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(11)(21) **3 140 972**

(12) **BREVET CANADIEN**
CANADIAN PATENT

(13) **C**

(86) **Date de dépôt PCT/PCT Filing Date:** 2020/05/15
(87) **Date publication PCT/PCT Publication Date:** 2020/11/26
(45) **Date de délivrance/Issue Date:** 2024/06/18
(85) **Entrée phase nationale/National Entry:** 2021/11/17
(86) **N° demande PCT/PCT Application No.:** IB 2020/054637
(87) **N° publication PCT/PCT Publication No.:** 2020/234726
(30) **Priorité/Priority:** 2019/05/20 (US62/850,133)

(51) **Cl.Int./Int.Cl.** ***A61K 31/454*** (2006.01), ***A61K 31/444*** (2006.01), ***A61K 31/4545*** (2006.01), ***A61K 31/46*** (2006.01), ***A61K 31/506*** (2006.01), ***A61K 45/06*** (2006.01), ***A61P 1/16*** (2006.01), ***A61P 3/04*** (2006.01), ***A61P 3/10*** (2006.01)

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(54) **Titre : COMBINAISONS COMPRENANT DU BENZODIOXOL EN TANT QU'AGONISTES DE GLP-1R DESTINEES A ETRE UTILISEES DANS LE TRAITEMENT DE LA NASH/NAFLD ET DE MALADIES ASSOCIEES**

(54) **Title: COMBINATIONS COMPRISING BENZODIOXOL AS GLP-1R AGONISTS FOR USE IN THE TREATMENT OF NASH/NAFLD AND RELATED DISEASES**

(57) **Abrégé/Abstract:**

In part, the invention provides a new combination comprising (1) a GLP-1R agonist and (2) an ACC inhibitor or a DGAT2 inhibitor, or a KHK inhibitor or FXR agonist. The invention further provides new methods for treating diseases and disorders, for example, fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, obesity, and type 2 diabetes, for example, using the new combination described herein.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 November 2020 (26.11.2020)

(10) International Publication Number
WO 2020/234726 A1

(51) International Patent Classification:
A61K 31/454 (2006.01) *A61P 3/04* (2006.01)
A61K 31/4545 (2006.01) *A61P 3/10* (2006.01)
A61K 31/46 (2006.01) *A61K 31/444* (2006.01)
A61K 31/506 (2006.01) *A61K 45/06* (2006.01)
A61P 1/16 (2006.01)

(21) International Application Number: PCT/IB2020/054637

(22) International Filing Date: 15 May 2020 (15.05.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/850,133 20 May 2019 (20.05.2019) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- — *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- — *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

- — *with international search report (Art. 21(3))*
- — *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

WO 2020/234726 A1

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

COMBINATIONS COMPRISING BENZODIOXOL AS GLP-1R AGONISTS FOR USE IN THE TREATMENT OF NASH/NAFLD AND RELATED DISEASES

The invention relates to combinations and methods for treating fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease. In part, the invention provides a new combination comprising a GLP-1R agonist and in the same or a separate composition comprising an ACC inhibitor. The invention also provides a new pharmaceutical composition comprising a GLP-1R agonist and in the same or a separate composition comprising a DGAT2 inhibitor. The invention also provides a new combination comprising a GLP-1R agonist and in the same or a separate composition comprising a KHK inhibitor. The invention also provides a new combination comprising a GLP-1R agonist and in the same or a separate composition comprising a FXR agonist. The invention further provides new methods for treating fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, for example, using the new combination described herein.

BACKGROUND OF THE INVENTION

Nonalcoholic steatohepatitis (NASH) is a clinical and histological subset of non-alcoholic fatty liver disease (NAFLD, defined as presence of >5% hepatic steatosis) that is associated with increased all cause mortality, cirrhosis and end stage liver disease, increased cardiovascular mortality, and increased incidence of both liver related and non liver related cancers (Sanyal et al, *Hepatology* 2015;61(4):1392-1405). NAFLD is the most common cause of chronic liver disease in the Western world. It is the hepatic manifestation of metabolic syndrome, and is a spectrum of hepatic conditions encompassing steatosis, NASH, fibrosis, cirrhosis, end stage liver disease, and ultimately hepatocellular carcinoma. NAFLD and NASH are considered the primary fatty liver diseases as they account for the greatest proportion of individuals with elevated hepatic lipids. The severity of NAFLD/NASH is based on the presence of lipid, inflammatory cell infiltrate, hepatocyte ballooning, and the degree of fibrosis. Although not all individuals with steatosis progress to NASH, a substantial portion do. At the present time, treatment options are limited to lifestyle modification including exercise and diet (EASL-EASD-EASO Clinical Practice Guidelines, *J. Hepatol.* 2016;64(6):1388-1402).

Alterations in lipid metabolism have been hypothesized to contribute to the molecular pathogenesis of NAFLD and NASH. Steatosis is a necessary but not sufficient component of the pathogenesis of NASH (Day C, and James O., Hepatology. 1998; 27(6):1463-6). Consistent with this, multiple studies have demonstrated that the severity of steatosis predicts the risk of concomitant steatohepatitis as well as the risk of progression to cirrhosis (Sorensen et al, *Lancet*. 1984; 2(8397): 241-4; Wanless I and Lentz J, *Hepatology* 1990;12(5):1106-10; Reeves H, et al, *J. Hepatol.* 1996; 25(5): 677-83). Hepatic steatosis is a consequence of an imbalance in TG production/uptake into the liver and clearance/removal (Cohen JC, et al, *Science*. 2011; 332(6037):1519-1523). It is hypothesized that reducing steatosis, the metabolic driver underpinning the development of NAFLD/NASH, will result in subsequent improvements in hepatic inflammation and fibrosis.

Savage, et al., demonstrated that ACC1 and ACC2 are both involved in regulating fat oxidation in hepatocytes while ACC1, the dominant isoform in rat liver, is the sole regulator of fatty acid synthesis. Furthermore, in their model, combined reduction of both isoforms is required to significantly lower hepatic malonyl-CoA levels, increase fat oxidation in the fed state, reduce lipid accumulation, and improve insulin action *in vivo*. Thus, hepatic ACC1 and ACC2 inhibitors may be useful in the treatment of NAFLD and hepatic insulin resistance. See, Savage, D. B., et al., "Reversal of diet-induced hepatic steatosis and hepatic insulin resistance by antisense oligonucleotide inhibitors of acetyl-CoA carboxylases 1 and 2" *J. Clin. Invest.* 2006;116(3):817-24. See also, Oh, W., et al., "Glucose and fat metabolism in adipose tissue of acetyl-CoA carboxylase 2 knockout mice" *PNAS*, 102(5) 1384-1389 (2005).

Acetyl-CoA Carboxylase (ACC) play a key role in regulating lipid metabolism. ACC catalyzes an essential and rate limiting step in the process of de novo lipogenesis (DNL) (Saggerson D, *Annu. Rev. Nutr.* 2008; 28:253-72.). Further, ACC also regulates mitochondrial beta-oxidation of fatty acids through allosteric regulation of the enzyme carnitine palmitoyltransferase 1 (CPT1) (Saggerson, 2008; Waite M, and Wakil SJ. *J. Biol. Chem.* 1962;237:2750-2757.). Emerging data also suggest that suppression of DNL through ACC inhibition may directly reduce inflammation by restraining the formation of the inflammatory interleukin-17 (IL-17) secreting T-cells of the T helper 17 lineage (Th17 cells) and favoring the development of anti-inflammatory FoxP3(+) regulatory T (Treg) cells (Berod L, et al. *Nat. Med.* 2014; 20(11): 1327-33). Recently, ACC inhibtion has also been shown to suppress primary human hepatic stellate cell activation in-vitro and reduce hepatic fibrosis in rat models (Ross et al, Abstract PS-132 Journal of Hepatology 2019 vol. 70 page e86).

Inhibition of ACC activity is hypothesized to be beneficial to patients with NASH by at least three independent mechanisms. As summarized above, humans with NAFLD show marked elevations in hepatic DNL and normalization of this increased flux through pharmacologic hepatic ACC inhibition is hypothesized to reduce steatosis. Consistent with this, ACC inhibitors have been shown to inhibit DNL. In addition, the effect of ACC inhibtions to increase fatty acid oxidation may also contribute to reduce liver fat content. . See Griffith DA, et al. *J. Med. Chem.* 2014;57(24):10512-10526; Kim CW, et al. *Cell Metab.* 2017;26, 394-406; Stiede K,, et al. *Hepatology.* 2017;66(2):324-334; Lawitz EJ, et al. *Clin Gastroenterol Hepatol.*

2018 (https://doi.org/10.1016/j.cgh.2018.04.042). In addition, inhibition of DNL in IL-17 secreting T-cells is expected to suppress hepatic inflammation by restraining the formation of the inflammatory Th17 cells (Berod et al., 2014), a pathway that may be important in NASH pathogenesis (Rau M, et al. *J. Immunol.* 2016;196(1):97-105), and favoring the development of anti-inflammatory Treg cells. Further, ACC inhibition may reduce stellate cell activation and fibrosis (Ross et al., 2019)

4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid is a selective ACC inhibitor and was prepared as the free acid in Example 9 of U.S. Patent No. 8,859,577, which is the U.S. national phase of International Application No. PCT/IB2011/054119. Crystal forms of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid, including an anhydrous mono-tris form (Form 1) and a trihydrate of the mono-tris salt (Form 2), are described in International PCT Application No. PCT/IB2018/058966.

Triglycerides or triacylglycerols (TG) represent a major form of energy storage in mammals. TG's are formed by the sequential esterification of glycerol with three fatty acids of varying chain lengths and degrees of saturation (Coleman, R. A., and Mashek, D. G. 2011. *Chem. Rev.* 111: 6359-6386). TG synthesized in the intestine or liver are packaged into chylomicrons or very low-density lipoprotein (VLDL), respectively, and exported to peripheral tissues where they are hydrolysed to their constituent fatty acids and glycerol by lipoprotein lipase (LPL). The resultant non-esterified fatty acids (NEFA) can either be metabolised further to produce energy or reesterified and stored.

Under normal physiological conditions, the energy-dense TG remains sequestered in various adipose depots until there is a demand for its release, whereupon, it is hydrolyzed to glycerol and free fatty acids which are then released into the blood stream. This process is tightly regulated by the opposing actions of insulin and hormones such as catecholamines which promote the deposition and mobilization of TG stores under various physiological conditions. In the post-prandial setting, insulin acts to inhibit lipolysis, thereby, restraining the release of energy in the form of NEFA and ensuring the appropriate storage of dietary lipids in adipose depots. However, in patients with type 2 diabetes, the ability of insulin to suppress lipolysis is impaired and NEFA flux from adipocytes is inappropriately elevated. This, in turn, results in increased delivery of lipid to tissues such as muscle and liver. In the absence of energetic demand the TG and other lipid metabolites, such as diacylglycerol (DAG) can accumulate and cause a loss of insulin sensitivity (Erion, D. M., and Shulman, G. I. 2010. Nat Med 16: 400-402). Insulin resistance in muscle is characterized by reduced glucose uptake and glycogen storage, whilst in the liver, loss of insulin signaling gives rise to dysregulated glucose output and over-production of TG-rich VLDL, a hallmark of type 2 diabetes (Choi, S. H., and Ginsberg, H. N. 2011. *Trends Endocrinol. Metab.* 22: 353-363). Elevated secretion of TG-enriched VLDL, so called VLDL1 particles, is thought to stimulate the production of small, dense low-density lipoprotein (sdLDL), a proatherogenic subfraction of LDL that is associated with elevated risk of coronary heart disease (St-Pierre, A. C.et.al. 2005. *Arterioscler. Thromb. Vasc. Biol.* 25: 553-559).

In mammals, two diacylglycerol acyltransferases (DGAT) enzymes (DGAT1 and DGAT2) have been characterized. Although these enzymes catalyze the same enzymatic reaction, their respective amino acid sequences are unrelated and they occupy distinct gene families. Mice harboring a disruption in the gene encoding DGAT1 are resistant to diet-induced obesity and have elevated energy expenditure and activity (Smith, S. J. et. al., 2000. *Nat Genet* 25: 87-90). Dgat1-/- mice exhibit dysregulated postaborpative release of chylomicrons and accumulate lipid in the enterocytes (Buhman, K. K. et.al. 2002. *J. Biol. Chem.* 277: 25474-25479). The metabolically favorable phenotype observed in these mice is suggested to be driven by loss of DGAT1 expression in the intestine (Lee, B., et.al. 2010. *J. Lipid Res.* 51: 1770-1780). Importantly, despite a defect in lactation in female Dgat1-/- mice, these animals retain the capacity to synthesize TG suggesting the existence of additional DGAT enzymes. This observation and the isolation of a second DGAT from the fungus *Mortierella rammaniana* led to the identification and characterization of DGAT2 (Yen, C. L. et.al. 2008. J. Lipid Res. 49: 2283-2301).

DGAT2 is highly expressed in liver and adipose, and unlike DGAT1, exhibits exquisite substrate specificity for DAG (Yen, C.L., 2008). Deletion of the DGAT2 gene in rodents results in defective intraunterine growth, severe lipemia, impaired skin barrier function, and early post-natal death (Stone, S. J. et.al. 2004. *J. Biol. Chem.* 279: 11767-11776). Due to the lethality caused by loss of DGAT2, much of our understanding of the physiological role of DGAT2 derives from studies performed with antisense oligonucleotides (ASO) in rodent models of metabolic disease. In this setting, inhibition of hepatic DGAT2 resulted in improvements in plasma lipoprotein profile (decrease in total cholesterol and TG) and a reduction of hepatic lipid burden which was accompanied by improved insulin sensitivity and whole-body glucose control (Liu, Y. et.al. 2008. *Biochim. Biophys. Acta* 1781: 97-104; Choi, C. S. et.al. 2007. *J. Biol. Chem.* 282: 22678-22688; Yu, X. X. et.al. 2005. *Hepatology* 42: 362-371). Although the molecular mechanisms underlying these observations are not fully elucidated, it is clear that suppression of DGAT2 results in a down-regulation of the expression of multiple genes encoding proteins involved in lipogensis, including sterol regulatory element-binding proteins 1c (SREBP1c) and stearoyl CoA-desaturase 1 (SCD1) (Choi, 2007; Yu, 2005). In parallel, oxidative pathways are induced as evidenced by increased expression of genes such as carnitine palmitoyl transfersase 1 (CPT1) (Choi, 2007). The net result of these changes is to decrease the levels of hepatic DAG and TG lipid which, in turn, leads to improved insulin responsiveness in the liver. Furthermore, DGAT2 inhibition suppresses hepatic VLDL TG secretion and reduction in circulating cholesterol levels. Finally, plasma apolipoprotein B (APOB) levels were suppressed, possibly due to decreased supply of TG for lipidation of the newly synthesized APOB protein (Liu, 2008; Yu, 2005). The beneficial effects of DGAT2 inhibition on both glycemic control and plasma cholesterol profile suggest that this target might be valuable in the treatment of metabolic disease (Choi, 2007). In addition, the observation that suppression of DGAT2 activity results in reduced hepatic lipid accumulation suggests that inhibitors of this enzyme might have utility in the treatment of NASH.

(S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide [including its crystalline solid forms (Form 1 and Form 2)] is a DGAT2 inhibitor described in Example 1 of U.S. Patent No. 10,071,992.

Ketohexokinase (KHK) is the principal enzyme in fructose metabolism and catalyzes the conversion of fructose to fructose-1-phosphate (F1P). KHK is expressed as two alternative mRNA splice variants, denoted KHKa and KHKc, resulting from alternative splicing of the third exon. The affinity and capacity of KHKc for fructose phosphorylation is much greater than KHKa as evidenced by a much lower Km (Ishimoto, Lanaspa et al., *PNAS* 109, 4320-4325, 2012). While KHKa is ubiquitously expressed, the expression of KHKc is highest in the liver, kidney and intestines, the primary sites of fructose metabolism in the body (Diggle CP, et al. (2009) *J Histochem Cytochem* 57:763–774; Ishimoto, Lanaspa, et al., *PNAS* 109, 4320-4325, 2012). Additionally, loss of function mutations have been reported in humans and termed Essential Fructosuria (OMIM #229800), with no adverse effects except the appearance of fructose in the urine after ingestion of the sugar.

A more severe condition involved in fructose metabolism is Hereditary Fructose Intolerance (HFI, OMIM #229600) which is caused by defects in aldolase B (GENE: ALDOB) which is the enzyme responsible for breaking down F1P and is immediately downstream of the KHK step in the pathway (Bouteldja N, et. al, *J. Inherit. Metab. Dis.* 2010 Apr;33(2):105-12; Tolan, DR, *Hum Mutat.* 1995;6(3):210-8; http://www.omim.org/entry/229600). It is a rare disorder which affects an estimated 1 in 20,000 people, and mutations result in accumulation of F1P, depletion of ATP, and increase in uric acid, the combination of which causes hypoglycemia, hyperuricemia, and lactic acidosis, among other metabolic derangements. HFI impairs the body's ability to metabolize dietary fructose resulting in acute symptoms such as vomiting, severe hypoglycemia, diarrhea, and abdominal distress, leading to long term growth defects, liver and kidney damage and potentially death (Ali M et al, *J. Med. Genet.* 1998 May:35(5):353-65). Patients generally suffer through the first years of life prior to diagnosis, and the only course of treatment is avoiding fructose in the diet. This is made challenging by the presence of this macronutrient in a majority of food items. In addition to physical symptoms, many patients experience emotional and social isolation as a consequence of their unusual diet, and constantly struggle to adhere to strict dietary limitations. Even when they appear non-symptomatic, some patients develop NAFLD and kidney disease, which underscores the inadequacy of self-imposed dietary restriction as the only treatment option, and the high unmet medical need for this condition.

In hyperglycemic conditions, endogenous fructose production occurs through the polyol pathway, a pathway by which glucose is converted to fructose with sorbitol as an intermediate. The activity of this pathway increases with hyperglycemia. In these studies, the authors demonstrated that the KHK null mice were protected from glucose induced weight gain, insulin resistance and hepatic steatosis suggesting that under hyperglycemic conditions, endogenously produced fructose may contribute to insulin resistance and hepatic steatosis (Lanaspa, M.A., et al., *Nature Comm.* 4, 2434, 2013). Therefore, the inhibition of KHK is anticipated to benefit many diseases where alterations of either or both of endogenous or ingested fructose are involved.

[(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid (including a crystalline free acid form thereof) is a ketohexokinase inhibitor and is described in Example 4 of U.S. Patent No. 9,809,579.

Currently, various pharmacological approaches are available for treating hyperglycemia and subsequently, Type 2 diabetes mellitus, also known as,T2DM (Hampp, C. et al. *Use of Antidiabetic Drugs in the U.S.*, 2003-2012, *Diabetes Care* 2014, 37, 1367-1374). These may be grouped into six major classes, each acting through a different primary mechanism: (A) Insulin secretogogues, including sulphonyl-ureas (e.g., glipizide, glimepiride, glyburide), meglitinides (e.g., nateglidine, repaglinide), dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin, vildagliptin, alogliptin, dutogliptin, linagliptin, saxogliptin), and glucagon-like peptide-1 receptor (GLP-1R) agonists (e.g., liraglutide, albiglutide, exenatide, lixisenatide, dulaglutide, semaglutide), which enhance secretion of insulin by acting on the pancreatic beta-cells. Sulphonyl-ureas and meglitinides have limited efficacy and tolerability, cause weight gain and often induce hypoglycemia. DPP-IV inhibitors have limited efficacy. Marketed GLP-1R agonists are peptides administered by subcutaneous injection. Liraglutide is additionally approved for the treatment of obesity. (B) Biguanides (e.g., metformin) are thought to act primarily by decreasing hepatic glucose production. Biguanides often cause gastrointestinal disturbances and lactic acidosis, further limiting their use. (C) Inhibitors of alpha-glucosidase (e.g., acarbose) decrease intestinal glucose absorption. These agents often cause gastrointestinal disturbances. (D) Thiazolidinediones (e.g., pioglitazone, rosiglitazone) act on a specific receptor (peroxisome proliferator-activated receptor-gamma) in the liver, muscle and fat tissues. They regulate lipid metabolism subsequently enhancing the response of these tissues to the actions of insulin. Frequent use of these drugs may lead to weight gain and may induce edema and anemia. (E) Insulin is used in more severe cases, either alone or in combination with the above agents, and frequent use may also lead to weight gain and carries a risk of hypoglycemia. (F) sodium-glucose linked transporter cotransporter 2 (SGLT2) inhibitors (e.g., dapagliflozin, empagliflozin, canagliflozin, ertugliflozin) inhibit reabsorption of glucose in the kidneys and thereby lower glucose levels in the blood. This emerging class of drugs may be associated with ketoacidosis and urinary tract infections.

However, with the exception of GLP-1R agonists and SGLT2 inhibitors, the drugs for T2DM have limited efficacy and do not address the most important problems, the declining β-cell function and the associated obesity.

Obesity is a chronic disease that is highly prevalent in modern society and is associated with numerous medical problems including hypertension, hypercholesterolemia, and coronary heart disease. It is further highly correlated with T2DM and insulin resistance, the latter of which is generally accompanied by hyperinsulinemia or hyperglycemia, or both. In addition, T2DM is associated with a two to fourfold increased risk of coronary artery disease. Presently, the only treatment that eliminates obesity with high efficacy is bariatric surgery, but this treatment is costly and risky. Pharmacological intervention is generally less efficacious and associated with side effects. There is therefore an obvious need for more efficacious pharmacological intervention with fewer side effects and convenient administration.

Although T2DM is most commonly associated with hyperglycemia and insulin resistance, other diseases associated with T2DM include hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, obesity, dyslipidemia, hypertension, hyperinsulinemia and nonalcoholic fatty liver disease (NAFLD).

NAFLD is the hepatic manifestation of metabolic syndrome, and is a spectrum of hepatic conditions encompassing steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and ultimately hepatocellular carcinoma. NAFLD and NASH are considered the primary fatty liver diseases as they account for the greatest proportion of individuals with elevated hepatic lipids. The severity of NAFLD/NASH is based on the presence of lipid, inflammatory cell infiltrate, hepatocyte ballooning, and the degree of fibrosis. Although not all individuals with steatosis progress to NASH, a substantial portion does.

GLP-1 is a 30 amino acid long incretin hormone secreted by the L-cells in the intestine in response to ingestion of food. GLP-1 has been shown to stimulate insulin secretion in a physiological and glucose-dependent manner, decrease glucagon secretion, inhibit gastric emptying, decrease appetite, and stimulate proliferation of beta-cells. In non-clinical experiments GLP-1 promotes continued beta-cell competence by stimulating transcription of genes important for glucose-dependent insulin secretion and by promoting beta-cell neogenesis (Meier, et al. *Biodrugs.* 2003; 17 (2): 93-102).

In a healthy individual, GLP-1 plays an important role regulating post-prandial blood glucose levels by stimulating glucose-dependent insulin secretion by the pancreas resulting in increased glucose absorption in the periphery. GLP-1 also suppresses glucagon secretion, leading to reduced hepatic glucose output. In addition, GLP-1 delays gastric emptying and slows small bowel motility delaying food absorption. In people with T2DM, the normal post-prandial rise in GLP-1 is absent or reduced (Vilsboll T, et al. *Diabetes.* 2001. 50; 609-613).

Holst (*Physiol. Rev.* 2007, 87, 1409) and Meier (*Nat. Rev. Endocrinol.* 2012, 8, 728) describe that GLP-1 receptor agonists, such as GLP-1, liraglutide and exendin-4, have 3 major pharmacological activities to improve glycemic control in patients such as those with T2DM by reducing fasting and postprandial glucose (FPG and PPG): (i) increased glucose-dependent insulin secretion (improved first- and second-phase), (ii) glucagon suppressing activity under hyperglycemic conditions, (iii) delay of gastric emptying rate resulting in retarded absorption of meal-derived glucose.

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically salt thereof [such as its 2-amino-2-(hydroxymethyl)propane-1,3-diol salt, also known as its tris salt] is a GLP-1R agonist described in U.S. Patent No.10,208,019 (see Example 4A-01 of the patent).

Additional GLP-1R agonists that are useful for the present invention are described in U.S. Provisional Patent Application No. 62/684,696 filed June 13, 2018, and U.S. Provisional Patent Application No. 62/846,944 filed May 13, 2019.

The farnesoid X receptor (FXR) is a member of the nuclear hormone receptor superfamily and is primarily expressed in the liver, kidney and intestine (see, e.g., Seol et al. (1995) Mol. Endocrinol. 9:72-85 and Forman et al. (1995) Cell 81:687-693). It functions as a heterodimer with the retinoid X receptor (RXR) and binds to response elements in the promoters of target genes to regulate gene transcription. The FXR-RXR heterodimer binds with highest affinity to an inverted repeat-1 (IR-1) response element, in which consensus receptor-binding hexamers are separated by one nucleotide. FXR is part of an interrelated process, in that FXR is activated by bile acids (the end product of cholesterol metabolism) (see, e.g., Makishima et al. (1999) Science 284: 1362-1365, Parks et al. (1999) Science 284:1365-1368, Wang et al. (1999) Mol. Cell. 3:543-553), which serve to inhibit cholesterol catabolism. See also, Urizar et al. (2000) J. Biol. Chem. 275:39313-39317.

FXR is a key regulator of cholesterol homeostasis, triglyceride synthesis and lipogenesis. (Crawley, Expert Opinion Ther. Patents (2010), 20(8): 1047-1057). In addition to the treatment of dyslipidemia, multiple indications for FXR have been described, including treatment of liver disease, diabetes, vitamin D-related diseases, drug-induced side effects and hepatitis. (Crawley, supra). While advances have been made in the development of novel FXR agonists, significant room for improvement remains.

The FXR agonist Tropifexor or a pharmaceutically acceptable salt thereof is described in, e.g., Example 1-1B of U.S. Patent No. 9,150,568. The chemical name of Tropifexor is 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid.

In view of the above, there exists a need for medicaments, for example, oral medicaments, containing combination of GLP-1R agonist and ACC1 and/or ACC2 inhibitors; combination of GLP-1R agonist and DGAT2 inhibitor; combination of GLP-1R agonist and KHK inhibitor; and/or combination of GLP-1R agonist and FXR agonist to treat diseases or disorders including NAFLD, and NASH. The specific combinations described herein satisfy the existing need.

SUMMARY OF THE INVENTION

The invention relates to combinations and methods for treating fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease. In part, the invention provides a new combination comprising a GLP-1R agonist in a pharmaceutical composition and in the same or a separate composition comprising an ACC inhibitor. The invention also provides a new combination comprising a GLP-1R agonist in a pharmaceutical composition and in the same or a separate composition comprising a DGAT2 inhibitor. The invention also provides a new combination comprising a GLP-1R agonist in a pharmaceutical composition and in the same or a separate composition comprising a KHK inhibitor. The invention also provides a new combination comprising a GLP-1R agonist in a pharmaceutical composition and in the same or a separate composition comprising a FXR agonist. The invention further provides new methods for treating fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, for example, using the new combination described herein.

In one embodiment, the present invention provides a combination comprising a therapeutically effective amount of a composition comprising (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) and in the same or a separate composition (2) 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-

5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment A) of the present invention provides a combination comprising (1) GLP-1R agonist and (2) 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a method for treating a disease or condition in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) and (2) 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment B) of the present invention provides a method for treating a disease or condition in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist and (2) 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof, wherein:

the disease or condition selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, obesity, and type 2 diabetes; and

the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a method for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity or reducing the medical consequences of nonalcoholic steatohepatitis in a patient, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) and (2) 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment C) of the present invention provides a method for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity or reducing the medical consequences of nonalcoholic steatohepatitis in a patient, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist and (2) 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a combination comprising (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) in a pharmaceutical composition and (2) in the same or a separate composition [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment D) of the present invention provides a combination comprising (1) GLP-1R agonist and (2) [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a method for treating a disease or condition a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) and (2) [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment E) of the present invention provides a method for treating a disease or condition in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist and (2) [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable salt thereof, wherein:

the disease or condition selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, obesity, and type 2 diabetes; and

the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a method for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity or reducing the medical consequences of nonalcoholic steatohepatitis in a patient, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) and (2) [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment F) of the present invention provides a method for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity or reducing the medical consequences of nonalcoholic steatohepatitis in a patient, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist and (2) [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a combination comprising a therapeutically effective amount of (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) in a pharmaceutical composition and (2) in the same or a separate composition (S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment G), the present invention provides a combination comprising (1) GLP-1R agonist and (2) (S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a method for treating a disease or condition a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) and (2) (S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment H) of the present invention provides a method for treating a disease or condition in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist and (2) (S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof, wherein:

the disease or condition selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, obesity, and type 2 diabetes; and

the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a method for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity or reducing the medical consequences of nonalcoholic steatohepatitis in a patient, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) and (2) (S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment I) of the present invention provides a method for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity or reducing the medical consequences of nonalcoholic steatohepatitis in a patient, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist and (2) (S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a combination comprising a therapeutically effective amount of (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) in a pharmaceutical composition and (2) in the same or a separate composition 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment J) of the present invention provides a combination comprising (1) GLP-1R agonist and (2) 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a method for treating a disease or condition a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) and (2) (2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment K) of the present invention provides a method for treating a disease or condition in a patient in need thereof, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist and (2) 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof, wherein:

the disease or condition selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, obesity, and type 2 diabetes; and

the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a method for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity or reducing the medical consequences of nonalcoholic steatohepatitis in a patient, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist (e.g. one of the compounds of Examples 1 to 103, or pharmaceutically acceptable salt thereof) and (2) 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-

azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof.

One embodiment (Embodiment L) of the present invention provides a method for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity or reducing the medical consequences of nonalcoholic steatohepatitis in a patient, which method comprises administering to the patient a therapeutically effective amount of a combination comprising (1) GLP-1R agonist and (2) 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

Any one of the combinations of the invention described here may further optionally comprise at least one other pharmaceutical agent.

Any one of the methods of use/treatment of the invention described here may further optionally comprise administration of at least one other pharmaceutical agent.

In some ebodiments, the at least one other pharmaceutical agent (in the combination of the presention, including both the pharmaceutical compositions of the invention and method of use of the invention) is selected from the group consisting of an acetyl-CoA carboxylase- (ACC) inhibitor, a diacylglycerol *O*-acyltransferase 1 (DGAT-1) inhibitor, monoacylglycerol O-acyltransferase inhibitors, a phosphodiesterase (PDE)-10 inhibitor, an AMPK activator, a sulfonylurea, a meglitinide, an α-amylase inhibitor, an α-glucoside hydrolase inhibitor, an α-glucosidase inhibitor, a PPARγ agonist, a PPAR α/γ agonist , a biguanide, a glucagon-like peptide 1 (GLP-1) modulator, liraglutide, albiglutide, exenatide, albiglutide, lixisenatide, dulaglutide, semaglutide, a protein tyrosine phosphatase-1B (PTP-1B) inhibitor, SIRT-1 activator, a dipeptidyl peptidease IV (DPP-IV) inhibitor, an insulin secreatagogue, a fatty acid oxidation inhibitor, an A2 antagonist, a c-jun amino-terminal kinase (JNK) inhibitor, glucokinase activators (GKa), insulin, an insulin mimetic, a glycogen phosphorylase inhibitor, a VPAC2 receptor agonist, SGLT2 inhibitors, a glucagon receptor modulator, GPR119 modulators, FGF21 derivatives or analogs, TGR5 receptor modulators, GPBAR1 receptor modulators, GPR40 agonists, GPR120 modulators, high affinity nicotinic acid receptor (HM74A) activators, SGLT1 inhibitors, inhibitors or modulators of carnitine palmitoyl transferase enzymes, inhibitors of fructose 1,6-diphosphatase, inhibitors of aldose reductase, mineralocorticoid receptor inhibitors, inhibitors of TORC2, inhibitors of CCR2 and/or CCR5, inhibitors of PKC isoforms (e.g. PKCα, PKCβ, PKCγ), inhibitors of fatty acid synthetase, inhibitors of serine palmitoyl transferase, modulators of GPR81, GPR39, GPR43, GPR41, GPR105, Kv1.3, retinol binding protein 4, glucocorticoid receptor, somatostain receptors, inhibitors or modulators of PDHK2 or PDHK4, inhibitors of MAP4K4, modulators of IL1 family including IL1beta, HMG-CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, choesterol absorption inhibitors, PCSK9 modulators, cholesteryl ester transfer protein inhibitors and modulators of RXRalpha.

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

The invention also includes:

any one of the combinations of the invention, for use as a medicament;

any one of the combinations of the invention, for treating fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, or nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease;

use of any one of the combinations of the invention for treating fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, or nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease; and

use of any one of the combinations of the invention for the manufacture of a medicament for treating fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, or nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a characteristic x-ray powder diffraction pattern showing crystalline Form 1 of Example DGAT2i Compound (Vertical Axis: Intensity (CPS); Horizontal Axis: Two theta (degrees)).

FIG. 2 is a characteristic x-ray powder diffraction pattern showing crystalline Form 2 of Example DGAT2i Compound (Vertical Axis: Intensity (CPS); Horizontal Axis: Two theta (degrees)).

FIG. 3 shows an illustrative PXRD pattern of Form 1 of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid (Example ACCi compound) carried out on a Bruker AXS D4 Endeavor diffractometer equipped with a Cu radiation source.

FIG. 4 shows an illustrative Raman spectra of Form 1 of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid (Example ACCi compound) collected using a Nicolet NXR FT-Raman accessory attached to the FT-IR bench.

FIG. 5 shows an illustrative ^{13}C ssNMR pattern of Form 1 of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid (Example ACCi compound) conducted on a Bruker-BioSpin CPMAS probe positioned into a Bruker-BioSpin Avance III 500 MHz (^{1}H frequency) NMR spectrometer.

FIG. 6 shows an illustrative PXRD pattern of Form 2 of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid (Example ACCi compound) carried out on a Bruker AXS D4 Endeavor diffractometer equipped with a Cu radiation source.

FIG. 7 shows an illustrative Raman spectra of Form 2 of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid (Example ACCi compound) collected using a Nicolet NXR FT-Raman accessory attached to the FT-IR bench.

FIG. 8 shows an illustrative ^{13}C ssNMR pattern of Form 2 of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid (Example ACCi compound) conducted on a Bruker-BioSpin CPMAS probe positioned into a Bruker-BioSpin Avance III 500 MHz (^{1}H frequency) NMR spectrometer.

