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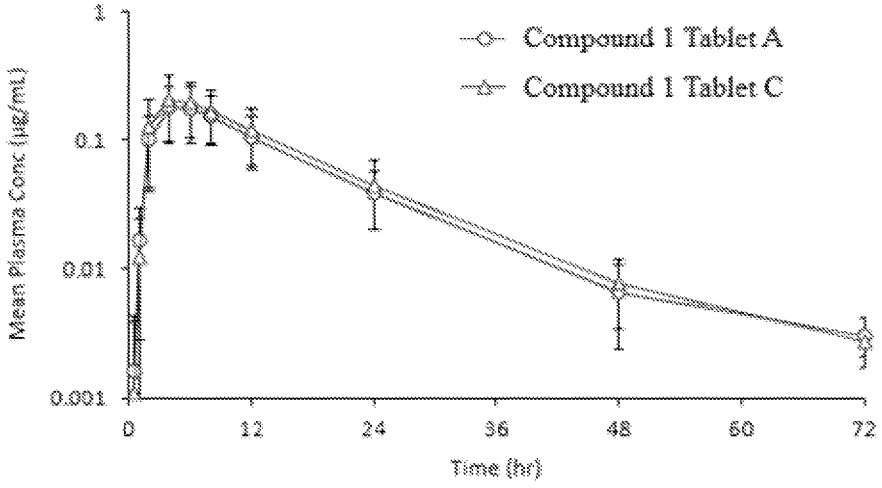
(54) Title: FORMULATIONS OF A FARNESOID X RECEPTOR AGONIST

Fig. 1



(57) Abstract: Described herein are pharmaceutical formulations of a farnesoid X receptor agonist, 4-((4-(1-(tert-butyl)-1H-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, and methods of using such pharmaceutical formulations in the treatment of conditions, diseases, or disorders associated with farnesoid X receptor activity.

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FORMULATIONS OF A FARNESOID X RECEPTOR AGONIST

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Patent Application No. 62/991,216, filed on March 18, 2020, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are spray-dried solid dispersions of farnesoid X receptor agonists, pharmaceutical formulations comprising such spray-dried solid dispersions, and methods of using such spray-dried solid dispersions and pharmaceutical formulations 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 OF THE INVENTION

[0004] In one aspect, provided herein is a spray-dried solid dispersion comprising: (a) 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, and (b) a pharmaceutically acceptable polymer; wherein 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 is dispersed in a polymer matrix formed from the pharmaceutically acceptable polymer. In some embodiments, the pharmaceutically acceptable polymer is selected from PVP/VA 64, PVP 30, HPMCAS-L, HPMCAS-M, HPMCAS-H, Eudragit L100-55, Eudragit L100, Eudragit EPO, HPMC E15, HPMC E3, HPMC E5, HPMCP-HP55, and Soluplus. In some embodiments, the pharmaceutically acceptable polymer is selected from PVP/VA 64 and HPMCAS-M. In some embodiments, the pharmaceutically acceptable polymer is PVP/VA 64. In some embodiments, the pharmaceutically acceptable polymer is HPMCAS-M. In some embodiments, the weight ratio of 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 to the pharmaceutically acceptable polymer is from 9:1 to 1:9. In some embodiments, the weight ratio of 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 to the pharmaceutically acceptable polymer is from 3:1 to 1:3. In some embodiments, the weight ratio of 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 to the pharmaceutically acceptable polymer is about 2:1. In some embodiments, the weight ratio of 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 to the pharmaceutically acceptable polymer is about 1.5:1. In some embodiments, the weight ratio of 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 to the pharmaceutically acceptable polymer is about 1:1. In some embodiments, the spray-dried solid dispersion further comprises a non-aqueous solvent. In some embodiments, the non-aqueous solvent is selected from the group consisting of tert-butanol, n-propanol, n-butanol, isopropanol, ethanol, methanol, acetone, ethyl acetate, dimethyl carbonate, acetonitrile, dichloromethane, methyl ethyl ketone, methyl isobutyl ketone, 1-pentanol, methyl acetate, carbon tetrachloride, dimethyl sulfoxide, hexafluoroacetone, chlorobutanol, dimethyl sulfone, acetic acid, cyclohexane, and mixtures thereof. In some embodiments, the non-aqueous solvent is selected from the group consisting of ethanol, methanol, propanol, butanol, isopropanol, tert-butanol, dichloromethane, and mixtures thereof. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol. In some embodiments of the spray-dried solid dispersion, 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 is substantially amorphous. In some embodiments of the spray-dried solid dispersion, 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 is substantially crystalline.

[0005] In another aspect, provided herein is a pharmaceutical formulation comprising a spray-dried solid dispersion described herein, further comprising one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more binders, one or more lubricants, one or more glidants, and one or more surfactants. In some embodiments, the one or more pharmaceutical acceptable ingredients are selected from the group consisting of microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, mannitol, crospovidone, and sodium stearyl fumarate. In some embodiments, the one or more pharmaceutical acceptable ingredients are selected from the group consisting of microcrystalline cellulose, lactose

monohydrate, croscarmellose sodium, magnesium stearate, and colloidal silicon dioxide. In some embodiments, the pharmaceutical formulation is in tablet form. In some embodiments, the tablet comprises about 1% by weight to about 30% by weight of the spray-dried solid dispersion. In some embodiments, the tablet comprises about 5% by weight to about 25% by weight of the spray-dried solid dispersion. In some embodiments, the tablet comprises about 1% by weight to about 20% by weight of 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. In some embodiments, the tablet comprises about 1 mg, about 5 mg, about 12 mg, or about 25 mg of 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. In some embodiments, the pharmaceutical formulation is in capsule form.

[0006] In another aspect, provided herein is a method of treating or preventing a liver disease or condition in a mammal, comprising administering to the mammal in need thereof a therapeutically effective amount of a spray-dried solid dispersion or pharmaceutical formulation described herein. In some embodiments, the disease or condition is a metabolic condition. In some embodiments, the disease or condition is a liver condition.

[0007] In some embodiments, the spray-dried solid dispersion described herein is administered to the mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration. In some embodiments, the pharmaceutical formulation described herein is administered to the mammal by intravenous administration, subcutaneous administration, oral administration, inhalation, nasal administration, dermal administration, or ophthalmic administration.

[0008] In another aspect, 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 spray-dried solid dispersion or pharmaceutical formulation described herein to a mammal in need thereof.

[0009] In another aspect, 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 spray-dried solid dispersion or pharmaceutical formulation described herein to the mammal in need thereof. In other embodiments, the metabolic or liver condition is amenable to treatment with a FXR agonist. In some embodiments, the method further comprises administering a second therapeutic agent to the mammal in addition to the spray-dried solid dispersion described herein, or a pharmaceutically acceptable salt, or solvate thereof.

[0010] In another aspect, described herein is a method of treating or preventing a liver disease or condition in a mammal, comprising administering to the mammal a spray-dried solid dispersion

or pharmaceutical formulation described herein. In some embodiments, the liver disease or condition is an alcoholic or non-alcoholic liver disease. In some embodiments, the liver disease or condition is primary biliary cirrhosis, primary sclerosing cholangitis, cholestasis, nonalcoholic steatohepatitis (NASH), or nonalcoholic fatty liver disease (NAFLD). In some embodiments, the alcoholic liver disease or condition is fatty liver (steatosis), cirrhosis, or alcoholic hepatitis. In some embodiments, the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH), or nonalcoholic fatty liver disease (NAFLD). In some embodiments, the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH). In some embodiments, the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH) and is accompanied by liver fibrosis. In some embodiments, the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH) without liver fibrosis. In some embodiments, the non-alcoholic liver disease or condition is intrahepatic cholestasis or extrahepatic cholestasis. In some embodiments, the liver disease or condition is steatohepatitis, cholangitis, fatty liver disease, cholestasis, cirrhosis, fibrotic liver disease, liver inflammation, primary biliary cholangitis, biliary atresia, Alagille syndrome, IFALD (intestinal failure associated liver disease), parental nutrition associated liver disease (PNALD), hepatitis, hepatocellular carcinoma, cholangiocarcinoma, or combinations thereof.

[0011] In another aspect, described herein is a method of treating or preventing a liver fibrosis in a mammal, comprising administering to the mammal a spray-dried solid dispersion or pharmaceutical formulation described herein. In some embodiments, 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), primary biliary cirrhosis (PBC), or biliary cirrhosis. In some embodiments, the mammal is diagnosed with nonalcoholic steatohepatitis (NASH).

[0012] In another aspect, described herein is a method of treating or preventing a liver inflammation in a mammal, comprising administering to the mammal a spray-dried solid dispersion or pharmaceutical formulation described herein. In some embodiments, 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), primary biliary cirrhosis (PBC), or biliary cirrhosis. In some embodiments, the mammal is diagnosed with nonalcoholic steatohepatitis (NASH). In some embodiments, the liver inflammation is associated with inflammation in the gastrointestinal tract. In some embodiments, the mammal is diagnosed with inflammatory bowel disease.

[0013] In another aspect, described herein is a method of treating or preventing a gastrointestinal disease or condition in a mammal, comprising administering to the mammal a spray-dried solid dispersion or pharmaceutical formulation described herein. In some embodiments, 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 embodiments, 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).

[0014] In another aspect, described herein is a method of treating or preventing a renal disease or condition in a mammal, comprising administering to the mammal a spray-dried solid dispersion or pharmaceutical formulation described herein. In some embodiments, 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.

[0015] In another aspect, described herein is a method of treating or preventing a metabolic inflammation-mediated disease or disorder in a mammal, comprising administering to the mammal a spray-dried solid dispersion or pharmaceutical formulation described herein. In some embodiments, the metabolic inflammation-mediated disease or disorder is diabetes mellitus.

[0016] In another aspect, described herein is a method of treating or preventing a lipid disease or disorder in a mammal, comprising administering to the mammal a spray-dried solid dispersion or pharmaceutical formulation described herein. In some embodiments, the lipid disease or disorder in a mammal is dyslipidemia.

[0017] In another aspect, described herein is a method of treating or preventing cancer in a mammal, comprising administering to the mammal a spray-dried solid dispersion or pharmaceutical formulation described herein. In some embodiments, the cancer is prostate cancer, colorectal cancer, or hepatocellular carcinoma.

[0018] In another aspect, 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 spray-dried solid dispersion or pharmaceutical formulation described herein. In some embodiments, the methods described herein further comprise administering at least one additional therapeutic agent in addition to the spray-dried solid dispersion or pharmaceutical formulation described herein.

INCORPORATION BY REFERENCE

[0019] All publications and patent applications mentioned in this specification are herein incorporated by reference to the extent applicable and relevant.

BRIEF DESCRIPTION OF THE FIGURES

[0020] **Fig. 1** depicts the pharmacokinetic profile of Compound **1** tablets A and C in monkeys.

[0021] **Fig. 2** depicts the release profiles of Compound **1** 12 mg tablets containing 5% and 10% croscarmellose sodium.

DETAILED DESCRIPTION OF THE INVENTION

[0022] 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 4alpha (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.

[0023] In some embodiments, elevated levels of bile acids have been associated with insulin resistance. For example, insulin resistance sometimes leads to a decreased uptake of glucose

from the blood and increased *de novo* glucose production in the liver. In some instances, intestinal sequestration of bile acids has been shown to improve insulin resistance by promoting the secretion of glucagon-like peptide-1 (GLP1) from intestinal L-cells. GLP-1 is an incretin derived from the transcription product of the proglucagon gene. It is released in response to the intake of food and exerts control in appetite and gastrointestinal function and promotes insulin secretion from the pancreas. The biologically active forms of GLP-1 include GLP-1-(7-37) and GLP-1-(7-36)NH_2, which result from selective cleavage of the proglucagon molecule. In such cases, activation of FXR leading to decreased production of bile acids correlates to a decrease in insulin resistance.

[0024] In some embodiments, the activation of FXR also correlates to the secretion of pancreatic polypeptide-fold such as peptide YY (PYY or PYY3-36). In some instances, peptide YY is a gut hormone peptide that modulates neuronal activity within the hypothalamic and brainstem, regions of the brain involved in reward processing. In some instances, reduced level of PYY correlates to increased appetite and weight gain.

[0025] In some instances, the activation of FXR indirectly leads to a reduction of plasma triglycerides. The clearance of triglycerides from the bloodstream is due to lipoprotein lipase (LPL). LPL activity is enhanced by the induction of its activator apolipoprotein CII, and the repression of its inhibitor apolipoprotein CIII in the liver occurs upon FXR activation.

