CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating or preventing a liver disease or condition, a lipid disease or disorder, a metabolic inflammation-mediated disease or disorder, or a combination thereof, comprising administering to a subject in need thereof a compound that is 4-((4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)carbamoyl)cyclohexyl 3-hydroxyazetidine-*trans*-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof.
2. The method of claim 1, wherein the liver disease or condition is steatohepatitis, cholangitis, fatty liver disease, cholestasis, cirrhosis, fibrotic liver disease, liver inflammation, biliary atresia, Alagille syndrome, IFALD (intestinal failure associated liver disease), parental nutrition associated liver disease (PNALD), hepatitis, hepatocellular carcinoma, cholangiocarcinoma, or combinations thereof.
3. The method of claim 2, wherein the steatohepatitis is nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), or HIV-associated steatohepatitis.
4. The method of claim 1, wherein the liver disease or condition is nonalcoholic steatohepatitis (NASH).
5. The method of claim 4, wherein the liver disease or condition is NASH that is accompanied by liver fibrosis.
6. The method of claim 4, wherein the liver disease or condition is NASH without liver fibrosis.
7. The method of claim 2, wherein the cholangitis is primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC).
8. The method of claim 2, wherein the fatty liver disease is non-alcoholic fatty liver disease (NAFLD) or alcohol-related fatty liver disease.
9. The method of claim 2, wherein the cholestasis is intrahepatic cholestasis or extrahepatic cholestasis.
10. The method of claim 2, wherein the cholestasis is intrahepatic cholestasis of pregnancy or progressive familial intrahepatic cholestasis (PFIC).
11. The method of claim 2, wherein the cirrhosis is HIV-associated cirrhosis.
12. The method of claim 1, wherein the metabolic inflammation-mediated disease or disorder is diabetes mellitus.
13. The method of claim 12, wherein the diabetes mellitus is diabetes mellitus type 2.
14. The method of claim 1, wherein the lipid disease or disorder is dyslipidemia.

15. The method according to claim 2, wherein the fibrotic liver disease is a fibrotic liver disease resulting from nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), non-alcoholic fatty liver disease (NAFLD), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), hepatitis C virus (HCV), cirrhosis, Wilson's disease, HIV associated steatohepatitis, HIV associated cirrhosis, or congenital hepatic fibrosis.

16. The method of claim 2, wherein the liver inflammation is acute hepatitis, chronic hepatitis, fulminant hepatitis, viral hepatitis, bacterial hepatitis, parasitic hepatitis, toxic- and drug-induced hepatitis, alcoholic hepatitis, autoimmune hepatitis, non-alcoholic steatohepatitis (NASH), neonatal hepatitis, or ischemic hepatitis.

17. The method according to claim 2, wherein the hepatitis is autoimmune hepatitis.

18. The method according to claim 2, wherein the liver disease or condition is Alagille syndrome.

19. The method according to claim 2, wherein the liver disease or condition is biliary atresia.

20. The method according to claim 2, wherein the liver disease or condition is hepatocellular carcinoma.

21. The method according to claim 2, wherein the liver disease or condition is cholangiocarcinoma.

22. The method of any one of claims 1-21, wherein treating the liver disease or condition, lipid disease or disorder, metabolic inflammation-mediated disease or disorder, or a combination thereof, comprises an increase in serum FGF-19 levels, a reduction in serum 7α-hydroxy-4-cholesten-3-one (C4) levels, a reduction in serum bile acid levels, or a combination thereof.

23. A method of treating or preventing fatty liver disease in a subject comprising administering to the subject with fatty liver disease a compound that is 4-((4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)carbamoyl)cyclohexyl 3-hydroxyazetidine-*trans*-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof.

24. The method of claim 23, wherein the fatty liver disease is nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or alcoholic steatohepatitis (ASH).

25. The method of claim 23 or claim 24, wherein treating fatty liver disease comprises liver fat reductions, improvements in liver histology, improvements in liver blood tests, improvements in cholestatic pruritis, or a combination thereof.

26. The method of any one of claims 23-25, wherein treating fatty liver disease comprises an increase in serum FGF-19 levels, a reduction in serum 7α-hydroxy-4-cholesten-3-one (C4) levels, a reduction in serum bile acid levels, or a combination thereof.
27. The method of any one of claims 23-26, wherein the subject has diabetes mellitus.
28. The method of claim 27, wherein the diabetes mellitus is diabetes mellitus type 2.
29. A method of treating or preventing a gastrointestinal disease or condition, comprising administering to a subject in need thereof a compound that is 4-((4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)carbamoyl)cyclohexyl 3-hydroxyazetidine-*trans*-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof.
30. The method of claim 29, wherein the gastrointestinal disease or condition is necrotizing enterocolitis, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), gastroenteritis, radiation induced enteritis, pseudomembranous colitis, enteritis, celiac disease, post-surgical inflammation of the intestines, graft versus host disease, bile acid reflux or colorectal cancer.
31. The method of claim 29, wherein the gastrointestinal disease or condition is inflammatory bowel disease (IBD).
32. The method of claim 31, wherein the inflammatory bowel disease (IBD) is Crohn's disease or ulcerative colitis.
33. The method of claim 30, wherein the irritable bowel syndrome (IBS) is 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).
34. The method of claim 33, wherein the IBS-D is due to bile acid malabsorption.
35. The method of claim 29, wherein the gastrointestinal disease or condition is ulcerative colitis, microscopic colitis, or pseudomembranous colitis.
36. The method of claim 30, wherein the enteritis is radiation-induced enteritis or chemotherapy-induced enteritis.
37. The method of claim 30, wherein the gastroenteritis is idiopathic gastroenteritis.
38. The method of claim 29, wherein the gastrointestinal disease or condition is bile acid reflux that is accompanied by gastro-esophageal reflux disease (GERD).
39. The method of claim 29, wherein the gastrointestinal disease or condition is bile acid reflux without GERD.
40. The method of any one of claims 29-39, wherein treating the gastrointestinal disease or condition comprises an increase in serum FGF-19 levels, a reduction in serum 7α-