FIG. 9 shows an illustrative single crystal structure of Form 2 of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid (Example ACCi compound) .

FIG. 10 summarizes the effects of oral administration as monotherapy and in combination of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide on plasma triglyceride levels in Western diet fed Sprague Dawley rats, measured at the fed state.

FIG. 11 summarizes the effects of oral administration as monotherapy and in combination 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide on plasma triglyceride levels in Western diet fed Sprague Dawley rats measured at the fasted state.

FIG. 12 summarizes the effect of administration of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide as monotherapy and in combination on SREBP-1 nuclear localization in Western diet fed rats.

FIG. 13 summarizes the effect of administration of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-

carboxamide as monotherapy and in combination on hepatic lipogenic gene expression in Western diet fed rats, specifically acetyl-CoA carboxylase (ACC1).

FIG. 14 summarizes the effect of administration of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide as monotherapy and in combination on hepatic lipogenic gene expression in Western diet fed rats, specifically fatty acid synthase (FASN).

FIG. 15 summarizes the effect of administration of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide as monotherapy and in combination on hepatic lipogenic gene expression in Western diet fed rats, specifically sterol-CoA desaturase (SCD1).

FIG. 16 summarizes the effect of administration of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide as monotherapy and in combination on hepatic lipogenic gene expression in Western diet fed rats, specifically sterol regulatory element-binding protein 1c (SREBP-1c).

FIG. 17 summarizes the effect of administration of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide as monotherapy and in combination on hepatic lipogenic gene expression in Western diet fed rats, specifically proprotein convertase subtilisin/kexin type 9 (PCSK9).

FIG. 18 summarizes the effects of oral administration as monotherapy and in combination of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide on hepatic triglyceride levels in Western diet fed Sprague Dawley rats.

Figure 19 summarizes the effects of oral administration as monotherapy and in combination of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide on elasticity of the liver, a marker of hepatic inflammation and fibrosis, in choline deficient and high fat diet (CDAHFD) fed Male Wistar Hann rats.

Figure 20 summarizes the effects of oral administration as monotherapy and in combination of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide on hepatic alpha smooth actin (αSMA) immunohistochemisrty, a marker of myofibroblast activation and fibrogenesis, in CDAHFD fed Male Wistar Hann rats.

Figure 21 summarizes the effects of oral administration as monotherapy and in combination of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide on hepatic Picosirius red staining in CDAHFD fed Male Wistar Hann rats.

Figure 22 summarizes the effects of oral administration as monotherapy and in combination of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide on hepatic alpha smooth actin (αSMA) gene expression in CDAHFD fed Male Wistar Hann rats.

Figure 23 summarizes the effects of oral administration as monotherapy and in combination of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide on hepatic collagen 1A1 gene expression in CDAHFD fed Male Wistar Hann rats.

Figure 24 represents an observed powder X-ray diffraction pattern for an anhydrous (anhydrate) crystal form (Form 1) of tris salt of compound Example 7.

Figure 25 represents an observed powder X-ray diffraction pattern for an anhydrous (anhydrate) crystal form (Form A) of tris salt of compound Example 10.

DETAILED DESCRIPTION OF THE INVENTION

The invention may be understood more readily by reference to the following detailed description of exemplary embodiments of the invention and the examples included therein.

It is to be understood that this invention is not limited to specific synthetic methods of making that may of course vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. In this specification and in the claims that follow, reference will be made to a number of terms that shall be defined to have the following meanings:

As used herein in the specification, "a" or "an" may mean one or more. As used herein in the claim(s), when used in conjunction with the word "comprising", the words "a" or "an" may mean one or more than one. As used herein "another" may mean at least a second or more.

The term “about” refers to a relative term denoting an approximation of plus or minus 10% of the nominal value it refers, in one embodiment, to plus or minus 5%, in another embodiment, to plus or minus 2%. For the field of this disclosure, this level of approximation is appropriate unless the value is specifically stated to require a tighter range.

"Compounds" when used herein includes any pharmaceutically acceptable derivative or variation, including conformational isomers (e.g., cis and trans isomers) and all optical isomers (e.g., enantiomers and diastereomers), racemic, diastereomeric and other mixtures of such isomers, as well as solvates, hydrates, isomorphs, polymorphs, tautomers, esters, salt forms, and prodrugs. The expression "prodrug" refers to compounds that are drug precursors which following administration, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form). Exemplary prodrugs upon cleavage release the corresponding free acid, and such hydrolyzable ester-forming residues of the compounds of the invention include but are not limited to those having a carboxyl moiety wherein the free hydrogen is replaced by $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_7)$alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-$(C_1\text{-}C_2)$alkylamino$(C_2\text{-}C_3)$alkyl (such as β-dimethylaminoethyl), carbamoyl-$(C_1\text{-}C_2)$alkyl, N,N-di$(C_1\text{-}C_2)$alkylcarbamoyl-$(C_1\text{-}C_2)$alkyl and piperidino-, pyrrolidino- or morpholino$(C_2\text{-}C_3)$alkyl.

As used herein, an arrowhead , "  " or wavy line,"  " denotes a point of attachment of a substituent to another group.

"Patient" refers to warm blooded animals such as, for example, guinea pigs, mice, rats, gerbils, cats, rabbits, dogs, cattle, goats, sheep, horses, monkeys, chimpanzees, and humans. A "mammal" is a patient.

By "pharmaceutically acceptable" is meant that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

As used herein, the following terms have the general meaning for administration of pharmaceutical agetns: QD means once daily and BID means twice daily.

As used herein, the expressions "reaction-inert solvent" and "inert solvent" refer to a solvent or a mixture thereof which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

As used herein, the term "selectivity" or "selective" refers to a greater effect of a compound in a first assay, compared to the effect of the same compound in a second assay. For example, in "gut selective" compounds, the first assay is for the half life of the compound in the intestine and the second assay is for the half life of the compound in the liver.

“Therapeutically effective amount” means an amount of all pharmalogical agents in the combination therapy described herein that treats the particular disease, condition, or disorder described herein.

The term "treating", "treat" or "treatment" as used herein embraces preventative, i.e., prophylactic; palliative treatment, i.e., relieve, alleviate, or slow the progression of the patient’s disease (or condition) or any tissue damage associated with the disease (or condition); and reversal where the patient’s disease (or condition) is not only alleviated but any tissue damage associated with the disease (or condition) is placed in a better state then when treatment was initiated. This latter could occur, for example and not limitation, from any one or more of the following: demonstration of NASH resolution and/or from an improvement in the fibrosis score based on liver biopsy; lower incidence of progression to cirrhosis, hepatocellular carcinoma, and/or other liver related outcomes; a reduction or improvement of the level of serum or imaging based markers of nonalcoholic steatohepatitis activity; reduction or improvement of nonalcoholic steatohepatitis disease activity; or reduction in the medical consequences of nonalcoholic steatohepatitis.

It appears that the administration of an ACC inhibitor may have positive effects to lower hepatic TGs and potentially other beneficiall effects on treatment of NASH. Increases in circulating TG levels has been reported to be a mechanistic consequence of hepatic ACC inhibition (Kim et al, 2017), though doses of ACC inhibitors that only partially inhibit DNL may not produce elevations in circulating TGs (Bergman et al., (2018) *J. of Hepatology*, Volume 68, S582). It has been discovered that administration of 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid, optionally administered as a pharmaceutically acceptable salt, has a potential to result in elevations in circulating TGs (generally measured from plasma) in Western diet fed Sprague Dawley rats as was observed in human subjects.

The compounds of the invention may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. Unless specified otherwise, it is intended that all stereoisomeric forms of the compounds of the invention as well as mixtures thereof, including racemic mixtures, form part of the invention. In addition, the invention embraces all geometric and positional isomers. For example, if a compound of the invention incorporates a double bond or a fused ring, both the *cis*- and *trans*- forms, as well as mixtures, are embraced within the scope of the invention.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically high pressure liquid chromatography (HPLC) or supercritical fluid chromatography (SFC), on a resin with an asymmetric stationary phase and with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to

5% of an alkylamine, typically 0.1% diethylamine (DEA) or isopropylamine. Concentration of the eluent affords the enriched mixture.

Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g. chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g. hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column. Alternatively, the specific stereoisomers may be synthesized by using an optically active starting material, by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one stereoisomer into the other by asymmetric transformation.

Where the compounds of the invention possess two or more stereogenic centers and the absolute or relative stereochemistry is given in the name, the designations R and S refer respectively to each stereogenic center in ascending numerical order (1, 2, 3, etc.) according to the conventional IUPAC number schemes for each molecule. Where the compounds of the invention possess one or more stereogenic centers and no stereochemistry is given in the name or structure, it is understood that the name or structure is intended to encompass all forms of the compound, including the racemic form.

It is also possible that the intermediates and compounds of the invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible *via* a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions *via* migration of a proton, such as keto-enol and imine-enamine isomerizations.

Valence tautomers include interconversions by reorganization of some of the bonding electrons.

Included within the scope of the claimed compounds invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of the invention, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

The invention includes all pharmaceutically acceptable isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I, ^{124}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Tomography (PET) studies for examining substrate receptor occupancy.

Isotopically-labelled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labelled ~~reagents~~ reagent in place of the non-labelled reagent previously employed.

The compounds of the invention may be isolated and used *per se,* or when possible, in the form of its pharmaceutically acceptable salt. The term "salts" refers to inorganic and organic salts of a compound of the invention. These salts can be prepared *in situ* during the final isolation and purification of a compound, or by separately treating the compound with a suitable organic or inorganic acid or base and isolating the salt thus formed. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, (i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulphonate, hexafluorophosphate, benzene sulfonate, tosylate, formate, trifluoroacetate, oxalate, besylate, palmitiate, pamoate, malonate, stearate, laurate, malate, borate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3- naphthoate)) salts.

The invention also relates to base addition salts of the compounds of the invention. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of the invention that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., lithium, potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines. See e.g. Berge, et al. *J. Pharm. Sci.* **66**, 1-19 (1977).

Certain compounds of the invention may exist in more than one crystal form (generally referred to as "polymorphs"). Polymorphs may be prepared by crystallization under various conditions, for example, using different solvents or different solvent mixtures for recrystallization; crystallization at different temperatures; and/or various modes of cooling, ranging from very fast to very slow cooling during crystallization. Polymorphs may also be obtained by heating or melting the compound of the invention followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

In a further embodiment, the composition further includes at least one additional pharmaceutical agent selected from the group consisting of an anti-inflammation agent, an anti-diabetic agent, an anti-fibrotic agent, an anti-steatiotic agent, and a cholesterol/lipid modulating agent.

In another embodiment, the method for treating a condition selected from the group consisting of hyperlipidemia, Type I diabetes, Type II diabetes mellitus, idiopathic Type I diabetes (Type Ib), latent autoimmune diabetes in adults (LADA), early-onset Type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance, hyper apo B lipoproteinemia, Alzheimer's, schizophrenia, impaired cognition, inflammatory bowel disease, ulcerative colitis, Crohn's disease, and irritable bowel syndrome, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), includes the administration of a therapuetically effective amount of a combination described herein.

In a further embodiment, the method for treating a metabolic or metabolic-related disease, condition or disorder includes the step of administering to a patient in need of such treatment a combination comprising at least two separate pharmaceutical compositions

(i) a first composition that includes (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide, or a pharmaceutically acceptable salt thereof, present in a therapeutically effective amount, in admixture with at least one pharmaceutically acceptable excipient;

(ii) a second composition that includes 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid, or a pharmaceutically acceptable salt thereof, present in a therapeutically effective amount, in admixture with at least one pharmaceutically acceptable excipient; and optionally

(iii) a third composition comprising at least one additional pharmaceutical agent selected from the group consisting of an anti-inflammatory agent, an anti-diabetic agent, an anti-fibrotic agent, an anti-steatiotic agent, and a cholesterol/lipid modulating agent and an anti-diabetic agent, and at least one pharmaceutically acceptable excipient.

In yet a further embodiment, the method of the invention is performed when said first composition, said second composition, and said third composition are administered simultaneously.

In yet another embodiment, the method of the invention is performed when first composition, said second composition, and said third composition are administered separately or sequentially and in any order.

In one embodiment, when three compositions are administered, the first composition and the second composition are administered simultaneously and the third composition is administered sequentially. In another embodiment, the three separate compositions are administered sequentially and in any order.

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available *via* the Beilstein online database)). A preparation of (S)-

2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide is presented in Example 1 of US 2018-0051012A1, hereby incorporated herein by reference in its entireties for all purposes. A preparation of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid is in Example 9 of US 8,859,577, hereby incorporated herein by reference in its entireties for all purposes.

GLP-1R agonist / ACCi combination

Embodiments A, B, and C relate to combinations of a GLP-1R agonist (including those described herein) and the ACC inhibitor 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof.

Embodiment A1 is a further embodiment of Embodiment A, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment A2 is a further embodiment of Embodiment A or A1, the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment A3 is a further embodiment of Embodiment A2, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment A4 is a further embodiment of Embodiment A, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agonist is a pharmaceutically acceptable salt.

Embodiment A5 is a further embodiment of Embodiment A4, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agonist is a pharmaceutically acceptable salt.

Embodiment A6 is a further embodiment of Embodiment A5, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment A7 is a further embodiment of any one of Embodiment A or Embodiments A1 to A5, wherein the 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or pharmaceutically acceptable salt thereof is 2-amino-2-(hydroxymethyl)propane-1,3-diol salt of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid.

Embodiment A8 is a further embodiment of Embodiment A7, wherein the 2-amino-2-(hydroxymethyl)propane-1,3-diol salt of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid is a crystal form.

Embodiment A9 is a further embodiment of Embodiment A8, wherein the ratio of 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and 2-amino-2-(hydroxymethyl)propane-1,3-diol in the crystal form is 1:1.

Embodiment A10 is a further embodiment of Embodiment A8 or A9, wherein the crystal form is an anhydrous crystal form.

Embodiment A11 is a further embodiment of Embodiment A10, wherein the anhydrous crystal form has a PXRD pattern comprising peaks at diffraction angles of 9.6, 10.7, and 11.3 2Θ, ± 0.2° 2Θ.

Embodiment A12 is a further embodiment of Embodiment A10 or A11, wherein the anhydrous crystal form has a Raman spectrum comprising peak shifts at 1511, 1561, and 1615 cm^{-1}, ± 2 cm^{-1}.

Embodiment A13 is a further embodiment of any one of Embodiments A10 to A12, wherein the anhydrous crystal form has a ^{13}C ssNMR spectrum comprising chemical shifts at 22.9, 146.2, and 161.9 ppm, ± 0.2 ppm.

Embodiment A14 is a further embodiment of Embodiment A13, wherein the anhydrous crystal form has an analytical parameter selected from the group consisting of a Raman spectrum comprising peak shifts at 1511 and 1615 cm^{-1}, ± 2 cm^{-1}, and a ^{13}C ssNMR spectrum comprising at least one chemical shift at 22.9, 146.2, or 161.9 ppm, ± 0.2 ppm.

Embodiment A15 is a further embodiment of Embodiment A8 or A9, wherein the crystal form is a trihydrate crystal form.

Embodiment A16 is a further embodiment of Embodiment A15, wherein the trihydrate crystal form has a PXRD pattern comprising peaks at diffraction angles of 8.4, 9.0, and 10.5 2Θ, ± 0.2° 2Θ.

Embodiment A17 is a further embodiment of Embodiment A15 or A16, wherein the trihydrate crystal form has a Raman spectrum comprising peak shifts at 1507, 1557, and 1610 cm^{-1}, ± 2 cm^{-1}.

Embodiment A18 is a further embodiment of any one of Embodiment A15 to A17, wherein the trihydrate crystal form has a ^{13}C ssNMR spectrum comprising chemical shifts at 19.2, 149.5, and 163.8 ppm, ± 0.2 ppm.

Embodiment A19 is a further embodiment of Embodiment A18, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of

a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ,

a Raman spectrum comprising peak shifts at 1557 and 1610 cm^{-1}, ± 2 cm^{-1}, and

a ^{13}C ssNMR spectrum comprising at least one chemical shift at 19.2, 149.5, or 163.8 ppm, ± 0.2 ppm.

Embodiment A20 is a further embodiment of Embodiment A18, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ, and a Raman spectrum comprising at least one peak shift at 1507, 1557, or 1610 cm^{-1}, ± 2 cm^{-1}.

Embodiment A21 is a further embodiment of Embodiment A18, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ, and a ^{13}C ssNMR spectrum comprising at least one chemical shift at 19.2, 149.5, or 163.8 ppm, ± 0.2 ppm.

Embodiment A22 is a further embodiment of Embodiment A or any one of Embodiments A1 to A12, the composition further comprises at least one other pharmaceutical agent.

Embodiment A23 is a further embodiment of Embodiment A22, wherein the at least one other pharmaceutical agent is selected from the group consisting of an acetyl-CoA carboxylase-(ACC) inhibitor, a diacylglycerol *O*-acyltransferase 1 (DGAT-1) inhibitor, monoacylglycerol O-acyltransferase inhibitors, a phosphodiesterase (PDE)-10 inhibitor, an AMPK activator, a sulfonylurea, a meglitinide, an α-amylase inhibitor, an α-glucoside hydrolase inhibitor, an α-glucosidase inhibitor, a PPARγ agonist, a PPAR α/γ agonist , a biguanide, a glucagon-like peptide 1 (GLP-1) modulator, liraglutide, albiglutide, exenatide, albiglutide, lixisenatide, dulaglutide, semaglutide, a protein tyrosine phosphatase-1B (PTP-1B) inhibitor, SIRT-1 activator, a dipeptidyl peptidease IV (DPP-IV) inhibitor, an insulin secreatagogue, a fatty acid oxidation inhibitor, an A2 antagonist, a c-jun amino-terminal kinase (JNK) inhibitor, glucokinase activators (GKa), insulin, an insulin mimetic, a glycogen phosphorylase inhibitor, a VPAC2 receptor agonist, SGLT2 inhibitors, a glucagon receptor modulator, GPR119 modulators, FGF21 derivatives or analogs, TGR5 receptor modulators, GPBAR1 receptor modulators, GPR40 agonists, GPR120 modulators, high affinity nicotinic acid receptor (HM74A) activators, SGLT1 inhibitors, inhibitors or modulators of carnitine palmitoyl transferase enzymes, inhibitors of fructose 1,6-diphosphatase, inhibitors of aldose reductase, mineralocorticoid receptor inhibitors, inhibitors of TORC2, inhibitors of CCR2 and/or CCR5, inhibitors of PKC isoforms (e.g. PKCα, PKCβ, PKCγ), inhibitors of fatty acid synthetase, inhibitors of serine palmitoyl transferase, modulators of GPR81, GPR39, GPR43, GPR41, GPR105, Kv1.3, retinol binding protein 4, glucocorticoid receptor, somatostain receptors, inhibitors or modulators of PDHK2 or PDHK4, inhibitors of MAP4K4, modulators of IL1 family including IL1beta, HMG-CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, choesterol absorption inhibitors, PCSK9 modulators, cholesteryl ester transfer protein inhibitors and modulators of RXRalpha.

Embodiment B1 is a further embodiment of Embodiment B, wherein the disease or condition is fatty liver.

Embodiment B2 is a further embodiment of Embodiment B, wherein the disease or condition is nonalcoholic fatty liver disease.

Embodiment B3 is a further embodiment of Embodiment B, wherein the disease or condition is nonalcoholic steatohepatitis.

Embodiment B4 is a further embodiment of Embodiment B, wherein the disease or condition is nonalcoholic steatohepatitis with liver fibrosis.

Embodiment B5 is a further embodiment of Embodiment B,, wherein the disease or condition is nonalcoholic steatohepotitis with cirrhosis.

Embodiment B6 is a further embodiment of Embodiment B, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma.

Embodiment B7 is a further embodiment of Embodiment B, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with a metabolic-related disease.

Embodiment B8 is a further embodiment of Embodiment B or any one of Embodiments B1 to B7, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment B9 is a further embodiment of Embodiment B8, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment B10 is a further embodiment of Embodiment B9, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment B11 is a further embodiment of Embodiment B or any one of Embodiments B1 to B7, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

Embodiment B12 is a further embodiment of Embodiment B11, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agaonist a pharmaceutically acceptable salt.

Embodiment B13 is a further embodiment of Embodiment B12, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment B14 is a further embodiment of any one of Embodiment B or Embodiment B1 to B13, wherein the 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or pharmaceutically acceptable salt thereof is 2-amino-2-(hydroxymethyl)propane-1,3-diol salt of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid.

Embodiment B15 is a further embodiment of Embodiment B14, wherein the 2-amino-2-(hydroxymethyl)propane-1,3-diol salt of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid is a crystal form.

Embodiment B16 is a further embodiment of Embodiment B15, wherein the ratio of 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and 2-amino-2-(hydroxymethyl)propane-1,3-diol in the crystal form is 1:1.

Embodiment B17 is a further embodiment of Embodiment B15 or B16, wherein the crystal form is an anhydrous crystal form.

Embodiment B18 is a further embodiment of Embodiment B17, wherein the anhydrous crystal form has a PXRD pattern comprising peaks at diffraction angles of 9.6, 10.7, and 11.3 2Θ, ± 0.2° 2Θ.

Embodiment B19 is a further embodiment of Embodiment B17 or B18, wherein the anhydrous crystal form has a Raman spectrum comprising peak shifts at 1511, 1561, and 1615 cm^{-1}, ± 2 cm^{-1}.

Embodiment B20 is a further embodiment of any one of Embodiments B17 to B19, wherein the anhydrous crystal form has a ^{13}C ssNMR spectrum comprising chemical shifts at 22.9, 146.2, and 161.9 ppm, ± 0.2 ppm.

Embodiment B21 is a further embodiment of Embodiment B20, wherein the anhydrous crystal form has an analytical parameter selected from the group consisting of a Raman spectrum comprising peak shifts at 1511 and 1615 cm^{-1}, ± 2 cm^{-1}, and a ^{13}C ssNMR spectrum comprising at least one chemical shift at 22.9, 146.2, or 161.9 ppm, ± 0.2 ppm.

Embodiment B22 is a further embodiment of Embodiment B15 or B16, wherein the crystal form is a trihydrate crystal form.

Embodiment B23 is a further embodiment of Embodiment B22, wherein the trihydrate crystal form has a PXRD pattern comprising peaks at diffraction angles of 8.4, 9.0, and 10.5 2Θ, ± 0.2° 2Θ.

Embodiment B24 is a further embodiment of Embodiment B22 or B23, wherein the trihydrate crystal form has a Raman spectrum comprising peak shifts at 1507, 1557, and 1610 cm^{-1}, ± 2 cm^{-1}.

Embodiment B25 is a further embodiment of any one of Embodiment B22 to B24, wherein the trihydrate crystal form has a ^{13}C ssNMR spectrum comprising chemical shifts at 19.2, 149.5, and 163.8 ppm, ± 0.2 ppm.

Embodiment B26 is a further embodiment of Embodiment B25, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of

a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ,

a Raman spectrum comprising peak shifts at 1557 and 1610 cm^{-1}, ± 2 cm^{-1}, and

a ^{13}C ssNMR spectrum comprising at least one chemical shift at 19.2, 149.5, or 163.8 ppm, ± 0.2 ppm.

Embodiment B27 is a further embodiment of Embodiment B25, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ, and a Raman spectrum comprising at least one peak shift at 1507, 1557, or 1610 cm^{-1}, ± 2 cm^{-1}.

Embodiment B28 is a further embodiment of Embodiment B25, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ, and a ^{13}C ssNMR spectrum comprising at least one chemical shift at 19.2, 149.5, or 163.8 ppm, ± 0.2 ppm.

Embodiment B29 is a further embodiment of Embodiment B or any one of Embodiments B1 to B28, the method further comprises administration of at least one other pharmaceutical agent.

Embodiment C1 is a further embodiment of Embodiment C, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment C2 is a further embodiment of Embodiment C1, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment C3 is a further embodiment of Embodiment C2, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment C4 is a further embodiment of Embodiment C, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

Embodiment C5 is a further embodiment of Embodiment C4, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agaonist a pharmaceutically acceptable salt.

Embodiment C6 is a further embodiment of Embodiment C5, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment C7 is a further embodiment of any one of Embodiment C or Embodiment C1 to B6, wherein the 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or pharmaceutically acceptable salt thereof is 2-amino-2-(hydroxymethyl)propane-1,3-diol salt of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid.

Embodiment C8 is a further embodiment of Embodiment C7, wherein the 2-amino-2-(hydroxymethyl)propane-1,3-diol salt of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid is a crystal form.

Embodiment C9 is a further embodiment of Embodiment C8, wherein the ratio of 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and 2-amino-2-(hydroxymethyl)propane-1,3-diol in the crystal form is 1:1.

Embodiment C10 is a further embodiment of Embodiment C8 or C9, wherein the crystal form is an anhydrous crystal form.

Embodiment C11 is a further embodiment of Embodiment C10, wherein the anhydrous crystal form has a PXRD pattern comprising peaks at diffraction angles of 9.6, 10.7, and 11.3 2Θ, ± 0.2° 2Θ.

Embodiment C12 is a further embodiment of Embodiment C10 or C11, wherein the anhydrous crystal form has a Raman spectrum comprising peak shifts at 1511, 1561, and 1615 cm^{-1}, ± 2 cm^{-1}.

Embodiment C13 is a further embodiment of any one of Embodiments C10 to C12, wherein the anhydrous crystal form has a ^{13}C ssNMR spectrum comprising chemical shifts at 22.9, 146.2, and 161.9 ppm, ± 0.2 ppm.

Embodiment 14 is a further embodiment of Embodiment C13, wherein the anhydrous crystal form has an analytical parameter selected from the group consisting of a Raman spectrum comprising peak shifts at 1511 and 1615 cm^{-1}, ± 2 cm^{-1}, and a ^{13}C ssNMR spectrum comprising at least one chemical shift at 22.9, 146.2, or 161.9 ppm, ± 0.2 ppm.

Embodiment C15 is a further embodiment of Embodiment C8 or BC9, wherein the crystal form is a trihydrate crystal form.

Embodiment C16 is a further embodiment of Embodiment C15, wherein the trihydrate crystal form has a PXRD pattern comprising peaks at diffraction angles of 8.4, 9.0, and 10.5 2Θ, ± 0.2° 2Θ.

Embodiment C17 is a further embodiment of Embodiment C15 or C16, wherein the trihydrate crystal form has a Raman spectrum comprising peak shifts at 1507, 1557, and 1610 cm^{-1}, ± 2 cm^{-1}.

Embodiment C18 is a further embodiment of any one of Embodiment C15 to C16, wherein the trihydrate crystal form has a ^{13}C ssNMR spectrum comprising chemical shifts at 19.2, 149.5, and 163.8 ppm, ± 0.2 ppm.

Embodiment C19 is a further embodiment of Embodiment C18, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of

a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ,

a Raman spectrum comprising peak shifts at 1557 and 1610 cm^{-1}, ± 2 cm^{-1}, and

a ^{13}C ssNMR spectrum comprising at least one chemical shift at 19.2, 149.5, or 163.8 ppm, ± 0.2 ppm.

Embodiment C20 is a further embodiment of Embodiment C18, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ, and a Raman spectrum comprising at least one peak shift at 1507, 1557, or 1610 cm^{-1}, ± 2 cm^{-1}.

Embodiment C21 is a further embodiment of Embodiment C18, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ, and a ^{13}C ssNMR spectrum comprising at least one chemical shift at 19.2, 149.5, or 163.8 ppm, ± 0.2 ppm.

Embodiment C22 is a further embodiment of Embodiment C or any one of Embodiments C1 to C21, the method further comprises administration of at least one other pharmaceutical agent.

In each of embodiments of the methods of treatment of the invention (including Embodiment B, Embodiments B1 to B29, Embodiment C, and Embodiments C1 to C29), each of the GLP-1R agonist and the ACC inhibitor be can present in a same composition or in separate compositions. The combined amount of the GLP-1R agonist and the ACC inhibitor is therapeutically effective for the methods decribed herein. Even when the GLP-1R agonist and the ACC inhibitor are present in separate compositions, they can be administered simultaneously or sequentially; and when they are administered sequentially, they can be administered in any order.

GLP-1R agonist / KHKi combination

Embodiments D, E, and F relate to combination of GLP-1R agonist (including those described herein) and the KHKi inhibitor [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof.

Embodiment D1 is a further embodiment of Embodiment D, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment D2 is a further embodiment of Embodiment D or D1, the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment D3 is a further embodiment of Embodiment D2, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment D4 is a further embodiment of Embodiment D, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

Embodiment D5 is a further embodiment of Embodiment D4, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agaonist a pharmaceutically acceptable salt.

Embodiment D6 is a further embodiment of Embodiment D5, wherein the pharmaceutically acceptable salt is a tris salt. In some further embodiments, the tris salt is a crystal form, for example, as one described herein.

Embodiment D7 is a further embodiment of any one of Embodiment D or Embodiments D1 to D6, wherein the [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof is [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid.

Embodiment D8 is a further embodiment of Embodiment D7, wherein the [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid is a crystal form.

Embodiment D9 is a further embodiment of Embodiment D8, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 9.0, 10.4, 15.0, and 21.4 2Θ, ± 0.2° 2Θ.

Embodiment D10 is a further embodiment of Embodiment D8, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 9.0, 15.0 19.6, 21.4, and 26.5 2Θ, ± 0.2° 2Θ.

Embodiment D11 is a further embodiment of Embodiment D8, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 10.4, 11.5, 15.0, 19.6, and 26.5 2Θ, ± 0.2° 2Θ.

Embodiment D12 is a further embodiment of any one of Embodiment D or Embodiments D1 to D11, wherein the composition further comprises at least one other pharmaceutical agent.

Embodiment E1 is a further embodiment of Embodiment E, wherein the disease or condition is fatty liver.

Embodiment E2 is a further embodiment of Embodiment E, wherein the disease or condition is nonalcoholic fatty liver disease.

Embodiment E3 is a further embodiment of Embodiment E, wherein the disease or condition is nonalcoholic steatohepatitis.

Embodiment E4 is a further embodiment of Embodiment E, wherein the disease or condition is nonalcoholic steatohepatitis with liver fibrosis.

Embodiment E5 is a further embodiment of Embodiment E, wherein the disease or condition is nonalcoholic steatohepotitis with cirrhosis.

Embodiment E6 is a further embodiment of Embodiment E, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma.

Embodiment E7 is a further embodiment of Embodiment E, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with a metabolic-related disease.

Embodiment E8 is a further embodiment of Embodiment E or any one of Embodiments E1 to E7, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment E9 is a further embodiment of Embodiment E8, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment E10 is a further embodiment of Embodiment E9, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment E11 is a further embodiment of Embodiment E or any one of Embodiments E1 to E7, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

Embodiment E12 is a further embodiment of Embodiment E11, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agaonist a pharmaceutically acceptable salt.

Embodiment E13 is a further embodiment of Embodiment E12, wherein the pharmaceutically acceptable salt is a tris salt. In some further embodiments, the tris salt is a crystal form, for example, as one described herein.

Embodiment E14 is a further embodiment of any one of Embodiment E or Embodiments E1 to E13, wherein the [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof is [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid (free acid).

Embodiment E15 is a further embodiment of Embodiment E14, wherein the [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid is a crystal form.

Embodiment E16 is a further embodiment of Embodiment E15, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 9.0, 10.4, 15.0, and 21.4 2Θ, ± 0.2° 2Θ.

Embodiment E17 is a further embodiment of Embodiment E15, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 9.0, 15.0 19.6, 21.4, and 26.5 2Θ, ± 0.2° 2Θ.

Embodiment E18 is a further embodiment of Embodiment E15, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 10.4, 11.5, 15.0, 19.6, and 26.5 2Θ, ± 0.2° 2Θ.

Embodiment E19 is a further embodiment of Embodiment E or any one of Embodiments E1 to E18, the method further comprises administration of at least one other pharmaceutical agent.

Embodiment F1 is a further embodiment of Embodiment F, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment F2 is a further embodiment of Embodiment F1, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment F3 is a further embodiment of Embodiment F2, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment F4 is a further embodiment of Embodiment F, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

Embodiment F5 is a further embodiment of Embodiment F4, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agaonist a pharmaceutically acceptable salt.

Embodiment F6 is a further embodiment of Embodiment F5, wherein the pharmaceutically acceptable salt is a tris salt. In some further embodiments, the tris salt is a crystal form, for example, as one described herein.

Embodiment F7 is a further embodiment of any one of Embodiment F or Embodiments F1 to F6, wherein the [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof is

[(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid.

Embodiment F8 is a further embodiment of Embodiment F7, wherein the [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid is a crystal form.

Embodiment F9 is a further embodiment of Embodiment F8, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 9.0, 10.4, 15.0, and 21.4 2Θ, ± 0.2° 2Θ.

Embodiment F10 is a further embodiment of Embodiment F8, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 9.0, 15.0 19.6, 21.4, and 26.5 2Θ, ± 0.2° 2Θ.

Embodiment F11 is a further embodiment of Embodiment F8, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 10.4, 11.5, 15.0, 19.6, and 26.5 2Θ, ± 0.2° 2Θ.

Embodiment F12 is a further embodiment of Embodiment F or any one of Embodiments F1 to F11, wherein the method further comprises administration of at least one other pharmaceutical agent.

In each of embodiments of the methods of treatment of the invention (including Embodiment E, Embodiments E1 to E19, Embodiment F, and Embodiments F1 to F12), each of the GLP-1R agonist and the KHK inhibitor be can present in a same composition or in separate compositions. The combined amount of the GLP-1R agonist and the KHK inhibitor is therapeutically effective for the methods decribed herein. Even when the GLP-1R agonist and the KHK inhibitor are present in separate compositions, they can be administered simultaneously or sequentially; and when they are administered sequentially, they can be administered in any order.

GLP-1R agonist / DGAT2 inhibitor combination

Embodiments G, H, and I relate to combination of GLP-1R agonist (including those described herein) and the DGAT2 inhibitor (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof.

Embodiment G1 is a further embodiment of Embodiment G, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment G2 is a further embodiment of Embodiment G or G1, the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment G3 is a further embodiment of Embodiment G2, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment G4 is a further embodiment of Embodiment G, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

Embodiment G5 is a further embodiment of Embodiment G4, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agaonist a pharmaceutically acceptable salt.

Embodiment G6 is a further embodiment of Embodiment G5, wherein the pharmaceutically acceptable salt is a tris salt. In some further embodiments, the tris salt is a crystal form, for example, as one described herein.