[0026] In some cases, the activation of FXR further modulates energy expenditure such as adipocyte differentiation and function. Adipose tissue comprises adipocytes or fat cells. In some instances, adipocytes are further differentiated into brown adipose tissue (BAT) or white adipose tissue (WAT). The function of BAT is to generate body heat, while WAT functions as fat storing tissues.

[0027] In some instances, FXR is widely expressed in the intestine. In some cases, the activation of FXR has been shown to induce the expression and secretion of FGF19 (or FGF15 in mouse) in the intestine. FGF19 is a hormone that regulates bile acid synthesis as well as exerts an effect on glucose metabolism, lipid metabolism, and on energy expenditure. In some instances, FGF19 has also been observed to modulate adipocyte function and differentiation. Indeed, a study has shown that the administration of FGF19 to high-fat diet-fed mice increased energy expenditure, modulated adipocytes differentiation and function, reversed weight gain, and improved insulin resistance (see, Fu *et al.,* "Fibroblast growth factor 19 increases metabolic rate and reverses dietary and leptin-deficient diabetes." *Endocrinology* **145**:2594-2603 (2004)).

[0028] In some cases, intestinal FXR activity has also been shown to be involved in reducing overgrowth of the microbiome, such as during feeding (Li *et al., Nat Commun* 4:2384, 2013). For example, a study had shown that activation of FXR correlated with increased expression of

several genes in the ileum such as *Ang2*, *iNos*, and *Il18*, which have established antimicrobial actions (Inagaki *et al., Proc Natl Acad Sci U S A* 103:3920-3925, 2006).

[0029] In some cases, FXR has been implicated in barrier function and immune modulation in the intestine. FXR modulates transcription of genes involved in bile salt synthesis, transport and metabolism in the liver and intestine, and in some cases has been shown to lead to improvements in intestinal inflammation and prevention of bacterial translocation into the intestinal tract (Gadaleta et al., *Gut. 2011 Apr; 60(4):463-72*).

[0030] In some cases, over production of bile acids or improper transport and re-cycling of bile acids can lead to diarrhea. FXR modulates transcription of genes involved in bile salt synthesis, transport and metabolism in the liver and intestine, and in some cases may lead to improvements in diarrhea Camilleri, *Gut Liver. 2015 May; 9(3): 332–339.*

[0031] G protein-coupled bile acid receptor 1 (also known as GPBAR2, GPCR19, membrane-type receptor for bile acids or M-BAR, or TGR5) is a cell surface receptor for bile acids. Upon activation with bile acid, TGR5 induces the production of intracellular cAMP, which then triggers an increase in triiodothyronine due to the activation of deiodinase (DIO2) in BAT, resulting in increased energy expenditure.

[0032] Hence in some embodiments, regulation of metabolic processes such as bile acid synthesis, bile-acid circulation, glucose metabolism, lipid metabolism, or insulin sensitivity is modulated by the activation of FXR. Furthermore, in some embodiments, dis-regulation of metabolic processes such as bile acid synthesis, bile-acid circulation, glucose metabolism, lipid metabolism, or insulin sensitivity results in metabolic diseases such as diabetes or diabetes-related conditions or disorders, alcoholic or non-alcoholic liver disease or condition, intestinal inflammation, or cell proliferative disorders.

[0033] Disclosed herein, in certain embodiments, are compounds that have activity as FXR agonists. In some embodiments, the FXR agonists described herein are structurally distinct from bile acids, other synthetic FXR ligands, and other natural FXR ligands.

[0034] In some embodiments, also disclosed herein are methods of treating or preventing a metabolic disorder, such as diabetes, obesity, impaired glucose tolerance, dyslipidemia, or insulin resistance by administering a therapeutically effective amount of an FXR agonist. In some instances, the compounds are administered to the GI tract of a subject.

[0035] In additional embodiments, disclosed herein are methods for treating or preventing alcoholic or non-alcoholic liver disease or conditions (*e.g.*, cholestasis, primary biliary cirrhosis, steatosis, cirrhosis, alcoholic hepatitis, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), primary sclerosing cholangitis (PSC) or elevated liver enzymes) by administering a therapeutically effective amount of an FXR agonist to a subject in need thereof

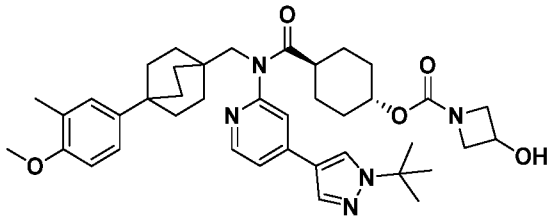
(*e.g.*, via the GI tract). In additional embodiments, disclosed herein include methods for treating or preventing cholestasis, cirrhosis, primary biliary cirrhosis, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), or primary sclerosing cholangitis (PSC) by administering a therapeutically effective amount of an FXR agonist to a subject in need thereof. In some embodiments, disclosed herein include methods for treating or preventing cholestasis by administering a therapeutically effective amount of an FXR agonist to a subject in need thereof. In some embodiments, disclosed herein include methods for treating or preventing primary biliary cirrhosis by administering a therapeutically effective amount of an FXR agonist to a subject in need thereof. In some embodiments, disclosed herein include methods for treating or preventing NASH by administering a therapeutically effective amount of an FXR agonist to a subject in need thereof. In some embodiments, disclosed herein include methods for treating or preventing NAFLD by administering a therapeutically effective amount of an FXR agonist to a subject in need thereof.

[0036] In further embodiments, disclosed herein include methods for treating or preventing inflammation in the intestines and/or a cell proliferative disorder, such as cancer, by administering a therapeutically effective amount of an FXR agonist to a subject in need thereof (*e.g.*, via the GI tract).

[0037] In still further embodiments, disclosed herein include FXR agonists that modulate one or more of the proteins or genes associated with a metabolic process such as bile acid synthesis, glucose metabolism, lipid metabolism, or insulin sensitivity, such as for example, increase in the activity of FGF19 (FGF15 in mouse), increase in the secretion of GLP-1, or increase in the secretion of PYY.

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)

[0038] Described herein is the FXR agonist compound, 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). "Compound 1" or "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" refers to the compound with the following structure:



[0039] In some embodiments, Compound **1** is in the form of pharmaceutically acceptable salt. In some embodiments, Compound **1** is a free base. In addition, Compound **1** can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of Compound **1** presented herein are also considered to be disclosed herein. In some embodiments, Compound **1** is solvated. In some embodiments, Compound **1** is unsolvated. In some embodiments, Compound **1** is crystalline. In some embodiments, Compound **1** is amorphous.

[0040] Compound **1** has a non-bile acid chemical structure. In some embodiments, Compound **1** has sustained exposure when administered to a mammal. In some embodiments, Compound **1** has continuous target engagement with FXR. In some embodiments, Compound **1** is suitable for once-daily oral dosing.

[0041] Obeticholic acid (OCA) is an FXR agonist that contains a bile acid chemical structure. In published clinical studies, OCA has demonstrated clinical efficacy as an FXR agonist but is associated with adverse side effects at higher administered doses, such as pruritis, increased LDL cholesterol and liver toxicity. In some embodiments, in a suitable *in vitro* assay assessing FXR agonist binding to FXR, Compound **1** demonstrated at least thirty-fold more potency than OCA. In some embodiments, the increased potency of Compound **1** indicates a wider potential therapeutic window relative to OCA.

[0042] In some embodiments, Compound **1** displayed sustained FXR engagement in preclinical animal models based on pharmacokinetics and pharmacodynamic markers. In some embodiments, Compound **1** demonstrates sustained FXR engagement that permits once a day dosing of Compound **1**.

[0043] "Pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material is administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0044] The term "pharmaceutically acceptable salt" refers to a form of a therapeutically active agent that consists of a cationic form of the therapeutically active agent in combination with a suitable anion, or in alternative embodiments, an anionic form of the therapeutically active agent in combination with a suitable cation. Handbook of Pharmaceutical Salts: Properties, Selection

and Use. International Union of Pure and Applied Chemistry, Wiley-VCH 2002. S.M. Berge, L.D. Bighley, D.C. Monkhouse, J. Pharm. Sci. 1977, 66, 1-19. P. H. Stahl and C. G. Wermuth, editors, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Weinheim/Zürich: Wiley-VCH/VHCA, 2002. Pharmaceutical salts typically are more soluble and more rapidly soluble in stomach and intestinal juices than non-ionic species and so are useful in solid dosage forms. Furthermore, because their solubility often is a function of pH, selective dissolution in one or another part of the digestive tract is possible, and this capability can be manipulated as one aspect of delayed and sustained release behaviors. Also, because the salt-forming molecule can be in equilibrium with a neutral form, passage through biological membranes can be adjusted.

[0045] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of isolating or purifying the compound with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein optionally exist in unsolvated as well as solvated forms.

Certain Terminology

[0046] Unless otherwise stated, the following terms used in this application have the definitions given below. The use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range varies between 1% and 15% of the stated number or numerical range. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0047] The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[0048] The term “modulate” as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[0049] The term “modulator” as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an

agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is an agonist.

[0050] The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally.

[0051] The terms “co-administration” or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[0052] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered, which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[0053] The terms “enhance” or “enhancing,” as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term “enhancing” refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An “enhancing-effective amount,” as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[0054] The term “pharmaceutical combination” as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, e.g. Compound **1**, or a pharmaceutically acceptable salt thereof, and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, e.g. Compound **1**, or a pharmaceutically acceptable salt thereof, and a co-agent, are administered to a patient as separate

entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[0055] The terms "kit" and "article of manufacture" are used as synonyms.

[0056] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[0057] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Pharmaceutical compositions

[0058] In some embodiments, spray-dried solid dispersions of Compound **1** described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[0059] In some embodiments, a spray-dried solid dispersion of Compound **1** described herein is administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition. Administration of a spray-dried solid dispersion of Compound **1** described herein, and pharmaceutical compositions thereof, can be affected by any method that enables delivery of the compound to the site of action. These methods include, though are not limited to delivery via oral administration.

[0060] In some embodiments, Compound **1** pharmaceutical compositions suitable for oral administration are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules.

[0061] Pharmaceutical compositions which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. In some embodiments, the tablets are coated or scored and are formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to characterize different combinations of active compound doses.

[0062] Conventional techniques to manufacture solid oral dosage forms include, but are not limited to, one or a combination of methods: (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, or (5) wet granulation. See, e.g., Lachman *et al.*, *The Theory and Practice of Industrial Pharmacy* (1986). Other methods include, e.g., spray drying, pan coating, melt granulation, granulation, fluidized bed spray drying or coating (e.g., wurster coating), tangential coating, top spraying, tableting, extruding and the like.

[0063] It should be understood that in addition to the ingredients particularly mentioned above, the compounds and compositions described herein may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0064] Provided herein are tablets comprising Compound **1**, or a pharmaceutically acceptable salt thereof. In some embodiments, the tablet comprises: Compound **1** dispersed in a polymer

matrix formed from a pharmaceutically acceptable polymer; one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more lubricants, one or more glidants; and optionally one or more film coating agents.

[0065] In some embodiments, described herein is a spray-dried solid dispersion comprising (a) Compound **1**; and (b) a pharmaceutically acceptable polymer; wherein Compound **1** is dispersed in a polymer matrix formed from the pharmaceutically acceptable polymer.

[0066] In some embodiments, described herein are tablets prepared with the spray-dried solid dispersions described herein.

Compound 1 Spray Dried Solid Dispersion Formulations

[0067] In some embodiments described herein, the Compound **1** pharmaceutical composition is a spray-dried solid dispersion formulation. In some embodiments, provided herein is a spray-dried solid dispersion comprising: (a) 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, and (b) a pharmaceutically acceptable polymer; wherein 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 is dispersed in a polymer matrix formed from the pharmaceutically acceptable polymer. In some embodiments, the pharmaceutically acceptable polymer is selected from PVP/VA 64, PVP 30, HPMCAS-L, HPMCAS-M, HPMCAS-H, Eudragit L100-55, Eudragit L100, Eudragit EPO, HPMC E15, HPMC E3, HPMC E5, HPMCP-HP55, and Soluplus. In some embodiments, the pharmaceutically acceptable polymer is selected from PVP/VA 64 and HPMCAS-M. In some embodiments, the pharmaceutically acceptable polymer is PVP/VA 64. In some embodiments, the pharmaceutically acceptable polymer is HPMC-AS-M. In some embodiments, the pharmaceutically acceptable polymer is PVP 30. In some embodiments, the pharmaceutically acceptable polymer is HPMC-AS-L. In some embodiments, the pharmaceutically acceptable polymer is HPMC-AS-H. In some embodiments, the pharmaceutically acceptable polymer is Eudragit L100-55. In some embodiments, the pharmaceutically acceptable polymer is Eudragit L100. In some embodiments, the pharmaceutically acceptable polymer is Eudragit EPO. In some embodiments, the pharmaceutically acceptable polymer is HPMC E15. In some embodiments, the pharmaceutically acceptable polymer is HPMC E3. In some embodiments, the pharmaceutically acceptable polymer is HPMC E5. In some embodiments, the pharmaceutically acceptable polymer is HPMCP-HP55. In some embodiments, the pharmaceutically acceptable polymer is Soluplus. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically

acceptable polymer is from 9:1 to 1:9. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is from 7:1 to 1:7. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is from 5:1 to 1:5. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is from 4:1 to 1:4. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is from 3:1 to 1:3. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is from 2:1 to 1:2. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is 4:1. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is 3:1. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is 2:1. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is 1.5:1. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is 1:1. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is 1:1.5. In some embodiments, the weight ratio of Compound **1** to the pharmaceutically acceptable polymer is 1:2. In some embodiments, the spray-dried solid dispersion further comprises a non-aqueous solvent. In some embodiments, the non-aqueous solvent is selected from the group consisting of tert-butanol, n-propanol, n-butanol, isopropanol, ethanol, methanol, acetone, ethyl acetate, dimethyl carbonate, acetonitrile, dichloromethane, methyl ethyl ketone, methyl isobutyl ketone, 1-pentanol, methyl acetate, carbon tetrachloride, dimethyl sulfoxide, hexafluoroacetone, chlorobutanol, dimethyl sulfone, acetic acid, cyclohexane, and mixtures thereof. In some embodiments, the non-aqueous solvent is selected from the group consisting of ethanol, methanol, propanol, butanol, isopropanol, tert-butanol, dichloromethane, and mixtures thereof. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 15/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 14/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 13/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 12/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 11/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 10/1. In some embodiments, the non-aqueous solvent is a mixture of

dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 9/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 8/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 7/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 6/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 5/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 4/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 3/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 2/1. In some embodiments, the non-aqueous solvent is a mixture of dichloromethane and methanol, wherein the weight ratio of dichloromethane to methanol is about 1/1. In some embodiments of the spray-dried solid dispersion, Compound **1** is substantially amorphous.

[0068] In another aspect, provided herein is a pharmaceutical formulation comprising a spray-dried solid dispersion described herein, further comprising one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more binders, one or more lubricants, one or more glidants, and one or more surfactants. In some embodiments, the one or more pharmaceutical acceptable ingredients are selected from the group consisting of microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, mannitol, crospovidone, and sodium stearyl fumarate. In some embodiments, the one or more pharmaceutical acceptable ingredients are selected from the group consisting of microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and colloidal silicon dioxide. In some embodiments, the pharmaceutical formulation is in tablet form. In some embodiments, the pharmaceutical formulation is in capsule form.

[0069] In one aspect, described herein is a tablet comprising: Compound **1**, or a pharmaceutically acceptable salt thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer; one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more lubricants, one or more glidants; and optionally one or more film coating agents.

[0070] In some embodiments, Compound **1**, or a pharmaceutically acceptable salt thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer is the spray-dried solid dispersion described herein.

[0071] In some embodiments, tablets comprise about 1% by weight to about 15% by weight of Compound **1**. In some embodiments, tablets comprise about 1% by weight to about 20% by weight of the polymer matrix formed from the pharmaceutically acceptable polymer.

[0072] In some embodiments, tablets comprise about 1% by weight to about 15% by weight of Compound **1**, dispersed in about 0.5% by weight to about 10% by weight of a polymer matrix formed from a pharmaceutically acceptable polymer.

[0073] In some embodiments, tablets comprise about 1% by weight to about 15% by weight of Compound **1** dispersed in about 0.5% by weight to about 10% by weight of a polymer matrix formed from a pharmaceutically acceptable polymer; about 70% by weight to about 99% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more lubricants, one or more glidants; and optionally less than about 2% by weight of one or more film coating agents.

[0074] In some embodiments, tablets comprises about 1% by weight to about 30% by weight of the spray-dried solid dispersion. In some embodiments, the tablet comprises about 5% by weight to about 25% by weight of the spray-dried solid dispersion. In some embodiments, the tablet comprises about 5% by weight to about 20% by weight of the spray-dried solid dispersion. In some embodiments, the tablet comprises about 5% by weight to about 15% by weight of the spray-dried solid dispersion. In some embodiments, the tablet comprises about 5% by weight to about 10% by weight of the spray-dried solid dispersion.

[0075] In some embodiments, in addition to the spray-dried solid dispersion, additional excipients in the tablets comprise one or more diluents, one or more disintegrants, one or more lubricants, one or more glidants, or any combination thereof. In some embodiments, in addition to the spray-dried solid dispersion, additional excipients in the tablets comprise microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide, and magnesium stearate.

[0076] In some embodiments, the tablet comprises one or more fillers/binders/diluents. Fillers/binders/diluents are selected from celluloses (such as microcrystalline cellulose, carboxymethylcellulose, ethyl cellulose and methyl cellulose), starch, gelatin, sugars (such as sucrose, glucose, dextrose, mannitol, and lactose), natural and synthetic gums (such as acacia, sodium alginate, panwar gum, and ghatti gum), polyvinylpyrrolidinone, polyethylene glycol, waxes, and any combinations thereof. In some embodiments, tablets comprise microcrystalline cellulose, and lactose monohydrate.

[0077] In some embodiments, the one or more fillers/binders/diluents in the tablets described herein comprise between about 40% and about 95% by weight of the total tablet weight. In some embodiments, the one or more fillers/binders/diluents in the tablets described herein comprise between about 60% and about 95% by weight of the total tablet weight. In some embodiments, the one or more fillers/binders/diluents in the tablets described herein comprise between about 65% and about 95% by weight of the total tablet weight. In some embodiments, the one or more fillers/binders/diluents in the tablets described herein comprise between about 75% and about 95% by weight of the total tablet weight. In some embodiments, the one or more fillers/binders/diluents in the tablets described herein comprise about 50%, about 55%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% by weight of the total tablet weight. In some embodiments, the one or more fillers/binders/diluents in the tablets described herein comprise about 58% by weight of the total tablet weight. In some embodiments, less than 95% by weight, less than 85% by weight, less than 75% by weight, less than 65% by weight, or less than 60% by weight of the total tablet weight comprise one or more fillers/binders/diluents.

[0078] In some embodiments, tablets comprise one or more disintegrants. Disintegrants are selected from croscarmellose sodium, crospovidone, sodium starch glycolate, veegum HV, methylcellulose, agar, bentonite, cellulose, carboxymethyl cellulose, and any combination thereof. In some embodiments, tablets comprise croscarmellose sodium.

[0079] In some embodiments, the one or more disintegrants in the tablets described herein comprise between about 2% and about 20% by weight of the total tablet weight. In some embodiments, the one or more disintegrants in the tablets described herein comprise between about 5% and about 10% by weight of the total tablet weight. In some embodiments, the one or more disintegrants in the tablets described herein comprise about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, or about 20% by weight of the total tablet weight. In some embodiments, the one or more disintegrants in the tablets described herein comprise about 5% by weight of the total tablet weight. In some embodiments, the one or more disintegrants in the tablets described herein comprise about 10% by weight of the total tablet weight. In some embodiments, less than 20% by weight of the total tablet weight comprise one or more disintegrants.

[0080] In some embodiments, tablets comprise one or more lubricants. Lubricants are selected from talc, magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, and any combinations thereof. In some embodiments, tablets comprise magnesium stearate.

[0081] In some embodiments, the one or more lubricants in the tablets described herein comprise between about 0.1 % and about 5% by weight of the total tablet weight. In some embodiments, the one or more lubricants in the tablets described herein comprise between about 0.1% and about 2% by weight of the total tablet weight. In some embodiments, the one or more lubricants in the tablets described herein comprise between about 0.1% and about 1% by weight of the total tablet weight. In some embodiments, the one or more lubricants in the tablets described herein comprise about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, or about 1% by weight of the total tablet weight. In some embodiments, the one or more lubricants in the tablets described herein comprise about 1% by weight of the total tablet weight. In some embodiments, less than 2% by weight of the total tablet weight comprise one or more lubricants.

[0082] In some embodiments, tablets comprise one or more glidants. A glidant is a substance that is added to a powder to improve its flowability. Examples of glidants include magnesium stearate, colloidal silicon dioxide, starch and talc. In some embodiments, tablets comprise colloidal silicon dioxide.

[0083] In some embodiments, the one or more lubricants in the tablets described herein comprise between about 0.1 % and about 5% by weight of the total tablet weight. In some embodiments, the one or more lubricants in the tablets described herein comprise between about 0.1% and about 2% by weight of the total tablet weight. In some embodiments, the one or more lubricants in the tablets described herein comprise between about 0.5% and about 1.5% by weight of the total tablet weight. In some embodiments, the one or more lubricants in the tablets described herein comprise about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, or about 2% by weight of the total tablet weight. In some embodiments, the one or more lubricants in the tablets described herein comprise about 1% by weight of the total tablet weight. In some embodiments, less than 2% by weight of the total tablet weight comprise one or more lubricants.

Additional Excipients

[0084] In some embodiments, the tablet described herein comprises additional excipients including, but not limited, to buffering agents, glidants, preservatives, and coloring agents. Additional excipients such as bulking agents, tonicity agents, and chelating agents are within the scope of the embodiments.

[0085] Non-limiting examples of buffering agents include, but are not limited to, sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium glucomate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, a

mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer. Additional buffering agents include sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts.

[0086] In some embodiments, the tablet described herein comprises a preservative. Preservatives include anti-microbials, anti-oxidants, and agents that enhance sterility. Exemplary preservatives include ascorbic acid, ascorbyl palmitate, BHA, BHT, citric acid, erythorbic acid, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium bisulfate, sodium metabisulfite, sodium sulfite, parabens (methyl-, ethyl-, butyl-), benzoic acid, potassium sorbate, vanillin, and the like.

[0087] In some embodiments, the tablet described herein comprises a coloring agent for identity and/or aesthetic purposes of the resultant liquid form. Suitable coloring agents illustratively include FD&C Red No. 3, FD&C Red No. 20, FD&C Red No. 40, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, caramel, ferric oxide and mixtures thereof.

[0088] Additional excipients are contemplated in the tablet embodiments. These additional excipients are selected based on function and compatibility with the tablet compositions described herein and may be found, for example in *Remington: The Science and Practice of Pharmacy,* Nineteenth Ed (Easton, PA: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences,* (Easton, PA: Mack Publishing Co 1975); Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms* (New York, NY: Marcel Decker 1980); and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed (Lippincott Williams & Wilkins 1999), herein incorporated by reference in their entirety.

[0089] In further embodiments, the tablets described herein are coated tablets, such as enteric-coated tablets, sugar-coated, or film-coated tablets.

[0090] In one embodiment, the individual unit dosages also include film coatings, which disintegrate upon oral ingestion or upon contact with diluent. In one embodiment, these formulations are manufactured by conventional techniques.

[0091] Compressed tablets are solid dosage forms prepared by compacting the bulk blend formulations described above. In various embodiments, compressed tablets which are designed to dissolve in the mouth will include one or more flavoring agents. In other embodiments, the compressed tablets will include a film surrounding the final compressed tablet. In some

embodiments, the film coating aids in patient compliance (e.g., Opadry® coatings or sugar coating). Film coatings comprising Opadry® typically range from about 1% to about 5% of the tablet weight. In other embodiments, the compressed tablets include one or more excipients.

[0092] Provided herein are film-coated tablets forms, which comprise: a combination of an active ingredient (e.g. Compound **1**, or a pharmaceutically acceptable salt thereof) and one or more tabletting excipients to form a tablet core and subsequently coating the core. The tablet cores are produced using conventional tabletting processes and with subsequent compression and coating.

[0093] Enteric-coatings are coatings that resist the action of stomach acid but dissolve or disintegrate in the intestine.

[0094] In one aspect, the oral solid dosage form disclosed herein include an enteric coating(s). Enteric coatings include one or more of the following: cellulose acetate phthalate; methyl acrylate-methacrylic acid copolymers; cellulose acetate succinate; hydroxy propyl methyl cellulose phthalate; hydroxy propyl methyl cellulose acetate succinate (hypromellose acetate succinate); polyvinyl acetate phthalate (PVAP); methyl methacrylate-methacrylic acid copolymers; methacrylic acid copolymers, cellulose acetate (and its succinate and phthalate version); styrol maleic acid co-polymers; polymethacrylic acid/acrylic acid copolymer; hydroxyethyl ethyl cellulose phthalate; hydroxypropyl methyl cellulose acetate succinate; cellulose acetate tetrahydrophtalate; acrylic resin; shellac.

[0095] An enteric coating is a coating put on a tablet, pill, capsule, pellet, bead, granule, particle, etc. so that it doesn't dissolve until it reaches the small intestine.

[0096] Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation.

[0097] Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets. In some embodiments, tablets are coated with water soluble, pH independent film coating which allows for immediate disintegration for fast, active release (e.g. Opadry products).

Dosage in the Tablet

[0098] In some embodiments, the amount of Compound **1** in the tablet is between about 1 mg and about 25 mg. In some embodiments, the amount of Compound **1** in the tablet is about 1 mg.

In some embodiments, the amount of Compound **1** in the tablet is about 5 mg. In some embodiments, the amount of Compound **1** in the tablet is about 12 mg. In some embodiments, the amount of Compound **1** in the tablet is about 25 mg.

Methods of Dosing and Treatment Regimens

[0099] In one embodiment, Compound **1** described herein, or a pharmaceutically acceptable salt thereof, is used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from administration of a FXR agonist. Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment, involves administration of pharmaceutical compositions (i.e., formulations) that include Compound **1** described herein, or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said mammal.

[00100] Disclosed herein, are methods of administering a FXR agonist in combination with an additional therapeutic agent. In some embodiments, the additional therapeutic agent comprises a therapeutic agent for treatment of diabetes or diabetes related disorder or conditions, alcoholic or non-alcoholic liver disease, inflammation related intestinal conditions, or cell proliferative disorders.

[00101] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00102] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in patients, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of the disease being treated and is currently in remission, a pharmaceutical composition comprising a

Compound **1**, or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00103] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion, the Compound **1** is administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00104] In certain embodiments wherein a patient's status does improve, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, or more than 28 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00105] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00106] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00107] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-500 mg per day. In one aspect, doses employed for adult human treatment are from about 1 mg to about 500 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00108] In one embodiment, the daily dosages appropriate for Compound **1** described herein, or a pharmaceutically acceptable salt thereof, are from about 0.01 to about 50 mg/kg per body weight. In some embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a

number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00109] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} and the ED_{50}. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD_{50} and ED_{50}. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED_{50} with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

[00110] In any of the aforementioned aspects are further embodiments in which the effective amount of Compound **1** 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 injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

[00111] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of Compound **1**, including further embodiments in which (i) the compound is administered once a day; or (ii) the compound is administered to the mammal multiple times over the span of one day.

[00112] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of Compound **1**, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

[00113] In certain instances, it is appropriate to administer Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with one or more other therapeutic agents.

[00114] In one embodiment, the therapeutic effectiveness of Compound **1** is enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant has minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, in some embodiments, the benefit experienced by a patient is increased by administering one of the compounds described herein with another agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[00115] In one specific embodiment, Compound **1**, or a pharmaceutically acceptable salt thereof, is co-administered with a second therapeutic agent, wherein Compound **1**, or a pharmaceutically acceptable salt thereof, and the second therapeutic agent modulate different aspects of the disease, disorder or condition being treated, thereby providing a greater overall benefit than administration of either therapeutic agent alone.

EXAMPLES

List of abbreviations

[00116] As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN or MeCN	acetonitrile
Bn	benzyl
BOC or Boc	*tert*-butyl carbamate
t-Bu	*tert*-butyl
Cy	cyclohexyl
DCE	dichloroethane ($ClCH_2CH_2Cl$)
DCM	dichloromethane (CH_2Cl_2)
DIPEA or DIEA	diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	dimethylformamide
DMA	*N,N*-dimethylacetamide
DMSO	dimethylsulfoxide
equiv	equivalent(s)
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol

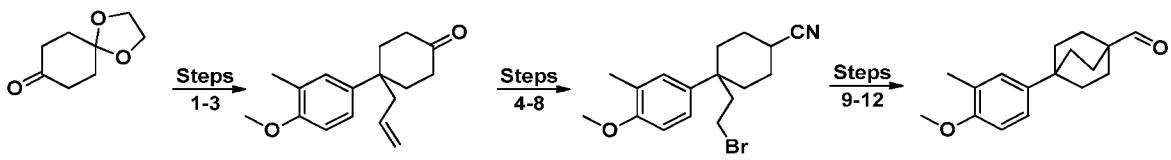
EtOAc	ethyl acetate
HPLC	high performance liquid chromatography
Me	methyl
MeOH	methanol
MS	mass spectroscopy
NMR	nuclear magnetic resonance
RP-HPLC	reverse phase-high pressure liquid chromatography
T3P	2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide
TBME	methyl *tert*-butyl ether
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

I. Chemical Synthesis

[00117] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Anhydrous solvents and oven-dried glassware were used for synthetic transformations sensitive to moisture and/or oxygen. Yields were not optimized. Reaction times are approximate and were not optimized. Column chromatography and thin layer chromatography (TLC) were performed on silica gel unless otherwise noted.

Example 1: Preparation of 4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octane-1-carbaldehyde

(Intermediate 1)



Step 1: 8-(4-Methoxy-3-methylphenyl)-1,4-dioxaspiro[4.5]decan-8-ol

[00118] 3 batches were run in parallel: *n*-BuLi (762 mL, 1.90 mol, 2.5 M in *n*-hexane) was added dropwise over 1 h to a solution of 4-bromo-1-methoxy-2-methylbenzene (333 g, 1.66 mol) and dry THF (2 L) at -60 °C under N_2. The reaction was stirred at -60 °C for 1 h, and then a solution of 1,4-dioxaspiro[4.5]decan-8-one (284.53 g, 1.82 mol) and dry THF (1 L) was added dropwise over 45 min. The reaction was stirred at -60 °C for 1 h, and then the 3 batches were poured into sat. aq. NH_4Cl (3 L). This mixture was extracted with EtOAc (5 L × 2). The combined organic layers were washed with brine (5 L), dried over Na_2SO_4, filtered, concentrated, and then triturated in *n*-hexane (1.2 L) at rt overnight. The mixture was filtered, and the filter cake was

washed with cool n-hexane (200 mL × 2) and then dried under vacuum to give 8-(4-methoxy-3-methylphenyl)-1,4-dioxaspiro[4.5]decan-8-ol (1100 g, 82%) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.30-7.20 (m, 2H), 6.74 (d, 1H), 4.02-3.87 (m, 4H), 3.78 (s, 3H), 2.18 (s, 3H), 2.15-2.00 (m, 4H), 1.82-1.73 (m, 2H), 1.68-1.60 (m, 2H), 1.48 (s, 1H).

Step 2: 8-Allyl-8-(4-methoxy-3-methylphenyl)-1,4-dioxaspiro[4.5]decane

[00119] 4 batches were run in parallel: BF_3•Et_2O (376.95 g, 2.65 mol) was added to a solution of 8-(4-methoxy-3-methylphenyl)-1,4-dioxaspiro[4.5]decan-8-ol (275 g, 0.99 mol), allyltrimethylsilane (180.62 g, 1.58 mol), and dry DCM (3 L) at -65 °C under N_2, The reaction mixture was stirred at -65 °C for 1 h, and then the 4 batches were carefully poured into sat. aq. $NaHCO_3$ (10 L). This mixture was extracted with DCM (5 L × 3). The combined organic layers were washed with brine (5 L), dried over Na_2SO_4, filtered, and concentrated to give 8-allyl-8-(4-methoxy-3-methylphenyl)-1,4-dioxaspiro[4.5]decane (1350 g) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.17-7.01 (m, 2H), 6.85-6.75 (m, 1H), 5.53-5.37 (m, 1H), 5.01-4.85 (m, 2H), 3.99-3.87 (m, 4H), 3.82 (s, 3H), 2.37-2.29 (m, 1H), 2.28-2.21 (m, 5H), 2.20-2.10 (m, 2H), 1.82-1.71 (m, 2H), 1.70-1.52 (m, 3H).

Step 3: 4-Allyl-4-(4-methoxy-3-methylphenyl)cyclohexanone

[00120] 3 batches were run in parallel: Water (450 mL) and then formic acid (285.95 g, 5.95 mol) were added to a solution of 8-allyl-8-(4-methoxy-3-methylphenyl)-1,4-dioxaspiro[4.5]decane (450 g) and THF (1.8 L) at rt. The reaction mixture was refluxed overnight, allowed to cool to rt, and then the 3 batches were poured into sat. aq. $NaHCO_3$ (3 L). This mixture was extracted with EA (3 L × 3). The combined organic layers were washed with brine (3 L), dried over Na_2SO_4, filtered, concentrated, and then purified by chromatography on silica gel (petroleum ether/EtOAc = 1/0-50/1) to give 4-allyl-4-(4-methoxy-3-methylphenyl)cyclohexanone (800 g, 69.3% over 2 steps) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.16-7.06 (m, 2H), 6.80-6.73 (m, 1H), 5.48-5.30 (m, 1H), 4.96-4.79 (m, 2H), 3.77 (s, 3H), 2.48-2.35 (m, 2H), 2.32-2.05 (m, 9H), 1.89-1.77 (m, 2H).

Step 4: 4-Allyl-4-(4-methoxy-3-methylphenyl)cyclohexanecarbonitrile

[00121] 3 batches were run in parallel: *t*-BuOK (299.69 g, 2.67 mol) was added portionwise over 1 h (keeping internal temp. < 5 °C) to a solution of 4-allyl-4-(4-methoxy-3-methylphenyl)cyclohexanone (230 g, 890.25 mmol), Tos-MIC (260.72 g, 1.34 mol), and DME (2 L) at 0 °C under N_2. The mixture was stirred at rt for 2 h, and then the 3 batches were poured into sat. aq. NH_4Cl (5 L). The mixture was extracted with EtOAc (5 L × 2). The combined organic layers were washed with brine (5 L), dried over Na_2SO_4, filtered, concentrated, and then purified by chromatography on silica gel (petroleum ether/EtOAc = 1/0-50/1) to give 4-allyl-4-(4-methoxy-3-methylphenyl)cyclohexanecarbonitrile (508 g, 70.6%) as a yellow oil. ^{1}H NMR

(400MHz, $CDCl_3$): δ 7.13-6.99 (m, 2H), 6.83-6.75 (m, 1H), 5.51-5.31 (m, 1H), 5.03-4.85 (m, 2H), 3.84 (s, 3H), 2.58-2.48 (m, 1H), 2.38-2.02 (m, 7H), 1.98-1.79 (m, 2H), 1.78-1.56 (m, 3H), 1.54-1.40 (m, 1H).

Step 5: 4-(2,3-Dihydroxypropyl)-4-(4-methoxy-3-methylphenyl)cyclohexanecarbonitrile

[00122] 3 batches were run in parallel: NMO (242.66 g, 2.07 mol) and then $K_2OsO_4•2H_2O$ (7.63 g, 20.71 mmol) were added to a solution of 4-allyl-4-(4-methoxy-3-methylphenyl)cyclohexanecarbonitrile (186 g, 690.47 mmol), acetone (2 L), and H_2O (250 mL) at 0 °C. The reaction was allowed to warm to rt and stirred for 2 h. The 3 batches were poured into sat. aq. Na_2SO_3 (4 L), and the mixture was extracted with EtOAc (3 L × 2). The combined organic layers were washed with brine (3 L), dried over Na_2SO_4, filtered, concentrated, and then purified by chromatography on silica gel (petroleum ether/EtOAc = 5/1-1/2) to give 4-(2,3-dihydroxypropyl)-4-(4-methoxy-3-methylphenyl)cyclohexanecarbonitrile (600 g, 95.4%) as a yellow oil. ^1H NMR (400MHz, $CDCl_3$): δ 7.21-7.01 (m, 2H), 6.87-6.74 (m, 1H), 3.83 (s, 3H), 3.65-3.49 (m, 1H), 3.35-3.17 (m, 2H), 2.60-2.45 (m, 1H), 2.41-2.11 (m, 5H), 2.01-1.81 (m, 4H), 1.79-1.38 (m, 6H).

Step 6: 4-(4-Methoxy-3-methylphenyl)-4-(2-oxoethyl)cyclohexanecarbonitrile

[00123] 3 batches were run in parallel: $NaIO_4$ (169.20 g, 791.05 mmol) was added portionwise over 30 min (keeping internal temp. < 5 °C) to a solution of 4-(2,3-dihydroxypropyl)-4-(4-methoxy-3-methylphenyl)cyclohexanecarbonitrile (200 g, 659.21 mmol), THF (2 L), and H_2O (1 L) at 0 °C. The mixture was stirred at rt for 3 h, and then the 3 batches were poured into water (2 L). The mixture was extracted with EtOAc (2 L × 2). The combined organic layers were washed with brine (2 L), dried over Na_2SO_4, filtered, and concentrated to give 4-(4-methoxy-3-methylphenyl)-4-(2-oxoethyl)cyclohexanecarbonitrile (510 g) as a colorless oil. ^1H NMR (400MHz, $CDCl_3$): δ 9.43-9.22 (m, 1H), 7.20-6.99 (m, 2H), 6.87-6.71 (m, 1H), 3.82 (s, 3H), 2.63-2.48 (m, 2H), 2.46-2.36 (m, 1H), 2.33-2.13 (m, 4H), 2.02-1.71 (m, 5H), 1.71-1.57 (m, 2H).

Step 7: 4-(2-Hydroxyethyl)-4-(4-methoxy-3-methylphenyl)cyclohexanecarbonitrile

[00124] 3 batches were run in parallel: $NaBH_4$ (35.55 g, 939.73 mmol) was added to a solution of 4-(4-methoxy-3-methylphenyl)-4-(2-oxoethyl)cyclohexanecarbonitrile (170 g) and THF (1.7 L) at 0 °C under N_2. The mixture was stirred at rt for 3 h, and then the 3 batches were poured into ice-cold water (3 L). This mixture was extracted with EtOAc (1.5 L × 2). The combined organic layers were washed with brine (2 L), dried over Na_2SO_4, filtered, concentrated to give 4-(2-hydroxyethyl)-4-(4-methoxy-3-methylphenyl)cyclohexanecarbonitrile (495 g) as a colorless oil. ^1H NMR (400MHz, $CDCl_3$): δ 7.18-6.97 (m, 2H), 6.88-6.71 (m, 1H), 3.85-3.78 (m, 3H), 3.76-3.70 (m, 1H), 3.44-3.33 (m, 2H), 2.71-2.69 (m, 0.5H), 2.60-2.48 (m, 0.5H), 2.37-2.35 (m, 0.5H),

2.27-2.19 (m, 3H), 2.14-2.12 (m, 0.5H), 1.96-1.79 (m, 5H), 1.78-1.61 (m, 3H), 1.58-1.45 (m, 1H).

Step 8: 4-(2-Bromoethyl)-4-(4-methoxy-3-methylphenyl)cyclohexanecarbonitrile

[00125] 3 batches were run in parallel: A solution of PPh_3 (316.62 g, 1.21 mol) and DCM (1 L) was added dropwise over 1 h to a solution of 4-(2-hydroxyethyl)-4-(4-methoxy-3-methyl-phenyl)cyclohexanecarbonitrile (165 g), CBr_4 (300.24 g, 905.37 mmol), and DCM (1.5 L) at 0 °C under N_2. The mixture was stirred at rt for 1.5 h, combined with the other 2 batches, and concentrated. The crude product was triturated in MTBE (5 L) at rt overnight. The solid was removed by filtration, the cake was washed with MTBE (500 mL × 2), and the filtrate was concentrated and then purified by chromatography on silica gel (petroleum ether/EtOAc = 30/1) to give 4-(2-bromoethyl)-4-(4-methoxy-3-methylphenyl)cyclohexanecarbonitrile (530 g, 80%) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.11-6.96 (m, 2H), 6.86-6.73 (m, 1H), 3.87-3.73 (m, 3H), 3.09-2.93 (m, 2H), 2.78-2.68 (m, 0.5H), 2.62-2.50 (m, 0.5H), 2.38-2.34 (m, 1H), 2.28-2.18 (m, 3H), 2.17-2.10 (m, 2H), 2.08-1.99 (m, 1H), 1.99-1.79 (m, 3H), 1.77-1.45 (m, 3H).

Step 9: 4-(4-Methoxy-3-methylphenyl)bicyclo[2.2.2]octane-1-carbonitrile

[00126] 3 batches were run in parallel: LDA (420 mL, 840 mmol, 2 M in THF) was added dropwise over 1 h to a solution of 4-(2-bromoethyl)-4-(4-methoxy-3-methyl-phenyl)cyclohexanecarbonitrile (143 g, 425.26 mmol), HMPA (381.03 g, 2.13 mol), and THF (1430 mL) at -65 °C under N_2. The mixture was stirred at -65 °C for 3 h, and then the 3 batches were poured into sat. aq. NH_4Cl (5 L). This mixture was extracted with EtOAc (3 L × 2). The combined organic layers were washed with water (3 L), washed with brine (3 L), dried over Na_2SO_4, filtered, concentrated, and then triturated in EA:Hexane (1:30, 775 mL) at rt overnight. The mixture was filtered, and the filter cake was washed with EA:Hexane (1:30, 150 mL) and dried under vacuum to give 4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octane-1-carbonitrile (240 g, 73%) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.13-6.98 (m, 2H), 6.83-6.73 (m, 1H), 3.82 (s, 3H), 2.22 (s, 3H), 2.12-1.98 (m, 6H), 1.94-1.80 (m, 6H).

Step 10: 4-(4-Methoxy-3-methylphenyl)bicyclo[2.2.2]octane-1-carbaldehyde

[00127] 3 batches were run in parallel: DIBAL-H (1 M PhMe, 830 mL, 830 mmol) was added to a solution of 4-(4-methoxy-3-methyl-phenyl)bicyclo[2.2.2]octane-1-carbonitrile (106 g, 415.11 mmol) in DCM (1 L) at -65 °C under N_2. The mixture was stirred at -65 °C for 1 h, and then the 3 batches were poured into sat. aq. NaK tartrate (3 L) and diluted by DCM (1.5 L). This mixture was stirred at rt for 3 h. The organic layer was separated, and the aqueous phase was extracted with DCM (2 L × 2). The organic layers were combined, washed with brine (3 L), dried over Na_2SO_4, filtered, and concentrated to give 4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octane-1-carbaldehyde (336 g) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 9.50-9.43 (m, 1H),

7.11-7.00 (m, 2H), 6.83-6.79 (m, 1H), 3.77-3.68 (m, 3H), 2.18-2.02 (m, 3H), 1.82-1.72 (m, 6H), 1.71-1.60 (m, 6H).

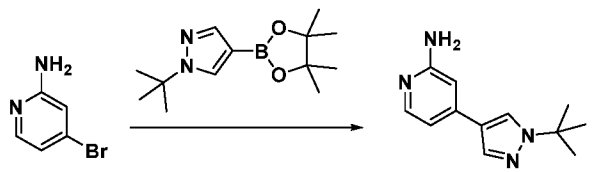
Step 11: Potassium-hydroxy(4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methanesulfonate

[00128] 6 batches were run in parallel: Aqueous potassium metabisulfite (2 M, 54 mL, 108 mmol) was added over 10 min to a solution of 4-(4-methoxy-3-methyl-phenyl)bicyclo[2.2.2]octane-1-carbaldehyde (56 g) in THF (300 mL) at 45 °C. The mixture was stirred for 3.5 h at 45 °C, allowed to cool to rt, and then stirred at rt overnight. The 6 batches were filtered, and the filter cake was washed with PE (400 mL) and dried under vacuum to give potassium-hydroxy(4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methanesulfonate (381 g, 81% over 2 steps) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) 7.12-6.97 (m, 2H), 6.88-6.71 (m, 1H), 4.51 (d, 1H), 3.73 (s, 3H), 3.56 (d, 1H), 2.11 (s, 3H), 1.88-1.56 (m, 12H).

Step 12: 4-(4-Methoxy-3-methylphenyl)bicyclo[2.2.2]octane-1-carbaldehyde

[00129] 6 batches were run in parallel: Saturated aq. Na_2CO_3 (300 mL) was added to a mixture of potassium-hydroxy(4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methanesulfonate (63.5 g, 167.76 mmol) and DCM (300 mL) at rt under N_2. The mixture was stirred for 1 h, and then the 6 batches were poured into a mixture of DCM (1500 mL) and H_2O (1500 mL). The organic layer was separated, and the aqueous phase was extracted with DCM (1500 mL × 3). The combined organic layers were washed with brine (2 L), dried over Na_2SO_4, filtered, and concentrated to give 4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octane-1-carbaldehyde (240.3 g, 92%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 9.52-9.41 (m, 1H), 7.14 - 7.02 (m, 2H), 6.84-7.80 (m, 1H), 3.73 (s, 3H), 2.12 (s, 3H), 1.83-1.72 (m, 6H), 1.71-1.56 (m, 6H); LCMS: 259.1 $[M+H]^+$.

Example 2: Preparation of 4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)pyridin-2-amine (Intermediate 2)



[00130] 2-Methyltetrahydrofuran (10 mL), Pd(dppf)Cl_2, and then aq. K_2CO_3 (3 M, 10 mL, 30 mmol) were added to 4-bromopyridin-2-amine (1.87 g, 10.8 mmol) and 1-(*tert*-butyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2.50 g, 10.0 mmol) in a 40 mL vial. The reaction was degassed with 3 vacuum/N_2 cycles, heated at 50 °C for 21 h, and then allowed to cool to rt. The layers were separated, and the organic layer was washed with sat'd aq. NaK tartrate (25 mL) and then washed with brine (25 mL). The aqueous layers were back extracted with 2-methyltetrahydrofuran (25 mL). The combined organics were dried ($MgSO_4$), filtered,

concentrated, and then dried under vacuum for 1 h. A suspension of the crude material and MTBE (25 mL) was refluxed for 2 h, allowed to cool to rt overnight, and then filtered. The filter cake was washed with MTBE (2 x 3 mL) and then dried under vacuum to give 4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)pyridin-2-amine (1.15 g, 53%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (s, 1H), 7.86-7.82 (m, 2H), 6.74 (d, 1H), 6.61 (s, 1H), 5.77 (s, 2H), 1.54 (s, 9H); LCMS: 217.1 $[M+H]^+$.

