Claims

1. A pharmaceutical composition comprising (S)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide, or a pharmaceutically acceptable salt thereof, in combination with at least 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid, or a pharmaceutically acceptable salt thereof, each present in therapeutically effective amounts, in admixture with a pharmaceutically acceptable excipient.

2. A pharmaceutical composition comprising (S)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof, 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

3. The composition of claim 2, further comprising at least one additional pharmaceutical agent selected from the group consisting of an anti inflammatory agent, an anti-diabetic agent, and a cholesterol/lipid modulating agent.

4. Use of (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof, in combination with at least a therapeutically effective amount of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease or condition selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepatitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, wherein a therapeutically effective amount of the medicament is to be administered to a patient in need of such treatment.

5. Use of (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof, and 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease or condition selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepatitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, wherein a therapeutically effective amount of the medicament is to be administered to a human in need of such treatment.

6. The use of claim 5, wherein the disease or condition is fatty liver.

7. The use of claim 5, wherein the disease or condition is nonalcoholic fatty liver disease.

8. The use of claim 5, wherein the disease or condition is nonalcoholic Steatohepatitis.

9. The use of claim 5, wherein the disease or condition is nonalcoholic steatohepatitis with liver fibrosis.

10. The use of claim 5, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis.

11. The use of claim 10, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma.

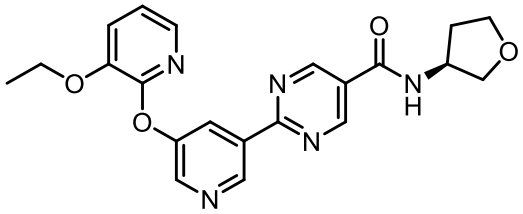
12. The use of claim 5, wherein the treatment comprises of a further administration of a therapeutically effective amount of at least one other pharmaceutical agent selected from the group consisting of an acetyl-CoA carboxylase-(ACC) inhibitor, a diacylglycerol *O*-

acyltransferase 1 (DGAT-1) inhibitor, monoacylglycerol O-acyltransferase inhibitors, a phosphodiesterase (PDE)-10 inhibitor, an AMPK activator, a sulfonylurea, a meglitinide, an α-amylase inhibitor, an α-glucoside hydrolase inhibitor, an α-glucosidase inhibitor, a PPARγ agonist, a PPAR α/γ agonist , a biguanide, a glucagon-like peptide 1 (GLP-1) modulator, liraglutide, albiglutide, exenatide, albiglutide, lixisenatide, dulaglutide, semaglutide, a protein tyrosine phosphatase-1B (PTP-1B) inhibitor, SIRT-1 activator, a dipeptidyl peptidase IV (DPP-IV) inhibitor, an insulin secreatagogue, a fatty acid oxidation inhibitor, an A2 antagonist, a c-jun amino-terminal kinase (JNK) inhibitor, glucokinase activators (GKa), insulin, an insulin mimetic, a glycogen phosphorylase inhibitor, a VPAC2 receptor agonist, SGLT2 inhibitors, a glucagon receptor modulator, GPR119 modulators, FGF21 derivatives or analogs, TGR5 receptor modulators, GPBAR1 receptor modulators, GPR40 agonists, GPR120 modulators, high affinity nicotinic acid receptor (HM74A) activators, SGLT1 inhibitors, inhibitors or modulators of carnitine palmitoyl transferase enzymes, inhibitors of fructose 1,6-diphosphatase, inhibitors of aldose reductase, mineralocorticoid receptor inhibitors, inhibitors of TORC2, inhibitors of CCR2 and/or CCR5, inhibitors of PKCα, inhibitors of PKCβ, inhibitors of PKCγ), inhibitors of fatty acid synthetase, inhibitors of serine palmitoyl transferase, modulators of GPR81, GPR39, GPR43, GPR41, GPR105, Kv1.3, retinol binding protein 4, glucocorticoid receptor, somatostatin receptors, inhibitors or modulators of PDHK2 or PDHK4, inhibitors of MAP4K4, modulators of IL1beta, HMG-CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, cholesterol absorption inhibitors, PCSK9 modulators, cholesteryl ester transfer protein inhibitors and modulators of RXRalpha.

13. Use of a first and second agent, and optionally a third agent in the manufacture of a medicament for the treatment of fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepatitis with cirrhosis, or nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma in humans, wherein a therapeutically effective amount is to be administered to a human in need of such treatment; and
wherein:

a. the first agent comprises (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof;
b. the second agent comprises 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof; and
c. the third agent comprises a pharmaceutical agent selected from the group consisting of an anti-inflammatory agent, an anti-diabetic agent, an anti-fibrotic agent, an anti-steatiotic agent, a cholesterol/lipid modulating agent and an anti-diabetic agent.