Embodiment G7 is a further embodiment of any one of Embodiment G or Embodiments G1 to G6, wherein the (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof is (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide.

Embodiment G8 is a further embodiment of Embodiment G7, wherein the (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide is a crystal form.

Embodiment G9 is a further embodiment of Embodiment G8, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 5.3, 7.7, 15.4 2Θ, ± 0.2° 2Θ (Form 1).

Embodiment G10 is a further embodiment of Embodiment G8, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 6.5, 9.3, 13.6 2Θ, ± 0.2° 2Θ (Form 2).

Embodiment G11 is a further embodiment of any one of Embodiment G or Embodiments G1 to G10, wherein the composition further comprises at least one other pharmaceutical agent.

Embodiment H1 is a further embodiment of Embodiment H, wherein the disease or condition is fatty liver.

Embodiment H2 is a further embodiment of Embodiment H, wherein the disease or condition is nonalcoholic fatty liver disease.

Embodiment H3 is a further embodiment of Embodiment H, wherein the disease or condition is nonalcoholic steatohepatitis.

Embodiment H4 is a further embodiment of Embodiment H, wherein the disease or condition is nonalcoholic steatohepatitis with liver fibrosis.

Embodiment H5 is a further embodiment of Embodiment H, wherein the disease or condition is nonalcoholic steatohepotitis with cirrhosis.

Embodiment H6 is a further embodiment of Embodiment H, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma.

Embodiment H7 is a further embodiment of Embodiment H, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with a metabolic-related disease.

Embodiment H8 is a further embodiment of Embodiment H or any one of Embodiments H1 to H7, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment H9 is a further embodiment of Embodiment H8, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment H10 is a further embodiment of Embodiment H9, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment H11 is a further embodiment of Embodiment H or any one of Embodiments H1 to H7, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

Embodiment H12 is a further embodiment of Embodiment H11, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agaonist a pharmaceutically acceptable salt.

Embodiment H13 is a further embodiment of Embodiment H12, wherein the pharmaceutically acceptable salt is a tris salt. In some further embodiments, the tris salt is a crystal form, for example, as one described herein.

Embodiment H14 is a further embodiment of any one of Embodiment H or Embodiments H1 to H13, wherein the (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof is (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide.

Embodiment H15 is a further embodiment of Embodiment H14, wherein the (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide is a crystal form.

Embodiment H16 is a further embodiment of Embodiment H15, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 5.3, 7.7, 15.4 2Θ, ± 0.2° 2Θ (Form 1).

Embodiment H17 is a further embodiment of Embodiment H15, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 6.5, 9.3, 13.6 2Θ, ± 0.2° 2Θ (Form 2).

Embodiment H18 is a further embodiment of Embodiment H or any one of Embodiments H1 to E17, the method further comprises administration of at least one other pharmaceutical agent.

Embodiment I1 is a further embodiment of Embodiment I, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment I2 is a further embodiment of Embodiment I1, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment I3 is a further embodiment of Embodiment I2, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment I4 is a further embodiment of Embodiment I, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

Embodiment I5 is a further embodiment of Embodiment I4, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agaonist a pharmaceutically acceptable salt.

Embodiment I6 is a further embodiment of Embodiment I5, wherein the pharmaceutically acceptable salt is a tris salt. In some further embodiments, the tris salt is a crystal form, for example, as one described herein.

Embodiment I7 is a further embodiment of any one of Embodiment I or Embodiments I1 to I6, wherein the (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof is (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide.

Embodiment I8 is a further embodiment of Embodiment I7, wherein the (*S*)-2-(5-((3-ethoxypyridin-2-yl)oxy)pyridin-3-yl)-*N*-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide is a crystal form.

Embodiment I9 is a further embodiment of Embodiment I8, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 5.3, 7.7, 15.4 2Θ, ± 0.2° 2Θ (Form 1).

Embodiment I10 is a further embodiment of Embodiment I8, wherein the crystal form has a PXRD pattern comprising peaks at diffraction angles of 6.5, 9.3, 13.6 2Θ, ± 0.2° 2Θ (Form 2).

Embodiment I11 is a further embodiment of any one of Embodiment I or Embodiments I1 to I10, wherein the composition further comprises at least one other pharmaceutical agent.

In each of embodiments of the methods of treatment of the invention (including Embodiment E, Embodiments H1 to H18, Embodiment F, and Embodiments I1 to I11), each of the GLP-1R agonist and the DGAT2 inhibitor be can present in a same composition or in separate compositions. The combined amount of the GLP-1R agonist and the DGAT2 inhibitor is therapeutically effective for the methods decribed herein. Even when the GLP-1R agonist and the DGT2 inhibitor are present in separate compositions, they can be administered simultaneously or sequentially; and when they are administered sequentially, they can be administered in any order.

GLP-1R agonist / FXR agonist combination

Embodiments J, K, and L relate to combination of GLP-1R agonist (including those described herein) and the FXR agonist 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid (also known as Tropifexor) or a pharmaceutically acceptable salt thereof.

Embodiment J1 is a further embodiment of Embodiment J, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment J2 is a further embodiment of Embodiment J or J1, the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment J3 is a further embodiment of Embodiment J2, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment J4 is a further embodiment of Embodiment J, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

Embodiment J5 is a further embodiment of Embodiment J4, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agaonist a pharmaceutically acceptable salt.

Embodiment J6 is a further embodiment of Embodiment J5, wherein the pharmaceutically acceptable salt is a tris salt. In some further embodiments, the tris salt is a crystal form, for example, as one described herein.

Embodiment J7 is a further embodiment of any one of Embodiment J or Embodiments J1 to J6, wherein the 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof is 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid.

Embodiment J8 is a further embodiment of any one of Embodiment J or Embodiments J1 to J7, wherein the composition further comprises at least one other pharmaceutical agent.

Embodiment K1 is a further embodiment of Embodiment K, wherein the disease or condition is fatty liver.

Embodiment K2 is a further embodiment of Embodiment K, wherein the disease or condition is nonalcoholic fatty liver disease.

Embodiment K3 is a further embodiment of Embodiment K, wherein the disease or condition is nonalcoholic steatohepatitis.

Embodiment K4 is a further embodiment of Embodiment K, wherein the disease or condition is nonalcoholic steatohepatitis with liver fibrosis.

Embodiment K5 is a further embodiment of Embodiment K, wherein the disease or condition is nonalcoholic steatohepotitis with cirrhosis.

Embodiment K6 is a further embodiment of Embodiment K, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma.

Embodiment K7 is a further embodiment of Embodiment K, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with a metabolic-related disease.

Embodiment K8 is a further embodiment of Embodiment K or any one of Embodiments K1 to K7, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment K9 is a further embodiment of Embodiment K8, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment K10 is a further embodiment of Embodiment K9, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment K11 is a further embodiment of Embodiment K or any one of Embodiments K1 to K7, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

Embodiment K12 is a further embodiment of Embodiment K11, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agaonist a pharmaceutically acceptable salt.

Embodiment K13 is a further embodiment of Embodiment K12, wherein the pharmaceutically acceptable salt is a tris salt. In some further embodiments, the tris salt is a crystal form, for example, as one described herein.

Embodiment K14 is a further embodiment of any one of Embodiment K or Embodiments K1 to K13, wherein the 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof is 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid.

Embodiment K15 is a further embodiment of Embodiment K or any one of Embodiments K1 to K14, the method further comprises administration of at least one other pharmaceutical agent.

Embodiment L1 is a further embodiment of Embodiment L, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

Embodiment L2 is a further embodiment of Embodiment L1, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

Embodiment L3 is a further embodiment of Embodiment L2, wherein the pharmaceutically acceptable salt is a tris salt.

Embodiment L4 is a further embodiment of Embodiment L, wherein the GLP-1R agonist selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

Embodiment L5 is a further embodiment of Embodiment L4, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof. In a further embodiment, the GLP-1R agaonist a pharmaceutically acceptable salt.

Embodiment L6 is a further embodiment of Embodiment L5, wherein the pharmaceutically acceptable salt is a tris salt. In some further embodiments, the tris salt is a crystal form, for example, as one described herein.

Embodiment L7 is a further embodiment of any one of Embodiment L or Embodiments L1 to L6, wherein the 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof is 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid.

Embodiment L8 is a further embodiment of any one of Embodiment L or Embodiments L1 to L7, wherein the composition further comprises at least one other pharmaceutical agent.

In each of embodiments of the methods of treatment of the invention (including Embodiment K, Embodiments K1 to K15, Embodiment L, and Embodiments L1 to L8), each of the GLP-1R agonist and the FXR agonist be can present in a same composition or in separate compositions. The combined amount of the GLP-1R agonist and the FXR agonist is therapeutically effective for the methods decribed herein. Even when the GLP-1R agonist and the FXR agonist are present in separate compositions, they can be administered simultaneously or sequentially; and when they are administered sequentially, they can be administered in any order.

COMBINATION AGENTS

The compounds in the combination of the invention (either in composition or method) can be administered separately or together as separate agents or in a fixed-dose comibination or in combination with one or more additional therapeutic agents. When administered in combination, each component may be administered at the same time (i.e. simultaneously) or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Thus, the methods of treatment described herein include use of combination agents to adiminister two or more agents in combination.

The combination agents are administered to a patient or mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of the compounds of the invention that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to treat the desired disease/condition e.g., NASH.

Examples of suitable anti-diabetic agents include (e.g. insulins, metfomin, DPPIV inhibitors, GLP-1 agonists, analogues and mimetics, SGLT1 and SGLT2 inhibitors). Suitable anti-diabetic agents include an acetyl-CoA carboxylase- (ACC) inhibitor such as those described in WO2009144554, WO2003072197, WO2009144555 and WO2008065508, a diacylglycerol *O*-acyltransferase 1 (DGAT-1) inhibitor, such as those described in WO09016462 or WO2010086820, AZD7687 or LCQ908, monoacylglycerol O-acyltransferase inhibitors, a phosphodiesterase (PDE)-10 inhibitor, an AMPK activator, a sulfonylurea (e.g., acetohexamide, chlorpropamide, diabinese, glibenclamide, glipizide, glyburide, glimepiride, gliclazide, glipentide, gliquidone, glisolamide, tolazamide, and tolbutamide), a meglitinide, an α-amylase inhibitor (e.g., tendamistat, trestatin and AL-3688), an α-glucoside hydrolase inhibitor (e.g., acarbose), an α-glucosidase inhibitor (e.g., adiposine, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, and salbostatin), a PPARγ agonist (e.g., balaglitazone, ciglitazone, darglitazone, englitazone, isaglitazone, pioglitazone and rosiglitazone), a PPAR α/γ agonist (e.g., CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-796449, LR-90, MK-0767 and SB-219994), a biguanide (e.g., metformin), a glucagon-like peptide 1 (GLP-1) modulator such as an agonist (e.g., exendin-3 and exendin-4), liraglutide, albiglutide, exenatide (Byetta®), albiglutide, lixisenatide, dulaglutide, semaglutide, NN-9924, TTP-054, a protein tyrosine phosphatase-1B (PTP-1B) inhibitor (e.g., trodusquemine, hyrtiosal extract, and compounds disclosed by Zhang, S., et al., Drug Discovery Today, 12(9/10), 373-381 (2007)), SIRT-1 activator (e.g., resveratrol, GSK2245840 or GSK184072), a dipeptidyl peptidease IV (DPP-IV) inhibitor (e.g., those in WO2005116014, sitagliptin, vildagliptin, alogliptin, dutogliptin, linagliptin and saxagliptin), an insulin secreatagogue, a fatty acid oxidation inhibitor, an A2 antagonist, a c-jun amino-terminal kinase (JNK) inhibitor, glucokinase activators (GKa) such as those described in WO2010103437, WO2010103438, WO2010013161, WO2007122482, TTP-399, TTP-355, TTP-547, AZD1656, ARRY403, MK-0599, TAK-329, AZD5658 or GKM-001, insulin, an insulin mimetic, a glycogen phosphorylase inhibitor (e.g. GSK1362885), a VPAC2 receptor agonist, SGLT2 inhibitors, such as those described in E.C. Chao et al. Nature Reviews Drug Discovery 9, 551-559 (July 2010) including dapagliflozin, canagliflozin, empagliflozin, tofogliflozin (CSG452), Ertugliflozin, ASP-1941, THR1474, TS-071, ISIS388626 and LX4211 as well as those in WO2010023594, a glucagon receptor modulator such as those described in Demong, D.E. et al. Annual Reports in Medicinal Chemistry 2008, 43, 119-137, GPR119 modulators, particularly agonists, such as those described in WO2010140092, WO2010128425, WO2010128414, WO2010106457, Jones, R.M. et al. in Medicinal Chemistry 2009, 44, 149-170 (e.g. MBX-2982, GSK1292263, APD597 and PSN821), FGF21 derivatives or analogs such as those described in Kharitonenkov, A. et al. et al., Current Opinion in Investigational Drugs 2009, 10(4)359-364, TGR5 (also termed GPBAR1) receptor modulators, particularly agonists, such as those described in Zhong, M., Current Topics in Medicinal Chemistry, 2010, 10(4), 386-396 and INT777, GPR40 agonists, such as those described in Medina, J.C., Annual Reports in Medicinal Chemistry, 2008, 43, 75-85, including but not limited to TAK-875, GPR120 modulators, particularly agonists, high affinity nicotinic acid receptor (HM74A) activators, and SGLT1 inhibitors, such as GSK1614235. A further representative listing of anti-diabetic agents that can be combined with the compounds of the invention can be found, for example, at page 28, line 35 through page 30, line 19 of WO2011005611. Preferred anti-diabetic agents are metformin and DPP-IV inhibitors (e.g., sitagliptin, vildagliptin, alogliptin, dutogliptin, linagliptin and saxagliptin). Other antidiabetic agents could include inhibitors or modulators of carnitine palmitoyl transferase enzymes, inhibitors of fructose 1,6-diphosphatase, inhibitors of aldose reductase, mineralocorticoid receptor inhibitors, inhibitors of TORC2, inhibitors of CCR2 and/or

CCR5, inhibitors of PKC isoforms (e.g. PKCα, PKCβ, PKCγ), inhibitors of fatty acid synthetase, inhibitors of serine palmitoyl transferase, modulators of GPR81, GPR39, GPR43, GPR41, GPR105, Kv1.3, retinol binding protein 4, glucocorticoid receptor, somatostain receptors (e.g. SSTR1, SSTR2, SSTR3 and SSTR5), inhibitors or modulators of PDHK2 or PDHK4, inhibitors of MAP4K4, modulators of IL1 family including IL1beta, modulators of RXRalpha. In addition suitable anti-diabetic agents include mechanisms listed by Carpino, P.A., Goodwin, B. Expert Opin. Ther. Pat, 2010, 20(12), 1627-51.

Suitable anti-obesity agents include 11β-hydroxy steroid dehydrogenase-1 (11β-HSD type 1) inhibitors, stearoyl-CoA desaturase-1 (SCD-1) inhibitor, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (such as sibutramine), sympathomimetic agents, β_3 adrenergic agonists, dopamine agonists (such as bromocriptine), melanocyte-stimulating hormone analogs, 5HT2c agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e. orlistat), anorectic agents (such as a bombesin agonist), neuropeptide-Y antagonists (e.g., NPY Y5 antagonists), PYY_{3-36} (including analogs thereof), thyromimetic agents, dehydroepiandrosterone or an analog thereof, glucocorticoid agonists or antagonists, orexin antagonists, glucagon-like peptide-1 agonists, ciliary neurotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH), human agouti-related protein (AGRP) inhibitors, ghrelin antagonists, histamine 3 antagonists or inverse agonists, neuromedin U agonists, MTP/ApoB inhibitors (e.g., gut-selective MTP inhibitors, such as dirlotapide), opioid antagonist, orexin antagonist, the combination of naltrexone with buproprion and the like.

Preferred anti-obesity agents for use in the combination aspects of the invention include gut-selective MTP inhibitors (e.g., dirlotapide, mitratapide and implitapide, R56918 (CAS No. 403987) and CAS No. 913541-47-6), CCKa agonists (e.g., *N*-benzyl-2-[4-(1H-indol-3-ylmethyl)-5-oxo-1-phenyl-4,5-dihydro-2,3,6,10b-tetraaza-benzo[e]azulen-6-yl]-*N*-isopropyl-acetamide described in PCT Publication No. WO 2005/116034 or US Publication No. 2005-0267100 A1), 5HT2c agonists (e.g., lorcaserin), MCR4 agonist (e.g., compounds described in US 6,818,658), lipase inhibitor (e.g., Cetilistat), PYY_{3-36} (as used herein "PYY_{3-36}" includes analogs, such as peglated PYY_{3-36} e.g., those described in US Publication 2006/0178501), opioid antagonists (e.g., naltrexone), the combination of naltrexone with buproprion, oleoyl-estrone (CAS No. 180003-17-2), obinepitide (TM30338), pramlintide (Symlin®), tesofensine (NS2330), leptin, liraglutide, bromocriptine, orlistat, exenatide (Byetta®), AOD-9604 (CAS No. 221231-10-3), phentermine and topiramate (trade name: Qsymia), and sibutramine. Preferably, compounds of the invention and combination therapies are administered in conjunction with exercise and a sensible diet.

The compounds of the invention may be used in combination with cholesterol modulating agents (including cholesterol lowering agents) such as a lipase inhibitor, an HMG-

CoA reductase inhibitor, an HMG-CoA synthase inhibitor, an HMG-CoA reductase gene expression inhibitor, an HMG-CoA synthase gene expression inhibitor, an MTP/Apo B secretion inhibitor, a CETP inhibitor, a bile acid absorption inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a squalene synthetase inhibitor, a squalene epoxidase inhibitor, a squalene cyclase inhibitor, a combined squalene epoxidase/squalene cyclase inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant or an agent such as mipomersen.

Examples of suitable cholesterol/lipid lowering agents and lipid profile therapies include: HMG-CoA reductase inhibitors (e.g., pravastatin, lovastatin, atorvastatin, simvastatin, fluvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin); squalene synthetase inhibitors; fibrates; bile acid sequestrants (such as questran); ACAT inhibitors; MTP inhibitors; lipooxygenase inhibitors; choesterol absorption inhibitors; and cholesteryl ester transfer protein inhibitors. Other atherosclerotic agents include PCSK9 modulators.

In another embodiment, the compounds of the invention may be co-administered with agents for the treatment of non-alcoholic steatohepatitis (NASH) and/or non-alcoholic fatty liver disease (NAFLD), such as Orlistat, TZDs and other insulin sensitizing agents, FGF21 analogs, Metformin, Omega-3-acid ethyl esters (e.g. Lovaza), Fibrates, HMG CoA-reductase Inhibitors, Ezitimbe, Probucol, Ursodeoxycholic acid, TGR5 agonists, FXR agonists, Vitamin E, Betaine, Pentoxifylline, CB1 antagonists, Carnitine, *N*-acetylcysteine, Reduced glutathione, lorcaserin, the combination of naltrexone with buproprion, SGLT2 Inhibitors, Phentermine, Topiramate, Incretin (GLP and GIP) analogs and Angiotensin-receptor blockers.

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

Additional therapeutic agents include anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, thrombolytic or fibrinolytic agents, anti-arrythmic agents, anti-hypertensive agents, calcium channel blockers (L-type and T-type), cardiac glycosides, diruetics, mineralocorticoid receptor antagonists, NO donating agents such as organonitrates, NO promoting agents such as phosphodiesterase inhibitors, cholesterol/lipid lowering agents and lipid profile therapies, anti-diabetic agents, anti-depressants, anti-inflammatory agents (steroidal and non-steroidal), anti-osteoporosis agents, hormone replacement therapies, oral contraceptives, anti-obesity agents, anti-anxiety agents, anti-proliferative agents, anti-tumor agents, anti-ulcer and gastroesophageal reflux disease agents, growth hormone and/or growth hormone secretagogues, thyroid mimetics (including thyroid hormone receptor antagonist), anti-infective agents, anti-viral agents, anti-bacterial agents, and anti-fungal agents.

Agents used in an ICU setting are included, for example, dobutamine, dopamine, dpinephrine, nitroglycerin, nitroprusside etc.

Combination agents useful for treating vasculitis are included, for example, azathioprine, cyclophosphamide, mycophenolate, mofetil, rituximab etc.

In another embodiment, the invention provides a combination wherein an additional agent (the third agent) is at least one agent selected from a factor Xa inhibitor, an anti-coagulant agent, an anti-platelet agent, a thrombin inhibiting agent, a thrombolytic agent, and a fibrinolytic agent. Exemplary factor Xa inhibitors include apixaban and rivaroxaban. Examples of suitable anti-coagulants for use in combination with the compounds of the invention include heparins (e.g., unfractioned and low molecular weight heparins such as enoxaparin and dalteparin).

In another preferred embodiment the additional (the third agent) is at least one agent selected from warfarin, dabigatran, unfractionated heparin, low molecular weight heparin, synthetic pentasaccharide, hirudin, argatrobanas, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, melagatran, disulfatohirudin, tissue plasminogen activator, modified tissue plasminogen activator, anistreplase, urokinase, and streptokinase.

A preferred third agent is at least one anti-platelet agent. Especially preferred anti-platelet agents are aspirin and clopidogrel.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function, for example by inhibiting the aggregation, adhesion or granular secretion of platelets. Agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam, and pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA) and COX-2 inhibitors such as CELEBREX or piroxicam are preferred. Other suitable platelet inhibitory agents include IIb/IIIa antagonists (e.g., tirofiban, eptifibatide, and abciximab), thromboxane-A2-receptor antagonists (e.g., ifetroban), thromboxane-A2-synthetase inhibitors, PDE-III inhibitors (e.g., Pletal, dipyridamole), and pharmaceutically acceptable salts or prodrugs thereof.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, is also intended to include ADP (adenosine diphosphate) receptor antagonists, preferably antagonists of the purinergic receptors P_2Y_1 and P_2Y_{12}, with P_2Y_{12} being even more preferred. Preferred P_2Y_{12} receptor antagonists include ticagrelor, prasugrel, ticlopidine and clopidogrel, including pharmaceutically acceptable salts or prodrugs thereof. Clopidogrel is an even more preferred agent. Ticlopidine and clopidogrel are also preferred compounds since they are known to be gentle on the gastro-intestinal tract in use.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boropeptides, dabigatran, heparins, hirudin, argatroban, and melagatran, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal alpha-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. The term thrombolytics or fibrinolytic agents (or thrombolytics or fibrinolytics), as used herein, denote agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator (natural or recombinant) and modified forms thereof, anistreplase, urokinase, streptokinase, tenecteplase (TNK), lanoteplase (nPA), factor VIIa inhibitors, PAI-1 inhibitors (i.e., inactivators of tissue plasminogen activator inhibitors), alpha2-antiplasmin inhibitors, and anisoylated plasminogen streptokinase activator complex, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in EP 028,489. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Examples of suitable anti-arrythmic agents include: Class I agents (such as propafenone); Class II agents (such as metoprolol, atenolol, carvadiol and propranolol); Class III agents (such as sotalol, dofetilide, amiodarone, azimilide and ibutilide); Class IV agents (such as ditiazem and verapamil); K^+ channel openers such as I_{Ach} inhibitors, and I_{Kur} inhibitors (e.g., compounds such as those disclosed in WO01/40231).

The compounds of the invention may be used in combination with antihypertensive agents and such antihypertensive activity is readily determined by those skilled in the art according to standard assays (e.g., blood pressure measurements). Examples of suitable anti-hypertensive agents include: alpha adrenergic blockers; beta adrenergic blockers; calcium channel blockers (e.g., diltiazem, verapamil, nifedipine and amlodipine); vasodilators (e.g., hydralazine), diruetics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, torsemide, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone); renin inhibitors; ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril); AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan); ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265); Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389); neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., gemopatrilat and nitrates). An exemplary antianginal agent is ivabradine.

Examples of suitable calcium channel blockers (L-type or T-type) include diltiazem, verapamil, nifedipine and amlodipine and mybefradil.

Examples of suitable cardiac glycosides include digitalis and ouabain.

In one embodiment, the compounds of the invention may be co-administered with one or more diuretics. Examples of suitable diuretics include (a) loop diuretics such as furosemide (such as LASIX™), torsemide (such as DEMADEX™), bemetanide (such as BUMEX™), and ethacrynic acid (such as EDECRIN™); (b) thiazide-type diuretics such as chlorothiazide (such as DIURIL™, ESIDRIX™ or HYDRODIURIL™), hydrochlorothiazide (such as MICROZIDE™ or ORETIC™), benzthiazide, hydroflumethiazide (such as SALURON™), bendroflumethiazide, methychlorthiazide, polythiazide, trichlormethiazide, and indapamide (such as LOZOL™); (c) phthalimidine-type diuretics such as chlorthalidone (such as HYGROTON™), and metolazone (such as ZAROXOLYN™); (d) quinazoline-type diuretics such as quinethazone; and (e) potassium-sparing diuretics such as triamterene (such as DYRENIUM™), and amiloride (such as MIDAMOR™ or MODURETIC™).

In another embodiment, the compounds of the invention may be co-administered with a loop diuretic. In still another embodiment, the loop diuretic is selected from furosemide and torsemide. In still another embodiment, the compounds of the invention may be co-administered with furosemide. In still another embodiment, the compounds of the invention may be co-administered with torsemide which may optionally be a controlled or modified release form of torsemide.

In another embodiment, the compounds of the invention may be co-administered with a thiazide-type diuretic. In still another embodiment, the thiazide-type diuretic is selected from the group consisting of chlorothiazide and hydrochlorothiazide. In still another embodiment, the compounds of the invention may be co-administered with chlorothiazide. In still another embodiment, the compounds of the invention may be co-administered with hydrochlorothiazide.

In another embodiment, the compounds of the invention may be co-administered with a phthalimidine-type diuretic. In still another embodiment, the phthalimidine-type diuretic is chlorthalidone. Examples of suitable mineralocorticoid receptor antagonists include sprionolactone and eplerenone. Examples of suitable phosphodiesterase inhibitors include: PDE III inhibitors (such as cilostazol); and PDE V inhibitors (such as sildenafil).

Those skilled in the art will recognize that the compounds of this invention may also be used in conjunction with other cardiovascular or cerebrovascular treatments including PCI, stenting, drug eluting stents, stem cell therapy and medical devices such as implanted pacemakers, defibrillators, or cardiac resynchronization therapy.

The dosage of each therapeutic agent, e.g., the GLP-1R agonist described herein, and any additional therapeutic agent, is generally dependent upon a number of factors including the health of the subject being treated, the extent of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and the nature of the effect desired. In general, the dosage range of each therapeutic agent is in the range of from about 0.001 mg to about 100 mg per kilogram body weight of the individual per day, preferably from about 0.1 mg to about 10 mg per kilogram body weight of the individual per day. However, some variability in the general dosage range may also be required depending upon the age and weight of the subject being treated, the intended route of administration, the particular anti-obesity agent being administered and the like. The determination of dosage ranges and optimal dosages for a particular patient is also well within the ability of one of ordinary skill in the art having the benefit of the instant disclosure.

According to the methods of treatment of the invention, a compound of the invention or a combination of a compound of the invention and at least one additional pharmaceutical agent (referred to herein as a "combination") is administered to a subject in need of such treatment, preferably in the form of a pharmaceutical composition. In the combination aspect of the invention, the compound of the invention and at least one other pharmaceutical agent (e.g., another anti-obesity agent,) may be administered either separately or in a pharmaceutical composition comprising both. It is generally preferred that such administration be oral.

When a combination of a compound of the invention and at least one other pharmaceutical agent are administered together, such administration may be sequential in time or simultaneous. Simultaneous administration of drug combinations is generally preferred. For sequential administration, a compound of the invention and the additional pharmaceutical agent may be administered in any order. It is generally preferred that such administration be oral. It is especially preferred that such administration be oral and simultaneous. When a compound of the invention and the additional pharmaceutical agent are administered sequentially, the administration of each may be by the same or by different methods.

According to the methods of the invention, a compound of the invention or a combination is preferably administered in the form of a pharmaceutical composition. Accordingly, a compound of the invention or a combination can be administered to a patient separately or together in any conventional oral, rectal, transdermal, parenteral (e.g., intravenous, intramuscular or subcutaneous), intracisternal, intravaginal, intraperitoneal, topical (e.g., powder, ointment, cream, spray or lotion), buccal or nasal dosage form (e.g., spray, drops or inhalant).

The compounds of the invention or combinations can be administered alone but will generally be administered in an admixture with one or more suitable pharmaceutical excipients, adjuvants, diluents or carriers known in the art and selected with regard to the intended route of administration and standard pharmaceutical practice. The compound of the invention or combination may be formulated to provide immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release dosage forms depending on the desired route of administration and the specificity of release profile, commensurate with therapeutic needs.

The pharmaceutical composition comprises a compound of the invention or a combination in an amount generally in the range of from about 1% to about 75%, 80%, 85%, 90% or even 95% (by weight) of the composition, usually in the range of about 1%, 2% or 3% to about 50%, 60% or 70%, more frequently in the range of about 1%, 2% or 3% to less than 50% such as about 25%, 30% or 35%.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known to those skilled in this art. For examples, see Remington: The Practice of Pharmacy, Lippincott Williams and Wilkins, Baltimore Md. 20.sup.th ed. 2000.

Compositions suitable for parenteral injection generally include pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers or diluents (including solvents and vehicles) include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, triglycerides including vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. A prefrerred carrier is Miglyol.RTM. brand caprylic/capric acid ester with glycerine or propylene glycol (e.g., Miglyol.RTM. 812, Miglyol.RTM. 829, Miglyol.RTM. 840) available from Condea Vista Co., Cranford, N.J. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions for parenteral injection may also contain excipients such as preserving, wetting, emulsifying, and dispersing agents. Prevention of microorganism contamination of the compositions can be accomplished with various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged absorption of injectable pharmaceutical compositions can be brought about by the use of agents capable of delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, chews, lozenges, pills, powders, and multi-particulate preparations (granules). In such solid dosage forms, a compound of the invention or a combination is admixed with at least one inert excipient, diluent or carrier. Suitable excipients, diluents or carriers include materials such as sodium citrate or dicalcium phosphate and/or (a) one or more fillers or extenders (e.g., microcrystalline cellulose (available as Avicel.TM. from FMC Corp.) starches, lactose, sucrose, mannitol, silicic acid, xylitol, sorbitol, dextrose, calcium hydrogen phosphate, dextrin, alpha-cyclodextrin, beta-cyclodextrin, polyethylene glycol, medium chain fatty acids, titanium oxide, magnesium oxide, aluminum oxide and the like); (b) one or more binders (e.g., carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, alginates, gelatin, polyvinylpyrrolidone, sucrose, acacia and the like); (c) one or more humectants (e.g., glycerol and the like); (d) one or more disintegrating agents (e.g., agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, sodium carbonate, sodium lauryl sulphate, sodium starch glycolate (available as Explotab.TM.from Edward Mendell Co.), cross-linked polyvinyl pyrrolidone, croscarmellose sodium A-type (available as Ac-di-sol.TM.), polyacrilin potassium (an ion exchange resin) and the like); (e) one or more solution retarders (e.g., paraffin and the like); (f) one or more absorption accelerators (e.g., quaternary ammonium compounds and the like); (g) one or more wetting agents (e.g., cetyl alcohol, glycerol monostearate and the like); (h) one or more adsorbents (e.g., kaolin, bentonite and the like); and/or (i)one or more lubricants (e.g., talc, calcium stearate, magnesium stearate, stearic acid, polyoxyl stearate, cetanol, talc, hydrogenated caster oil, sucrose esters of fatty acid, dimethylpolysiloxane, microcrystalline wax, yellow beeswax, white beeswax, solid polyethylene glycols, sodium lauryl sulfate and the like). In the case of capsules and tablets, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be used as fillers in soft or hard filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, and granules may be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may also contain opacifying agents, and can also be of such composition that they release the compound of the invention and/or the additional pharmaceutical agent in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The drug may also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

For tablets, the active agent will typically comprise less than 50% (by weight) of the formulation, for example less than about 10% such as 5% or 2.5% by weight. The predominant portion of the formulation comprises fillers, diluents, disintegrants, lubricants and optionally, flavors. The composition of these excipients is well known in the art. Frequently, the fillers/diluents will comprise mixtures of two or more of the following components: microcrystalline cellulose, mannitol, lactose (all types), starch, and di-calcium phosphate. The filler/diluent mixtures typically comprise less than 98% of the formulation and preferably less than 95%, for example 93.5%. Preferred disintegrants include Ac-di-sol.TM., Explotab.TM., starch and sodium lauryl sulphate. When present a disintegrant will usually comprise less than 10% of the formulation or less than 5%, for example about 3%. A preferred lubricant is magnesium stearate. When present a lubricant will usually comprise less than 5% of the formulation or less than 3%, for example about 1%.

Tablets may be manufactured by standard tabletting processes, for example, direct compression or a wet, dry or melt granulation, melt congealing process and extrusion. The tablet cores may be mono or multi-layer(s) and can be coated with appropriate overcoats known in the art.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the compound of the invention or the combination, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame seed oil and the like), Miglyole.RTM. (available from CONDEA Vista Co., Cranford, N.J.), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition may also include excipients, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Oral liquid forms of the compounds of the invention or combinations include solutions, wherein the active compound is fully dissolved. Examples of solvents include all pharmaceutically precedented solvents suitable for oral administration, particularly those in which the compounds of the invention show good solubility, e.g., polyethylene glycol, polypropylene glycol, edible oils and glyceryl- and glyceride-based systems. Glyceryl- and glyceride-based systems may include, for example, the following branded products (and corresponding generic products): Captex.TM. 355 EP (glyceryl tricaprylate/caprate, from Abitec, Columbus Ohio), Crodamol.TM. GTC/C (medium chain triglyceride, from Croda, Cowick Hall, UK) or Labrafac.TM. CC (medium chain triglyides, from Gattefosse), Captex.TM. 500P (glyceryl triacetate i.e. triacetin, from Abitec), Capmul.TM. MCM (medium chain mono- and diglycerides, fromAbitec), Migyol.TM. 812 (caprylic/capric triglyceride, from Condea, Cranford N.J.), Migyol.TM. 829 (caprylic/capric/succinic triglyceride, from Condea), Migyol.TM. 840 (propylene glycol dicaprylate/dicaprate, from Condea), Labrafil.TM. M1944CS (oleoyl macrogol-6 glycerides, from Gattefosse), Peceol.TM. (glyceryl monooleate, from Gattefosse) and Maisine.TM. 35-1 (glyceryl monooleate, from Gattefosse). Of particular interest are the medium chain (about C.sub.8 to C.sub.10) triglyceride oils. These solvents frequently make up the predominant portion of the composition, i.e., greater than about 50%, usually greater than about 80%, for example about 95% or 99%. Adjuvants and additives may also be included with the solvents principally as taste-mask agents, palatability and flavoring agents, antioxidants, stabilizers, texture and viscosity modifiers and solubilizers.