Example 3: Preparation of *trans*-4-((*tert*-butyldimethylsilyl)oxy)cyclohexanecarboxylic acid (Intermediate 3)

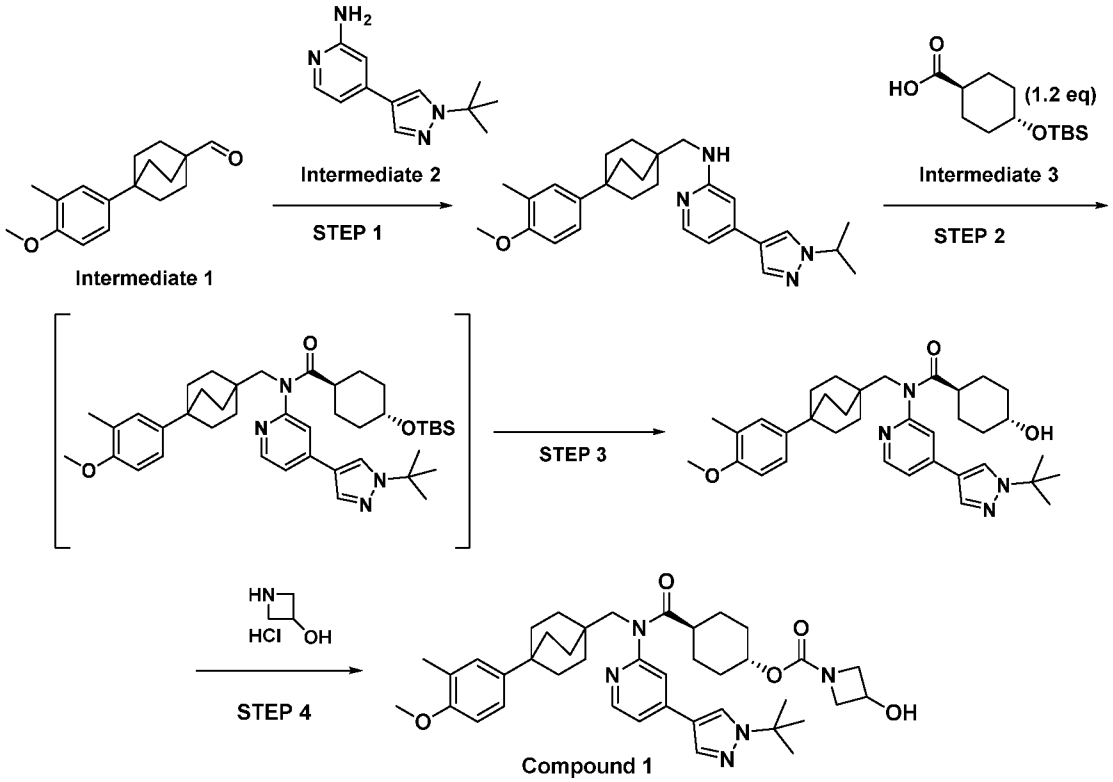
Step 1: *trans-tert*-Butyldimethylsilyl 4-((*tert*-butyldimethylsilyl)oxy)cyclohexanecarboxylate

[00131] *tert*-Butyldimethylsilyl chloride (31.47 g, 208.8 mmol) was added to a mixture of *trans*-4-hydroxy-cyclohexanecarboxylic acid (10.03 g, 69.57 mmol), imidazole (18.96 g, 278.5 mmol), and DMF (140 mL) at rt under N_2 (reaction exothermed to 32 °C). The reaction was stirred at rt for 2 h and then diluted with diethyl ether (300 mL). The organic layer was washed (2×300 mL 1 N HCl and then 300 mL brine), dried (Na_2SO_4), filtered, and concentrated to give *trans-tert*-butyldimethylsilyl 4-((*tert*-butyldimethylsilyl)oxy)cyclohexanecarboxylate (31.5 g) as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.61-3.53 (m, 1H), 2.26-2.18 (m, 1H), 2.04-1.96 (m, 2H), 1.92-1.85 (m, 2H), 1.51-1.39 (m, 2H), 1.39-1.27 (m, 2H), 0.94 (s, 9H), 0.89 (s, 9H), 0.26 (s, 6H), 0.06 (s, 6H).

Step 2: *trans*-4-((*tert*-Butyldimethylsilyl)oxy)cyclohexanecarboxylic Acid

[00132] Potassium carbonate (58.01 g, 419.7 mmol) in H_2O (300 mL) was added to a mixture of *trans-tert*-butyldimethylsilyl 4-((*tert*-butyldimethylsilyl)oxy)cyclohexanecarboxylate (31.5 g crude, 69.6 mmol), ethanol (1000 mL) and THF (300 mL) at rt under N_2. The reaction was stirred at rt for 3 h, concentrated until 300 mL remained, diluted with brine (600 mL), and then acidified to *p*H 2-3 with 20% $NaHSO_4$ (550 mL). The aqueous layer was extracted with diethyl ether (800 mL). The organic layer was washed (800 mL brine), dried (Na_2SO_4), filtered, concentrated, and dried under high vacuum (to remove silanol byproducts) to give *trans*-4-((*tert*-butyldimethylsilyl)oxy)cyclohexanecarboxylic acid (17.3 g, 96% over 2 steps) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.30 (br s, 1H), 3.59-3.51 (m, 1H), 2.15-2.05 (m, 1H), 1.88-1.74 (m, 4H), 1.41-1.29 (m, 2H), 1.28-1.16 (m, 2H), 0.84 (s, 9H), 0.02 (s, 6H).

Example 4: Preparation of 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)



Step 1: 4-(1-(*tert*-Butyl)-1*H*-pyrazol-4-yl)-*N*-((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)pyridin-2-amine

[00133] A mixture of intermediate **1** (1.0 equiv) and intermediate **2** (1.1 equiv) in methanol (7.5 vol) and acetic acid (0.33 equiv) was heated at 55 °C for at least 3 h. The reaction mixture was cooled to room temperature and 2-methylpyridine borane complex (1.0 equiv) was added as a solid over at least 20 minutes. The reaction was stirred at rt overnight and water (12.0 vol) was added within at least 60 minutes. The suspension was stirred for at least 2 h. A solid was collected by filtration, washed with water/methanol (2:1) (2 x 1 vol), TBME (2 x 2 vol), and heptane (2 x 2 vol), and dried in a rotary evaporator at 50 °C to afford 4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)-*N*-((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)pyridin-2-amine.

Steps 2 and 3: *trans*-*N*-(4-(1-(*tert*-Butyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-4-hydroxy-*N*-((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)cyclohexanecarboxamide

[00134] To a mixture of 4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)-*N*-((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)pyridin-2-amine (1.0 equiv) and intermediate **3** (1.2 equiv) in dichloromethane (7.5 vol) and triethylamine (4.0 equiv) at 0 °C was added a T3P solution in dichloromethane (2.0 equiv) over 0.5 h. The reaction mixture was warmed to room temperature and stirred at least 12 h. The reaction mixture was cooled to 5 °C and quenched with the addition of water in 2 portions (0.05 vol and 6.0 vol). The mixture was warmed to room temperature and stirred for at least 2 h. The organic layer was collected and washed with water. The dichloromethane solvent was replaced with 2-methyltetrahyrdrofuran (5.4 vol) *in vacuo*.

Methanol (2.4 vol) and water (2 vol) were added to the solution followed by aqueous HCl (32%) (1.9 equiv). The reaction mixture was stirred at room temperature for at least 2 h. To the mixture was added 9.5% aqueous $NaHCO_3$ solution (4 vol). The organic layer was collected, washed with brine, dried over Na_2SO_4, and filtered over Celite. The filtrate was concentrated *in vacuo* and TBME (9 vol) was added. A solid was collected by filtration, washed with TBME and heptane, and dried *in vacuo* at 60 °C to afford *trans*-*N*-(4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-4-hydroxy-*N*-((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)cyclohexanecarboxamide.

Step 4: 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)

[00135] To a solution of *trans*-*N*-(4-(1-(*tert*-butyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-4-hydroxy-*N*-((4-(4-methoxy-3-methylphenyl)bicyclo[2.2.2]octan-1-yl)methyl)cyclohexanecarboxamide in dichloromethane (8.0 vol) was added 1,1'-carbonyldiimidazole (1.5 equiv). The mixture was stirred at room temperature for at least 3.5 h. 3-Hydroxy azetidine hydrochloride (3.0 equiv) and then iPr_2NEt (7.0 equiv) were added to this solution at room temperature. The reaction mixture was stirred at room temperature for at least 2.5 h. The reaction was quenched with 4.5% $NaHCO_3$ aqueous solution (6.0 vol). The organic layer is collected and the aqueous layer extracted one time with dichloromethane (2.0 vol). Methanol (0.8 vol) was added and the combined organic layers were washed twice with 20% NH_4Cl solution (4.0 vol) and twice with water (4.0 vol). The organic layer was dried (Na_2SO_4) and the dichloromethane solvent was exchanged for ethyl acetate (4 vol). Heptane was added slowly (4 vol). The crude product was collected by filtration and washed with ethyl acetate:heptane (1:1). The crude product was dried *in vacuo* at 55 °C. The crude product is purified in a hot slurry in ethyl acetate (5 vol) and collected by filtration. The product was washed with ethyl acetate and dried *in vacuo* at 55 °C to give 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**).

II. Compound 1 Spray-Dried Dispersions

Example 5: Compound 1 / Polymer Combinations Screen

[00136] A polymeric based spray dried dispersion for Compound **1** was developed. Several Compound **1** / polymer combinations were screened and evaluated using computational models. The evaluated polymers were PVP/VA 64, PVP 30, HPMCAS-L, HPMCAS-M, HPMCAS-H, Eudragit L100-55, Eudragit L100, Eudragit EPO, HPMC E15, HPMC E3, HPMC E5, HPMCP-HP55, and Soluplus. The Compound **1** / polymer combinations were evaluated for: 1) Miscibility

assessment – *In silico* simulations to assess phase separation propensity with different stabilizing carriers and drug loadings; 2) API / Polymer solubility confirmation – for each lead condition, a series of compatible solvent systems were tested; 3) Solvent casting – Solvent casting trials with different stabilizing carriers and drug loadings to further narrow the formulation variables; and 4) Supersaturation studies – Evaluation of the precipitation inhibition of different stabilizing carriers using a solvent-shift method. Based on the screening studies Compound **1** and PVP/VA 64 60% (w/w) and Compound **1** and HPMCAS-M 60% (w/w) were scaled up.

Example 6: Compound 1 / Polymer Combination Lab-Scale Prototype Manufacturing

[00137] Spray drying. A lab-scale spray drier (Buchi B-290 Spray Dryer), was used to dry the feed solution. The unit was equipped with a two fluid nozzle with a nozzle tip and cap 0.7 and 1.5 mm, respectively. The spray-drying unit was operated with nitrogen in open-loop configuration (i.e., without recirculation of the drying nitrogen) and the aspirator blowing at 100% capacity.

[00138] Secondary drying. A lab-scale vacuum tray dryer was used to reduce the residual solvents content of the wet spray dried dispersions. Secondary drying was carried out for 48 hours at 50 °C under vacuum and with nitrogen sweep.

[00139] Solution preparation. Solutions for prototype manufacturing of a spray dried dispersion using PVP/VA 64 and HPMCAS-M were prepared according to the following general procedure: the total amount of solvent was charged to an empty vessel; the total amount of polymer was slowly added under stirring; stirring was continued until the polymer was completely dissolved; the total amount of Compound **1** was slowly added under stirring; and stirring was continued until Compound **1** was completely dissolved. Representative solutions of Compound **1** and HPMCAS-M, and Compound **1** and PVP/VA 64 were prepared according to the quantities and ratios in **Table 1** below (where "C_feed" = solids content in the feed mixture [% w/w], and "C_Compound **1**" = Compound **1** content in the feed mixture [% w/w]):

Table 1. Solutions for prototype manufacture of spray dried dispersions

Quantities and Ratios		Compound **1**/(HPMCAS-M)	Compound **1**/(PVP/VA 64)
Compound **1**	g	19	24
HPMCAS M	g	12.66	-
PVP/VA 64	g	-	16
Methylene chloride	g	254.4	324
Methanol	g	28.5	36
Total solids	g	31.66	40.0
Total liquids	g	284.9	360
Compound **1** load	% w/w	60	60
C_feed	% w/w	10	10
C_Compound **1**	% w/w	6	6

Results

[00140] The main process data and analytical results are summarized in **Table 2** below (where "T_feed" = temperature of the feed solution [°C], "F_drying" = flow rate of drying gas in the spray drier [kg/h], "F_atom" = atomization gas flow rate [g/min], "T_out" = drying gas temperature at the outlet of the drying chamber [°C], "F_feed" = flow rate of feed solution to the spray dryer [kg/h], "GC" = gas chromatography, "KF" = Karl Fisher, "TFN" = two fluid nozzle, and "PSD" = particle size distribution):

Table 2. Main process data and analytical results from prototype manufacture of spray dried dispersions

Feed solution parameters			
Formulation		Compound **1**:HPMCAS-M	Compound **1**:PVP/VA 64
T_feed	°C	room temperature	room temperature
Spray drying parameters			
Nozzle (orifice / core)	mm	TFN (0.7 / 1.5)	TFN (0.7 / 1.5)
F_drying	kg/h	20	20
F_atom	kg/h	1.0	1.0
T_out	°C	40	40
F_feed	kg/h	1.0	1.0
Process throughput and yield			
Drying time	hh:mm	00:18	00:26
Yield (wet basis)	g	26.2	37.7
Yield (wet basis)	% w/w	82.6	94.2
Secondary drying conditions			
Vacuum	-	yes	yes
Temperature	°C	50	50
Drying time	h	72	72
Analytical results after secondary drying			
Methylene chloride by GC	ppm	<30	<30
Methanol by GC	ppm	86	<30
Water by KF	% w/w	1.74	2.65
Description		White to off white solid	White to off white solid
XRPD	-	Amorphous form	Amorphous form
PSD D_{v10}	µm	1.9	1.6
PSD D_{v50}	µm	5.3	4.1
PSD D_{v90}	µm	12.2	8.3

[00141] Both spray dried dispersions (Compound **1**:HPMCAS-M and Compound **1**: PVP/VA 64) were amorphous after secondary drying, as indicated by the absence of crystalline peaks (XRPD) and melting endotherms characteristic of crystalline material (DSC).

Example 7: Compound 1 Spray Dried Dispersions Stability Study

[00142] The two Compound **1** spray dried dispersions (Compound **1**:HPMCAS-M and Compound **1**: PVP/VA 64) were stored for 1 month in capped vials at 40°C/75% RH. No chemical degradation was observed for either spray dried dispersion. In addition, the amorphous state for each spray dried dispersion was maintained.

Example 8: Development of Compound 1 SDI Tablet Formulation

[00143] First, the compatibility of Compound **1** API (amorphous form) was evaluated in various excipients. These compatibility studies were conducted for one month at 40°C/75% RH in a closed container. At the conclusion of the study, no detectable changes in assay, related substances or appearance was detected. Compound **1** API was determined to be compatible with: Avicel (microcrystalline cellulose), Tablettose (lactose monohydrate), Pearlitol (mannitol), Compitrol (glyceryl behenate), Acdisol (croscarmellose sodium), Polyplasdone XL (crospovidone), Magnesium stearate, Cab-o-sil (colloidal silicone dioxide).

[00144] Next four Compound **1** formulation matrices were prepared using the spray-dried intermediates (SDIs) PVP/VA and HPMCAS, as outlined in **Table 3**. The tablet formulation blends and tablets were prepared and evaluated with regards to a tabletability profile, compressibility profile, disintegration time, friability and biorelevant dissolution. The only difference between the two formulations tested with each SDI was the disintegrant. Disintegrants are important ingredients in tablets that contain SDIs since SDI polymers can also function as binders. Disintegrants can be critical in overcoming the binder effect of the SDI polymer to promote drug release.

Table 3. Formulation Matrix for Compound 1 Tablet Formulations

Ingredient	Function	Formulation (% w/w)			
		A	B	C	D
Compound 1 API PVP/VA HPMCAS	Active Ingredient Stabilizing Polymer Stabilizing Polymer	5.0 3.3 -	5.0 3.3 -	5.0 - 3.3	5.0 - 3.3
Microcrystalline cellulose	Filler/Binder	44.7	44.7	44.7	44.7
Lactose Monohydrate	Filler/Compaction Aid	40.0	40.0	40.0	40.0
Croscarmellose Sodium (Acdisol)	Disintegrant	5.0	-----	5.0	-----
Crospovidone (Polyplasdone XL)	Disintegrant	-----	5.0	-----	5.0
Colloidal Silicon Dioxide	Glidant	1.0	1.0	1.0	1.0
Magnesium stearate, vegetable grade	Lubricant	1.0	1.0	1.0	1.0
	TOTAL	100.0%	100.0%	100.0%	100.0%

SDI: Spray dried intermediate; API: Active pharmaceutical ingredient

[00145] Tabletability and compressibility curves were obtained for each of the four formulations. All four formulations produced tablets of high tensile strength (such as a hardness ≥ 1.7 MPa) using typical compaction pressures such as 100-200 MPa. Biorelevant dissolution profiles for

the four tablet formulations showed that all formulations can be compressed into high quality tablets.

[00146] Two prototype 5 mg tablets were prepared from tablet formulations A and C. These tablets were used in a pharmacokinetic study in monkeys (n=12 per formulation). Compound **1** was well absorbed from both tablet formulations (**Fig. 1**).

Example 9: Compound 1 SDI Tablet Formulation – 5 mg and 25 mg tablets

[00147] The ingredients in Example 8, Formulation A, were increased 5-fold to produce 25 mg tablets.

Table 4. Formulation for Compound 1 Tablet Formulations, 5 mg and 25 mg

Ingredient	Function	Formulation (% w/w)	mg per tablet	
		5 mg & 25 mg	5-mg	25-mg
Compound 1 API PVP/VA	Active Ingredient Stabilizing Polymer	5.0 3.3	5.0 3.3	25.0 16.5
Microcrystalline cellulose	Filler/Binder	44.7	44.7	223.5
Lactose Monohydrate	Filler/Compaction Aid	40.0	40.0	200.0
Croscarmellose Sodium (Acdisol)	Disintegrant	5.0	5.0	25.0
Colloidal Silicon Dioxide	Glidant	1.0	1.0	5.0
Magnesium stearate, vegetable grade	Lubricant	1.0	1.0	5.0
	TOTAL	100.0%	100.0 mg	500.0 mg

API: Active pharmaceutical ingredient

Example 10: Compound 1 SDI Tablet Formulation – 1 mg tablet

[00148] Since the amount of Compound 1 SDI in the 1-mg blend is less than 2%, the blend was prepared by a three-stage geometric dilution to provide a uniform mixture. The process entailed the following steps:

1. Pre-blend #1: Sieve the batch required amount of Compound 1 SDI and double the amount of microcrystalline cellulose (MCC). The pre-blend #1 is mixed.

2. Pre-blend #2: MCC corresponding to double the weight of the Pre-blend #1 is added, then mixed.

3. Pre-blend #3: MCC corresponding to double the weight of the Pre-blend #2 is added to the blend, then mixed.

4. The remaining batch required amount of MCC, lactose monohydrate, croscarmellose sodium and colloidal silicon dioxide are added to the blend and mixed. This blend is evaluated for blend uniformity analysis (BUA).

5. Once BUA meets requirements, half the batch amount of magnesium stearate is sieved, added to the blend from step 4 and mixed.

6. The blend from step 5 is granulated via roller compaction. A sample is removed to measure bulk density (BD), Tapped Density (TD) and Particle Size Distribution (PSD). Then, the remaining half of the batch required magnesium stearate is added to the dry-granulated blend and mixed.

7. The blend from step 6 is compressed into tablets (round; 100 mg target weight).

8. The compressed tablets are coated in a pan coater.

9. The final coated tablets are sampled for quality testing, stability and the remaining bulk is bottled and capped.

Table 5. Formulation for Compound 1 Tablet Formulations, 1 mg

Ingredient	**Function**		
		Formulation (% w/w)	**mg per tablet**
		1-mg	**1-mg**
Compound 1 API PVP/VA	Active Ingredient Stabilizing Polymer	1.0 0.67	1.0 0.67
Microcrystalline cellulose	Filler/Binder	45.67	45.67
Lactose Monohydrate	Filler/Compaction Aid	45.66	45.66
Croscarmellose Sodium (Acdisol)	Disintegrant	5.0	5.0
Colloidal Silicon Dioxide	Glidant	1.0	1.0
Magnesium stearate, vegetable grade	Lubricant	1.0	1.0
	TOTAL	100.0%	100.0 mg

Example 11: Compound 1 SDI Tablet Formulation – 12 mg tablet

[00149] As tablet strength increased beyond 5 mg Compound 1 and 3.3 mg PVP/VA per 100 mg tablet, the increased amount of polymer inhibited drug release by acting as a binder. As a result, the amount of croscarmellose sodium was increased from 5% to 10% and the percentage of microcrystalline cellulose and lactose monohydrate were decreased, which gave an improved Compound 1 release profile (**Fig. 2**).

Table 6. Formulation for Compound 1 Tablet Formulations, 12 mg

Ingredient	Function	Formulation (% w/w)	
		12-mg	12-mg
Compound 1 API PVP/VA	Active Ingredient Stabilizing Polymer	12.0 8.0	12.0 8.0
Microcrystalline cellulose	Filler/Binder	34.0	31.5
Lactose Monohydrate	Filler/Compaction Aid	34.0	31.5
Croscarmellose Sodium (Acdisol)	Disintegrant	10.0	10.0
Sodium chloride	Salt	-----	5.0
Colloidal Silicon Dioxide	Glidant	1.0	1.0
5.Magnesium stearate, vegetable grade	Lubricant	1.0	1.0
	TOTAL	100.0%	100.0%

III. Compound 1 FXR Activity

Example 12: *In Vitro* FXR Assay (TK)

Seeding

[00150] CV-1 cells were seeded at a density of 2,000,000 cells in a T175 flask with DMEM + 10% charcoal double-stripped FBS and incubated at 37 °C in 5% CO_2 for 18 h (O/N).

Transfection

[00151] After 18 h of incubation, the medium in the T175 flask was changed with fresh DMEM + 10% charcoal super-stripped serum. In a polypropylene tube, 2500 µL OptiMEM (Life Technologies, Cat # 31985-062) was combined with expression plasmids for hFXR, hRXR, TK-ECRE-luc and pCMX-YFP. The tube was then briefly vortexed and incubated at room temperature for 5 minutes. Transfection reagent (X-tremeGENE HP from Roche, Cat # 06 366 236 001) was added to the OptiMEM/plasmid mixture vortexed and incubated at room temperature for 20 minutes. Following incubation, the transfection reagent/DNA mixture

complex was added to cells in the T175 flask and the cells were incubated at 37 °C in 5% CO_2 for 18 h (O/N).

Addition of Compound 1

[00152] Compound **1** was serially diluted in DMSO and added to transfected CV-1 cells. The cells were then incubated for 18 hrs. The next day cells were lysed and examined for luminescence. Compound 1 TK hFXR: $EC_{50} \leq 0.01$ μM.

CLAIMS

We Claim:

1. A spray-dried solid dispersion, comprising: (a) 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, and (b) a pharmaceutically acceptable polymer; wherein 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 is dispersed in a polymer matrix formed from the pharmaceutically acceptable polymer.
2. The spray-dried solid dispersion of claim 1, wherein the pharmaceutically acceptable polymer is selected from PVP/VA 64, PVP 30, HPMCAS-L, HPMCAS-M, HPMCAS-H, Eudragit L100-55, Eudragit L100, Eudragit EPO, HPMC E15, HPMC E3, HPMC E5, HPMCP-HP55, and Soluplus.
3. The spray-dried solid dispersion of claim 1 or claim 2, wherein the pharmaceutically acceptable polymer is selected from PVP/VA 64 and HPMCAS-M.
4. The spray-dried solid dispersion of any one of claims 1-3, wherein the pharmaceutically acceptable polymer is PVP/VA 64.
5. The spray-dried solid dispersion of any one of claims 1-3, wherein the pharmaceutically acceptable polymer is HPMCAS-M.
6. The spray-dried solid dispersion of any one of claims 1-5, wherein the weight ratio of 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 to the pharmaceutically acceptable polymer is from 9:1 to 1:9.
7. The spray-dried solid dispersion of any one of claims 1-6, wherein the weight ratio of 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 to the pharmaceutically acceptable polymer is from 3:1 to 1:3.
8. The spray-dried solid dispersion of any one of claims 1-7, wherein the weight ratio of 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 to the pharmaceutically acceptable polymer is about 2:1.
9. The spray-dried solid dispersion of any one of claims 1-7, wherein the weight ratio of 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 to the pharmaceutically acceptable polymer is about 1.5:1.

10. The spray-dried solid dispersion of any one of claims 1-7, wherein the weight ratio of 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 to the pharmaceutically acceptable polymer is about 1:1.
11. The spray-dried solid dispersion of any one of claims 1-10, further comprising a non-aqueous solvent.
12. The spray-dried solid dispersion of claim 11, wherein the non-aqueous solvent is selected from the group consisting of tert-butanol, n-propanol, n-butanol, isopropanol, ethanol, methanol, acetone, ethyl acetate, dimethyl carbonate, acetonitrile, dichloromethane, methyl ethyl ketone, methyl isobutyl ketone, 1-pentanol, methyl acetate, carbon tetrachloride, dimethyl sulfoxide, hexafluoroacetone, chlorobutanol, dimethyl sulfone, acetic acid, cyclohexane, and mixtures thereof.
13. The spray-dried solid dispersion of claim 11 or claim 12, wherein the non-aqueous solvent is selected from the group consisting of ethanol, methanol, propanol, butanol, isopropanol, tert-butanol, dichloromethane, and mixtures thereof.
14. The spray-dried solid dispersion of any one of claims 11-13, wherein the non-aqueous solvent is a mixture of dichloromethane and methanol.
15. The spray-dried solid dispersion of any one of claims 1-14, wherein 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 is substantially amorphous.
16. The spray-dried solid dispersion of any one of claims 1-14, wherein 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 is crystalline.
17. A pharmaceutical formulation comprising a spray-dried solid dispersion of any one of claims 1-16 and optionally one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more binders, one or more lubricants, one or more glidants, and one or more surfactants.
18. The pharmaceutical formulation of claim 17, wherein the one or more pharmaceutical acceptable ingredients are selected from the group consisting of microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, mannitol, crospovidone, and sodium stearyl fumarate.
19. The pharmaceutical formulation of claim 18, wherein the one or more pharmaceutical acceptable ingredients are selected from the group consisting of microcrystalline cellulose,

lactose monohydrate, croscarmellose sodium, magnesium stearate, and colloidal silicon dioxide.

20. The pharmaceutical formulation of any one of claims 17-19, wherein the pharmaceutical formulation is in tablet form.
21. The pharmaceutical formulation of claim 20, wherein the tablet comprises about 1% by weight to about 30% by weight of the spray-dried solid dispersion.
22. The pharmaceutical formulation of claim 20 or claim 21, wherein the tablet comprises about 5% by weight to about 25% by weight of the spray-dried solid dispersion.
23. The pharmaceutical formulation of any one of claims 20-22, wherein the tablet comprises about 1% by weight to about 20% by weight of 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.
24. The pharmaceutical formulation of any one of claims 20-22, wherein the tablet comprises about 1 mg, about 5 mg, about 12 mg, or about 25 mg of 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.
25. The pharmaceutical formulation of any one of claims 17-19, wherein the pharmaceutical formulation is in capsule form.
26. A method of treating or preventing a liver disease or condition in a mammal, comprising administering to the mammal a spray-dried solid dispersion of any one of claims 1-16 or a pharmaceutical formulation of any one of claims 17-25.
27. The method of claim 26, wherein the liver disease or condition is an alcoholic or non-alcoholic liver disease or condition.
28. The method of claim 26, wherein the liver disease or condition is primary biliary cirrhosis, primary sclerosing cholangitis, cholestasis, nonalcoholic steatohepatitis (NASH), or nonalcoholic fatty liver disease (NAFLD).
29. The method of claim 27, wherein the alcoholic liver disease or condition is fatty liver (steatosis), cirrhosis, or alcoholic hepatitis.
30. The method of claim 27, wherein the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH), or nonalcoholic fatty liver disease (NAFLD).
31. The method of claim 27, wherein the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH).
32. The method of claim 27, wherein the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH) and is accompanied by liver fibrosis.

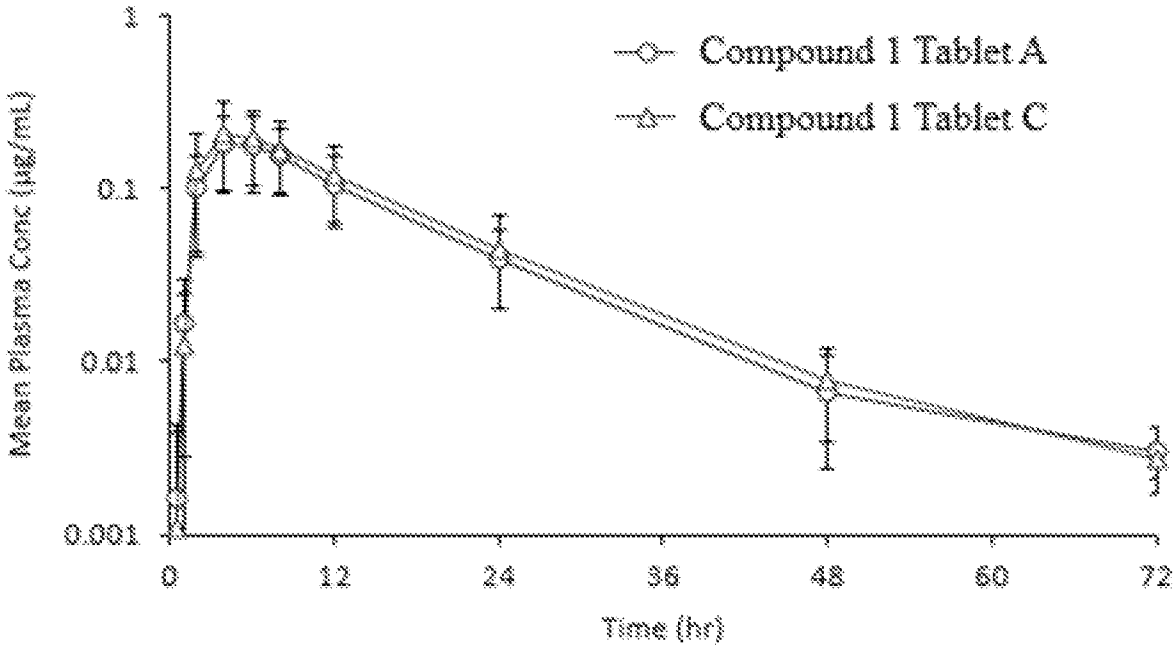
33. The method of claim 27, wherein the non-alcoholic liver disease or condition is nonalcoholic steatohepatitis (NASH) without liver fibrosis.
34. The method of claim 27, wherein the non-alcoholic liver disease or condition is intrahepatic cholestasis or extrahepatic cholestasis.
35. The method of claim 26, wherein the liver disease or condition is steatohepatitis, cholangitis, fatty liver disease, cholestasis, cirrhosis, fibrotic liver disease, liver inflammation, primary biliary cholangitis, biliary atresia, Alagille syndrome, IFALD (intestinal failure associated liver disease), parental nutrition associated liver disease (PNALD), hepatitis, hepatocellular carcinoma, cholangiocarcinoma, or combinations thereof.
36. A method of treating or preventing a liver fibrosis in a mammal, comprising administering to the mammal a spray-dried solid dispersion of any one of claims 1-16 or a pharmaceutical formulation of any one of claims 17-25.
37. The method of claim 36, wherein 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), primary biliary cirrhosis (PBC), or biliary cirrhosis.
38. The method of claim 36, wherein the mammal is diagnosed with nonalcoholic steatohepatitis (NASH).
39. A method of treating or preventing a liver inflammation in a mammal, comprising administering to the mammal a spray-dried solid dispersion of any one of claims 1-16 or a pharmaceutical formulation of any one of claims 17-25.
40. The method of claim 39, wherein 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), primary biliary cirrhosis (PBC), or biliary cirrhosis.
41. The method of claim 39, wherein the mammal is diagnosed with nonalcoholic steatohepatitis (NASH).
42. The method of claim 39, wherein the liver inflammation is associated with inflammation in the gastrointestinal tract.
43. The method of claim 39, wherein the mammal is diagnosed with inflammatory bowel disease.

44. A method of treating or preventing a gastrointestinal disease or condition in a mammal, comprising administering to the mammal a spray-dried solid dispersion of any one of claims 1-16 or a pharmaceutical formulation of any one of claims 17-25.
45. The method of claim 44, wherein 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.
46. The method of claim 44, wherein the gastrointestinal disease or condition 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).
47. A method of treating or preventing a renal disease or condition in a mammal, comprising administering to the mammal a spray-dried solid dispersion of any one of claims 1-16 or a pharmaceutical formulation of any one of claims 17-25.
48. The method of claim 47, 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.
49. A method of treating or preventing a metabolic inflammation-mediated disease or disorder in a mammal, comprising administering to the mammal a spray-dried solid dispersion of any one of claims 1-16 or a pharmaceutical formulation of any one of claims 17-25.
50. The method of claim 49, wherein the metabolic inflammation-mediated disease or disorder is diabetes mellitus.
51. A method of treating or preventing a lipid disease or disorder in a mammal, comprising administering to the mammal a spray-dried solid dispersion of any one of claims 1-16 or a pharmaceutical formulation of any one of claims 17-25.
52. The method of claim 51, wherein the lipid disease or disorder in a mammal is dyslipidemia.
53. A method of treating or preventing cancer in a mammal, comprising administering to the mammal a spray-dried solid dispersion of any one of claims 1-16 or a pharmaceutical formulation of any one of claims 17-25.
54. The method of claim 53, wherein the cancer is prostate cancer, colorectal cancer, or hepatocellular carcinoma.
55. 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 spray-

dried solid dispersion of any one of claims 1-16 or a pharmaceutical formulation of any one of claims 17-25.

56. The method of any one of claims 26-55, further comprising administering at least one additional therapeutic agent in addition to a spray-dried solid dispersion of any one of claims 1-16.

Fig. 1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Compound 1 Tablet C
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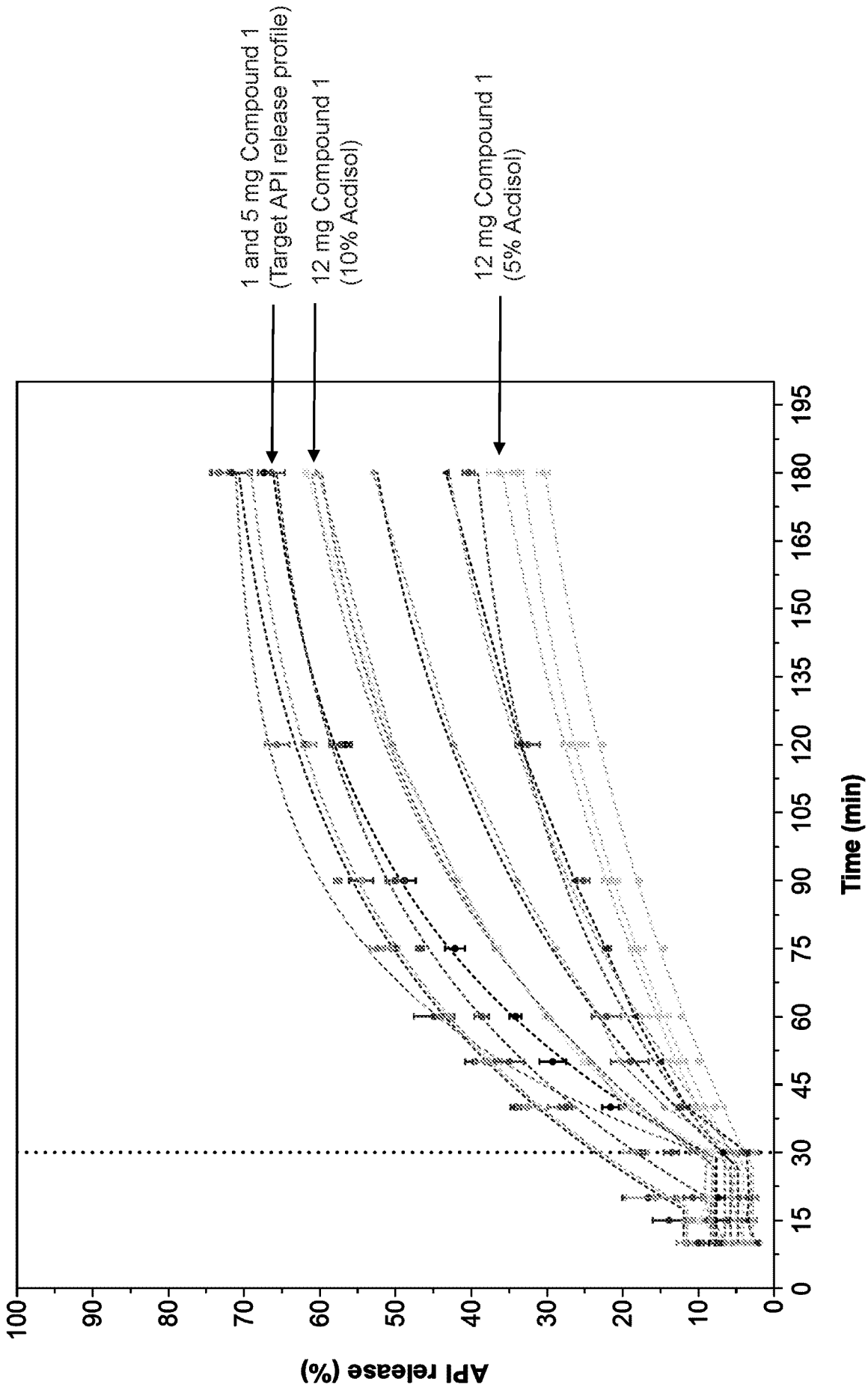
0.01
0.001
0
12
24
36
48
60
72
Time (hr)

Fig. 2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(Target API release profile)
12 mg Compound 1
(10% Acdisol)
12 mg Compound 1
(5% Acdisol)
API release (%)
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20
30
40
50
60
70
80
90
100
0
15
30
45
60
75
90
105
120
135
150
165
180
195