14. Theuse according to claim 5, wherein (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide is a crystalline solid of structure:

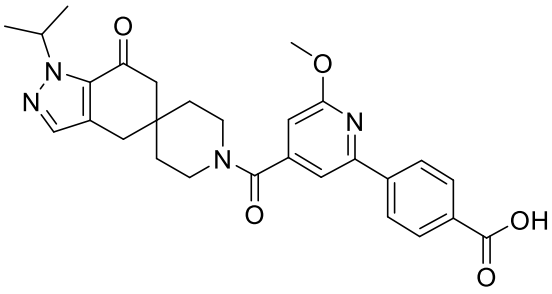


or a pharmaceutically acceptable salt thereof.

15. The use of claim 14, wherein the crystalline solid has a powder x-ray diffraction pattern comprising 2-theta values of (CuKα radiation, wavelength of 1. 54056 Å) 5.3 ± 0.2, 7.7 ± 0.2, and 15.4 ± 0.2.

16. The use of claim 14, wherein the crystalline solid has a powder x-ray diffraction pattern comprising 2-theta values of (CuKα radiation, wavelength of 1. 54056Å) 6.5 ± 0.2, 9.3 ± 0.2, and 13.6 ± 0.2.

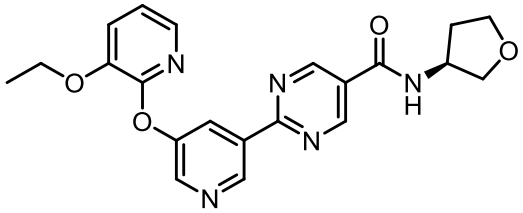
17. A use according to claim 5, wherein 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid is a crystalline solid of structure:



or a pharmaceutically acceptable salt thereof.

18. The use of claim 17, wherein the crystalline solid is 2-amino-2-(hydroxymethyl)propane-1,3-diol salt of 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid.

19. The pharmaceutical composition as recited in claim 2, wherein (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide is a crystalline solid of structure:

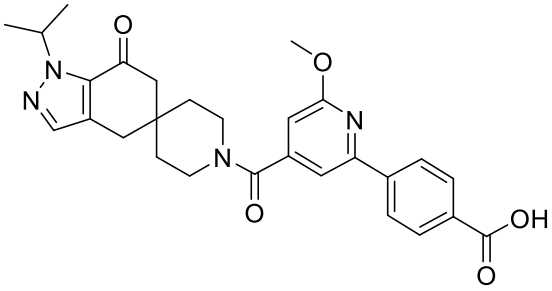


or a pharmaceutically acceptable salt thereof.

20. The pharmaceutical composition as recited in claim 19, wherein the crystalline solid has a powder x-ray diffraction pattern comprising 2-theta values of (CuKα radiation, wavelength of 1. 54056 Å) 5.3 ± 0.2, 7.7 ± 0.2, and 15.4 ± 0.2.:

21. The pharmaceutical composition as recited in claim 19, wherein the crystalline solid has a powder x-ray diffraction pattern comprising 2-theta values of (CuKα radiation, wavelength of 1. 54056Å) 6.5 ± 0.2, 9.3 ± 0.2, and 13.6 ± 0.2.

22. The pharmaceutical composition as recited in claim 2, wherein 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid is a crystalline solid of structure:



or a pharmaceutically acceptable salt thereof.

23. The pharmaceutical composition as recited in claim 22, wherein the crystalline solid is 2-amino-2-(hydroxymethyl)propane-1,3-diol salt of 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid.

24. The pharmaceutical composition as recited in claim 22,, wherein at least one other pharmaceutical agent is used and is selected from the group consisting of [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid; 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid; or 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof. (Original) A method of treating hepatocellular carcinoma, kidney renal clear cell carcinoma, head and neck squamous cell carcinoma, colorectal adenocarcinoma, mesothelioma, stomach adenocarcinoma, adrenocortical carcinoma, kidney papillary cell carcinoma, cervical and endocervical carcinoma, bladder urothelial carcinoma, lung adenocarcinoma comprising administering to a human in need of such treatment a therapeutically effective amount of (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof, and 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof.

25. Use of the composition according to claim 2 in the manufacture of a medicament for the treatment of a disease or condition selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepatitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, wherein the medicament is to be administered to a human in need of such treatment.

26. (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof, in combination with at least a therapeutically effective amount of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof for use in the treatment of a disease or condition selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepatitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease.

27. The composition according to claim 2 for use in the treatment of a disease or condition selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepatitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease.