

R^{14} is C_1-C_6alkyl or $-C_1$-C_6alkyl-OR^{17};

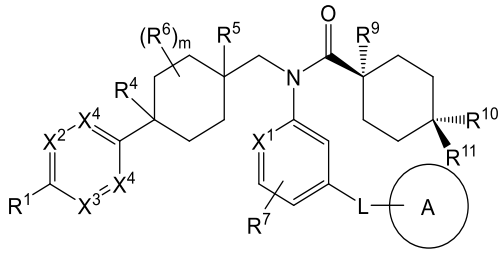
R^{15} is C_1-C_6alkyl, $-C_1$-C_6alkyl-OR^{17}, or C_2-C_6heterocycloalkyl;

R^{16} is H or C_1-C_6alkyl;

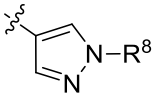
each R^{17} is independently H or C_1-C_6alkyl; and

m is 0, 1, or 2.

2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIa).

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein ring A is 

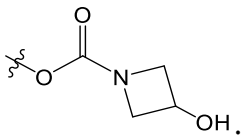
.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein R^8 is $-C(CH_3)_3$.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is N.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is $-OC(=O)N(R^{12})(R^{13})$.

7. The compound of claim 6, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{12} and R^{13} are taken together to form a 4-membered or 5-membered heterocycloalkyl ring optionally containing an additional heteroatom selected from O, S, and N and optionally substituted with 1 or 2 groups selected from -OH, $-N(C_1\text{-}C_4alkyl)_2$, $C_1\text{-}C_6$alkyl, and $C_1\text{-}C_6$alkoxy.

8. The compound of claim 7, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is .

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein:

each X^4 is CH;

X^3 is CH; and

X^2 is CR^2.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is $C_1\text{-}C_4$alkyl.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $C_1\text{-}C_4$alkoxy.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein:

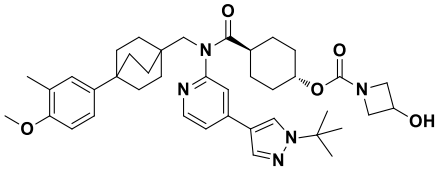
m is 0;

R^9 is H;

R^{11} is H; and

R^7 is H.

13. The compound of claim 1 that is:

;

or a pharmaceutically acceptable salt or solvate thereof.

14. A pharmaceutical composition comprising a compound of any one of claims 1-13, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

15. Use of a compound of any one of claims 1-13, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating or preventing:
a liver disease or condition in a mammal;
a liver fibrosis in a mammal;
a liver inflammation in a mammal; or
a gastrointestinal disease or condition in a mammal.