Suspensions, in addition to the compound of the invention or the combination, may further comprise carriers such as suspending agents, e.g., ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal or vaginal administration preferably comprise suppositories, which can be prepared by mixing a compound of the invention or a combination with suitable non-irritating excipients or carriers, such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ordinary room temperature, but liquid at body temperature, and therefore, melt in the rectum or vaginal cavity thereby releasing the active component(s).

Dosage forms for topical administration of the compounds of the invention or combinations include ointments, creams, lotions, powders and sprays. The drugs are admixed with a pharmaceutically acceptable excipient, diluent or carrier, and any preservatives, buffers, or propellants that may be required.

When compounds are poorly soluble in water, e.g., less than about 1 .mu.g/mL, liquid compositions in solubilizing, non-aqueous solvents such as the medium chain triglyceride oils discussed above are a preferred dosage form for these compounds.

Solid amorphous dispersions, including dispersions formed by a spray-drying process, are also a preferred dosage form for the poorly soluble compounds of the invention. By "solid amorphous dispersion" is meant a solid material in which at least a portion of the poorly soluble compound is in the amorphous form and dispersed in a water-soluble polymer. By "amorphous" is meant that the poorly soluble compound is not crystalline. By "crystalline" is meant that the compound exhibits long-range order in three dimensions of at least 100 repeat units in each dimension. Thus, the term amorphous is intended to include not only material which has essentially no order, but also material which may have some small degree of order, but the order is in less than three dimensions and/or is only over short distances. Amorphous material may be characterized by techniques known in the art such as powder x-ray diffraction (PXRD) crystallography, solid state NMR, or thermal techniques such as differential scanning calorimetry (DSC).

Preferably, at least a major portion (i.e., at least about 60 wt %) of the poorly soluble compound in the solid amorphous dispersion is amorphous. The compound can exist within the solid amorphous dispersion in relatively pure amorphous domains or regions, as a solid solution of the compound homogeneously distributed throughout the polymer or any combination of these states or those states that lie intermediate between them. Preferably, the solid amorphous dispersion is substantially homogeneous so that the amorphous compound is dispersed as homogeneously as possible throughout the polymer. As used herein, "substantially homogeneous" means that the fraction of the compound that is present in relatively pure amorphous domains or regions within the solid amorphous dispersion is relatively small, on the order of less than 20 wt %, and preferably less than 10 wt % of the total amount of drug.

Water-soluble polymers suitable for use in the solid amorphous dispersions should be inert, in the sense that they do not chemically react with the poorly soluble compound in an adverse manner, are pharmaceutically acceptable, and have at least some solubility in aqueous solution at physiologically relevant pHs (e.g. 1-8). The polymer can be neutral or ionizable, and should have an aqueous-solubility of at least 0.1 mg/mL over at least a portion of the pH range of 1-8.

Water-soluble polymers suitable for use with the invention may be cellulosic or non-cellulosic. The polymers may be neutral or ionizable in aqueous solution. Of these, ionizable and cellulosic polymers are preferred, with ionizable cellulosic polymers being more preferred.

Exemplary water-soluble polymers include hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl methyl cellulose phthalate (HPMCP), carboxy methyl ethyl cellulose (CMEC), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), polyvinylpyrrolidone (PVP), hydroxypropyl cellulose (HPC), methyl cellulose (MC), block copolymers of ethylene oxide and propylene oxide (PEO/PPO, also known as poloxamers), and mixtures thereof. Especially preferred polymers include HPMCAS, HPMC, HPMCP, CMEC, CAP, CAT, PVP, poloxamers, and mixtures thereof. Most preferred is HPMCAS. See European Patent Application Publication No. 0 901 786 A2.

The solid amorphous dispersions may be prepared according to any process for forming solid amorphous dispersions that results in at least a major portion (at least 60%) of the poorly soluble compound being in the amorphous state. Such processes include mechanical, thermal and solvent processes. Exemplary mechanical processes include milling and extrusion; melt processes including high temperature fusion, solvent-modified fusion and melt-congeal processes; and solvent processes including non-solvent precipitation, spray coating and spray drying. See, for example, the following U.S. Patents: Nos. 5,456,923 and 5,939,099, which describe forming dispersions by extrusion processes; Nos. 5,340,591 and 4,673,564, which describe forming dispersions by milling processes; and Nos. 5,707,646 and 4,894,235, which describe forming dispersions by melt congeal processes. In a preferred process, the solid amorphous dispersion is formed by spray drying, as disclosed in European Patent Application Publication No. 0 901 786 A2. In this process, the compound and polymer are dissolved in a solvent, such as acetone or methanol, and the solvent is then rapidly removed from the solution by spray drying to form the solid amorphous dispersion. The solid amorphous dispersions may be prepared to contain up to about 99 wt % of the compound, e.g., 1 wt %, 5 wt %, 10 wt %, 25 wt %, 50 wt %, 75 wt %, 95 wt %, or 98 wt % as desired.

The solid dispersion may be used as the dosage form itself or it may serve as a manufacturing-use-product (MUP) in the preparation of other dosage forms such as capsules, tablets, solutions or suspensions. An example of an aqueous suspension is an aqueous suspension of a 1:1 (w/w) compound/HPMCAS-HF spray-dried dispersion containing 2.5 mg/mL of compound in 2% polysorbate-80. Solid dispersions for use in a tablet or capsule will generally be mixed with other excipients or adjuvants typically found in such dosage forms. For example, an exemplary filler for capsules contains a 2:1 (w/w) compound/HPMCAS-MF spray-dried dispersion (60%), lactose (fast flow) (15%), microcrystalline cellulose (e.g., Avicel.sup.(R0-102) (15.8%), sodium starch (7%), sodium lauryl sulfate (2%) and magnesium stearate (1%).

The HPMCAS polymers are available in low, medium and high grades as Aqoa.sup.(R)-LF, Aqoat.sup.(R)-MF and Aqoat.sup.(R)-HF respectively from Shin-Etsu Chemical Co., LTD, Tokyo, Japan. The higher MF and HF grades are generally preferred.

The following paragraphs describe exemplary formulations, dosages, etc. useful for non-human animals. The administration of a combination described herein can be effected orally or non-orally.

An amount of each of the components in a combination described herein, together or in combination with an another agent is administered such that an effective dose is received. Generally, a daily dose that is administered orally to an animal is between about 0.01 and about 1,000 mg/kg of body weight, e.g., between about 0.01 and about 300 mg/kg or between about 0.01 and about 100 mg/kg or between about 0.01 and about 50 mg/kg of body weight, or between about 0.01 and about 25 mg/kg, or about 0.01 and about 10 mg/kg or about 0.01 and about 5 mg/kg.

Conveniently, a compound of the invention (or combination) can be carried in the drinking water so that a therapeutic dosage of the compound is ingested with the daily water supply. The compound can be directly metered into drinking water, preferably in the form of a liquid, water-soluble concentrate (such as an aqueous solution of a water-soluble salt).

Conveniently, a compound of the invention (or combination) can also be added directly to the feed, as such, or in the form of an animal feed supplement, also referred to as a premix or concentrate. A premix or concentrate of the compound in an excipient, diluent or carrier is more commonly employed for the inclusion of the agent in the feed. Suitable excipients, diluents or carriers are liquid or solid, as desired, such as water, various meals such as alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal, corncob meal and corn meal, molasses, urea, bone meal, and mineral mixes such as are commonly employed in poultry feeds. A particularly effective excipient, diluent or carrier is the respective animal feed itself; that is, a small portion of such feed. The carrier facilitates uniform distribution of the compound in the finished feed with which the premix is blended. Preferably, the compound is thoroughly blended into the premix and, subsequently, the feed. In this respect, the compound may be dispersed or dissolved in a suitable oily vehicle such as soybean oil, corn oil, cottonseed oil, and the like, or in a volatile organic solvent and then blended with the carrier. It will be appreciated that the proportions of compound in the concentrate are capable of wide variation since the amount of the compound in the finished feed may be adjusted by blending the appropriate proportion of premix with the feed to obtain a desired level of compound.

High potency concentrates may be blended by the feed manufacturer with proteinaceous carrier such as soybean oil meal and other meals, as described above, to produce concentrated supplements, which are suitable for direct feeding to animals. In such instances, the animals are permitted to consume the usual diet. Alternatively, such concentrated supplements may be added directly to the feed to produce a nutritionally balanced, finished feed containing a therapeutically effective level of a compound of the invention. The mixtures are thoroughly blended by standard procedures, such as in a twin shell blender, to ensure homogeneity.

If the supplement is used as a top dressing for the feed, it likewise helps to ensure uniformity of distribution of the compound across the top of the dressed feed.

Drinking water and feed effective for increasing lean meat deposition and for improving lean meat to fat ratio are generally prepared by mixing a compound of the invention with a sufficient amount of animal feed to provide from about 10^{-3} to about 500 ppm of the compound in the feed or water.

The preferred medicated swine, cattle, sheep and goat feed generally contain from about 1 to about 400 grams of a compound of the invention (or combination) per ton of feed, the optimum amount for these animals usually being about 50 to about 300 grams per ton of feed.

The preferred poultry and domestic pet feeds usually contain about 1 to about 400 grams and preferably about 10 to about 400 grams of a compound of the invention (or combination) per ton of feed.

For parenteral administration in animals, the compounds of the invention (or combination) may be prepared in the form of a paste or a pellet and administered as an implant, usually under the skin of the head or ear of the animal in which increase in lean meat deposition and improvement in lean meat to fat ratio is sought.

Paste Formulations may be prepared by dispersing the drug in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil or the like.

Pellets containing a therapeutically effective amount of each of the components in a combination described herein, with a diluent such as carbowax, carnuba wax, and the like, and a lubricant, such as magnesium or calcium stearate, may be added to improve the pelleting process.

It is, of course, recognized that more than one pellet may be administered to an animal to achieve the desired dose level which will provide the increase in lean meat deposition and improvement in lean meat to fat ratio desired. Moreover, implants may also be made periodically during the animal treatment period in order to maintain the proper drug level in the animal's body.

The invention has several advantageous veterinary features. For the pet owner or veterinarian who wishes to increase leanness and/or trim unwanted fat from pet animals, the instant invention provides the means by which this may be accomplished. For poultry, beef and swine breeders, utilization of the method of the invention yields leaner animals that command higher sale prices from the meat industry.

EXAMPLES

Unless specified otherwise, starting materials are generally available from commercial sources such as Aldrich Chemicals Co. (Milwaukee, WI), Lancaster Synthesis, Inc. (Windham, NH), Acros Organics (Fairlawn, NJ), Maybridge Chemical Company, Ltd. (Cornwall, England) and Tyger Scientific (Princeton, NJ). Certain common abbreviations and acronyms have been employed which may include: AcOH (acetic acid), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), CDI (1,1'-carbonyldiimidazole), DCM (dichloromethane), DEA (diethylamine), DIPEA (*N,N*-diisopropylethylamine), DMAP (4-dimethylaminopyridine), DMF (*N,N'*-dimethylformamide), DMSO (dimethylsulfoxide), EDCI (*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide), Et_2O (diethyl ether), EtOAc (ethyl acetate), EtOH (ethanol), G or g (gram), HATU (2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium), HBTU

(*O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluoro phosphate), HOBT (1-hydroxybenzotriazole), H or h (hour), IPA (isopropyl alcohol), KHMDS (potassium hexamethyldisilazane), MeOH (methanol), L or l (liter), mL (milliliter) MTBE (*tert*-butyl methyl ether), mg (milligram), $NaBH(OAc)_3$ (sodium triacetoxyborohydride), NaHMDS (sodium hexamethyldisilazane), NMP (*N*-methylpyrrolidone), RH (relative humidity), RT or rt (room temperature which is the same as ambient temperature (about 20 to 25 °C)), SEM ([2-(Trimethylsilyl)ethoxy]methyl), TEA (triethylamine), TFA (trifluoroacetic acid), THF (tetrahydrofuran), and T_3P (propane phosphonic acid anhydride).

^1H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million (ppm) relative to the residual proton signal in the deuterated solvent ($CHCl_3$ at 7.27 ppm; CD_2HOD at 3.31 ppm) and are reported using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

ssNMR means solid-state NMR.

PXRD means Powder X-ray Diffraction.

The term “substantially the same” when used to describe X-ray powder diffraction patterns is mean to include patterns in which peaks are within a standard deviation of +/- 0.2° 2Θ.

As used herein, the term "substantially pure" with reference to a particular crystalline form means that the crystalline form includes less than 10%, preferably less than 5%, preferably less than 3%, preferably less than 1% by weight of any other physical form of the same compound.

Reactions were performed in air or, when oxygen- or moisture-sensitive reagents or intermediates were employed, under an inert atmosphere (nitrogen or argon). When appropriate, reaction apparatuses were dried under dynamic vacuum using a heat gun, and anhydrous solvents (Sure-Seal™ products from Aldrich Chemical Company, Milwaukee, Wisconsin or DriSolv™ products from EMD Chemicals, Gibbstown, NJ) were employed. Commercial solvents and reagents were used without further purification. When indicated, reactions were heated by microwave irradiation using Biotage Initiator or Personal Chemistry Emrys Optimizer microwaves. Reaction progress was monitored using thin layer chromatography (TLC), liquid chromatography-mass spectrometry (LCMS), high performance liquid chromatography (HPLC), and/or gas chromatography-mass spectrometry (GCMS) analyses. TLC was performed on pre-coated silica gel plates with a fluorescence indicator (254 nm excitation wavelength) and visualized under UV light and/or with I_2, $KMnO_4$, $CoCl_2$, phosphomolybdic acid, and/or ceric ammonium molybdate stains. LCMS data were acquired on an Agilent 1100 Series instrument with a Leap Technologies autosampler, Gemini C18 columns, MeCN/water gradients, and either TFA, formic acid, or ammonium hydroxide modifiers. The column eluent was analyzed using Waters ZQ mass spectrometer scanning in both positive and negative ion modes from 100 to 1200 Da. Other similar instruments were also used. HPLC data were acquired on an Agilent 1100 Series instrument using Gemini or XBridge C18 columns, MeCN/water gradients, and either TFA or ammonium hydroxide modifiers. GCMS data were acquired using a Hewlett Packard 6890 oven with an HP 6890 injector, HP-1 column (12 m×0.2 mm×0.33 μm), and helium carrier gas. The sample was analyzed on an HP 5973 mass selective detector scanning from 50 to 550 Da using electron ionization. Purifications were performed by medium performance liquid chromatography (MPLC) using Isco CombiFlash Companion, AnaLogix IntelliFlash 280, Biotage SP1, or Biotage Isolera One instruments and pre-packed Isco RediSep or Biotage Snap silica cartridges. Chiral purifications were performed by chiral supercritical fluid chromatography (SFC) using Berger or Thar instruments; ChiralPAK-AD, -AS, -IC, Chiralcel-OD, or –OJ columns; and CO_2 mixtures with MeOH, EtOH, iPrOH, or MeCN, alone or modified using TFA or $iPrNH_2$. UV detection was used to trigger fraction collection.

Mass spectrometry data are reported from LCMS analyses. Mass spectrometry (MS) was performed via atmospheric pressure chemical ionization (APCI), electrospray Ionization (ESI), electron impact ionization (EI) or electron scatter (ES) ionization sources. Mass spectrometry data is reported from either liquid chromatography-mass spectrometry (LCMS), atmospheric pressure chemical ionization (APCI) or gas chromatography-mass spectrometry (GCMS) instrumentation. The symbol ♦ denotes that the chlorine isotope pattern was observed in the mass spectrum. Proton nuclear magnetic spectroscopy (^1H NMR) chemical shifts are given in parts per million downfield from tetramethylsilane and were recorded on on 300, 400, 500, or 600 MHz Varian spectrometers. Chemical shifts are expressed in parts per million (ppm, δ) referenced to the deuterated solvent residual peaks. The peak shapes are described as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br s, broad singlet; app, apparent. Analytical SFC data were acquired on a Berger analytical instrument as described above. Optical rotation data were acquired on a PerkinElmer model 343 polarimeter using a 1 dm cell. Silica gel chromatography was performed primarily using a medium pressure Biotage or ISCO systems using columns pre-packaged by various commercial vendors including Biotage and ISCO. Microanalyses were performed by Quantitative Technologies Inc. and were within 0.4% of the calculated values.

Unless otherwise noted, chemical reactions were performed at room/ambient temperature (about 23 degrees Celsius).

The compounds and intermediates described below generally were named using the naming convention provided with ChemBioDraw Ultra, Version 12.0 (CambridgeSoft Corp., Cambridge, Massachusetts). The naming convention provided with ChemBioDraw Ultra, Version 12.0 are well known by those skilled in the art and it is believed that the naming convention provided with ChemBioDraw Ultra, Version 12.0 generally comports with the IUPAC (International Union for Pure and Applied Chemistry) recommendations on Nomenclature of Organic Chemistry and the CAS Index rules. Unless noted otherwise, all reactants were obtained commercially without further purifications or were prepared using methods known in the literature.

Chiral separations were used to separate enantiomers or diastereomers of some intermediates during the preparation of the compounds of the invention. When chiral separation was done, the separated enantiomers were designated as ENT-1 or ENT-2 (or DIAST-1 or DIAST-2), according to their order of elution. In some embodiments, enantiomers designated as ENT-1 or ENT-2 can be used as starting materials to prepare other enantiomers or diastereomers. In such situations, the resulting enantiomers prepared are designated as ENT-X1 and ENT-X2, respectively, according to their starting materials; similarly, the diastereomers prepared are designated as DIAST-X1 and DIAST-X2, respectively, (or DIAST-according to their starting materials. DIAST-Y and DIAST-Z nomenclature is used similarly, in syntheses employing multiple intermediates.

For compounds with two chiral centers, the stereoisomers at each stereocenter were separated at different times. The designation of ENT-1 or ENT-2 (or DIAST-1 or DIAST-2) of an intermediate or an example refers to the order of elution for the separation done at that step. It is recognized that when stereoisomers at a chiral center are separated in a compound with two or more centers, the separated enantiomers are diastereomers of each other. By way of example, but not limitation, Examples **15** and **16** have two chiral centers. The chiral center of the cyclopropyl moiety was separated when intermediate **C36** was separated into ENT-1, giving intermediate **P17,** and ENT-2, giving intermediate **P18**. **P18** was then used in preparing **C70**, which had one stereoisomer enriched at the cyclopropyl chiral carbon and a mixture of stereoisomers at the dioxolane carbon. **C70** was then separated into DIAST-Y1 at the dioxolane carbon, giving intermediate **C71**, and DIAST-Y2 at the dioxolane carbon, giving intermediate **C72**, where these intermediates are enriched in a single stereoisomer. **C71** was then used to prepare Example 15, which is identified by name as 2-{6-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-6-azaspiro[2.5]oct-1-yl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, DIAST-X1, trifluoroacetate salt [from **P18** via **C71**]. In these preparations, after a mixture is subjected to separation procedures, the chiral center is identified with “abs” near that center, with the understanding that the separated enantiomers may not be enantiomerically pure. Typically, the enriched enantiomer at each chiral center is >90% of the isolated material. Preferably, the enriched enantiomer at each center is >98% of the mixture.

In some examples, the optical rotation of an enantiomer was measured using a polarimeter. According to its observed rotation data (or its specific rotation data), an enantiomer with a clockwise rotation was designated as the (+)-enantiomer and an enantiomer with a counter-clockwise rotation was designated as the (-)-enantiomer. Racemic compounds are indicated either by the absence of drawn or described stereochemistry, or by the presence of (+/-) adjacent to the structure; in this latter case, indicated stereochemistry represents the relative (rather than absolute) configuration of the compound's substituents.

Reactions proceeding through detectable intermediates were generally followed by LCMS, and allowed to proceed to full conversion prior to addition of subsequent reagents. For syntheses referencing procedures in other Examples or Methods, reaction conditions (reaction time and temperature) may vary. In general, reactions were followed by thin-layer chromatography or mass spectrometry, and subjected to work-up when appropriate. Purifications may vary between experiments: in general, solvents and the solvent ratios used for eluents/gradients were chosen to provide appropriate R_fs or retention times. All starting materials in these Preparations and Examples are either commercially available or can be prepared by methods known in the art or as described herein.

The terms "concentrated", "evaporated", and "concentrated in vacuo" refer to the removal of solvent at reduced pressure on a rotary evaporator with a bath temperature less than 60°C. The abbreviation "min" and "h" stand for "minutes" and "hours" respectively. The term "TLC" refers to thin layer chromatography, "room temperature or ambient temperature" means a temperature between 18 to 25°C, "GCMS" refers to gas chromatography–mass spectrometry, "LCMS" refers to liquid chromatography–mass spectrometry, "UPLC" refers to ultra performance liquid chromatography and "HPLC" refers to high pressure liquid chromatography, "SFC" refers to supercritical fluid chromatography.

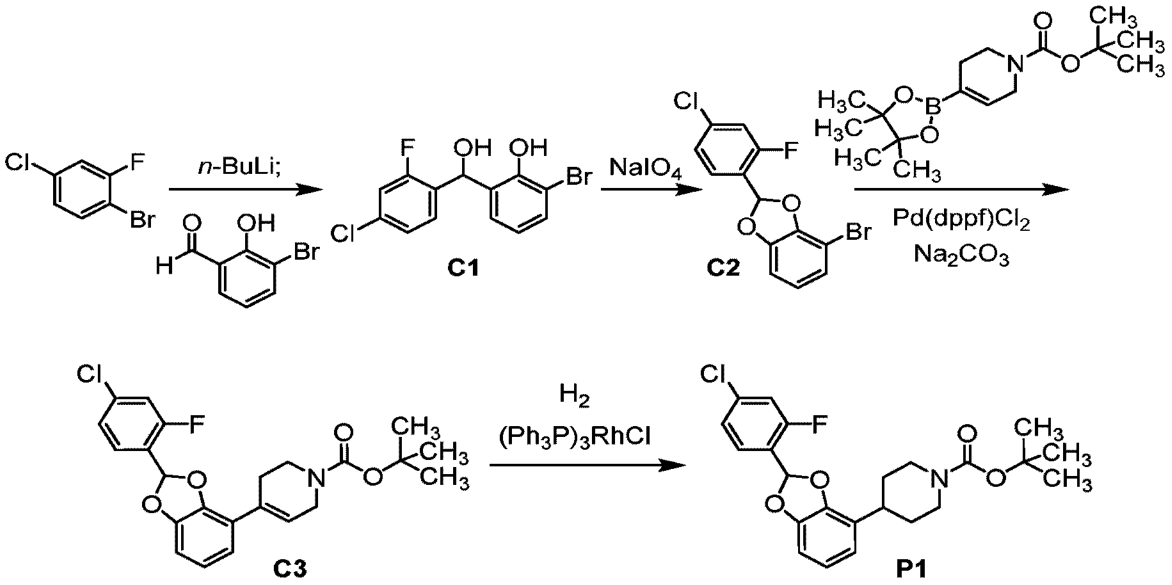
Hydrogenation may be performed in a Parr Shaker under pressurized hydrogen gas, or in Thales-nano H-Cube flow hydrogenation apparatus at full hydrogen and a flow rate between 1-2 mL/min at specified temperature.

HPLC, UPLC, LCMS, GCMS, and SFC retention times were measured using the methods noted in the procedures.

PREPARATION OF INTERMEDIATES AND EXAMPLES

Preparation P1

tert-*Butyl 4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidine-1-carboxylate **(P1)***



*Step 1. Synthesis of 2-bromo-6-[(4-chloro-2-fluorophenyl)(hydroxy)methyl]phenol (**C1**).*

This experiment was carried out in two batches of the same scale. *n*-Butyllithium (2.5 M solution in hexanes; 32.8 mL, 82.0 mmol) was slowly added to a −70 °C solution of 1-bromo-4-chloro-2-fluorobenzene (17.2 g, 82.1 mmol) in diethyl ether (100 mL), while the temperature of the reaction mixture was maintained below −60 °C. After the reaction mixture had been stirred at −70 °C for 20 minutes, a solution of 3-bromo-2-hydroxybenzaldehyde (5.5 g, 27 mmol) in diethyl ether (100 mL) was slowly added, while the reaction temperature was maintained below −60 °C. After a further 1 hour of stirring at −70 °C, the reaction was quenched by addition of aqueous ammonium chloride solution (50 mL) at −70 °C, and the resulting mixture was diluted with water (100 mL). The two batches were combined at this point and extracted with ethyl acetate (400 mL); the organic layer was washed with saturated aqueous sodium chloride solution (200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography (Gradient: 0% to 7% ethyl acetate in petroleum ether) afforded **C1** as a white solid. Combined yield: 15.7 g, 47.4 mmol, 88%. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.44 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.37 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.15 (br dd, *J* = 8.5, 2.1 Hz, 1H), 7.12 – 7.05 (m, 2H), 6.80 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.78 (s, 1H), 6.31 (d, *J* = 4.8 Hz, 1H), 3.02 (br d, *J* = 4.9 Hz, 1H).

*Step 2. Synthesis of 4-bromo-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxole (**C2**).*

To a solution of **C1** (15.7 g, 47.4 mmol) in methanol (450 mL) was added a solution of sodium periodate (25.4 g, 119 mmol) in water (105 mL), and the reaction mixture was stirred at 30 °C for 16 hours, whereupon it was concentrated *in vacuo*. After the residue had been diluted with dichloromethane (500 mL), it was washed with water (500 mL). The dichloromethane solution was then dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via silica gel chromatography (Eluent: petroleum ether) provided **C2** as a white solid. Yield: 10.0 g, 30.3 mmol, 64%. The following ^{1}H NMR data was obtained from an experiment carried out in the same manner but on smaller scale. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 – 7.61 (m, 2H), 7.50 (s, 1H), 7.43 (br dd, *J* = 8, 2 Hz, 1H), 7.09 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.01 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.1, 8.1 Hz, 1H).

Step 3. Synthesis of tert-*butyl 4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]-3,6-dihydropyridine-1(*2H*)-carboxylate (**C3**).*

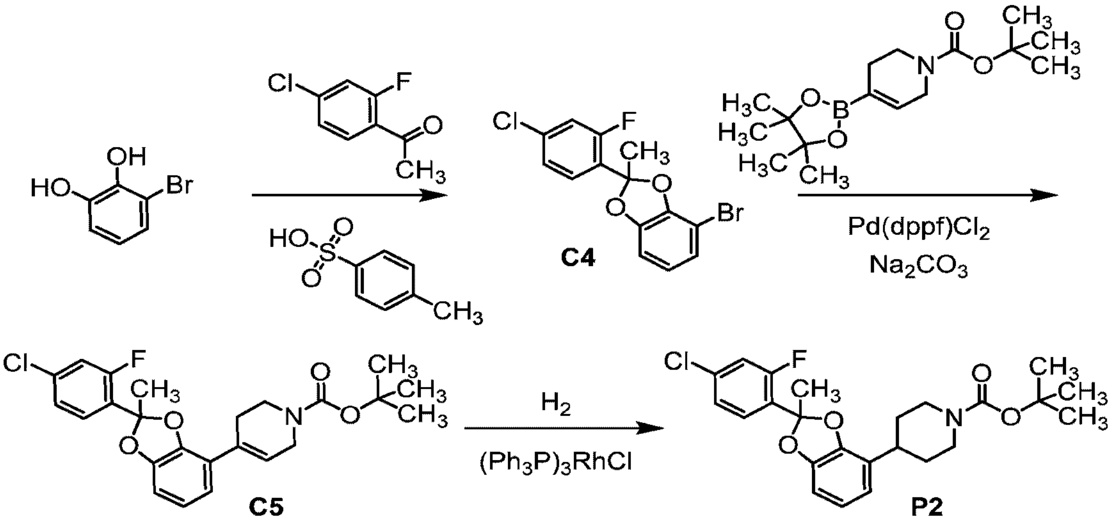
A reaction flask containing a suspension of **C2** (8.00 g, 24.3 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (9.01 g, 29.1 mmol), sodium carbonate (5.15 g, 48.6 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) [Pd(dppf)Cl_2; 888 mg, 1.21 mmol] in 1,4-dioxane (80 mL) and water (32 mL) was evacuated and charged with nitrogen. This evacuation cycle was repeated twice, and then the reaction mixture was stirred at 90 °C for 16 hours. After removal of solvent *in vacuo*, the residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was washed with saturated aqueous sodium chloride solution (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Chromatography on silica gel (Gradient: 0% to 4.3% ethyl acetate in petroleum ether) provided the product, which was combined with material from a similar reaction carried out using **C2** (2.00 g, 6.07 mmol) to afford **C3** as a light-yellow gum. Combined yield: 10.3 g, 23.8 mmol, 78%. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.53 (dd, *J* = 8.3, 7.8 Hz, 1H), 7.23 – 7.16 (m, 3H), 6.88 – 6.83 (m, 2H), 6.81 – 6.76 (m, 1H), 6.34 – 6.28 (br m, 1H), 4.10 – 4.05 (m, 2H), 3.61 (br dd, *J* = 6, 5 Hz, 2H), 2.59 – 2.50 (br m, 2H), 1.48 (s, 9H).

Step 4. Synthesis of tert-*butyl 4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (**P1**).*

A solution of **C3** (10.3 g, 23.8 mmol) and tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst; 1.54 g, 1.66 mmol) in methanol (100 mL) was stirred at 50 °C under hydrogen (45 psi) for 18 hours. The reaction mixture was then filtered through a pad of diatomaceous earth, and the filtrate was concentrated under reduced pressure and subjected to silica gel chromatography (Gradient: 0% to 9% ethyl acetate in petroleum ether). The resulting material was combined with that from a similar reaction carried out using **C3** (1.67 g, 3.87 mmol) to afford **P1** as a colorless gum. Combined yield: 10.3 g, 23.7 mmol, 86%. LCMS *m/z* 456.1♦ [M+Na^{+}]. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.52 (dd, *J* = 8.5, 7.6 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.16 (s, 1H), 6.83 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.78 – 6.69 (m, 2H), 4.35 – 4.10 (br m, 2H), 2.89 – 2.71 (m, 3H), 1.89 – 1.77 (m, 2H), 1.77 – 1.63 (m, 2H), 1.47 (s, 9H).

Preparation P2

tert-*Butyl 4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (**P2**)*



*Step 1. Synthesis of 4-bromo-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxole (**C4**).*

To a solution of 3-bromobenzene-1,2-diol (330 g, 1.75 mol) in toluene (1.5 L) were added 1-(4-chloro-2-fluorophenyl)ethanone (316 g, 1.83 mol) and *p*-toluenesulfonic acid (6.02 g, 35.0 mmol). The reaction apparatus was fitted with a Dean-Stark trap, and the reaction mixture was heated at 140 °C for 60 hours, whereupon the solution was concentrated *in vacuo* and purified using silica gel chromatography (Eluent: petroleum ether); **C4** was obtained as a mixture of yellow oil and solid. Yield: 158 g, 460 mmol, 26%. ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.54 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.17 – 7.10 (m, 2H), 6.95 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.75 (dd, component of ABX pattern, *J* = 7.8, 1.4 Hz, 1H), 6.70 (dd, component of ABX pattern, *J* = 7.9, 7.9 Hz, 1H), 2.11 (d, *J* = 1.1 Hz, 3H).

Step 2. Synthesis of tert-*butyl 4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-3,6-dihydropyridine-1(*2H*)-carboxylate (**C5**).*

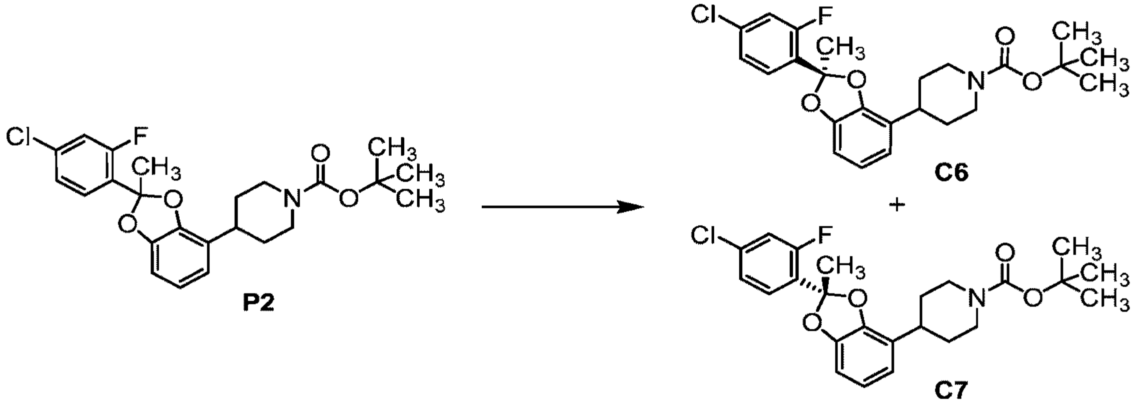
tert-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (62 g, 200 mmol) and sodium carbonate (100 g, 940 mmol) were added to a solution of **C4** (58.0 g, 169 mmol) in 1,4-dioxane (600 mL). After addition of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (6.0 g, 8.2 mmol), the reaction mixture was heated to 90 °C and stirred for 16 hours. Water (500 mL) was then added, and the resulting mixture was extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 x 500 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography (Gradient: 0% to 9% ethyl acetate in petroleum ether) provided **C5** as a yellow oil. Yield: 56.0 g, 126 mmol, 75%. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.50 (dd, *J* = 8.2, 8.2 Hz, 1H), 7.17 – 7.09 (m, 2H), 6.83 – 6.77 (m, 2H), 6.74 (dd, component of ABX pattern, *J* = 5.4, 3.6 Hz, 1H), 6.39 – 6.33 (br m, 1H), 4.14 – 4.08 (m, 2H), 3.70 – 3.56 (m, 2H), 2.66 – 2.45 (m, 2H), 2.07 (d, *J* = 1.1 Hz, 3H), 1.50 (s, 9H).

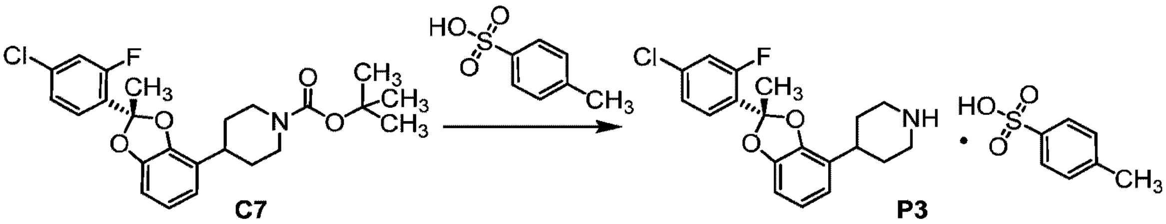
Step 3. Synthesis of tert-*butyl 4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (**P2**).*

To a solution of **C5** (56.0 g, 126 mmol) in methanol (200 mL) was added tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst; 8.10 g, 8.75 mmol), and the reaction mixture was heated to 50 °C for 18 hours under hydrogen (45 psi). It was then cooled to 25 °C and filtered through diatomaceous earth. The filtrate was concentrated *in vacuo*, and purified twice using silica gel chromatography (First column – Gradient: 0% to 9% ethyl acetate in petroleum ether; Second column – Gradient: 0% to 2% ethyl acetate in petroleum ether), affording **P2** as a yellow solid. Yield: 37.0 g, 82.6 mmol, 66%. LCMS *m/z* 392.1♦ [(M − 2-methylprop-1-ene)+H]$^{+}$. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.51 (dd, *J* = 8.3, 8.0 Hz, 1H), 7.17 – 7.09 (m, 2H), 6.77 (dd, component of ABC pattern, *J* = 7.8, 7.8 Hz, 1H), 6.70 (dd, component of ABC pattern, *J* = 7.7, 1.3 Hz, 1H), 6.66 (dd, component of ABC pattern, *J* = 7.8, 1.3 Hz, 1H), 4.37 – 4.13 (br m, 2H), 2.92 – 2.73 (m, 3H), 2.05 (d, *J* = 1.1 Hz, 3H), 1.90 – 1.63 (m, 4H), 1.49 (s, 9H).

Preparation P3

4-[(2S)-2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine, p-*toluenesulfonate salt (**P3**)*





Step 1. Isolation of tert-*butyl 4-[(2*R*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (**C6**) and* tert-*butyl 4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (**C7**).*

Separation of **P2** (75.2 g, 168 mmol) into its component enantiomers was carried out via SFC (supercritical fluid chromatography) [Column: Chiral Technologies Chiralpak AD-H, 5 µm; Mobile phase: 4:1 carbon dioxide / (2-propanol containing 0.2% 1-aminopropan-2-ol)]. The first-eluting compound was designated as **C6**, and the second-eluting enantiomer as **C7**. The indicated absolute configurations were assigned on the basis of a single-crystal X-ray structure determination carried out on **C8**, which was derived from **C6** (see below).

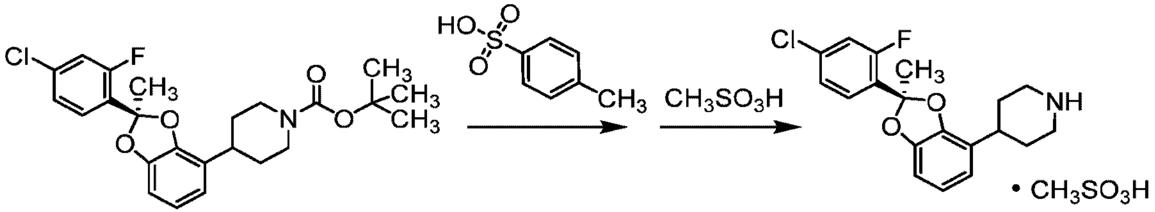
C6 - Yield: 38.0 g, 84.8 mmol, 50%. Retention time 3.64 minutes [Column: Chiral Technologies Chiralpak AD-H, 4.6 x 250 mm, 5 µm; Mobile phase A: carbon dioxide; Mobile phase B: 2-propanol containing 0.2% 1-aminopropan-2-ol; Gradient: 5% B for 1.00 minute, then 5% to 60% B over 8.00 minutes; Flow rate: 3.0 mL/minute; Back pressure: 120 bar].

C7 - Yield: 36.8 g, 82.2 mmol, 49%. Retention time 4.19 minutes (Analytical SFC conditions identical to those used for **C6**).

*Step 2. Synthesis of 4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine,* p-*toluenesulfonate salt (**P3**).*

A solution of **C7** (1.62 g, 3.62 mmol) in ethyl acetate (36 mL) was treated with *p*-toluenesulfonic acid monohydrate (791 mg, 4.16 mmol) and heated at 45 °C. After 23 hours, the reaction mixture was allowed to cool to room temperature and the solid was collected via filtration. It was rinsed with a mixture of ethyl acetate and heptane (1:1, 2 x 15 mL) to afford **P3** as a white solid. Yield: 1.37 g, 2.63 mmol, 73%. LCMS *m/z* 348.1♦ $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.53 (v br s, 1H), 8.29 (v br s, 1H), 7.65 – 7.55 (m, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.35 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.88 – 6.81 (m, 2H), 6.75 – 6.68 (m, 1H), 3.42 – 3.33 (m, 2H), 3.11 – 2.93 (m, 3H), 2.29 (s, 3H), 2.03 (s, 3H), 1.98 – 1.82 (m, 4H).

Conversion of C6 to 4-[(2*R*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine, methanesulfonate salt (C8) for determination of absolute stereochemistry



p-Toluenesulfonic acid (377 mg, 2.19 mmol) was added to a solution of **C6** (490 mg, 1.09 mmol) in ethyl acetate (5.5 mL), and the reaction mixture was stirred at room temperature overnight. After dilution with additional ethyl acetate, the reaction mixture was washed sequentially with aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Yield: 375 mg, 1.08 mmol, 99%. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.59 (dd, J = 8.3. 8.3 Hz, 1H), 7.27 (dd, J = 10.9, 2.0 Hz, 1H), 7.20 (br dd, J = 8.4, 2.1 Hz, 1H), 6.81 – 6.75 (m, 1H), 6.74 – 6.67 (m, 2H), 3.18 – 3.09 (m, 2H), 2.88 – 2.77 (m, 1H), 2.77 – 2.67 (m, 2H), 2.02 (d, J = 0.7 Hz, 3H), 1.85 – 1.73 (m, 4H).

A 0.1 M solution of this free base (4-[(2*R*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine) in ethyl acetate was prepared and subjected to a salt screen. Only the methanesulfonate salt formation is described here. A mixture of methanesulfonic acid (25 µL, 39 µmol) and the solution of substrate (0.1 M; 0.25 mL, 25 µmol) was stirred overnight. Sufficient methanol was then added to dissolve the solid present, and ethyl acetate (3 mL) was added. The resulting solution was allowed to evaporate slowly, without stirring, to afford crystals of **C8**; one of these was used for the single crystal X-ray structure determination described below.

*Single-crystal X-ray structural determination of **C8***

Single Crystal X-Ray Analysis

Data collection was performed on a Bruker D8 Quest diffractometer at room temperature. Data collection consisted of omega and phi scans.

The structure was solved by intrinsic phasing using SHELX software suite in the orthorhombic class space group $P2_12_12_1$. The structure was subsequently refined by the full-matrix least squares method. All non-hydrogen atoms were found and refined using anisotropic displacement parameters.

Formation of the methanesulfonate salt was confirmed via N1_H1X_O4 proton transfer.

The hydrogen atoms located on nitrogen and oxygen were found from the Fourier difference map and refined with distances restrained. The remaining hydrogen atoms were placed in calculated positions and were allowed to ride on their carrier atoms. The final refinement included isotropic displacement parameters for all hydrogen atoms.

Analysis of the absolute structure using likelihood methods (Hooft, 2008) was performed using PLATON (Spek). The results indicate that the absolute structure has been correctly assigned; the method calculates that the probability that the structure is correct is 100%. The Hooft parameter is reported as 0.02 with an esd of 0.0012 and the Parson's parameter is reported as 0.07 with an esd of 0.009. The absolute configuration at C7 was confirmed as (*R*).

The asymmetric unit is comprised of one molecule of the protonated free base of **C8** and one molecule of deprotonated methanesulfonic acid. The final R-index was 4.6%. A final difference Fourier revealed no missing or misplaced electron density.

Pertinent crystal, data collection, and refinement information is summarized in Table A. Atomic coordinates, bond lengths, bond angles, and displacement parameters are listed in Tables B – D.

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Table A. Crystal data and structure refinement for **C8**.

Empirical formula	$C_{20}H_{23}ClFNO_5S$	
Formula weight	443.90	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.5348(5) Å	α = 90°
	b = 9.3688(7) Å	β = 90°
	c = 35.214(3) Å	γ = 90°
Volume	2155.9(3) $Å^3$	
Z	4	
Density (calculated)	1.368 Mg/m^3	
Absorption coefficient	2.823 mm^{-1}	
F(000)	928	
Crystal size	0.480 x 0.100 x 0.040 mm^3	
Theta range for data collection	2.509 to 70.483°	
Index ranges	$-7<=h<=7$, $-11<=k<=8$, $-42<=l<=42$	
Reflections collected	16311	
Independent reflections	4035 [R_{int} = 0.0638]	
Completeness to theta = 67.679°	99.0%	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4035 / 2 / 271	
Goodness-of-fit on F^2	0.832	
Final R indices [$I>2\sigma(I)$]	$R1$ = 0.0463, $wR2$ = 0.1227	
R indices (all data)	$R1$ = 0.0507, $wR2$ = 0.1294	
Absolute structure parameter	−0.003(18)	
Extinction coefficient	0.0051(6)	
Largest diff. peak and hole	0.256 and −0.305 e.$Å^{-3}$	

Table B. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **C8**. U(eq) is defined as one-third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	3842(2)	9910(1)	5317(1)	57(1)
Cl(1)	-1625(2)	-718(1)	6588(1)	80(1)
O(1)	6138(4)	3727(3)	6876(1)	53(1)
F(1)	639(5)	3071(4)	7503(1)	89(1)
O(2)	3445(4)	5043(3)	7117(1)	57(1)
O(4)	2909(6)	11013(4)	5082(1)	78(1)
O(3)	3708(7)	10299(4)	5708(1)	83(1)
N(1)	10461(5)	2909(4)	5493(1)	56(1)
C(9)	5652(6)	4826(4)	6629(1)	44(1)
C(1)	3361(7)	1662(4)	6697(1)	53(1)
C(6)	2957(6)	2523(4)	7012(1)	49(1)
C(10)	4075(6)	5613(4)	6776(1)	47(1)
C(14)	6628(6)	5138(4)	6294(1)	47(1)
O(5)	5833(7)	9578(4)	5179(1)	96(1)
C(15)	8265(6)	4182(4)	6130(1)	49(1)
C(5)	1105(7)	2270(5)	7190(1)	59(1)
C(16)	7309(6)	3048(5)	5874(1)	54(1)
C(2)	1971(7)	670(4)	6567(1)	55(1)
C(4)	-286(7)	1288(5)	7080(1)	64(1)
C(7)	4448(6)	3667(4)	7142(1)	52(1)
C(13)	5876(8)	6374(5)	6113(1)	60(1)
C(11)	3359(7)	6819(4)	6602(1)	57(1)
C(8)	5296(8)	3485(6)	7537(1)	64(1)
C(19)	9905(7)	4976(6)	5902(1)	67(1)
C(17)	8902(7)	2063(5)	5702(1)	59(1)
C(12)	4316(8)	7178(5)	6263(1)	65(1)
C(3)	150(7)	497(4)	6756(1)	56(1)
C(18)	11476(7)	3977(6)	5738(1)	73(1)
C(20)	2328(14)	8399(7)	5260(2)	117(3)

Table C. Bond lengths [Å] and angles [°] for **C8**.

S(1)-O(5)	1.423(4)	C(4)-C(3)	1.389(6)
S(1)-O(3)	1.428(3)	C(4)-H(4)	0.9300
S(1)-O(4)	1.458(3)	C(7)-C(8)	1.506(6)
S(1)-C(20)	1.738(6)	C(13)-C(12)	1.373(7)
Cl(1)-C(3)	1.729(5)	C(13)-H(13)	0.9300
O(1)-C(9)	1.385(4)	C(11)-C(12)	1.388(7)
O(1)-C(7)	1.449(4)	C(11)-H(11)	0.9300
F(1)-C(5)	1.367(4)	C(8)-H(8A)	0.9600
O(2)-C(10)	1.376(4)	C(8)-H(8B)	0.9600
O(2)-C(7)	1.449(4)	C(8)-H(8C)	0.9600
N(1)-C(18)	1.478(6)	C(19)-C(18)	1.505(7)
N(1)-C(17)	1.486(5)	C(19)-H(19A)	0.9700
N(1)-H(1X)	0.99(2)	C(19)-H(19B)	0.9700
N(1)-H(1Y)	0.97(2)	C(17)-H(17A)	0.9700
C(9)-C(10)	1.369(5)	C(17)-H(17B)	0.9700
C(9)-C(14)	1.375(5)	C(12)-H(12)	0.9300
C(1)-C(2)	1.378(6)	C(18)-H(18A)	0.9700
C(1)-C(6)	1.395(5)	C(18)-H(18B)	0.9700
C(1)-H(1)	0.9300	C(20)-H(20A)	0.9600
C(6)-C(5)	1.384(6)	C(20)-H(20B)	0.9600
C(6)-C(7)	1.519(6)	C(20)-H(20C)	0.9600
C(10)-C(11)	1.369(5)		
C(14)-C(13)	1.409(6)	O(5)-S(1)-O(3)	116.2(3)
C(14)-C(15)	1.509(5)	O(5)-S(1)-O(4)	110.1(2)
C(15)-C(16)	1.527(5)	O(3)-S(1)-O(4)	109.9(2)
C(15)-C(19)	1.531(6)	O(5)-S(1)-C(20)	107.6(4)
C(15)-H(15)	0.9800	O(3)-S(1)-C(20)	106.6(3)
C(5)-C(4)	1.351(7)	O(4)-S(1)-C(20)	105.9(4)
C(16)-C(17)	1.518(6)	C(9)-O(1)-C(7)	105.0(3)
C(16)-H(16A)	0.9700	C(10)-O(2)-C(7)	105.2(3)
C(16)-H(16B)	0.9700	C(18)-N(1)-C(17)	112.3(3)
C(2)-C(3)	1.372(6)	C(18)-N(1)-H(1X)	107(3)
C(2)-H(2)	0.9300	C(17)-N(1)-H(1X)	113(3)
C(18)-N(1)-H(1Y)	113(3)	C(1)-C(2)-H(2)	120.3

C(17)-N(1)-H(1Y)	103(3)	C(5)-C(4)-C(3)	117.5(4)
H(1X)-N(1)-H(1Y)	108(4)	C(5)-C(4)-H(4)	121.2
C(10)-C(9)-C(14)	124.1(3)	C(3)-C(4)-H(4)	121.2
C(10)-C(9)-O(1)	109.6(3)	O(1)-C(7)-O(2)	105.7(3)
C(14)-C(9)-O(1)	126.3(3)	O(1)-C(7)-C(8)	108.7(3)
C(2)-C(1)-C(6)	121.9(4)	O(2)-C(7)-C(8)	108.8(3)
C(2)-C(1)-H(1)	119.0	O(1)-C(7)-C(6)	108.7(3)
C(6)-C(1)-H(1)	119.0	O(2)-C(7)-C(6)	108.6(3)
C(5)-C(6)-C(1)	115.3(4)	C(8)-C(7)-C(6)	115.8(3)
C(5)-C(6)-C(7)	123.0(3)	C(12)-C(13)-C(14)	122.4(4)
C(1)-C(6)-C(7)	121.7(4)	C(12)-C(13)-H(13)	118.8
C(9)-C(10)-C(11)	122.1(4)	C(14)-C(13)-H(13)	118.8
C(9)-C(10)-O(2)	110.3(3)	C(10)-C(11)-C(12)	115.6(4)
C(11)-C(10)-O(2)	127.5(4)	C(10)-C(11)-H(11)	122.2
C(9)-C(14)-C(13)	113.6(4)	C(12)-C(11)-H(11)	122.2
C(9)-C(14)-C(15)	122.1(3)	C(7)-C(8)-H(8A)	109.5
C(13)-C(14)-C(15)	124.2(3)	C(7)-C(8)-H(8B)	109.5
C(14)-C(15)-C(16)	110.4(3)	H(8A)-C(8)-H(8B)	109.5
C(14)-C(15)-C(19)	114.1(3)	C(7)-C(8)-H(8C)	109.5
C(16)-C(15)-C(19)	108.4(3)	H(8A)-C(8)-H(8C)	109.5
C(14)-C(15)-H(15)	107.9	H(8B)-C(8)-H(8C)	109.5
C(16)-C(15)-H(15)	107.9	C(18)-C(19)-C(15)	112.2(4)
C(19)-C(15)-H(15)	107.9	C(18)-C(19)-H(19A)	109.2
C(4)-C(5)-F(1)	117.2(4)	C(15)-C(19)-H(19A)	109.2
C(4)-C(5)-C(6)	125.0(4)	C(18)-C(19)-H(19B)	109.2
F(1)-C(5)-C(6)	117.9(4)	C(15)-C(19)-H(19B)	109.2
C(17)-C(16)-C(15)	112.2(3)	H(19A)-C(19)-H(19B)	107.9
C(17)-C(16)-H(16A)	109.2	N(1)-C(17)-C(16)	110.1(3)
C(15)-C(16)-H(16A)	109.2	N(1)-C(17)-H(17A)	109.6
C(17)-C(16)-H(16B)	109.2	C(16)-C(17)-H(17A)	109.6
C(15)-C(16)-H(16B)	109.2	N(1)-C(17)-H(17B)	109.6
H(16A)-C(16)-H(16B)	107.9	C(16)-C(17)-H(17B)	109.6
C(3)-C(2)-C(1)	119.4(4)	H(17A)-C(17)-H(17B)	108.2
C(3)-C(2)-H(2)	120.3	C(13)-C(12)-C(11)	122.1(4)
C(1)-C(2)-H(2)	120.3	C(13)-C(12)-H(12)	118.9
		C(11)-C(12)-H(12)	118.9

C(2)-C(3)-C(4)	120.8(4)	H(18A)-C(18)-H(18B)	108.2
C(2)-C(3)-Cl(1)	119.6(3)	S(1)-C(20)-H(20A)	109.5
C(4)-C(3)-Cl(1)	119.6(3)	S(1)-C(20)-H(20B)	109.5
N(1)-C(18)-C(19)	109.9(3)	H(20A)-C(20)-H(20B)	109.5
N(1)-C(18)-H(18A)	109.7	S(1)-C(20)-H(20C)	109.5
C(19)-C(18)-H(18A)	109.7	H(20A)-C(20)-H(20C)	109.5
N(1)-C(18)-H(18B)	109.7	H(20B)-C(20)-H(20C)	109.5
C(19)-C(18)-H(18B)	109.7		

Symmetry transformations used to generate equivalent atoms.

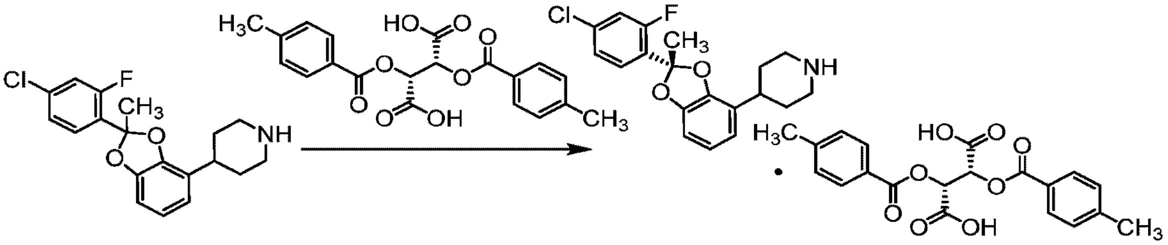
Table D. Anisotropic displacement parameters (Å^2 x 10^3) for **C8**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	73(1)	48(1)	48(1)	-2(1)	7(1)	-1(1)
Cl(1)	81(1)	78(1)	81(1)	-8(1)	1(1)	-8(1)
O(1)	54(1)	50(1)	56(1)	14(1)	10(1)	17(1)
F(1)	83(2)	103(2)	79(2)	-40(2)	38(2)	-6(2)
O(2)	66(2)	49(1)	54(1)	2(1)	11(1)	18(1)
O(4)	87(2)	84(2)	64(2)	19(2)	17(2)	21(2)
O(3)	122(3)	80(2)	47(1)	-3(1)	7(2)	-13(2)
N(1)	47(2)	73(2)	48(2)	7(2)	3(1)	11(2)
C(9)	51(2)	38(2)	44(2)	2(1)	-7(1)	2(2)
C(1)	63(2)	46(2)	50(2)	5(2)	21(2)	13(2)
C(6)	55(2)	47(2)	45(2)	5(1)	11(2)	19(2)
C(10)	55(2)	39(2)	46(2)	-5(1)	-4(2)	6(2)
C(14)	54(2)	46(2)	42(2)	0(1)	-9(2)	-5(2)
O(5)	88(2)	88(3)	113(3)	-24(2)	13(2)	21(2)
C(15)	47(2)	61(2)	40(2)	3(2)	-3(1)	-2(2)
C(5)	60(2)	62(2)	54(2)	-6(2)	19(2)	13(2)
C(16)	43(2)	53(2)	65(2)	-4(2)	8(2)	-6(2)
C(2)	72(3)	49(2)	45(2)	2(2)	16(2)	14(2)
C(4)	57(2)	68(3)	65(2)	-3(2)	23(2)	6(2)
C(7)	54(2)	50(2)	51(2)	7(2)	12(2)	16(2)

C(13)	81(3)	54(2)	46(2)	9(2)	-4(2)	4(2)
C(11)	70(3)	46(2)	54(2)	-8(2)	-14(2)	17(2)
C(8)	69(3)	71(3)	51(2)	4(2)	4(2)	15(2)
C(19)	54(2)	78(3)	70(3)	-13(2)	2(2)	-25(2)
C(17)	54(2)	57(2)	67(2)	-3(2)	8(2)	3(2)
C(12)	96(3)	43(2)	56(2)	5(2)	-14(2)	13(2)
C(3)	64(2)	52(2)	52(2)	4(2)	2(2)	14(2)
C(18)	43(2)	103(4)	73(3)	7(3)	3(2)	-18(2)
C(20)	153(7)	87(4)	110(5)	-14(4)	-6(5)	-57(5)

Preparation of P3, di-p-toluoyl-L-tartrate salt

*4-[(2S)-2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine, di-p-toluoyl-L-tartrate salt (**P3, di-p-toluoyl-L-tartrate salt**).*



C13, free base **P3, di-*p*-toluoyl-L-tartrate salt**

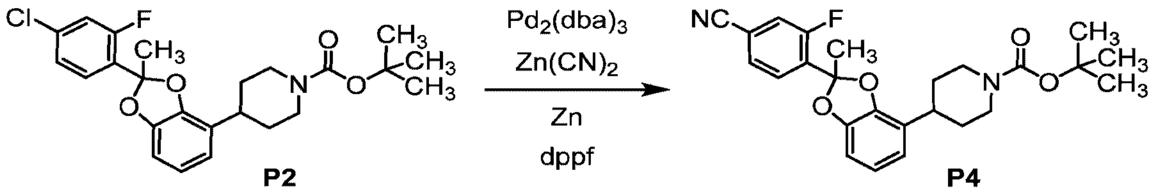
A solution of **C13, free base** (519 mg, 1.49 mmol) and di-*p*-toluoyl-L-tartaric acid (278 mg, 0.719 mmol) in acetonitrile (7.5 mL) was stirred at 50 °C for 1.5 hours. The mixture was allowed to cool to room temperature at 0.2 °C/minute. After 15 hours at room temperature, the mixture was heated to 65 °C and charged with acetonitrile (15 mL). The mixture was allowed to cool to room temperature at 0.2 °C/minute. After 15 hours at room temperature, the mixture was heated to 54 °C. After 3 hours, the solid was collected by filtration, and dried in a vacuum oven at 35 °C under nitrogen, providing **P3, di-*p*-toluoyl-L-tartrate salt** as a white solid (217 mg, 0.296 mmol, 20%, 82% ee).

A solution of **P3, di-*p*-toluoyl-L-tartrate salt** (217 mg, 0.296 mmol, 82% ee) in acetonitrile (8.0 mL) at 50 °C was allowed to cool to room temperature at 0.2 °C/minute. After 15 hours, the solid was collected by filtration, and dried in a vacuum oven at 35 °C under nitrogen, providing **P3, di-*p*-toluoyl-L-tartrate salt** as a white solid (190 mg, 0.259 mmol, 88%, 88% ee). LCMS *m/z* 348.1♦ $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.9 – 8.5 (br s, 2H), 7.79 (d, *J* = 8.1 Hz, 4H), 7.64 – 7.54 (m, 2H), 7.34 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 4H), 6.87 – 6.78 (m, 2H), 6.69 (dd, *J* = 6.7, 2.5 Hz, 1H), 5.58 (s, 2H), 3.37 – 3.28 (m, 2H, assumed; partially obscured by water peak), 3.05 – 2.89 (m, 3H), 2.33 (s, 6H), 2.02 (s, 3H), 1.92 – 1.80 (m, 4H).

Retention time: Peak 1 (4.97 minutes, minor) and Peak 2 (5.31 minutes, Major) {Column: Chiralpak IC-U 3.0 x 50 mm, 1.6 µm; Mobile phase A: carbon dioxide; Mobile phase B: 0.1% isopropylamine in methanol; Gradient: 10% B for 5.00 minutes, then 45% B for 0.6 minutes; Flow rate: 1.7 mL/minute; Back pressure: 130 bar}.

Preparation P4

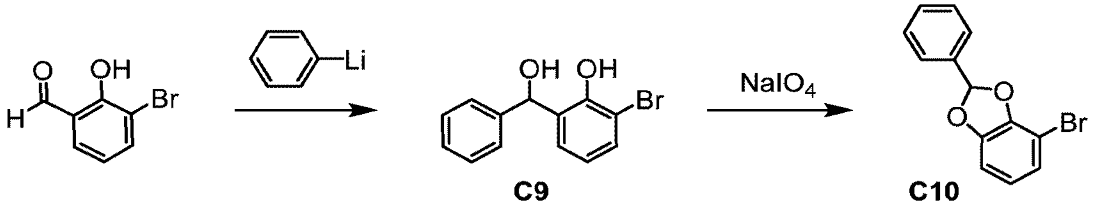
tert-*Butyl 4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (P4)*

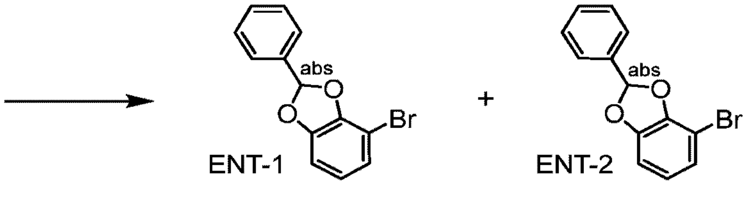


A suspension of **P2** (2.00 g, 4.46 mmol), zinc cyanide (734 mg, 6.25 mol), zinc (70.1 mg, 1.07 mmol), 1,1'-bis(diphenylphosphino)ferrocene (dppf; 198 mg, 0.357 mmol) and tris(dibenzylideneacetone)dipalladium(0) (164 mg, 0.179 mmol) in *N*,*N*-dimethylacetamide (20 mL) was stirred at 120 °C for 16 hours, whereupon it was filtered. The filtrate was mixed with water (50 mL) and extracted with ethyl acetate (3 x 50 mL); the combined organic layers were then washed sequentially with water (30 mL) and with saturated aqueous sodium chloride solution (20 mL), and concentrated *in vacuo*. Silica gel chromatography (Gradient: 0% to 30% ethyl acetate in petroleum ether) afforded a solid, which was treated with acetonitrile (15 mL) and water (15 mL) and subjected to lyophilization. This provided **P4** as a light yellow solid. Yield: 1.17 g, 2.67 mmol, 60%. LCMS *m/z* 461.3 [M+Na$^+$]. ^{1}H NMR (400 MHz, chloroform-*d*) 7.71 (dd, *J* = 7.7, 7.6 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.42 (dd, *J* = 10.0, 1.5 Hz, 1H), 6.79 (dd, component of ABC pattern, *J* = 7.7, 7.6 Hz, 1H), 6.72 (dd, component of ABC pattern, *J* = 7.8, 1.3 Hz, 1H), 6.68 (dd, component of ABC pattern, *J* = 7.8, 1.3 Hz, 1H), 4.37 – 4.14 (br m, 2H), 2.91 – 2.73 (m, 3H), 2.07 (d, *J* = 1.1 Hz, 3H), 1.89 – 1.62 (m, 4H), 1.49 (s, 9H).

Preparations P5 and P6

*4-Bromo-2-phenyl-1,3-benzodioxole, ENT-1 (**P5**) and 4-Bromo-2-phenyl-1,3-benzodioxole, ENT-2 (**P6**)*





P5 **P6**

*Step 1. Synthesis of 2-bromo-6-[hydroxy(phenyl)methyl]phenol (**C9**).*

Phenyllithium (1.9 M solution in 1-butoxybutane; 78.5 mL, 149 mmol) was slowly added to a −70 °C solution of 3-bromo-2-hydroxybenzaldehyde (10.0 g, 49.7 mmol) in tetrahydrofuran (70 mL), at a rate that maintained the reaction temperature below −60 °C. The resulting suspension was stirred at −70 °C for 1 hour, and then allowed to warm to room temperature overnight, whereupon it was poured into a 0 °C aqueous ammonium chloride solution (30 mL). This mixture was extracted with ethyl acetate (3 x 30 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography (Gradient: 0% to 5% ethyl acetate in petroleum ether) provided **C9** as a yellow solid. Yield: 6.11 g, 21.9 mmol, 44%. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.45 – 7.28 (m, 6H), 7.22 – 7.18 (m, 1H), 7.06 (br d, *J* = 7.7 Hz, 1H), 6.77 (dd, *J* = 7.9, 7.8 Hz, 1H), 6.06 (br s, 1H), 2.89 (br s, 1H).

*Step 2. Synthesis of 4-bromo-2-phenyl-1,3-benzodioxole (**C10**).*

To a solution of **C9** (6.11 g, 21.9 mmol) in methanol (370 mL) was added a solution of sodium periodate (11.7 g, 54.7 mmol) in water (175 mL). The reaction mixture was stirred at 30 °C for 40 hours, whereupon most of the methanol was removed via concentration *in vacuo*. The resulting mixture was extracted with dichloromethane (5 x 100 mL), and the combined organic layers were washed sequentially with aqueous sodium sulfite solution (100 mL) and saturated aqueous sodium chloride solution (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Chromatography on silica gel (Eluent: petroleum ether) provided **C10** as a colorless oil. Yield: 4.50 g, 16.2 mmol, 74%. LCMS *m/z* 278.5 (bromine isotope pattern observed) $[M+H]^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.62 – 7.57 (m, 2H), 7.49 – 7.43 (m, 3H), 7.04 (s, 1H), 7.00 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.79 (dd, component of ABX pattern, *J* = 7.8, 1.4 Hz, 1H), 6.75 (dd, component of ABX pattern, *J* = 7.9, 7.8 Hz, 1H).

*Step 3. Isolation of 4-bromo-2-phenyl-1,3-benzodioxole, ENT-1 (**P5**) and 4-bromo-2-phenyl-1,3-benzodioxole, ENT-2 (**P6**).*

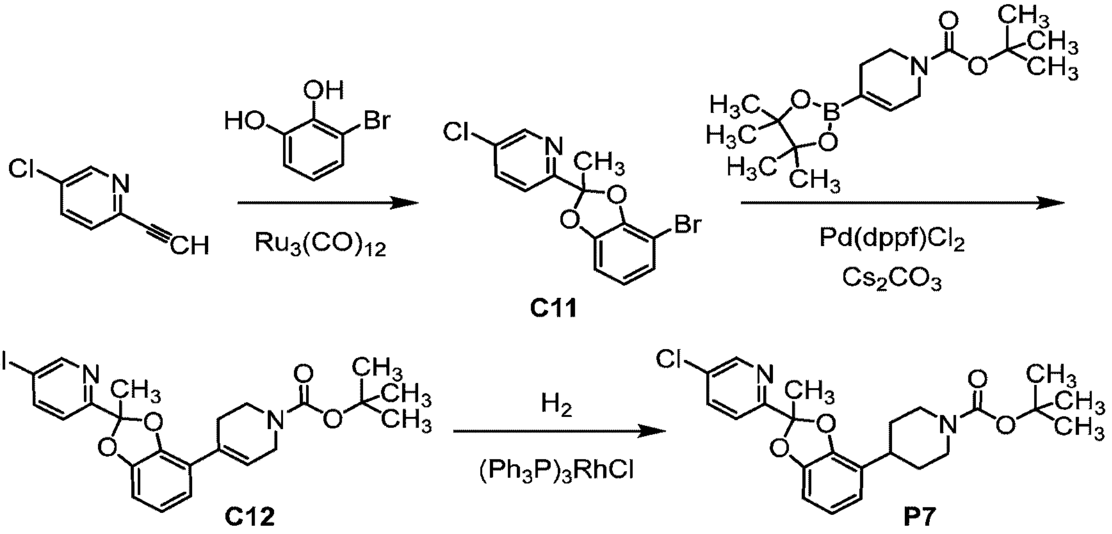
The enantiomers comprising **C10** (5.00 g, 18.0 mmol) were separated using SFC [Column: Chiral Technologies ChiralCel OD, 10 µm; Mobile phase: 3:1 carbon dioxide / (methanol containing 0.1% ammonium hydroxide)]. The first-eluting enantiomer was designated as ENT-1 (**P5**), and the second-eluting enantiomer as ENT-2 (**P6**); both were obtained as yellow oils.

P5 Yield: 2.20 g, 7.94 mmol, 44%. LCMS *m/z* 277.0 (bromine isotope pattern observed) $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 7.63 – 7.55 (m, 2H), 7.51 – 7.42 (m, 3H), 7.04 (s, 1H), 7.00 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.80 (dd, component of ABX pattern, *J* = 7.8, 1.4 Hz, 1H), 6.75 (dd, component of ABX pattern, *J* = 7.9, 7.8 Hz, 1H). Retention time 3.28 minutes (Column: Chiral Technologies ChiralCel OD-H, 4.6 x 150 mm, 5 µm; Mobile phase A: carbon dioxide; Mobile phase B: methanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 5.5 minutes; Flow rate: 2.5 mL/minute).

P6 Yield: 2.00 g, 7.22 mmol, 40%. LCMS *m/z* 276.9 (bromine isotope pattern observed) $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 7.63 – 7.55 (m, 2H), 7.50 – 7.42 (m, 3H), 7.04 (s, 1H), 7.00 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.80 (dd, component of ABX pattern, *J* = 7.8, 1.4 Hz, 1H), 6.75 (dd, component of ABX pattern, *J* = 7.9, 7.9 Hz, 1H). Retention time 3.73 minutes (Analytical conditions identical to those used for **P5**).

Preparation P7

tert-*Butyl 4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (**P7**)*



*Step 1. Synthesis of 2-(4-bromo-2-methyl-1,3-benzodioxol-2-yl)-5-chloropyridine (**C11**).*

A mixture of 5-chloro-2-ethynylpyridine (1.80 g, 13.1 mmol), 3-bromobenzene-1,2-diol (2.47 g, 13.1 mmol), and triruthenium dodecacarbonyl (167 mg, 0.261 mmol) in toluene (25 mL) was degassed for 1 minute and then heated at 100 °C for 16 hours. The reaction mixture was diluted with ethyl acetate (30 mL) and filtered through a pad of diatomaceous earth; the filtrate was concentrated *in vacuo* and purified using silica gel chromatography (Gradient: 0% to 1% ethyl acetate in petroleum ether) to provide **C11** as a yellow oil. Yield: 1.73 g, 5.30 mmol, 40%.

LCMS *m/z* 325.6 (bromine-chlorine isotope pattern observed) $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.63 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.71 (dd, component of ABX pattern, *J* = 8.4, 2.4 Hz, 1H), 7.60 (dd, component of ABX pattern, *J* = 8.4, 0.7 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.76 (dd, component of ABX pattern, *J* = 7.8, 1.4 Hz, 1H), 6.72 (dd, component of ABX pattern, *J* = 8.0, 7.8 Hz, 1H), 2.10 (s, 3H).

Step 2. Synthesis of tert-*butyl 4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]-3,6-dihydropyridine-1(*2H*)-carboxylate (**C12**).*

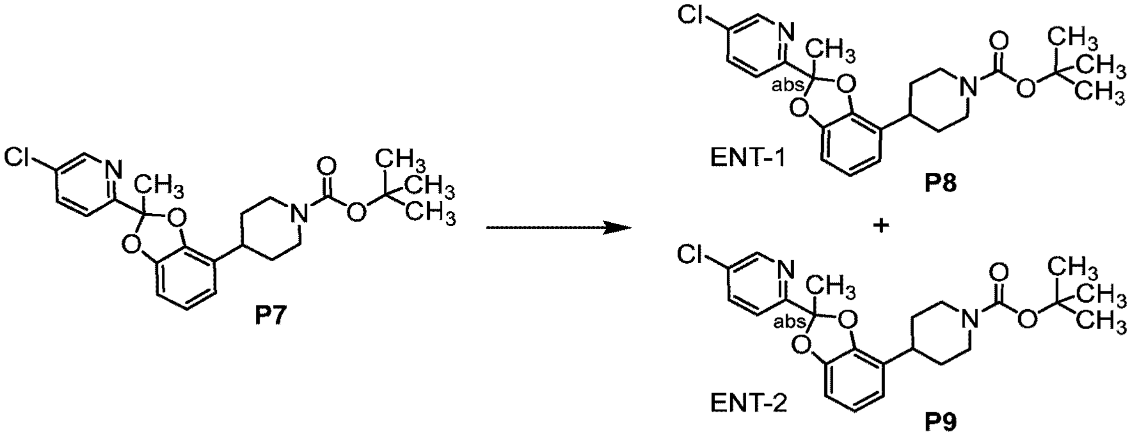
[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (388 mg, 0.530 mmol) was added to a suspension of **C11** (1.73 g, 5.30 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.64 g, 5.30 mmol), and cesium carbonate (5.18 g, 15.9 mmol) in 1,4-dioxane (35 mL) and water (6 mL). The reaction mixture was stirred at 90 °C for 4 hours, whereupon it was diluted with ethyl acetate (30 mL) and water (5 mL). The organic layer was concentrated *in vacuo* and the residue was subjected to silica gel chromatography (Gradient: 0% to 5% ethyl acetate in petroleum ether), affording **C12** as a yellow gum. Yield: 1.85 g, 4.31 mmol, 81%. LCMS *m/z* 451.0♦ $[M+Na^+]$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.62 (dd, *J* = 2.5, 0.8 Hz, 1H), 7.69 (dd, component of ABX pattern, *J* = 8.4, 2.4 Hz, 1H), 7.57 (dd, component of ABX pattern, *J* = 8.4, 0.8 Hz, 1H), 6.84 – 6.79 (m, 2H), 6.78 – 6.73 (m, 1H), 6.39 – 6.33 (br m, 1H), 4.13 – 4.07 (m, 2H), 3.68 – 3.58 (m, 2H), 2.60 – 2.51 (br m, 2H), 2.07 (s, 3H), 1.49 (s, 9H).

Step 3. Synthesis of tert-*butyl 4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (**P7**).*

A solution of **C12** (2.61 g, 6.08 mmol) and tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst; 563 mg, 0.608 mmol) in methanol (100 mL) was degassed under vacuum and then purged with hydrogen; this evacuation-purge cycle was carried out a total of three times. The reaction mixture was then stirred at 60 °C under hydrogen (50 psi) for 16 hours, whereupon it was filtered. The filtrate was concentrated *in vacuo*, and the residue was purified using silica gel chromatography (Gradient: 0% to 10% ethyl acetate in petroleum ether); the resulting material was combined with material from a similar hydrogenation carried out on **C12** (110 mg, 0.256 mmol) to provide **P7** as a light-yellow gum. Combined yield: 2.05 g, 4.76 mmol, 75%. LCMS *m/z* 431.3♦ $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.62 (d, *J* = 2.3 Hz, 1H), 7.69 (dd, component of ABX pattern, *J* = 8.4, 2.4 Hz, 1H), 7.57 (d, half of AB quartet, *J* = 8.4 Hz, 1H), 6.79 (dd, component of ABC pattern, *J* = 7.8, 7.7 Hz, 1H), 6.72 (dd, component of ABC pattern, *J* = 7.8, 1.3 Hz, 1H), 6.68 (br d, component of ABC pattern, *J* = 7.9 Hz, 1H), 4.32 – 4.12 (br m, 2H), 2.91 – 2.73 (m, 3H), 2.05 (s, 3H), 1.90 – 1.62 (m, 4H), 1.48 (s, 9H).

Preparations P8 and P9

tert-*Butyl 4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate, ENT-1 (**P8**) and* tert-*Butyl 4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate, ENT-2 (**P9**)*



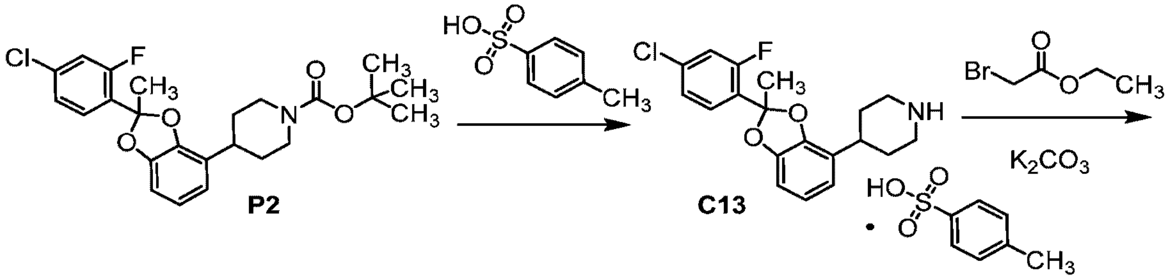
Separation of **P7** (500 mg, 1.16 mmol) into its component enantiomers was effected using SFC {Column: Phenomenex Lux Amylose-1, 5 µm; Mobile phase: 9:1 carbon dioxide / [2-propanol containing 0.2% (7 M ammonia in methanol)]}. The first-eluting enantiomer was designated as ENT-1 (**P8**), and the second-eluting enantiomer as ENT-2 (**P9**).

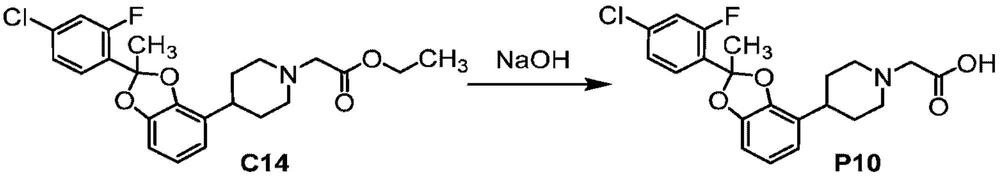
P8 Yield: 228 mg, 0.529 mmol, 46%. Retention time 4.00 minutes {Column: Phenomenex Lux Amylose-1, 4.6 x 250 mm, 5 µm; Mobile phase A: carbon dioxide; Mobile phase B: [2-propanol containing 0.2% (7 M ammonia in methanol)]; Gradient: 5% B for 1.00 minute, then 5% to 60% B over 8.00 minutes; Flow rate: 3.0 mL/minute; Back pressure: 120 bar}.

P9 Yield: 229 mg, 0.531 mmol, 46%. Retention time 4.50 minutes (Analytical conditions identical to those used for **P8**).

Preparation P10

*{4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}acetic acid (**P10**)*





Step 1. Synthesis of 4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine, p-*toluenesulfonate salt (**C13**).*

A solution of **P2** (5.0 g, 11 mmol) and *p*-toluenesulfonic acid (4.81 g, 27.9 mmol) in ethyl acetate (100 mL) was stirred at 60 °C for 2 hours, whereupon it was concentrated *in vacuo* to afford **C13** as a yellow gum. This material was taken directly into the following step. LCMS *m/z* 347.9♦ $[M+H]^+$.

*Step 2. Synthesis of ethyl {4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}acetate (**C14**).*

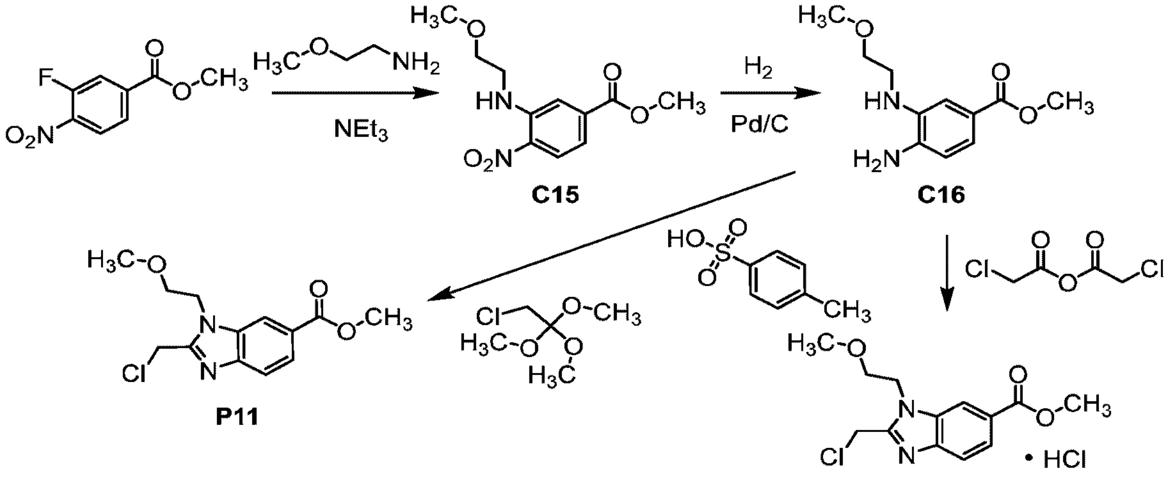
Potassium carbonate (7.71 g, 55.8 mmol) and ethyl bromoacetate (1.86 g, 11.2 mmol) were added to a solution of **C13** (from the previous step; ≤11 mmol) in acetonitrile (150 mL), and the reaction mixture was stirred at 55 °C for 16 hours. It was then filtered, and the filtrate was concentrated *in vacuo* and purified using silica gel chromatography (Gradient: 0% to 30% ethyl acetate in petroleum ether) to afford **C14** as a yellow gum. By ^1H NMR analysis, this material was not entirely pure. Yield: 3.57 g, 8.23 mmol, 75% over 2 steps. ^1H NMR (400 MHz, chloroform-*d*), **C14** peaks only: δ 7.52 (dd, *J* = 8.4, 8.0 Hz, 1H), 7.17 – 7.07 (m, 2H), 6.77 (dd, component of ABC pattern, *J* = 7.8, 7.8 Hz, 1H), 6.72 – 6.67 (m, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.27 (s, 2H), 3.07 (m, 2H), 2.70 (tt, *J* = 12.1, 3.8 Hz, 1H), 2.35 (ddd, *J* = 11.5, 11.5, 2.7 Hz, 2H), 2.04 (d, *J* = 1.1 Hz, 3H), 2.02 – 1.76 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H).

*Step 3. Synthesis of {4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}acetic acid (**P10**).*

A solution of **C14** (3.57 g, 8.23 mmol) and aqueous sodium hydroxide solution (3 M; 13.7 mL, 41.1 mmol) in a mixture of methanol (80 mL) and tetrahydrofuran (40 mL) was stirred at 25 °C for 16 hours. After removal of solvents *in vacuo*, the aqueous residue was acidified to pH 7 by addition of 1 M hydrochloric acid, and then extracted with a mixture of dichloromethane and methanol (10:1, 2 x 100 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide **P10** as a yellow solid. Yield: 2.95 g, 7.27 mmol, 88%. LCMS *m/z* 406.2♦ $[M+H]^+$. ^1H NMR (400 MHz, methanol-d_4) δ 7.61 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.29 (dd, *J* = 10.9, 2.0 Hz, 1H), 7.22 (ddd, *J* = 8.4, 2.0, 0.8 Hz, 1H), 6.82 (dd, component of ABC pattern, *J* = 8.3, 7.1 Hz, 1H), 6.78 – 6.72 (m, 2H), 3.65 – 3.54 (br m, 2H), 3.51 (s, 2H), 3.04 – 2.88 (m, 3H), 2.23 – 2.07 (m, 2H), 2.07 – 1.93 (m, 2H), 2.04 (d, *J* = 1.1 Hz, 3H).

Preparation P11

*Methyl 2-(chloromethyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate (**P11**)*



*Step 1. Synthesis of methyl 3-[(2-methoxyethyl)amino]-4-nitrobenzoate (**C15**).*

To a colorless solution of methyl 3-fluoro-4-nitrobenzoate (50 g, 250 mmol) in tetrahydrofuran (400 mL) was added triethylamine (40.7 g, 402 mmol, 55.8 mL) followed by addition of 2-methoxyethanamine (30.2 g, 402 mmol) in tetrahydrofuran (100 mL), drop-wise, at room temperature. The resultant yellow solution was stirred at 55 °C for 18 hours. The solution was cooled to room temperature and concentrated under reduced pressure to remove tetrahydrofuran. The resultant yellow solid was dissolved in ethyl acetate (800 mL) and washed with saturated aqueous ammonium chloride solution (250 mL). The aqueous phase was separated and extracted with ethyl acetate (200 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (3 x 250 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield **C15** (60.2 g, 94%) as a yellow solid. ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.23 (d, 1H), 8.17 (br s, 1H), 7.58 (d, 1H), 7.25 (dd, 1H), 3.95 (s, 3H), 3.69-3.73 (m, 2H), 3.56 (m, 2H), 3.45 (s, 3H); LCMS *m/z* 255.4 [M+H]$^+$.

*Step 2. Synthesis of methyl 4-amino-3-[(2-methoxyethyl)amino]benzoate (**C16**).*

To solution of **C15** (30 g, 118 mmol) in methanol (500 mL) was added Pd/C (10 g, 94 mmol). This reaction was stirred at room temperature under 15 psi hydrogen for 18 hours. The black suspension was filtered through diatomaceous earth and the filter cake was washed with methanol (500 mL). The combined filtrates were concentrated *in vacuo* to give **C16** (26.5 g, quantitative) as a brown oil, which solidified on standing. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.48 (dd, 1H), 7.36 (d, 1H), 6.69 (d, 1H), 3.87 (s, 3H), 3.77 (br s, 2H), 3.68 (t, 2H), 3.41 (s, 3H), 3.32 (t, 2H); LCMS *m/z* 224.7 [M+H]$^+$.

*Step 3. Synthesis of methyl 2-(chloromethyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate (**P11**).*

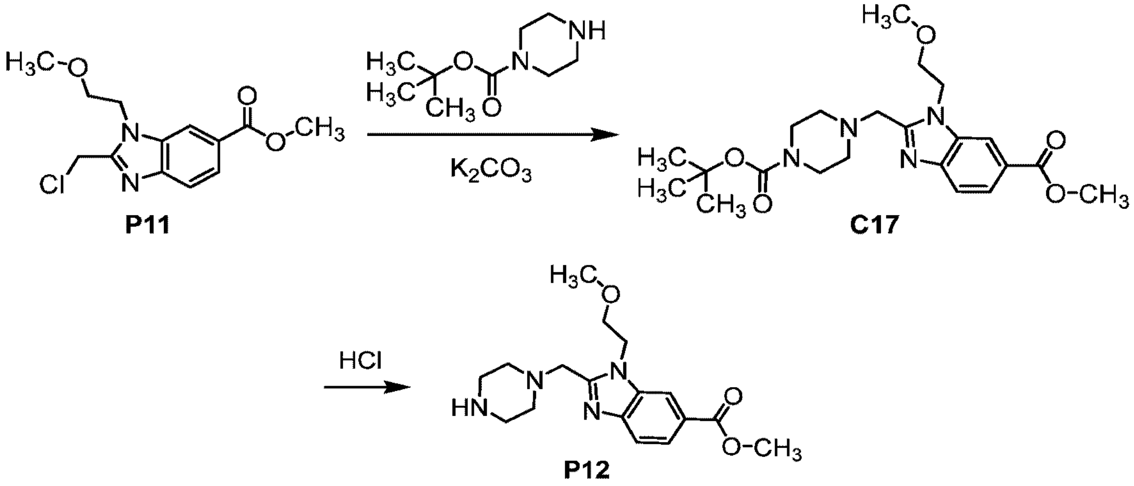
To a solution of **C16** (5.00 g, 22.3 mmol) in tetrahydrofuran (100 mL) was added 2-chloro-1,1,1-trimethoxyethane (3.31 mL, 24.6 mmol), followed by *p*-toluenesulfonic acid monohydrate (84.8 mg, 0.446 mmol). The reaction mixture was heated at 45 °C for 5 hours, whereupon it was concentrated *in vacuo*; the residual oil was dissolved in ethyl acetate (10 mL) and heated until a solution formed. This was slowly stirred while cooling to room temperature overnight. The precipitate was collected via filtration and washed with heptane to afford **P11** as a gray solid. Yield: 5.73 g, 20.3 mmol, 91%. ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.12 (br s, 1H), 8.01 (br d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 4.96 (s, 2H), 4.52 (t, *J* = 5.1 Hz, 2H), 3.96 (s, 3H), 3.74 (t, *J* = 5.1 Hz, 2H), 3.28 (s, 3H).

*Step 4. Synthesis of methyl 2-(chloromethyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, hydrochloride salt (**P11, HCl salt**).*

A solution of **C16** (5.0 g, 24 mmol) in 1,4-dioxane (100 mL) was heated to 100 °C, a solution of chloroacetic anhydride (4.1 g, 24.5 mmol) in 1,4-dioxane (60 mL) was added via addition funnel over a period of 10 hours, and the reaction mixture was stirred for another 12 hours at 100 °C. The following day, the reaction was cooled to room temperature and the 1,4-dioxane was removed under reduced pressure. The crude reaction mixture was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The ethyl acetate layer was separated, dried over sodium sulfate, and filtered. A solution of 4 M hydrogen chloride in 1,4-dioxane (1.1 equiv.) was added to the ethyl acetate solution with constant stirring. The hydrochloride salt of **P11** precipitated out as a pale yellow solid. The suspension was stirred for 1 hour and the hydrochloride salt of **P11** was then collected by filtration to give a yellow solid (6.1 g, 86%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.64 (s, 1H), 8.30 (d, 1H), 7.92 (d, 1H), 5.32 (s, 2H), 4.84 (m, 2H), 3.99 (s, 3H), 3.83 (t, 2H), 3.31 (s, 3H). LCMS *m/z* 283.2 [M+H]$^+$.

Preparation P12

*Methyl 1-(2-methoxyethyl)-2-(piperazin-1-ylmethyl)-1*H*-benzimidazole-6-carboxylate (**P12**)*



*Step 1. Synthesis of methyl 2-{[4-(*tert*-butoxycarbonyl)piperazin-1-yl]methyl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate (**C17**).*

Compound **P11** (1.59 g, 5.62 mmol) was added to a 15 °C mixture of *tert*-butyl piperazine-1-carboxylate (1.00 g, 5.37 mmol) and potassium carbonate (2.97 g, 21.5 mmol) in acetonitrile (15 mL), and the reaction mixture was stirred at 55 °C for 12 hours. It was then combined with a similar reaction carried out using **P11** and *tert*-butyl piperazine-1-carboxylate (200 mg, 1.07 mmol), and the mixture was filtered. After the filtrate had been concentrated *in vacuo*, the residue was purified via chromatography on silica gel (Gradient: 0% to 60% ethyl acetate in petroleum ether) to provide **C17** as a pale yellow solid. Combined yield: 2.30 g, 5.32 mmol, 83%. LCMS *m/z* 433.0 $[M+H]^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.12 (d, *J* = 1.5 Hz, 1H), 7.96 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 4.58 (t, *J* = 5.4 Hz, 2H), 3.95 (s, 3H), 3.89 (s, 2H), 3.73 (t, *J* = 5.4 Hz, 2H), 3.46 – 3.37 (br m, 4H), 3.28 (s, 3H), 2.54 – 2.44 (br m, 4H), 1.45 (s, 9H).

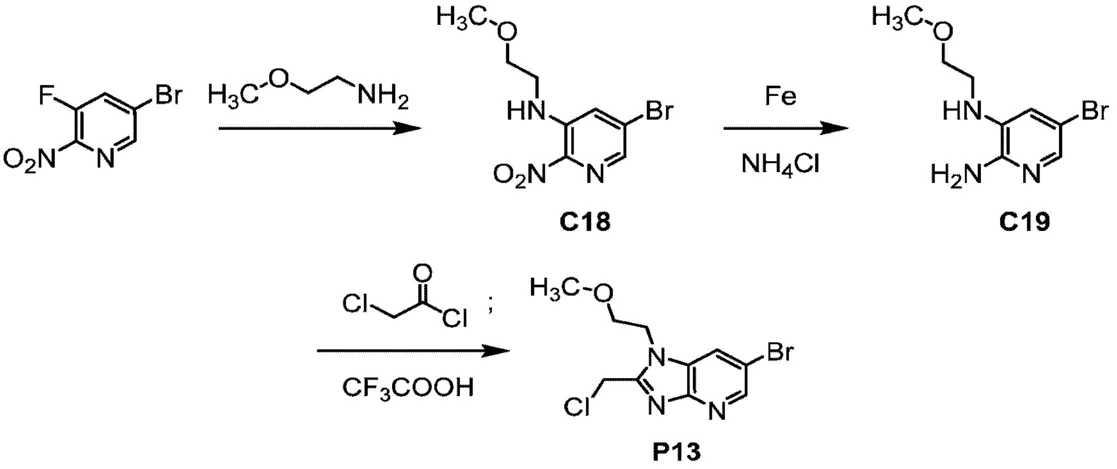
*Step 2. Synthesis of methyl 1-(2-methoxyethyl)-2-(piperazin-1-ylmethyl)-1*H*-benzimidazole-6-carboxylate (**P12**).*

To a solution of **C17** (2.30 g, 5.32 mmol) in dichloromethane (80 mL) was added a solution of hydrogen chloride in ethyl acetate (20 mL). The reaction mixture was stirred at 20 °C for 2 hours, whereupon it was concentrated *in vacuo*. The residue was diluted with water (20 mL), adjusted to a pH of 9 to 10 by addition of saturated aqueous sodium bicarbonate solution, and extracted with a mixture of ethyl acetate and methanol (10:1, 15 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford **P12** as a pale yellow solid. Yield: 1.68 g, 5.05 mmol, 95%. LCMS *m/z* 332.8 $[M+H]^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.13 (br s, 1H), 7.96 (br d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 4.59

(t, *J* = 5.5 Hz, 2H), 3.95 (s, 3H), 3.86 (s, 2H), 3.75 (t, *J* = 5.5 Hz, 2H), 3.29 (s, 3H), 2.87 (t, *J* = 4.8 Hz, 4H), 2.50 (br m, 4H).

Preparation P13

*6-Bromo-2-(chloromethyl)-1-(2-methoxyethyl)-1*H*-imidazo[4,5-*b*]pyridine (**P13**)*



*Step 1. Synthesis of 5-bromo-*N*-(2-methoxyethyl)-2-nitropyridin-3-amine (**C18**).*

A solution of 5-bromo-3-fluoro-2-nitropyridine (400 mg, 1.81 mmol) and 2-methoxyethanamine (408 mg, 5.43 mmol) in tetrahydrofuran (10 mL) was stirred at 25 °C for 2 hours, whereupon it was diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic layer was washed with saturated aqueous sodium chloride solution (50 mL), dried over magnesium sulfate, filtered, and concentrated to afford **C18** as a yellow solid. Yield: 430 mg, 1.56 mmol, 86%.

*Step 2. Synthesis of 5-bromo-*N^3*-(2-methoxyethyl)pyridine-2,3-diamine (**C19**).*

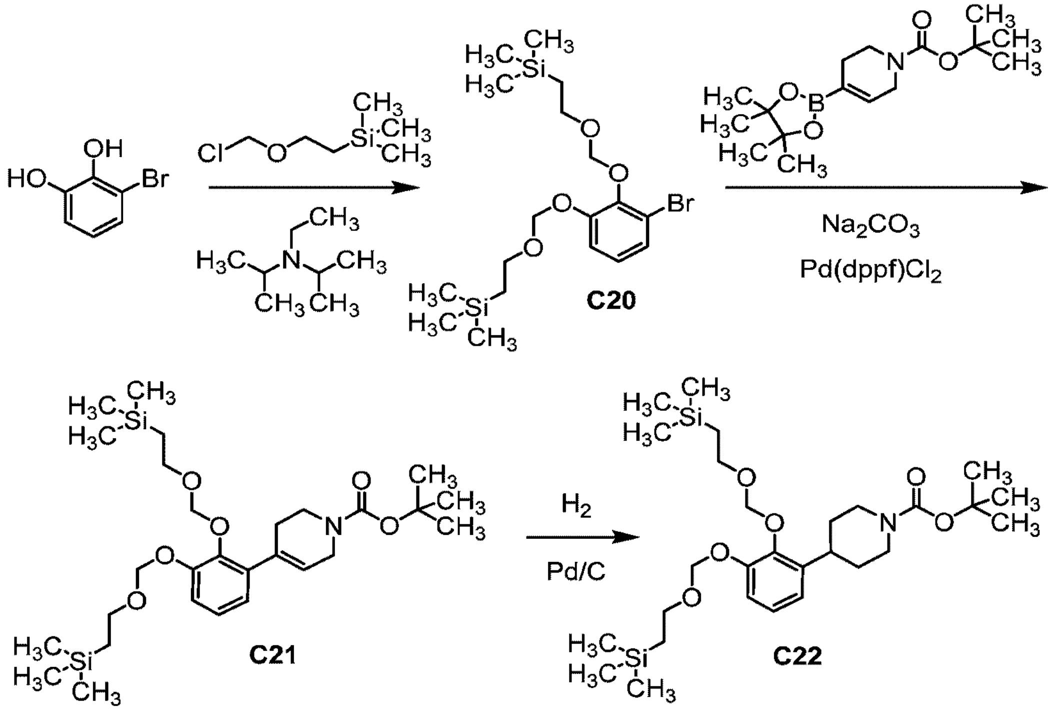
A solution of **C18** (430 mg, 1.56 mmol), ammonium chloride (833 mg, 15.6 mmol), and iron powder (870 mg, 15.6 mmol) in a mixture of methanol (10 mL) and water (2 mL) was stirred at 80 °C for 30 minutes. The resulting suspension was poured into water (50 mL) and extracted with ethyl acetate (2 x 50 mL); the combined organic layers were dried over magnesium sulfate, filtered, and concentrated to provide **C19** as a brown solid. Yield: 350 mg, 1.42 mmol, 91%. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.63 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 4.33 – 4.19 (br s, 2H), 3.65 (dd, *J* = 5.6, 4.6 Hz, 2H), 3.40 (s, 3H), 3.22 (br t, *J* = 5 Hz, 2H).

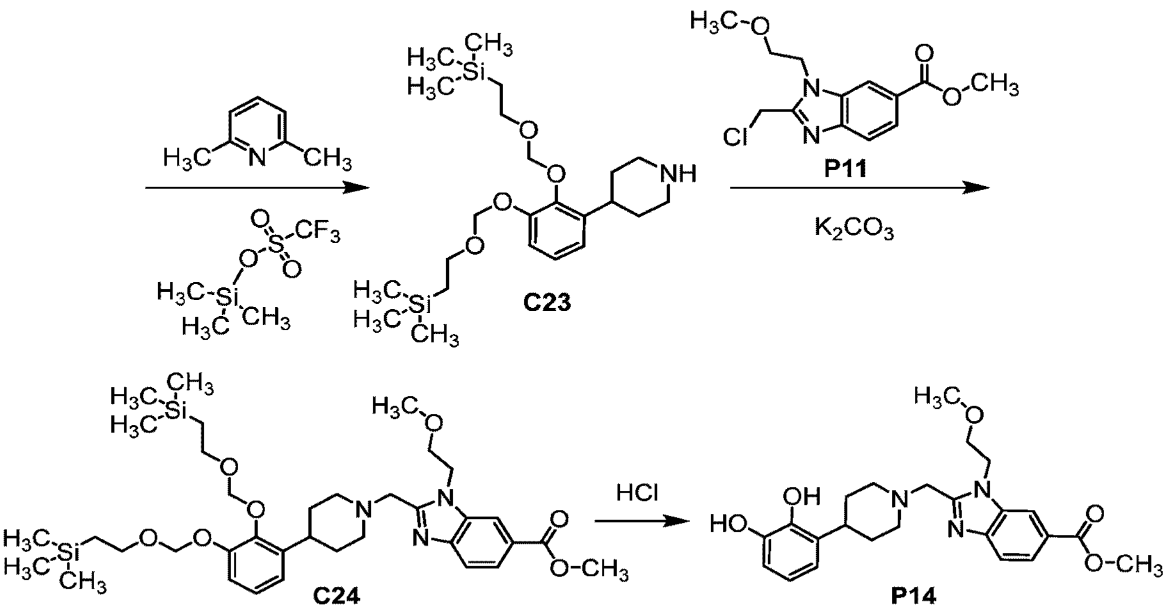
*Step 3. Synthesis of 6-bromo-2-(chloromethyl)-1-(2-methoxyethyl)-1*H*-imidazo[4,5-*b*]pyridine (**P13**).*

A solution of **C19** (400 mg, 1.63 mmol) in 1,4-dioxane (8 mL) was treated with chloroacetyl chloride (0.284 mL, 3.57 mmol) and stirred at room temperature until LCMS analysis indicated complete conversion of **C19** to the intermediate amide. After removal of the 1,4-dioxane *in vacuo*, the residue was dissolved in trifluoroacetic acid (8 mL) and heated at 80 °C for 18 hours, whereupon the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting oil was dissolved in ethyl acetate (50 mL) and neutralized by addition of saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography (Gradient: 0% to 80% ethyl acetate in heptane) afforded **P13** as a solid. Yield: 176 mg, 0.578 mmol, 35%. LCMS *m/z* 306.1 (bromine-chlorine isotope pattern observed) $[M+H]^+$. ^1H NMR (600 MHz, chloroform-*d*) δ 8.58 (br s, 1H), 7.89 (br s, 1H), 4.92 (s, 2H), 4.44 (t, *J* = 5.0 Hz, 2H), 3.71 (t, *J* = 5.0 Hz, 2H), 3.28 (s, 3H).

Preparation P14

*Methyl 2-{[4-(2,3-dihydroxyphenyl)piperidin-1-yl]methyl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate (**P14**)*





*Step 1. Synthesis of [(3-bromobenzene-1,2-diyl)bis(oxymethanediyloxyethane-2,1-diyl)]bis(trimethylsilane) (**C20**).*

This reaction was carried out in two batches of identical scale. *N,N*-Diisopropylethylamine (37.8 mL, 217 mmol) was added drop-wise to a solution of 3-bromobenzene-1,2-diol (10.0 g, 52.9 mmol) in tetrahydrofuran (300 mL). After the mixture had been stirred for 10 minutes at 20 °C, [2-(chloromethoxy)ethyl](trimethyl)silane (19.2 mL, 108 mmol) was added drop-wise over 5 minutes, and stirring was continued for 16 hours at room temperature (18 °C). *N,N*-Diisopropylethylamine (27.6 mL, 158 mmol) was again added, followed by drop-wise addition of [2-(chloromethoxy)ethyl](trimethyl)silane (14.0 mL, 79.1 mmol) at room temperature (18 °C). After another 2.5 hours at room temperature, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. At this point, the crude products from the two batches were combined and purified using silica gel chromatography (Gradient: 0% to 7% ethyl acetate in petroleum ether), to afford **C20** as a colorless oil. By ^{1}H NMR analysis, this material was not entirely pure. Combined yield: 22.9 g, 50.9 mmol, 48%. ^{1}H NMR (400 MHz, chloroform-*d*), **C20** peaks only: δ 7.19 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.12 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.90 (dd, *J* = 8.2. 8.2 Hz, 1H), 5.26 – 5.19 (m, 4H), 4.00 – 3.92 (m, 2H), 3.80 – 3.73 (m, 2H), 1.00 – 0.91 (m, 4H), 0.03 (s, 9H), 0.00 (s, 9H).

Step 2. Synthesis of tert-*butyl 4-(2,3-bis{[2-(trimethylsilyl)ethoxy]methoxy}phenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**C21**).*

A reaction vessel containing a suspension of **C20** (6.11 g, 13.6 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (5.04 g, 16.3 mmol), aqueous sodium carbonate solution (1 M; 40.8 mL, 40.8 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (497 mg, 0.679 mmol) in 1,4-dioxane (100 mL) was evacuated and charged with nitrogen. This evacuation cycle was repeated twice, and then the reaction mixture was stirred at 85 °C for 16 hours, whereupon the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via silica gel chromatography (Gradient: 0% to 8% methanol in dichloromethane) provided **C21** as a yellow oil. Yield: 5.47 g, 9.91 mmol, 73%. ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.10 (br d, *J* = 8.2 Hz, 1H), 6.98 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.81 (br d, *J* = 7.7 Hz, 1H), 5.79 (br s, 1H), 5.23 (s, 2H), 5.07 (s, 2H), 4.03 (br s, 2H), 3.83 – 3.74 (m, 4H), 3.59 (br s, 2H), 2.52 (br s, 2H), 1.49 (s, 9H), 1.01 – 0.89 (m, 4H), 0.01 (s, 9H), 0.01 (s, 9H).

Step 3. Synthesis of tert-*butyl 4-(2,3-bis{[2-(trimethylsilyl)ethoxy]methoxy}phenyl)piperidine-1-carboxylate (**C22**).*

A solution of **C21** (12.5 g, 22.6 mmol) in methanol (300 mL) was treated with 10% palladium on carbon (2.94 g, 2.76 mmol) and hydrogenated for 16 hours at 40 psi and 25 °C. LCMS analysis at this point indicated conversion to the product: LCMS *m/z* 576.0 [M+Na$^+$]. After the reaction mixture had been filtered, and the filter cake had been washed with methanol (2 x 100 mL), the combined filtrates were concentrated *in vacuo* to afford **C22** as a colorless oil. Yield: 11.2 g, 20.1 mmol, 89%. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.05 – 6.97 (m, 2H), 6.83 (dd, *J* = 6.9, 2.5 Hz, 1H), 5.22 (s, 2H), 5.13 (s, 2H), 4.38 – 4.10 (br m, 2H), 3.90 – 3.82 (m, 2H), 3.81 – 3.73 (m, 2H), 3.22 (tt, *J* = 12.2, 3.5 Hz, 1H), 2.79 (br dd, *J* = 12.8, 12.8 Hz, 2H), 1.78 (br d, *J* = 13 Hz, 2H), 1.65 – 1.52 (m, 2H), 1.48 (s, 9H), 1.04 – 0.91 (m, 4H), 0.03 (s, 9H), 0.00 (s, 9H).

*Step 4. Synthesis of 4-(2,3-bis{[2-(trimethylsilyl)ethoxy]methoxy}phenyl)piperidine (**C23**).*

To a room temperature (15 °C) solution of **C22** (7.23 g, 13.0 mmol) in dichloromethane (90 mL) was added 2,6-dimethylpyridine (2.39 g, 22.3 mmol), followed by drop-wise addition of trimethylsilyl trifluoromethanesulfonate (3.80 g, 17.1 mmol). The reaction mixture was stirred at 15 °C for 16 hours, whereupon additional 2,6-dimethylpyridine (909 mg, 8.48 mmol) and trimethylsilyl trifluoromethanesulfonate (1.45 g, 6.52 mmol) were added. After stirring at room temperature (15 °C) for another 5 hours, LCMS analysis of the reaction mixture indicated the presence of product: LCMS *m/z* 454.1 [M+H]$^+$. The reaction mixture was concentrated *in vacuo*, and the residue was washed sequentially with aqueous ammonium chloride solution (3 x 100 mL) and saturated aqueous sodium chloride solution (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford **C23** as a brown oil (6.6 g). This material was taken directly to the following step.

*Step 5. Synthesis of methyl 2-{[4-(2,3-bis{[2-(trimethylsilyl)ethoxy]methoxy}phenyl)piperidin-1-yl]methyl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate (**C24**).*

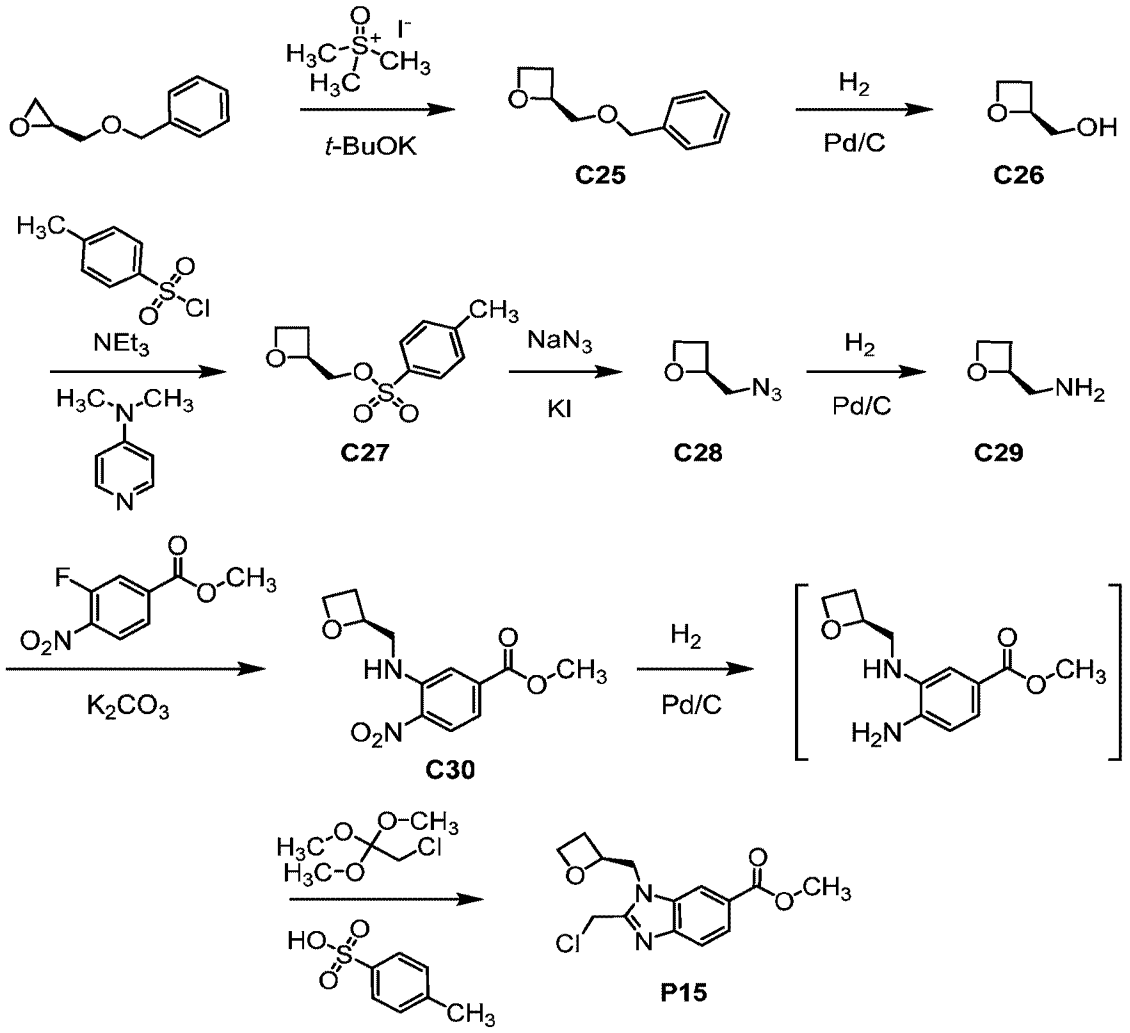
To a solution of **C23** (from the previous step; 6.6 g, ≤13 mmol) in acetonitrile (150 mL) was added **P11** (3.08 g, 10.9 mmol), followed by potassium carbonate (10.1 g, 73.1 mmol), and the reaction mixture was stirred at room temperature (15 °C) for 16 hours. LCMS analysis at this point indicated the presence of the product: LCMS *m/z* 700.2 $[M+H]^+$. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*; purification via silica gel chromatography (Gradient: 34% to 56% ethyl acetate in petroleum ether) afforded **C24** as a yellow oil. Yield: 5.4 g, 7.7 mmol, 59% over 2 steps. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.16 – 8.12 (m, 1H), 7.96 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.86 (dd, *J* = 6.7, 2.6 Hz, 1H), 5.21 (s, 2H), 5.12 (s, 2H), 4.63 (t, *J* = 5.5 Hz, 2H), 3.95 (s, 3H), 3.93 – 3.83 (m, 4H), 3.80 – 3.72 (m, 4H), 3.31 (s, 3H), 3.17 – 3.06 (m, 1H), 2.99 (br d, *J* = 11.2 Hz, 2H), 2.35 – 2.22 (m, 2H), 1.81 (br d, half of AB quartet, *J* = 12.6 Hz, 2H), 1.75 – 1.61 (m, 2H), 1.04 – 0.91 (m, 4H), 0.05 (s, 9H), −0.01 (s, 9H).

*Step 6. Synthesis of methyl 2-{[4-(2,3-dihydroxyphenyl)piperidin-1-yl]methyl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate (**P14**).*

A solution of hydrogen chloride in 1,4-dioxane (4 M; 96 mL, 384 mmol) was added to a room temperature (18 °C) solution of **C24** (6.40 g, 9.14 mmol) in 1,4-dioxane (120 mL). After completion of the addition, the reaction mixture was stirred at room temperature (18 °C) for 16 hours, combined with a similar reaction carried out using **C24** (1.00 g, 1.43 mmol), and concentrated *in vacuo*. The residue was treated with a mixture of dichloromethane and methanol (20:1, 150 mL) and stirred at room temperature (18 °C) for 1 hour, whereupon the solid (4.85 g) was collected via filtration. This material was treated with water (100 mL), and the mixture was adjusted to a pH of 7 to 8 by addition of aqueous sodium bicarbonate solution, stirred at room temperature (18 °C) for 30 minutes, and filtered. The filter cake was washed with water (2 x 20 mL), then mixed with methanol (100 mL) and concentrated *in vacuo*. The resulting material was treated with petroleum ether (100 mL) and stirred at room temperature (18 °C) for 30 minutes. After filtration, the filter cake was mixed with toluene (30 mL) and concentrated *in vacuo* to provide **P14** as a gray solid. Combined yield: 2.92 g, 6.64 mmol, 63%. LCMS *m/z* 440.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, *J* = 1.6 Hz, 1H), 7.81 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 6.64 – 6.51 (m, 3H), 4.63 (t, *J* = 5.3 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 2H), 3.75 (t, *J* = 5.3 Hz, 2H), 3.22 (s, 3H), 2.97 – 2.78 (m, 3H), 2.18 (br dd, *J* = 11, 11 Hz, 2H), 1.75 – 1.64 (m, 2H), 1.64 – 1.49 (m, 2H).

Preparation P15

*Methyl 2-(chloromethyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**P15**)*



This entire sequence was carried out on large scale. In general, before reactions, as well as after addition of reagents, reactors were evacuated to −0.08 to −0.05 MPa and then filled with nitrogen to normal pressure. This process was generally repeated 3 times, and then oxygen content was assessed to ensure that it was ≤1.0%. For the processes of extraction and washing of organic layers, mixtures were generally stirred for 15 to 60 minutes and then allowed to settle for 15 to 60 minutes before separation of layers.

*Step 1. Synthesis of (2*S*)-2-[(benzyloxy)methyl]oxetane (**C25**).*

This reaction was carried out in three batches of approximately the same scale. A 2000 L glass-lined reactor was charged with 2-methylpropan-2-ol (774.7 kg). Potassium *tert*-butoxide (157.3 kg, 1402 mol) was added via a solid addition funnel, and the mixture was stirred for 30 minutes. Trimethylsulfoxonium iodide (308.2 kg, 1400 mol) was then added in the same manner, and the reaction mixture was heated at 55 °C to 65 °C for 2 to 3 hours, whereupon (2*S*)-2-[(benzyloxy)methyl]oxirane (92.1 kg, 561 mol) was added at a rate of 5 to 20 kg/hour. After the reaction mixture had been maintained at 55 °C to 65 °C for 25 hours, it was cooled to 25 °C to 35 °C, and filtered through diatomaceous earth (18.4 kg). The filter cake was rinsed with *tert*-butyl methyl ether (3 x 340 kg), and the combined filtrates were transferred to a 5000 L reactor, treated with purified water (921 kg), and stirred for 15 to 30 minutes at 15 °C to 30 °C. The organic layer was then washed twice using a solution of sodium chloride (230.4 kg) in purified water (920.5 kg), and concentrated under reduced pressure (≤ −0.08 MPa) at ≤45 °C. *n*-Heptane (187 kg) was added, and the resulting mixture was concentrated under reduced pressure (≤ −0.08 MPa) at ≤45 °C; the organic phase was purified using silica gel chromatography (280 kg), with sodium chloride (18.5 kg) on top of the column. The crude material was loaded onto the column using *n*-heptane (513 kg), and then eluted with a mixture of *n*-heptane (688.7 kg) and ethyl acetate (64.4 kg). The three batches were combined, providing **C25** as an 85% pure light yellow oil (189.7 kg, 906 mmol, 54%). ^{1}H NMR (400 MHz, chloroform-*d*), **C25** peaks only: δ 7.40 – 7.32 (m, 4H), 7.32 – 7.27 (m, 1H), 4.98 (dddd, *J* = 8.1, 6.7, 4.9, 3.7 Hz, 1H), 4.72 – 4.55 (m, 4H), 3.67 (dd, component of ABX pattern, *J* = 11.0, 4.9 Hz, 1H), 3.62 (dd, component of ABX pattern, *J* = 11.0, 3.7 Hz, 1H), 2.72 – 2.53 (m, 2H).

*Step 2. Synthesis of (2S)-oxetan-2-ylmethanol (**C26**).*

10% Palladium on carbon (30.7 kg) was added through an addition funnel to a 10 °C to 30 °C solution of 85% pure **C25** (from previous step; 185.3 kg, 884.8 mol) in tetrahydrofuran (1270 kg) in a 3000 L stainless steel autoclave reactor. The addition funnel was rinsed with purified water and tetrahydrofuran (143 kg), and the rinses were added to the reaction mixture. After the reactor contents had been purged with nitrogen, they were similarly purged with hydrogen, increasing the pressure to 0.3 to 0.5 MPa and then venting to 0.05 MPa. This hydrogen purge was repeated 5 times, whereupon the hydrogen pressure was increased to 0.3 to 0.4 MPa. The reaction mixture was then heated to 35 °C to 45 °C. After 13 hours, during which the hydrogen pressure was maintained at 0.3 to 0.5 MPa, the mixture was vented to 0.05 MPa, and purged five times with nitrogen, via increasing the pressure to 0.15 to 0.2 MPa and then venting to 0.05 MPa. After the mixture had been cooled to 10 °C to 25 °C, it was filtered, and the reactor was rinsed with tetrahydrofuran (2 x 321 kg). The filter cake was soaked twice with this rinsing liquor and then filtered; concentration at reduced pressure (≤ −0.06 MPa) was carried out at ≤40 °C, affording **C26** (62.2 kg, 706 mol, 80%) in tetrahydrofuran (251 kg)

*Step 3. Synthesis of (2S)-oxetan-2-ylmethyl 4-methylbenzenesulfonate (**C27**).*

4-(Dimethylamino)pyridine (17.5 kg, 143 mol) was added to a 10 °C to 25 °C solution of **C26** (from the previous step; 62.2 kg, 706 mol) in tetrahydrofuran (251 kg) and triethylamine (92.7 kg, 916 mol) in dichloromethane (1240 kg). After 30 minutes, *p*-toluenesulfonyl chloride (174.8 kg, 916.9 mol) was added in portions at intervals of 20 to 40 minutes, and the reaction mixture was stirred at 15 °C to 25 °C for 16 hours and 20 minutes. Purified water (190 kg) was added; after stirring, the organic layer was washed with aqueous sodium bicarbonate solution (prepared using 53.8 kg of sodium bicarbonate and 622 kg of purified water), and then washed with aqueous ammonium chloride solution (prepared using 230 kg of ammonium chloride and 624 kg of purified water). After a final wash with purified water (311 kg), the organic layer was filtered through a stainless steel Nutsche filter that had been preloaded with silica gel (60.2 kg). The filter cake was soaked with dichloromethane (311 kg) for 20 minutes, and then filtered; the combined filtrates were concentrated at reduced pressure (≤ −0.05 MPa) and ≤40 °C until 330 to 400 L remained. Tetrahydrofuran (311 kg) was then added, at 15 °C to 30 °C, and the mixture was concentrated in the same manner, to a final volume of 330 to 400 L. The tetrahydrofuran addition and concentration was repeated, again to a volume of 330 to 400 L, affording a light yellow solution of **C27** (167.6 kg, 692 mmol, 98%) in tetrahydrofuran (251.8 kg). ^{1}H NMR (400 MHz, chloroform-*d*), **C27** peaks only: δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 4.91 (ddt, *J* = 8.0, 6.7, 3.9 Hz, 1H), 4.62 – 4.55 (m, 1H), 4.53 – 4.45 (m, 1H), 4.14 (d, *J* = 3.9 Hz, 2H), 2.75 – 2.63 (m, 1H), 2.60 – 2.49 (m, 1H), 2.44 (s, 3H).

*Step 4. Synthesis of (2S)-2-(azidomethyl)oxetane (**C28**).*

N,N-Dimethylformamide (473 kg), sodium azide (34.7 kg, 534 mol), and potassium iodide (5.2 kg, 31 mol) were combined in a 3000 L glass-lined reactor at 10 °C to 25 °C. After addition of **C27** (83.5 kg, 344.6 mol) in tetrahydrofuran (125.4 kg), the reaction mixture was heated to 55 °C to 65 °C for 17 hours and 40 minutes, whereupon it was cooled to 25 °C to 35 °C, and nitrogen was bubbled from the bottom valve for 15 minutes. *tert*-Butyl methyl ether (623 kg) and purified water (840 kg) were then added, and the resulting aqueous layer was extracted twice with *tert*-butyl methyl ether (312 kg and 294 kg). The combined organic layers were washed with purified water (2 x 419 kg) while maintaining the temperature at 10 °C to 25 °C, affording **C28** (31.2 kg, 276 mol, 80%) in a solution of the above organic layer (1236.8 kg).

*Step 5. Synthesis of 1-[(2S)-oxetan-2-yl]methanamine (**C29**).*

10% Palladium on carbon (3.7 kg) was added through an addition funnel to a 10 °C to 30 °C solution of **C28** [from the previous step; 1264 kg (31.1 kg of **C28**, 275 mol)] in tetrahydrofuran (328 kg) in a 3000 L stainless steel autoclave reactor. The addition funnel was rinsed with tetrahydrofuran (32 kg), and the rinse was added to the reaction mixture. After the reactor contents had been purged with nitrogen, they were similarly purged with hydrogen, increasing the pressure to 0.05 to 0.15 MPa and then venting to 0.03 to 0.04 MPa. This hydrogen purge was repeated 5 times, whereupon the hydrogen pressure was increased to 0.05 to 0.07 MPa. The reaction temperature was increased to 25 °C to 33 °C, and the hydrogen pressure was maintained at 0.05 to 0.15 MPa for 22 hours, while exchanging the hydrogen every 3 to 5 hours. The mixture was then purged five times with nitrogen, via increasing the pressure to 0.15 to 0.2 MPa and then venting to 0.05 MPa. After filtration, tetrahydrofuran (92 kg and 93 kg) was used to wash the reactor and then soak the filter cake. The combined filtrates were concentrated at reduced pressure (≤ -0.07 MPa) and ≤ 45 °C, affording **C29** (18.0 kg, 207 mol, 75%) in tetrahydrofuran (57.8 kg). ^{1}H NMR (400 MHz, DMSO-d_6), **C29** peaks only: δ 4.62 (ddt, *J* = 7.6, 6.6, 5.1 Hz, 1H), 4.49 (ddd, *J* = 8.6, 7.3, 5.6 Hz, 1H), 4.37 (dt, *J* = 9.1, 5.9 Hz, 1H), 2.69 (d, *J* = 5.1 Hz, 2H), 2.55 – 2.49 (m, 1H), 2.39 (m, 1H).

*Step 6. Synthesis of methyl 4-nitro-3-{[(2S)-oxetan-2-ylmethyl]amino}benzoate (**C30**).*

Potassium carbonate (58.1 kg, 420 mol) was added to a solution of methyl 3-fluoro-4-nitrobenzoate (54.8 kg, 275 mol) in tetrahydrofuran (148 kg) in a 100 L glass-lined reactor, and the mixture was stirred for 10 minutes. A solution of **C29** (29.3 kg, 336 mol) in tetrahydrofuran (212.9 kg) was added, and the reaction mixture was stirred at 20 °C to 30 °C for 12 hours, whereupon ethyl acetate (151 kg) was added, and the mixture was filtered through silica gel (29 kg). The filter cake was rinsed with ethyl acetate (150 kg and 151 kg), and the combined filtrates were concentrated at reduced pressure (≤ -0.08 MPa) and ≤ 45 °C to a volume of 222 to 281 L. After the mixture had been cooled to 10 °C to 30 °C, *n*-heptane (189 kg) was added, stirring was carried out for 20 minutes, and the mixture was concentrated at reduced pressure (≤ -0.08 MPa) and ≤ 45 °C to a volume of 222 L. *n*-Heptane (181 kg) was again added into the mixture at a reference rate of 100 to 300 kg/hour, and stirring was continued for 20 minutes. The mixture was sampled until residual tetrahydrofuran was $\leq 5\%$ and residual ethyl acetate was 10% to 13%. The mixture was heated to 40 °C to 45 °C and stirred for 1 hour, whereupon it was cooled to 15 °C to 25 °C at a rate of 5 °C to 10 °C per hour, and then stirred at 15 °C to 25 °C for 1 hour. Filtration using a stainless steel centrifuge provided a filter cake, which was rinsed with a mixture of ethyl acetate (5.0 kg) and *n*-heptane (34 kg), and then stirred with tetrahydrofuran (724 kg) at 10 °C to 30 °C for 15 minutes; filtration provided a yellow solid largely composed of **C30** (57.3 kg, 210 mol, 76%). ^{1}H NMR (400 MHz, DMSO-d_6) 8.34 (t, *J* = 5.8 Hz, 1H), 8.14 (d, *J* = 8.9 Hz, 1H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.13 (dd, *J* = 8.9, 1.8 Hz, 1H), 4.99 (dddd, *J* = 7.7, 6.7, 5.3, 4.1 Hz, 1H), 4.55 (ddd, *J* = 8.6, 7.3, 5.8 Hz, 1H), 4.43 (dt, *J* = 9.1, 6.0 Hz, 1H), 3.87 (s, 3H), 3.67 – 3.61 (m, 2H), 2.67 (dddd, *J* = 11.1, 8.6, 7.7, 6.2 Hz, 1H), 2.57 – 2.47 (m, 1H).

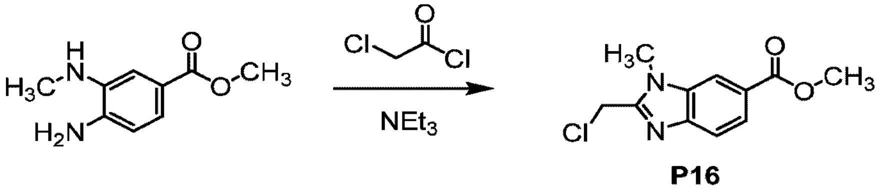
*Step 7. Synthesis of methyl 2-(chloromethyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylate (**P15**).*

A solution of **C30** (from the previous step; 51.8 kg, 190 mol) in tetrahydrofuran (678 kg), in a 3000 L autoclave reactor, was treated with 10% palladium on carbon (5.2 kg) at 10 °C to 30 °C. The addition pipe was rinsed with tetrahydrofuran (46 kg) and the rinse was added to the reaction mixture. After the reactor contents had been purged with nitrogen, they were similarly purged with hydrogen, increasing the pressure to 0.1 to 0.2 MPa and then venting to 0.02 to 0.05 MPa. This hydrogen purge was repeated 5 times, whereupon the hydrogen pressure was increased to 0.1 to 0.25 MPa. The reaction mixture was stirred at 20 °C to 30 °C, and every 2 to 3 hours, the mixture was purged with nitrogen three times, and then purged with hydrogen five times; after each final hydrogen exchange, the hydrogen pressure was increased to 0.1 to 0.25 MPa. After 11.25 hours total reaction time, the reaction mixture was vented to normal pressure, and purged five times with nitrogen, via increasing the pressure to 0.15 to 0.2 MPa and then venting to 0.05 MPa. It was then filtered, and the filter cake was rinsed twice with tetrahydrofuran (64 kg and 63 kg); the combined rinse and filtrate were concentrated under reduced pressure (≤ -0.08 MPa) and ≤ 40 °C to a volume of 128 to 160 L. Tetrahydrofuran (169 kg) was added, and the mixture was again concentrated to a volume of 128 to 160 L; this process was repeated a total of 4 times, affording a solution of the intermediate methyl 4-amino-3-{[(2*S*)-oxetan-2-ylmethyl]amino}benzoate.

Tetrahydrofuran (150 kg) was added to this solution, followed by 2-chloro-1,1,1-trimethoxyethane (35.1 kg, 227 mol) and *p*-toluenesulfonic acid monohydrate (1.8 kg, 9.5 mol). After the reaction mixture had been stirred for 25 minutes, it was heated at 40 °C to 45 °C for 5 hours, whereupon it was concentrated under reduced pressure to a volume of 135 to 181 L. 2-Propanol (142 kg) was added, and the mixture was again concentrated to a volume of 135 to 181 L, whereupon 2-propanol (36.5 kg) and purified water (90 kg) were added, and stirring was continued until a solution was obtained. This was filtered with an in-line liquid filter, and then treated with purified water (447 kg) at a reference rate of 150 to 400 kg/hour at 20 °C to 40 °C. After the mixture had been cooled to 20 °C to 30 °C, it was stirred for 2 hours, and the solid was collected via filtration with a centrifuge. The filter cake was rinsed with a solution of 2-propanol (20.5 kg) and purified water (154 kg); after drying, **P15** was obtained as a white solid (32.1 kg, 109 mol, 57%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14 – 8.11 (m, 1H), 8.01 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.79 (br d, *J* = 8.6 Hz, 1H), 5.26 – 5.18 (m, 1H), 5.04 (s, 2H), 4.66 – 4.58 (m, 2H), 4.53 (dd, component of ABX pattern, *J* = 15.7, 2.7 Hz, 1H), 4.34 (dt, *J* = 9.1, 6.0 Hz, 1H), 3.96 (s, 3H), 2.82 – 2.71 (m, 1H), 2.48 – 2.37 (m, 1H).

Preparation P16

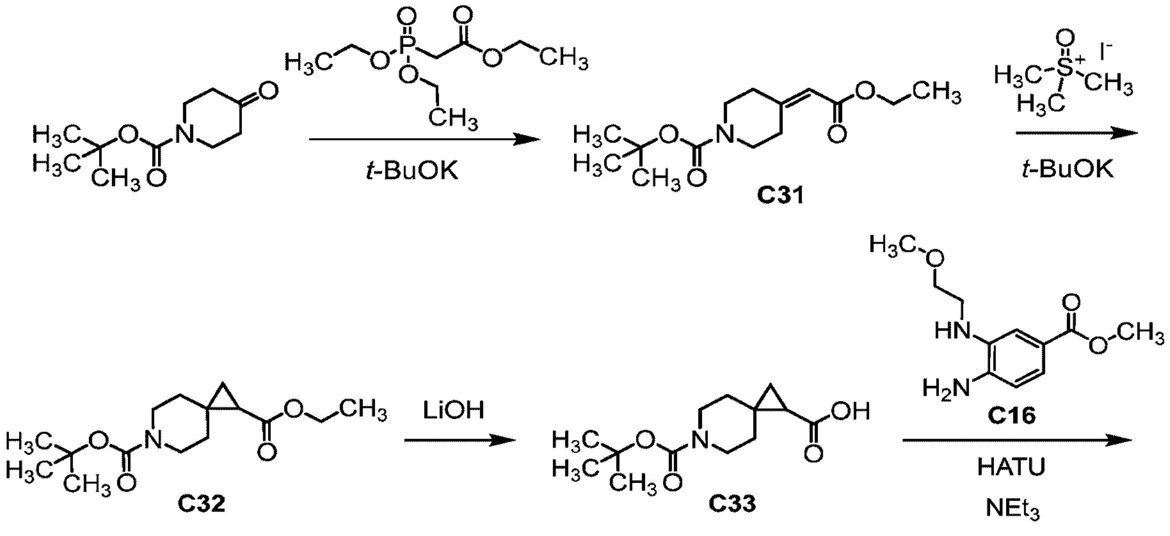
*Methyl 2-(chloromethyl)-1-methyl-1*H*-benzimidazole-6-carboxylate (**P16**)*

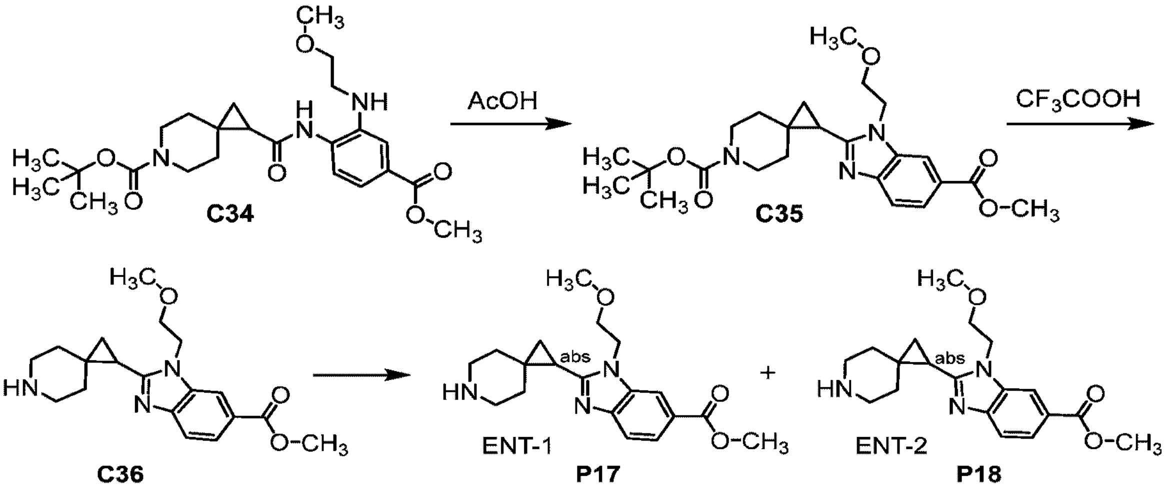


Methyl 4-amino-3-(methylamino)benzoate (206 mg, 1.14 mmol) was dissolved in 1,4-dioxane (11.5 mL) and treated with chloroacetyl chloride (109 µL, 1.37 mmol). The mixture was stirred at 100 °C for 3 hours and cooled to room temperature. Triethylamine (0.8 mL, 7 mmol) and heptane (10 mL) were added and filtered. The filtrate was concentrated under reduced pressure and the crude material was purified by chromatography on silica gel (Eluent: 40% ethyl acetate in heptane) to afford 120 mg of **P16** (44%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14 (s, 1H), 8.01 (d, 1H), 7.78 (d, 1H), 4.87 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H); LCMS *m/z* 239.1 [M+H]$^+$.

Preparations P17 and P18

*Methyl 2-(6-azaspiro[2.5]oct-1-yl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, ENT-1 (**P17**) and Methyl 2-(6-azaspiro[2.5]oct-1-yl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, ENT-2 (**P18**)*





Step 1. Synthesis of tert*-butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (**C31**).*

A solution of potassium *tert*-butoxide (65.9 g, 587 mmol) in tetrahydrofuran (500 mL) was added to a 0 °C solution of ethyl (diethoxyphosphoryl)acetate (132 g, 589 mmol) in tetrahydrofuran (500 mL), and the resulting suspension was stirred at 0 °C for 1 hour, whereupon it was cooled to −50 °C. A solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (90.0 g, 452 mmol) in tetrahydrofuran (1.5 L) was added drop-wise at −50 °C, and the reaction mixture was subsequently allowed to slowly warm to 20 °C, and then to stir for 16 hours at 20 °C. After addition of water (1 L), the mixture was concentrated *in vacuo* to remove tetrahydrofuran. The aqueous residue was extracted with ethyl acetate (2 x 800 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (500 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting material was washed several times with petroleum ether (200 mL) to provide **C31** as a white solid. Yield: 95.0 g, 353 mmol, 78%. ^{1}H NMR (400 MHz, chloroform-*d*) δ 5.71 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.55 – 3.43 (m, 4H), 2.94 (br t, *J* = 5.5 Hz, 2H), 2.28 (br t, *J* = 5.5 Hz, 2H), 1.47 (s, 9H), 1.28 (t, *J* = 7.0 Hz, 3H).

*Step 2. Synthesis of 6-*tert*-butyl 1-ethyl 6-azaspiro[2.5]octane-1,6-dicarboxylate (**C32**).*

To a solution of trimethylsulfoxonium iodide (140 g, 636 mmol) in dimethyl sulfoxide (800 mL) was added potassium *tert*-butoxide (71.2 g, 634 mmol) in one portion at 20 °C. After the reaction mixture had been stirred at 20 °C for 1.5 hours, a solution of **C31** (95.0 g, 353 mmol) in dimethyl sulfoxide (800 mL) was added drop-wise, and stirring was continued at 20 °C for 16 hours. Saturated aqueous sodium chloride solution (2.0 L) was then added; the resulting mixture was neutralized by addition of ammonium chloride, and extracted with ethyl acetate (3.0 L). The combined organic layers were washed sequentially with water (2 x 1.0 L) and with saturated aqueous sodium chloride solution (2.0 L), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via silica gel chromatography (Eluent: 10:1 petroleum ether / ethyl acetate) afforded **C32** as a yellow oil. ^{1}H NMR analysis indicated that extraneous aliphatic material was present. Yield: 80 g, 280 mmol, 79%. ^{1}H NMR (400 MHz, chloroform-*d*), **C32** peaks only: δ 4.19 – 4.09 (m, 2H), 3.55 – 3.39 (m, 3H), 3.27 (ddd, *J* = 13.0, 7.0, 4.5 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.56 (dd, *J* = 8.0, 5.5 Hz, 1H, assumed; partially obscured by water peak), 1.47 (s, 9H), 1.47 – 1.37 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.17 (dd, *J* = 5.0, 5.0 Hz, 1H), 0.93 (dd, *J* = 8.0, 4.5 Hz, 1H).

