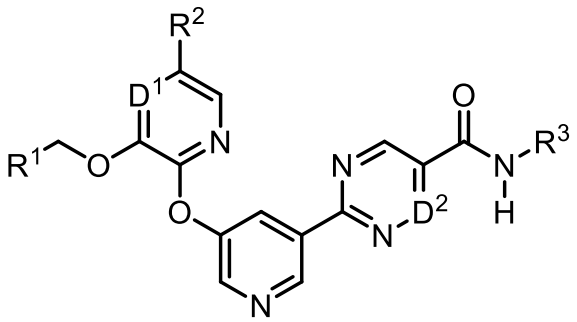
Claims

1. A compound of Formula (I)



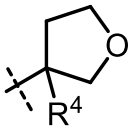
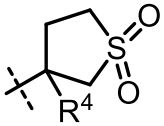
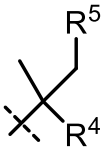
(I)

wherein

$D^1$and D^2 are each independently N or CH;

R^1 is H, or $(C_1\text{-}C_2)$alkyl optionally substituted with one or two substituents each independently selected from fluoro and $(C_3\text{-}C_6)$cycloalkyl;

R^2 is H or fluoro;

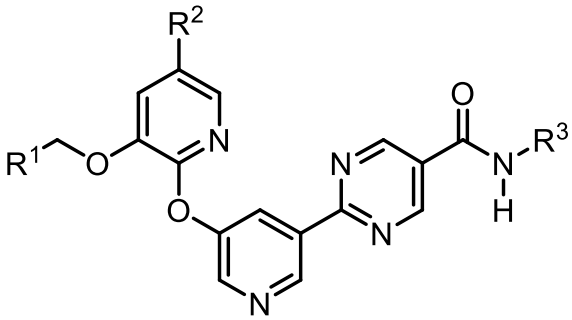
R^3 is,  ,  or  ;

R^4 is H, cyano, or $(C_1\text{-}C_4)$alkyl optionally substituted with one or two substituents each independently selected from –OH and $\text{-}S(O)_2R^6$;

R^5 is H or -OH; and

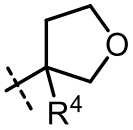
R^6 is $(C_1\text{-}C_4)$alkyl; or a pharmaceutically acceptable salt thereof.

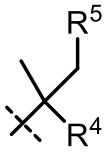
2. The compound of claim 1 having the Formula (Ia)



(Ia)

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^3 is  .

4. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^3 is  .

5. The compound of claim 3 or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl.

6. The compound of claim 4 or a pharmaceutically acceptable salt thereof wherein R^1 is methyl.

7. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein R^4 is H,-CH_2OH, or cyano.

8. The compound:

(*S*)-2-(5-((3-Ethoxy-5-fluoropyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide ;

N-(2-cyanopropan-2-yl)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)pyrimidine-5-carboxamide;

2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)pyrimidine-5-carboxamide;

2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)pyrimidine-5-carboxamide;

(*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide;

(*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(3-(hydroxymethyl)tetrahydrofuran-3-yl)pyrimidine-5-carboxamide;

(*R*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(3-(hydroxymethyl)tetrahydrofuran-3-yl)pyrimidine-5-carboxamide;

2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(2-methyl-1-(methylsulfonyl)propan-2-yl)pyrimidine-5-carboxamide;

(*S*)-2-(5-((3-(2-fluoroethoxy)pyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide;

3-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-triazine-6-carboxamide;

N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)pyrimidine-5-carboxamide;

(*S*)-3-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)-1,2,4-triazine-6-carboxamide;

N-(1,1-dioxidotetrahydrothiophen-3-yl)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)pyrimidine-5-carboxamide;

(*R*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide; or

2-(5-((3-ethoxypyrazin-2-yl)oxy)pyridin-3-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)pyrimidine-5-carboxamide;

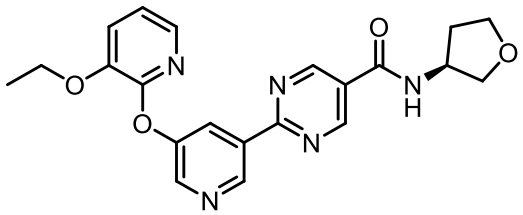
or a pharmaceutically acceptable salt thereof.

9. The compound:

(*R*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(3-(hydroxymethyl)tetrahydrofuran-3-yl)pyrimidine-5-carboxamide;(*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide; or

(*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(3-(hydroxymethyl)tetrahydrofuran-3-yl)pyrimidine-5-carboxamide, or a pharmaceutically acceptable salt thereof.

10. The compound having the structure:



or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound according to claim 1 or a pharmaceutically acceptable salt of said compound, present in a therapeutically effective amount, in admixture with at least one pharmaceutically acceptable excipient.

12. The composition of Claim 11 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.

13. The composition of Claim 12 wherein said additional pharmaceutical agent is 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 peptidease 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 PKC isoforms (e.g. PKCα, PKCβ, 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, somatostain receptors, inhibitors or modulators of PDHK2 or PDHK4, inhibitors of MAP4K4, modulators of IL1 family including IL1beta, HMG-CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, choesterol absorption inhibitors, PCSK9 modulators, cholesteryl ester transfer protein inhibitors and modulators of RXRalpha.

14. The composition of Claim 11 further comprising at least one additional pharmaceutical agent selected from the group consisting of cysteamine or a pharmaceutically acceptable salt thereof, cystamine or a pharmaceutically acceptable salt thereof, an anti-oxidant compound, lecithin, vitamin B complex, a bile salt preparations, an antagonists of Cannabinoid-1 (CB1) receptor, an inverse agonists of Cannabinoid-1 (CB1) receptor, a peroxisome proliferator-activated receptor) activity regulators, a benzothiazepine or benzothiepine compound, an RNA antisense construct to inhibit protein tyrosine phosphatase PTPRU, a heteroatom-linked substituted piperidine and derivatives thereof, an azacyclopentane derivative capable of inhibiting stearoyl-coenzyme alpha delta-9 desaturase, acylamide compound having secretagogue or inducer activity of adiponectin, a quaternary ammonium compound, Glatiramer acetate, pentraxin proteins, a HMG-CoA reductase inhibitor, n-acetyl cysteine, isoflavone compound, a macrolide antibiotic, a galectin inhibitor, an antibody, or any combination of thereof.

15. Use of a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt of said compound in the manufacture of a medicament for treating fatty liver, nonalcoholic fatty liver disease, nonalcoholic steato-hepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, or nonalcoholic steatohepatitis with cirrhosis and hepatocellular carcinoma in humans.

16. Use of a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt of said compound in the manufacture of a medicament for treating hyperlipidemia, Type I diabetes, Type II diabetes mellitus, idiopathic Type I diabetes (Type Ib), latent autoimmune diabetes in adults (LADA), early-onset Type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction, dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hyper-trophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis,

transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance, hyper apo B lipo-proteinemia, Alzheimer's, schizophrenia, impaired cognition, inflammatory bowel disease, ulcerative colitis, Crohn's disease, and irritable bowel syndrome, non-alcoholic steatohepatitis (NASH), or non-alcoholic fatty liver disease (NAFLD), in humans.

17. Use of a therapeutically effective amount of two separate pharmaceutical compositions comprising

(i) a first composition according to claim 12; and

(ii) a second composition 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 and at least one pharmaceutically acceptable excipient;.

in the manufacture of a medicament for treating fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, or nonalcoholic steatohepatitis with cirrhosis and hepatocellular carcinoma in humans.

18. The use of claim 17 wherein said first composition and said second composition are to be administered simultaneously.

19. The use of claim 17 wherein said first composition and said second compositionare are to be administered sequentially and in any order.

20. A compound according to claim 1 or a pharmaceutically acceptable salt of said compound for use in the reduction of at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reduction of the level of serum markers of nonalcoholic steatohepatitis activity, reduction of nonalcoholic steatohepatitis disease activity or reduction in the medical consequences of non-alcoholic steatohepatitis in humans.

21. A compound of claim 1 or a pharmaceutically acceptable salt of said compound for use in treating fatty liver, nonalcoholic fatty liver disease, nonalcoholic steato-

hepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, or nonalcoholic steatohepatitis with cirrhosis and hepatocellular carcinoma in humans.

22. A compound according to claim 1 or a pharmaceutically acceptable salt of said compound for use in treating hyperlipidemia, Type I diabetes, Type II diabetes mellitus, idiopathic Type I diabetes (Type Ib), latent autoimmune diabetes in adults (LADA), early-onset Type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction, dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyper-insulinemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance, hyper apo B lipoproteinemia, Alzheimer's, schizophrenia, impaired cognition, inflammatory bowel disease, ulcerative colitis, Crohn's disease, and irritable bowel syndrome, non-alcoholic steatohepatitis (NASH), or non-alcoholic fatty liver disease (NAFLD), in humans.

23. A therapeutically effective amount of two separate pharmaceutical compositions comprising

(i) a first composition according to claim 12; and

(ii) a second composition 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 and at least one pharmaceutically acceptable excipient;.

for use in treating fatty liver, nonalcoholic fatty liver disease, nonalcoholic steato-hepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, or nonalcoholic steatohepatitis with cirrhosis and hepatocellular carcinoma in humans.