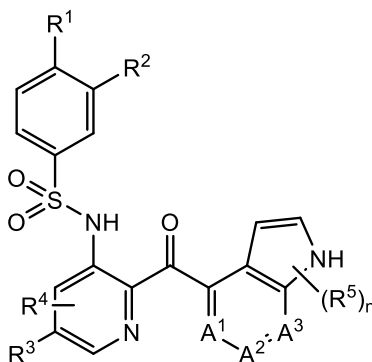


BRIEF SUMMARY

[0006] The present disclosure is directed to methods of treating liver fibrosis in a patient comprising administering to the patient in need thereof an effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R¹ is halogen or C₁₋₆ alkyl;

R² is hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, or -CN;

R³ is hydrogen, halogen, or C₁₋₆ alkyl;

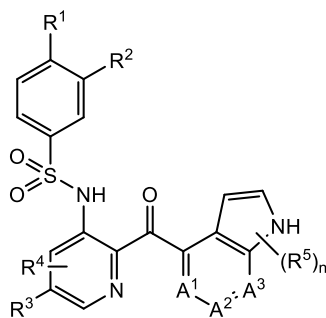
R⁴ is hydrogen, halogen, or C₁₋₆ alkyl;

each R⁵ is independently C₁₋₆ alkyl, -OH, or -NH₂;

n is 0, 1, 2, or 3; and

each of A¹, A², and A³ is -CH- or -N-, where at least one of A¹, A², or A³ is -N-.

[0006a] In an aspect, there is provided the use of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of liver fibrosis, wherein

R¹ is halogen or methyl alkyl;

R² is halogen, or C₁₋₆ haloalkyl;

R³ is halogen or C₁₋₆ alkyl;

R⁴ is hydrogen;

n is 0;

A¹ is –CH– or –N–;

A² is –CH–; and

A³ is –N–.

FIGURES

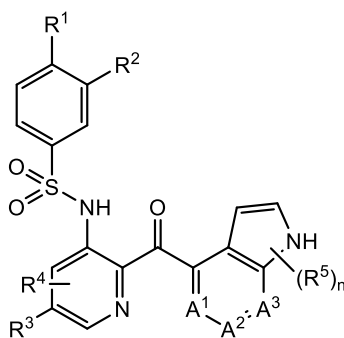
[0007] Figure 1 illustrates the change in body weight in the HFD/fructose-induced NASH model.

[0008] Figure 2 shows the serum ALT and AST levels in the HFD/fructose-induced NASH model.

[0009] Figure 3 shows representative images of Sirius, red-stained liver sections of animals treated with vehicle or Compound 1 in the FHD/fructose-induced NASH model.

Claims

1. Use of a compound of Formula I:

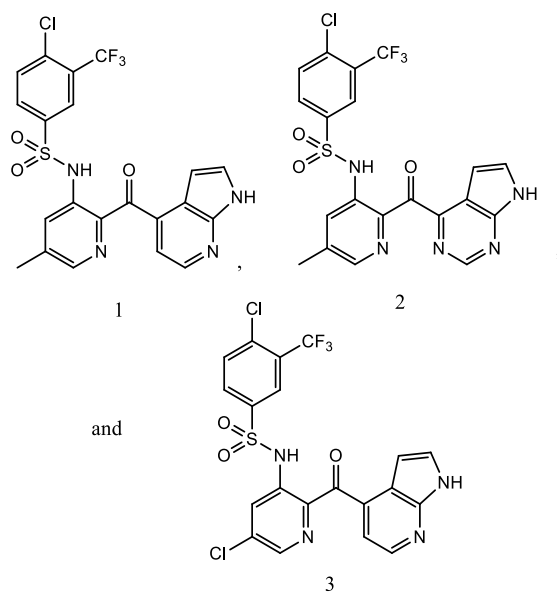


Formula I

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of liver fibrosis, wherein

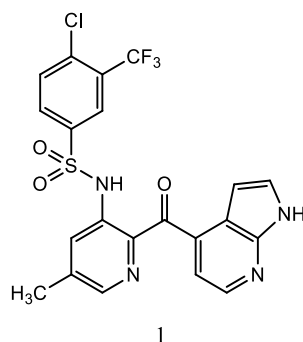
- R^1 is halogen or methyl alkyl;
- R^2 is halogen, or C_{1-6} haloalkyl;
- R^3 is halogen or C_{1-6} alkyl;
- R^4 is hydrogen;
- n is 0;
- A^1 is $-CH-$ or $-N-$;
- A^2 is $-CH-$; and
- A^3 is $-N-$.

2. The use of claim 1, wherein the compound is selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

3. The use of claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

4. The use of any one of claims 1 to 3, wherein the liver fibrosis is associated with non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), or one or more of emerging cirrhosis, primary biliary cholangitis, primary sclerosing cholangitis, biliary atresia, cholestatic liver disease, chronic liver disease, hepatitis C infection, alcoholic liver disease, hypercholesteremia, and hyperlipidemia.

5. The use of any one of claims 1 to 3, wherein the liver fibrosis is non-cirrhotic hepatic fibrosis.

6. The use of any one of claims 1 to 3, wherein the liver fibrosis is associated with non-alcoholic steatohepatitis (NASH), and wherein the NASH is associated with type 2 diabetes mellitus (T2DM) or metabolic syndrome (MS).