hydroxy-4-cholesten-3-one (C4) levels, a reduction in serum bile acid levels, or a combination thereof.

41. A method of treating or preventing a renal disease or condition, comprising administering to a subject in need thereof a compound that is 4-((4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)carbamoyl)cyclohexyl 3-hydroxyazetidine-*trans*-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof.

42. The method of claim 41, wherein the renal disease or condition is kidney fibrosis, acute kidney injury, chronic kidney injury, ischemic nephropathy, diabetic nephropathy, tubulointerstitial nephritis/nephropathy, glomerulonephritis/nephropathy, or combinations thereof.

43. A method of treating or preventing cancer, comprising administering to a subject in need thereof a compound that is 4-((4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)carbamoyl)cyclohexyl 3-hydroxyazetidine-*trans*-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof.

44. The method of claim 43, wherein the cancer is prostate cancer, colorectal cancer, cholangiocarcinoma or hepatocellular carcinoma.

45. The method of any one of claims 1-44, wherein Compound 1, or a pharmaceutically acceptable salt thereof is administered to the mammal at a dose of about 1 mg to about 300 mg of Compound 1.

46. The method of any one of claims 1-44, wherein Compound 1, or a pharmaceutically acceptable salt thereof is administered to the mammal at a dose of about 1 mg to about 30 mg of Compound 1.

47. The method of any one of claims 1-44, wherein Compound 1, or a pharmaceutically acceptable salt thereof is administered to the mammal at a dose of about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 15 mg, about 20 mg, or about 25 mg.

48. The method of any one of claims 1-44, wherein Compound 1, or a pharmaceutically acceptable salt thereof is administered to the mammal at a dose of about 3 mg or about 6 mg.

49. The method of any one of claims 1-48, wherein Compound 1, or a pharmaceutically acceptable salt thereof, is systemically administered to the subject.

50. The method of any one of claims 1-48, wherein Compound 1, or a pharmaceutically acceptable salt thereof, is orally administered to the subject.

51. The method of claim 50, wherein Compound 1, or a pharmaceutically acceptable salt thereof, is administered to the mammal in the form of an oral solution, oral suspension, powder, pill, tablet or capsule.

52. The method of any one of claims 29-40, wherein Compound 1, or a pharmaceutically acceptable salt thereof, is non-systemically administered to the subject.

53. The method of any one of claims 1-52, wherein Compound 1, or a pharmaceutically acceptable salt thereof, is administered to the mammal daily.

54. The method of any one of claims 1-53, wherein Compound 1, or a pharmaceutically acceptable salt thereof, is administered to the mammal once daily.

55. The method of any one of claims 1-54, wherein Compound 1, or a pharmaceutically acceptable salt thereof is orally administered to the mammal by following a titration schedule.

56. The method of claim 55, wherein the titration schedule comprises daily administration of an initial dose of Compound 1, or a pharmaceutically acceptable salt thereof, for an initial period of time followed by daily administration of a dose of Compound 1, or a pharmaceutically acceptable salt thereof, that is higher than the initial dose.

57. The method of claim 56, wherein the initial period of time comprises one day, about one week, about two weeks, about three weeks, about four weeks, about five weeks, about six weeks, about seven weeks, about eight weeks, about nine weeks, about ten weeks, about eleven weeks, or about 12 weeks.

58. The method of claim 55, wherein the titration schedule comprises the up-titration, or down-titration followed by an optional re-up-titration of Compound 1, or a pharmaceutically acceptable salt thereof.

59. The method of claim 55, wherein the titration schedule comprises administering Compound 1, or a pharmaceutically acceptable salt thereof, at an initial dose for about one week and, provided that the patient tolerates the initial dose, increasing the dose by an amount equal to a first incremental value or provided that the patient does not tolerate the initial dose, decreasing the dose by an amount equal to a first incremental value.

60. The method of claim 59, wherein the titration schedule further comprises: administering Compound 1, or a pharmaceutically acceptable salt thereof, at the increased dose for about one week and provided that the patient tolerates the increased dose, further increasing the dose by an amount equal to a second incremental value; or administering Compound 1, or a pharmaceutically acceptable salt thereof, at the decreased dose for about one week and provided that the patient tolerates the decreased dose, optionally increasing the dose by an amount equal to a second incremental value.