7. The use of any one of claims 1 to 6, wherein one or more additional therapeutic compound is administered, the one or more additional therapeutic compound being preferably selected from one or more of a sodium glucose transporter-2 inhibitor, a glucagon-like peptide 1 agonist, a galectin-3 inhibitor, a transaminase stimulator, an IL-10 agonist, an Insulin sensitizer, a PPAR gamma agonist, a thyroid hormone receptor beta agonist, a caspase inhibitor, a dipeptidyl peptidase IV inhibitor, a PPAR alpha agonist; a PPAR delta agonist, a PPAR agonist, farnesoid X receptor agonist, a lysyl oxidase homolog 2 inhibitor, a MEKK-5 protein kinase inhibitor, a methyl CpG binding protein 2 modulator, a transglutaminase inhibitor, a myelin basic protein stimulator, a chloride channel stimulator, a CCR3 chemokine antagonist, a CCR5 chemokine antagonist, an angiotensin II AT-1 receptor antagonist, a SREBP transcription factor 1 inhibitor, a PDGF receptor beta modulator, a FGF-21 ligand, an IL-17 antagonist, a rho associated protein kinase 2 inhibitor, an ileal sodium bile acid cotransporter inhibitor, a stearyl CoA desaturase-1 inhibitor, a FGF1 receptor agonist, a klotho beta stimulator, a connective tissue growth factor ligand inhibitor, a lipoprotein lipase inhibitor; a SREBP transcription factor inhibitor, a FGF-19 ligand, a CD3 antagonist, a caveolin 1 inhibitor, an amylin receptor agonist; a calcitonin agonist, a NAD-dependent deacetylase sirtuin stimulator, a PDE 5 inhibitor, a NADPH oxidase 1 inhibitor, a NADPH oxidase 4 inhibitor, a NADPH oxidase inhibitor, an hepatocyte growth factor agonist, an integrin alpha-V/beta-6 antagonist, TGF beta antagonist, a NAD-dependent deacetylase sirtuin stimulator, a nicotinic acid receptor 1 agonist, a phenylalanine hydroxylase stimulator, a membrane copper amine oxidase inhibitor, a ribosomal protein S6 kinase-1 inhibitor, a high mobility group protein B1 inhibitor, a TLR-4 antagonist, a cathepsin B inhibitor, a hepatocyte growth factor ligand, an interferon gamma ligand, an ACE inhibitor, a HMG CoA reductase inhibitor, or a pharmaceutically acceptable salt thereof.

8. The use of claim 7 wherein the one or more additional therapeutic compound is selected from one or more of a farnesoid X receptor (FXR) agonist, a dual TGR5/FXR agonist, a PPAR alpha agonist, a PPAR-gamma agonist, a PPAR-delta agonist, or a pharmaceutically acceptable salt thereof.

9. The use of claim 7 wherein the one or more additional therapeutic compound is selected from one or more of dapagliflozin propanediol, dapagliflozin, liraglutide, GR-MD-02, semaglutide, cenicriviroc, F-351, peg-ilodecakin, ipragliflozin, ursodeoxycholic acid, colessevelam, pioglitazone, VK-2809, emricasan, linagliptin, elafibranor, DS-102, Px-102, Px-103, GS-4997, simtuzumab, DUR-928, mercaptamine, olesoxime, cobiprostone, bertilimumab, MDV-4463, irbesartan, GS-9674, BOT-191, MGL-3196, BMS-986171, PEG-FGF21, LJN-452, CF-102, KD-025, volixibat, volixibat potassium ethanolate hydrate, aramchol, tielukast, NGM-313, FG-3019, CAT-2003, NGM-282, TRX-318, IONIS-DGAT2Rx, IMM-124-E, RG-125, norursodeoxycholic acid, KBP-042, leucine, metformin, sildenafil, A-4250, GKT-831, BB-3, saroglitazar, BG-00011, alipogene tiparvovec, MB-12066, Betaine anhydrous, ARI-3037MO, HepaStem, PXS-4728A, CIGB-500, oltipraz, omega-3 carboxylic acids, dapagliflozin, remogliflozin etabonate, remogliflozin, LC-280126, JKB-121, DWP-10292, VBY-376, VBY-825, icosapent ethyl ester, Fuzheng Huayu capsule, interferon gamma, acetylsalicylic acid, hydrochlorothiazide, enalapril, atorvastatin, NC-101, TCM-606F, obeticholic acid, INT-767, GNF-5120, cryptochinone-D, fexamine, caprylic triglyceride, evogliptin, GM-CT-01, high dose vitamin E (> 400 iU/d) or a pharmaceutically acceptable salt thereof.

10. The use of any one of claims 1 to 9, wherein the compound improves insulin sensitivity and/or glucose tolerance.

11. The use of any one of claims 1 to 9, wherein the compound lowers hepatic triglyceride accumulation.

12. The use of any one of claims 1 to 9, wherein the compound lowers alanine aminotransferase (ALT) concentration and/or aspartate aminotransferase (AST) concentration.

13. The use of any one of claims 1 to 9, wherein the compound lowers liver collagen content, hepatic macrophages content, adipose tissue macrophages content, and/or omental adipose tissue content.

14. The use of any one of claims 1 to 9, wherein the compound lowers liver cholesterol levels and/or bilirubin levels.