61. The method of any one of claims 58-60, wherein the titration schedule is repeated until an optimized dose is obtained.

62. The method of any one of claims 1-61, further comprising administering to the subject at least one additional therapeutic agent in addition to Compound 1, or a pharmaceutically acceptable salt thereof.

63. The method of claim 62, wherein the at least one additional therapeutic agent is an angiotensin type 2 receptor agonist, a Keto-hexo Kinase (KHK) inhibitor, a mitochondrial uncoupler or protonophore, a sodium-glucose transport protein 2 (SGLT2) inhibitor, a sodium-glucose transport protein 1/2 (SGLT1/2) co-inhibitor, a dihydroceramide desaturase 1 (DES-1) inhibitor, an integrin aVb1 inhibitor, an integrin aVb6 inhibitor, a NOD-like receptor protein 3 (NLRP3) inhibitor, a cyclophilin inhibitor, a Glucagon-like peptide-1 (GLP-1) agonist, a 17-beta-Hydroxysteroid dehydrogenase type 13 (17b-HSD type 13) inhibitor, a Thyroid hormone receptor beta (THR-beta) agonist, or combinations thereof.

64. The method of claim 62, wherein the at least one additional therapeutic agent is a sodium-glucose transport protein 2 (SGLT2) inhibitor, a sodium-glucose transport protein 1/2 (SGLT1/2) co-inhibitor, a Glucagon-like peptide-1 (GLP-1) agonist, or combinations thereof.

65. A method of evaluating the clinical response to treatment with 4-((4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)carbamoyl)cyclohexyl 3-hydroxyazetidine-*trans*-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, in a subject with fatty liver disease comprising:

(a) assessing the liver fat content (LFC) of the subject with fatty liver disease prior to the initiation of treatment with Compound 1;

(b) administering Compound 1 at an initial daily dose to the subject with fatty liver disease for an initial period of time;

(c) re-assessing the liver fat content (LFC) of the subject with fatty liver disease; and

(d) continuing the daily administrations of Compound 1 if the LFC in step (a) is higher than the LFC of step (b) or discontinuing treatment the daily administrations of the FXR agonist if the LFC in step (b) is substantially similar to the LFC in step (a).

66. The method of claim 65, wherein the initial period of time is about two weeks, about three weeks, or about four weeks.

67. The method of claim 65, wherein the initial period of time is about four weeks.

68. The method of any one of claims 65-67, wherein Compound 1 is administered to the subject by following a titration schedule.

69. The method of claim 68, wherein the titration schedule comprises one or more cycles of: administration of Compound 1 at a first daily amount for a period of about a week, followed by: administration of Compound 1 at an increased daily amount or administration of Compound 1 at a decreased daily amount optionally followed by increasing the daily amount of Compound 1 that is administered.

70. The method of claim 69, wherein the first daily amount is less than the initial daily amount of step (b).

71. The method of claim 69 or claim 70, wherein the cycle of administration is repeated.

72. The method of any one of claims 65-71, wherein the method further comprises:

(i) assessing the liver fat content (LFC) of the subject with fatty liver disease after about 12 weeks of treatment with Compound 1;

(ii) adjusting the daily dose amount of Compound 1 if the relative change in LFC between step (c) and step (i) is less than about 10%.

73. The method of claim 72, wherein adjusting the daily dose amount of Compound 1 comprises increasing the daily dose amount of Compound 1.

74. The method of claim 72, wherein adjusting the daily dose amount of Compound 1 comprises decreasing the daily dose amount of Compound 1.

75. The method of claim 72, wherein adjusting the daily dose amount of Compound 1 comprises increasing the daily dose amount of Compound 1 agonist if the relative change in LFC between step (c) and step (i) is less than 10%.

76. The method of claim 72, wherein adjusting the daily dose amount of Compound 1 comprises increasing the daily dose amount of Compound 1 if the relative change in LFC between step (c) and step (i) is less than 20%.

77. The method of claim 72, wherein adjusting the daily dose amount of Compound 1 comprises increasing the daily dose amount with a titration schedule.

78. The method of any one of claims 61-77, wherein the initial daily amount of Compound 1 in step (b) is about 1 mg to about 3 mg.

79. The method of any one of claims 65-77, wherein adjusting the daily dose amount of the FXR agonist comprises increasing the daily dose amount of Compound 1 from about 1 mg to about 3 mg to about 3 mg to about 12 mg if the relative change in LFC between step (c) and step (i) is less than 10%.

80. The method of any one of claims 65-77, wherein the initial daily amount of Compound 1 in step (b) is about 1 mg to about 6 mg.

81. The method of any one of claims 65-77, wherein adjusting the daily dose amount of the FXR agonist comprises increasing the daily dose amount of Compound 1 from about 1 mg to about 6 mg to about 3 mg to about 12 mg if the relative change in LFC between step (c) and step (i) is less than 10%.

82. The method of any one of claims 65-81, wherein the LFC is assessed with magnetic resonance imaging-proton density fat fraction (MRI-PDFF).