*Step 3. Synthesis of 6-(*tert*-butoxycarbonyl)-6-azaspiro[2.5]octane-1-carboxylic acid (**C33**).*

To a mixture of **C32** (80 g, 280 mmol) in tetrahydrofuran (500 mL) and water (500 mL) was added lithium hydroxide monohydrate (37.4 g, 891 mmol) in one portion. The reaction mixture was stirred at 25 °C for 16 hours, whereupon it was diluted with water (600 mL) and washed with ethyl acetate (3 x 300 mL). The organic layers were discarded, and the aqueous layer was acidified to pH 3 to 4 by addition of 6 M hydrochloric acid. The resulting mixture was extracted with ethyl acetate (3 x 600 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Trituration of the residue with petroleum ether (300 mL) provided **C33** as a white solid. Yield: 42.0 g, 164 mmol, 59%. LCMS *m/z* 278.2 [M+Na$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 – 12.03 (br s, 1H), 3.43 – 3.25 (m, 3H, assumed; partially obscured by water peak), 3.23 – 3.12 (m, 1H), 1.64 – 1.50 (m, 2H), 1.52 (dd, *J* = 7.5, 5.5 Hz, 1H), 1.39 (s, 9H), 1.39 – 1.28 (m, 2H), 0.96 – 0.88 (m, 2H).

Step 4. Synthesis of tert*-butyl 1-({4-(methoxycarbonyl)-2-[(2-methoxyethyl)amino]phenyl}carbamoyl)-6-azaspiro[2.5]octane-6-carboxylate (**C34**).*

A solution of **C33** (570 mg, 2.23 mmol), **C16** (500 mg, 2.23 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU; 1.27 g, 3.34 mmol) in *N,N*-dimethylformamide (10 mL) was stirred at 30 °C for 30 minutes, whereupon triethylamine (902 mg, 8.91 mmol) was added, and stirring was continued at 30 °C for 16 hours. The reaction mixture was then poured into water (60 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (3 x 50 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography (Eluent: 1:1 petroleum ether / ethyl acetate) afforded **C34** as a brown oil, which was taken directly into the following step.

*Step 5. Synthesis of methyl 2-[6-(*tert*-butoxycarbonyl)-6-azaspiro[2.5]oct-1-yl]-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate (**C35**).*

A solution of **C34** (from the previous step, ≤2.23 mmol) in acetic acid (15 mL) was stirred at 50 °C for 16 hours, whereupon it was concentrated *in vacuo* to provide **C35** as a brown oil. This material was used directly in the next step. LCMS *m/z* 444.1 [M+H]$^+$.

*Step 6. Synthesis of methyl 2-(6-azaspiro[2.5]oct-1-yl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate (**C36**).*

Trifluoroacetic acid (5 mL) was added to a solution of **C35** (from the previous step; ≤2.23 mmol) in dichloromethane (10 mL), and the reaction mixture was stirred at 25 °C for 2 hours. After removal of solvents *in vacuo*, the residue was basified via addition of saturated aqueous potassium carbonate solution (40 mL), and extracted with a mixture of dichloromethane and methanol (10:1, 3 x 40 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and subjected to silica gel chromatography (Eluent: 10:1:0.1 dichloromethane / methanol / concentrated ammonium hydroxide) to afford **C36** as a yellow solid. Yield: 640 mg, 1.86 mmol, 83% over three steps. LCMS *m/z* 344.1 [M+H]$^+$.

*Step 7. Isolation of methyl 2-(6-azaspiro[2.5]oct-1-yl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, ENT-1 (**P17**) and methyl 2-(6-azaspiro[2.5]oct-1-yl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, ENT-2 (**P18**).*

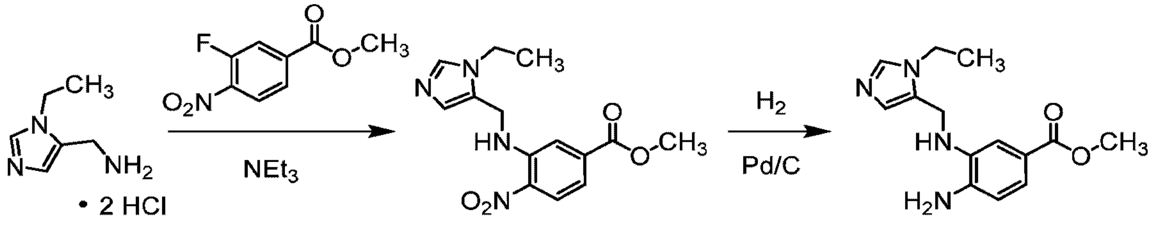
Separation of **C36** (630 mg, 1.83 mmol) into its component enantiomers was carried out using SFC [Column: Chiral Technologies Chiralpak AD, 10 µm; Mobile phase: 55:45 carbon dioxide / (ethanol containing 0.1% ammonium hydroxide)]. The first-eluting peak was designated as ENT-1 (**P17**), and the second-eluting enantiomer as ENT-2 (**P18**); both were isolated as pale yellow solids.

P17 Yield: 300 mg, 0.874 mmol, 48%. LCMS *m/z* 344.1 [M+H]$^+$. Retention time: 5.10 minutes (Column: Chiral Technologies Chiralpak AD-3, 4.6 x 150 mm, 3 µm; Mobile phase A: carbon dioxide; Mobile phase B: ethanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 5.5 minutes, then held at 40% B for 3.0 minutes; Flow rate: 2.5 mL/minute).

P18 Yield: 240 mg, 0.699 mmol, 38%. LCMS *m/z* 344.1 [M+H]$^+$. Retention time: 7.35 minutes (Analytical conditions identical to those used for **P17**).

Preparation P19

*Methyl 4-amino-3-{[(1-ethyl-1*H*-imidazol-5-yl)methyl]amino}benzoate (**P19**)*



C37 **P19**

*Step 1. Synthesis of methyl 3-{[(1-ethyl-1*H*-imidazol-5-yl)methyl]amino}-4-nitrobenzoate (**C37**).*

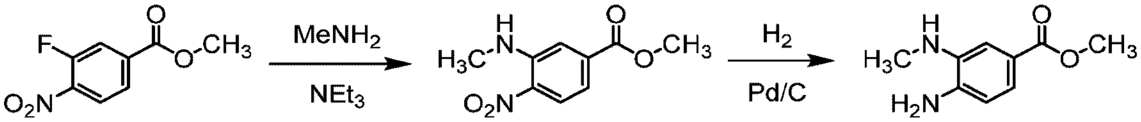
Triethylamine (3.65 mL, 26.2 mmol) was added to a solution of methyl 3-fluoro-4-nitrobenzoate (1.00 g, 5.02 mmol) and 1-(1-ethyl-1*H*-imidazol-5-yl)methanamine, dihydrochloride salt (1.00 g, 5.05 mmol) in a mixture of tetrahydrofuran (12 mL) and methanol (8 mL). The reaction mixture was stirred at 60 °C for 40 hours, whereupon it was concentrated *in vacuo* and purified using silica gel chromatography (Gradient: 0% to 2% methanol in dichloromethane) to afford **C37** as an orange solid. Yield: 1.27 g, 4.17 mmol, 83%. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.24 (d, *J* = 8.8 Hz, 1H), 7.98 – 7.91 (m, 1H), 7.68 (d, *J* = 1.7 Hz, 1H), 7.57 (br s, 1H), 7.33 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.11 (br s, 1H), 4.53 (d, *J* = 4.9 Hz, 2H), 3.99 (q, *J* = 7.3 Hz, 2H), 3.95 (s, 3H), 1.47 (t, *J* = 7.3 Hz, 3H).

*Step 2. Synthesis of methyl 4-amino-3-{[(1-ethyl-1*H*-imidazol-5-yl)methyl]amino}benzoate (**P19**).*

A mixture of wet palladium on carbon (144 mg) and **C37** (412 mg, 1.35 mmol) in methanol (13 mL) was stirred under a balloon of hydrogen for 16 hours at 25 °C. The reaction mixture was then filtered through a pad of diatomaceous earth and the filtrate was concentrated *in vacuo* to afford **P19** as a gray solid. Yield: 340 mg, 1.24 mmol, 92%. ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 7.66 (br s, 1H), 7.38 – 7.29 (m, 2H), 6.97 (br s, 1H), 6.67 (d, *J* = 7.9 Hz, 1H), 4.35 (s, 2H), 4.11 (q, *J* = 7.3 Hz, 2H), 3.81 (s, 3H), 1.44 (t, *J* = 7.3 Hz, 3H).

Preparation P20

*Methyl 4-amino-3-(methylamino)benzoate (**P20**)*



D1 **P20**

*Step 1. Synthesis of methyl 3-(methylamino)-4-nitrobenzoate (**D1**).*

To a solution of methyl 3-fluoro-4-nitrobenzoate (5.10 g, 25.6 mmol) in tetrahydrofuran (60 mL) was added methylamine (38.4 mL, 76.8 mmol, 2 M in tetrahydrofuran), drop-wise, over

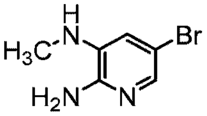
10 minutes. The pale yellow solution turned deep orange immediately upon addition and was stirred for 2 hours at room temperature. The reaction mixture was then diluted with diethyl ether (100 mL) and the organic layer was washed sequentially with water (50 mL) and saturated aqueous sodium chloride solution (50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 5.26 g of methyl 3-(methylamino)-4-nitrobenzoate (98%) as a deep orange solid. LCMS *m/z* 211.1 $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.22 (d, *J* = 8.9 Hz, 1H), 8.00 (br s, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.25 (dd, *J* = 8.9, 1.7 Hz, 1H, assumed; partially obscured by solvent peak), 3.95 (s, 3H), 3.09 (d, *J* = 5.1 Hz, 3H).

*Step 2. Synthesis of methyl 4-amino-3-(methylamino)benzoate (**P20**).*

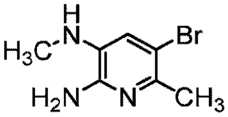
A solution of **D1** (5.26 g, 25.0 mmol) in ethanol (150 mL) was added to a 500 mL Parr® bottle previously charged with 10% palladium on carbon (50% water; 1 g). The mixture was shaken under 50 psi hydrogen atmosphere for 1 hour at room temperature, whereupon it was filtered and the filter cake was rinsed with ethanol (100 mL). The filtrate was concentrated under reduced pressure to yield 4.38 g of **P20** (97%) as an off-white solid. LCMS *m/z* 181.1 $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 7.46 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.34 (d, *J* = 1.8 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H), 3.72 (br s, 2H), 3.21 (br s, 1H), 2.91 (s, 3H).

Preparations P21 and P22

*5-Bromo-N^3-methylpyridine-2,3-diamine (**P21**)* and
*5-Bromo-N^3,6-dimethylpyridine-2,3-diamine (**P22**)*



P21

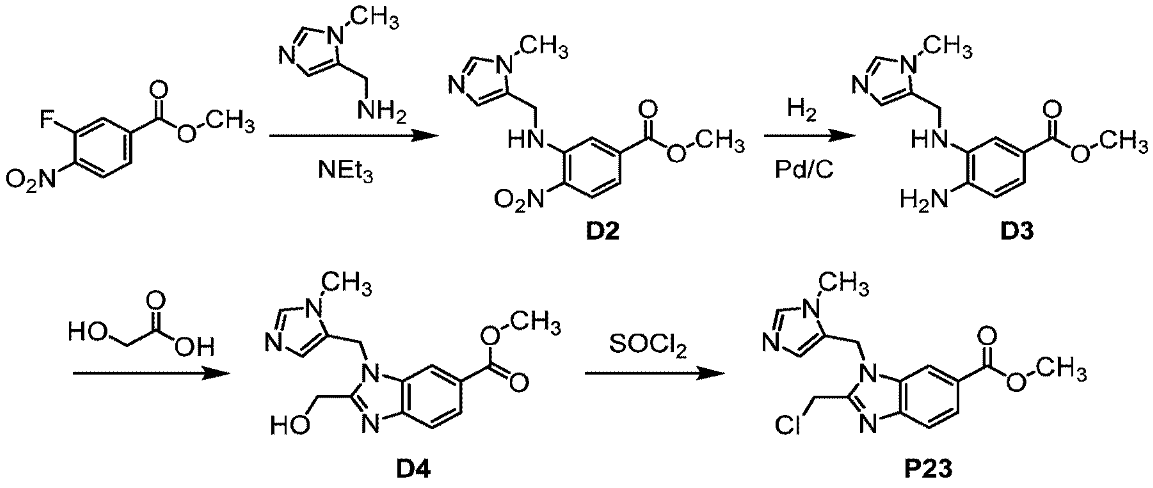


P22

Intermediate **P21** was synthesized according to the literature procedure (Choi, J. Y. et al. *J. Med. Chem.* **2012**, *55*, 852−870). Intermediate **P22** was synthesized using the same method.

Preparation P23

*Methyl 2-(chloromethyl)-1-[(1-methyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylate (**P23**)*



*Step 1. Synthesis of methyl 3-{[(1-methyl-1*H*-imidazol-5-yl)methyl]amino}-4-nitrobenzoate (**D2**).*

To a colorless solution of methyl 3-fluoro-4-nitrobenzoate (1.0 g, 5.0 mmol) in *N,N*-dimethylformamide (10 mL) was slowly added 1-(1-methyl-1*H*-imidazol-5-yl)methanamine (670 mg, 6.0 mmol) and triethylamine (762 mg, 7.53 mmol). The reaction mixture was stirred at 60 °C for 16 hours, whereupon it was poured into water (30 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (Eluent: 20% methanol in dichloromethane). The obtained yellow solid was triturated with 30:1 petroleum ether / ethyl acetate to deliver **D2** (1.2 g, 82%) as a yellow solid. LCMS *m/z* 290.9 $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.25 (d, *J* = 8.9 Hz, 1H), 7.98 – 7.92 (m, 1H), 7.70 (d, *J* = 1.7 Hz, 1H), 7.49 (s, 1H), 7.34 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.12 (s, 1H), 4.54 (d, *J* = 5.0 Hz, 2H), 3.96 (s, 3H), 3.67 (s, 3H).

*Step 2. Synthesis of methyl 4-amino-3-{[(1-methyl-1*H*-imidazol-5-yl)methyl]amino}benzoate (**D3**).*

To a suspension of **D2** (5.46 g, 18.8 mmol) in methanol (160 mL) was added wet 10% palladium on carbon (1 g). The mixture was stirred under 1 atmosphere of hydrogen for 36 hours at 20 °C. The reaction mixture was filtered and the filter cake was rinsed with methanol (200 mL). The filtrate was concentrated under reduced pressure to deliver **D3** (4.8 g, 98%) as a brown solid. LCMS *m/z* 260.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.56 (s, 1H), 7.18 (br d, *J* = 8.1 Hz, 1H), 7.12 (br s, 1H), 6.87 (s, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.50 (s, 2H), 4.84 (t, *J* = 5.2 Hz, 1H), 4.23 (d, *J* = 5.0 Hz, 2H), 3.73 (s, 3H), 3.63 (s, 3H).

*Step 3. Synthesis of methyl 2-(hydroxymethyl)-1-[(1-methyl-1*H*-imidazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylate (**D4**).*

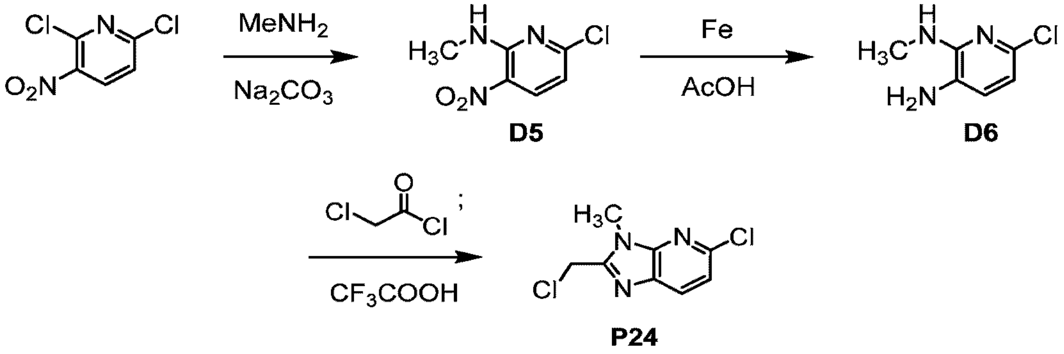
A mixture of **D3** (780 mg, 3.00 mmol) and 2-hydroxyacetic acid (342 mg, 4.49 mmol) in 1,3,5-trimethylbenzene (8 mL) was stirred at 140 °C for 14 hours and at 25 °C for 48 hours. The clear yellow solution was decanted off to give a brown residue that was dissolved in methanol (50 mL) and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (Eluent: 20% methanol in dichloromethane) to provide **D4** (318 mg, 35%) as a yellow foam. LCMS *m/z* 300.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.13 – 8.11 (m, 1H), 7.83 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.59 (s, 1H), 6.58 (s, 1H), 5.69 (s, 2H), 4.75 (s, 2H), 3.84 (s, 3H), 3.53 (s, 3H).

*Step 4. Synthesis of methyl 2-(chloromethyl)-1-[(1-methyl-1*H*-imidazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylate (**P23**).*

To a suspension of **D4** (500 mg, 1.66 mmol) in dichloromethane (10 mL) and *N,N*-dimethylformamide (3 mL) was added thionyl chloride (990 mg, 0.60 mL, 8.32 mmol), drop-wise, at room temperature. The reaction mixture was stirred at room temperature for 1 hour, then concentrated under reduced pressure. The resultant brown residue was triturated with dichloromethane (10 mL). The solids were collected by filtration and rinsed with dichloromethane (5 mL) to provide **P23** (431 mg, 73%) as an off-white solid. LCMS *m/z* 318.9♦ $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.31 (s, 1H), 7.93 (br d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.11 (s, 1H), 5.92 (s, 2H), 5.13 (s, 2H), 3.87 (s, 3H), 3.87 (s, 3H).

Preparation P24

*5-Chloro-2-(chloromethyl)-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (**P24**)*



*Step 1. Synthesis of 6-chloro-*N*-methyl-3-nitropyridin-2-amine (**D5**).*

To a suspension of 2,6-dichloro-3-nitropyridine (200 g, 1.04 mol) and Na_2CO_3 (132 g, 1.24 mol) in ethanol (1 L) was added a solution of methylamine in tetrahydrofuran (2.0 M; 622 mL,1.24 mol), drop-wise, at 0 °C via syringe. After completion of the addition, the reaction mixture was stirred at 18 °C for 6 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a yellow solid. The crude material was purified by silica gel chromatography (Gradient: 0% to 5% ethyl acetate in petroleum ether) to afford **D5** (158 g, 81% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (br s, 1H), 8.41 (d, *J* = 8.6 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 3.00 (d, *J* = 4.8 Hz, 3H).

*Step 2. Synthesis of 6-chloro-*N^2*-methylpyridine-2,3-diamine (**D6**).*

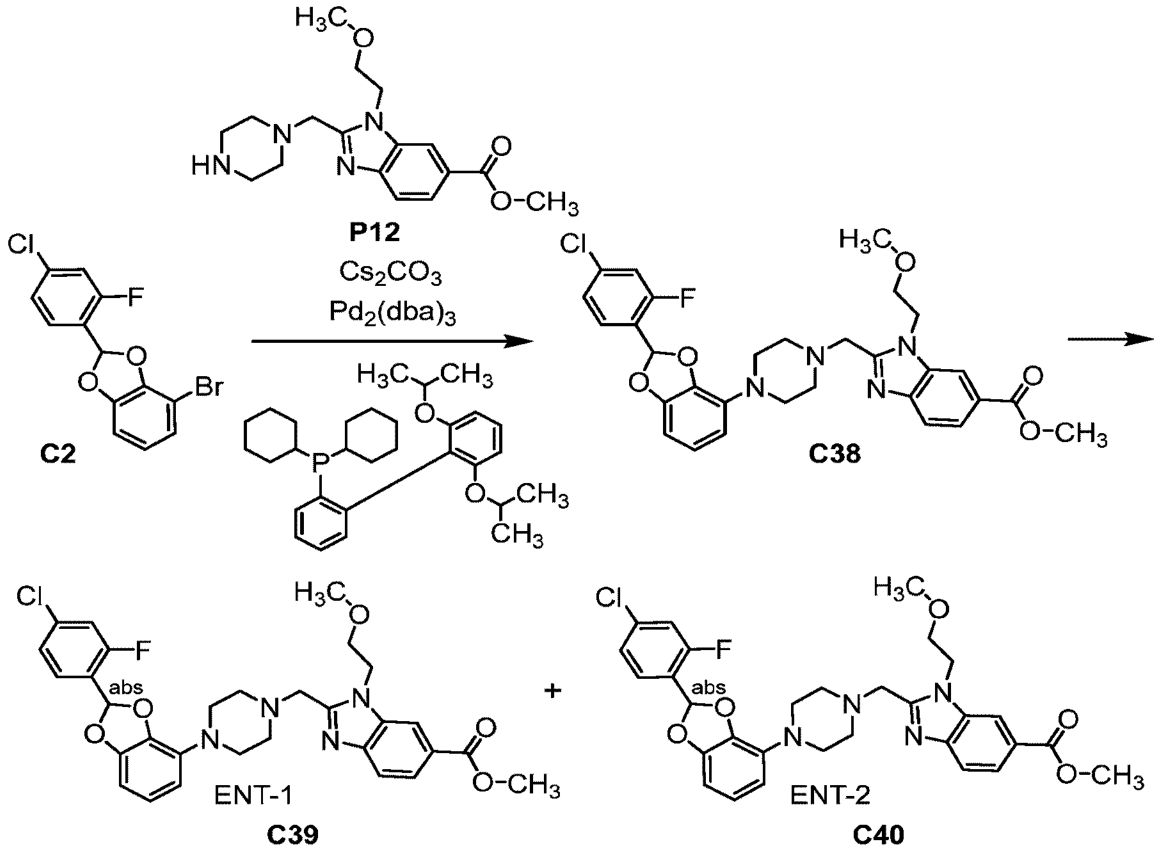
To a mixture of **D5** (15.8 g, 84.2 mmol) in acetic acid (100 mL) was added iron powder (15.4 g, 276 mmol). The reaction mixture was stirred at 80 °C for 3 hours, whereupon it was cooled to room temperature and filtered. The filter cake was washed with ethyl acetate (2 x 100). The combined organic layers were concentrated under reduced pressure and the crude material was purified by silica gel chromatography (Eluent: 1:1 ethyl acetate / petroleum ether) to afford **D6** (8.40 g, 63% yield) as a brown solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.79 (d, *J* = 7.7 Hz, 1H), 6.49 (d, *J* = 7.7 Hz, 1H), 3.00 (s, 3H).

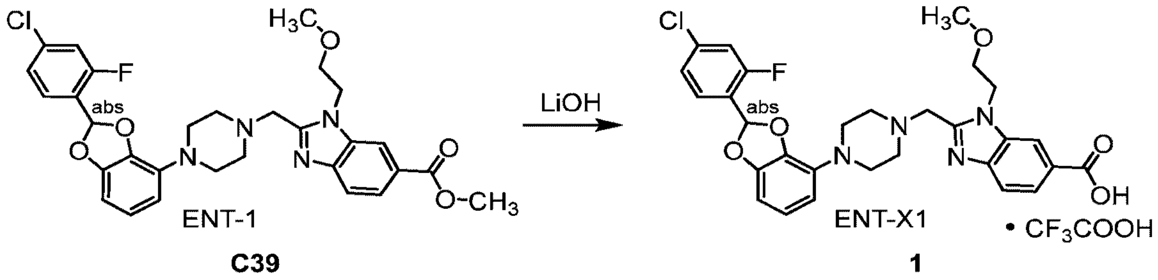
*Step 3. Synthesis of 5-chloro-2-(chloromethyl)-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (**P24**).*

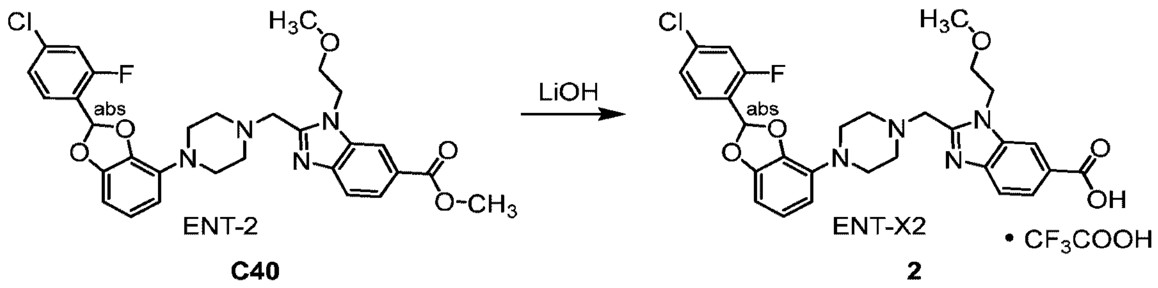
To a solution of **D6** (50.0 g, 317 mmol) in 1,4-dioxane (1.2 L) was added chloroacetyl chloride (55.5 mL, 698 mmol) and the reaction mixture was stirred at 15 °C for 50 minutes. It was then concentrated under reduced pressure to give a brown solid, which was taken up in trifluoroacetic acid (1.2 L) and stirred at 80 °C for 60 hours. The mixture was concentrated under reduced pressure to give a brown oil, which was diluted with ethyl acetate (1 L) and neutralized by addition of saturated aqueous sodium bicarbonate solution. When carbon dioxide evolution subsided, the layers were separated, and the aqueous layer was extracted with ethyl acetate (200 mL). The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (Gradient: 10% to 25% ethyl acetate in petroleum ether) to afford **P24** (61.0 g, 79% yield) as a yellow solid. LCMS *m/z* 215.7 (dichloro isotope pattern observed) $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, *J* = 8.3 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 5.11 (s, 2H), 3.84 (s, 3H).

Examples 1 and 2

*2-({4-[2-(4-Chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperazin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, ENT-X1, trifluoroacetate salt (**1**) [from **C39**]; and 2-({4-[2-(4-Chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperazin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, ENT-X2, trifluoroacetate salt (**2**) [from **C40**]*


P12
Cs$_2$CO$_3$
Pd$_2$(dba)$_3$
C2
C38
abs
ENT-1
C39
+
abs
ENT-2
C40


abs
ENT-1
C39
LiOH
abs
ENT-X1
• CF$_3$COOH
1


abs
ENT-2
C40
LiOH
abs
ENT-X2
• CF$_3$COOH
2

*Step 1. Synthesis of methyl 2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperazin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate (**C38**).*

This experiment was carried out in two batches of identical scale. A reaction vessel containing a mixture of **C2** (500 mg, 1.52 mmol), **P12** (530 mg, 1.59 mmol), [2',6'-bis(propan-2-yloxy)biphenyl-2-yl](dicyclohexyl)phosphane (Ruphos; 142 mg, 0.304 mmol), tris(dibenzylideneacetone)dipalladium(0) (139 mg, 0.152 mmol), and cesium carbonate (1.48 g, 4.54 mmol) in toluene (15 mL) was evacuated and charged with nitrogen. This evacuation cycle was repeated twice, whereupon the reaction mixture was stirred at 100 °C for 16 hours, combined with the second batch, and filtered. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (Gradient: 0% to 60% ethyl acetate in petroleum ether) followed by preparative thin-layer chromatography (Eluent: 1:1 petroleum ether / ethyl acetate) to afford **C38** as a pale yellow solid. Combined yield: 600 mg, 1.03 mmol, 34%. LCMS *m/z* 581.0♦ $[M+H]^+$.

*Step 2. Isolation of methyl 2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperazin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, ENT-1 (**C39**) and methyl 2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperazin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, ENT-2 (**C40**).*

Separation of **C38** (780 mg, 1.34 mmol) into its component enantiomers was effected using SFC [Column: Chiral Technologies Chiralpak AD, 10 µm; Mobile phase: 3:2 carbon dioxide / (ethanol containing 0.1% ammonium hydroxide)]. The first-eluting enantiomer, designated as ENT-1 (**C39**), was obtained as a white solid. Yield: 282 mg, 0.485 mmol, 36%. LCMS *m/z* 581.0♦ $[M+H]^+$. Retention time 1.90 minutes (Column: Chiral Technologies Chiralpak AD-3, 4.6 x 50 mm, 3 µm; Mobile phase A: carbon dioxide; Mobile phase B: ethanol containing 0.05% diethylamine; Gradient: 5% B for 0.20 minutes, then 5% to 40% B over 1.4 minutes, then held at 40% B for 1.05 minutes; Flow rate: 4.0 mL/minute).

The second-eluting enantiomer, designated as ENT-2, (**C40**), was subjected to a second purification using SFC [Column: Chiral Technologies Chiralpak AD, 10 µm; Mobile phase: 3:2 carbon dioxide / (ethanol containing 0.1% ammonium hydroxide)]. This provided **C40** as a pale brown solid. Yield: 280 mg, 0.482 mmol, 36%. LCMS *m/z* 581.0♦ $[M+H]^+$. Retention time 2.18 minutes (Analytical conditions identical to those used for **C39**).

*Step 3. Synthesis of 2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperazin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, ENT-X1, trifluoroacetate salt (**1**) [from **C39**].*

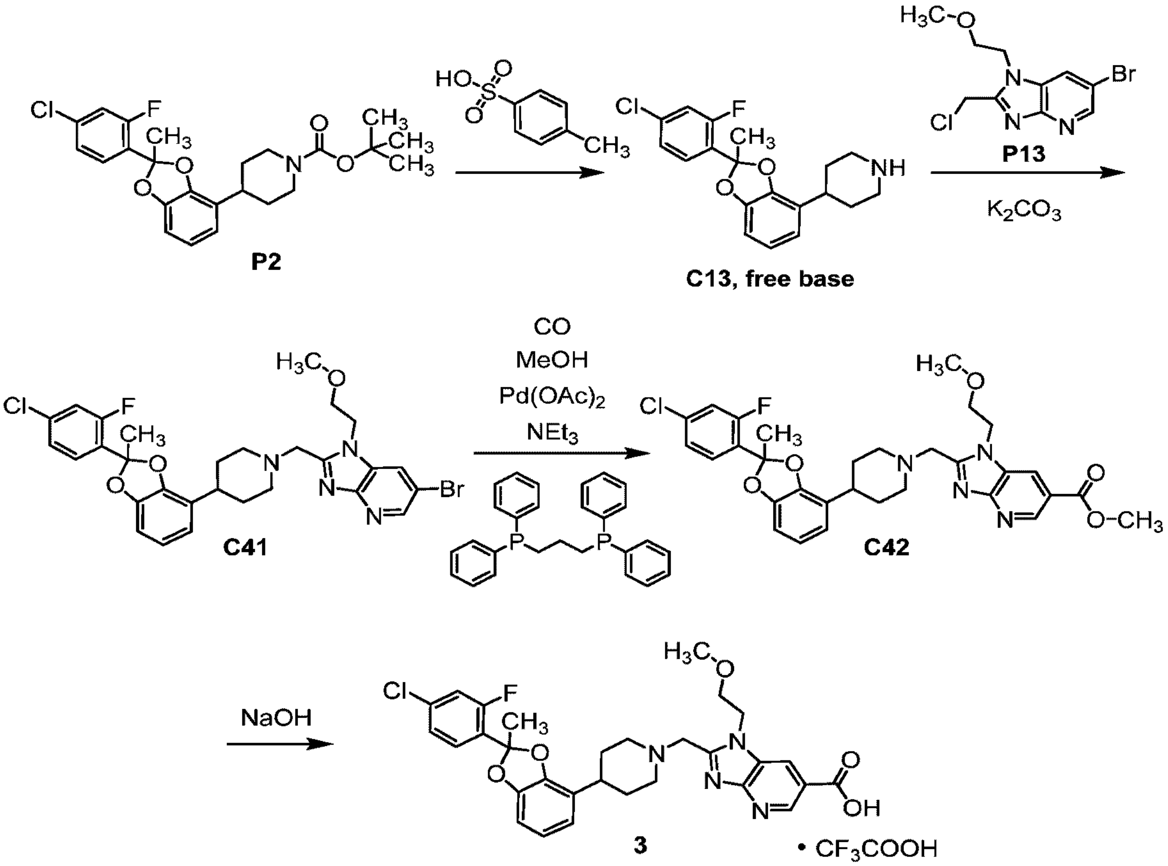
Aqueous lithium hydroxide solution (2 M; 0.30 mL, 0.60 mmol) was added to a solution of **C39** (70 mg, 0.12 mmol) in a mixture of methanol (3 mL) and tetrahydrofuran (3 mL). After the reaction mixture had been stirred at 25 °C for 16 hours, aqueous lithium hydroxide solution (2 M; 0.30 mL, 0.60 mmol) was again added, and stirring was continued for an additional 20 hours. The reaction mixture was then adjusted to pH 7 via addition of 1 M hydrochloric acid, and subsequently concentrated *in vacuo* to remove methanol and tetrahydrofuran. The residue was adjusted to a pH of 5 to 6 by addition of trifluoroacetic acid and then purified via reversed-phase HPLC (Column: Agela Durashell C18, 5 µm; Mobile phase A: 0.1% trifluoroacetic acid in water; Mobile phase B: acetonitrile; Gradient: 30% to 60% B) to afford **1** as a white solid. Yield: 40.5 mg, 59.5 µmol, 50%. LCMS *m/z* 567.0♦ $[M+H]^+$. ^1H NMR (400 MHz, methanol-d_4) δ 8.37 (br s, 1H), 8.07 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.59 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.34 (dd, *J* = 10.2, 2.0 Hz, 1H), 7.30 (br dd, *J* = 8.3, 2.0 Hz, 1H), 7.22 (s, 1H), 6.87 (dd, *J* = 8.1, 8.1 Hz, 1H), 6.63 (br d, *J* = 8 Hz, 1H), 6.60 (br d, *J* = 8 Hz, 1H), 4.70 (s, 2H), 4.65 (t, *J* = 4.8 Hz, 2H), 3.75 (t, *J* = 4.8 Hz, 2H), 3.59 – 3.42 (m, 8H), 3.29 (s, 3H).

*Step 4. Synthesis of 2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperazin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, ENT-X2, trifluoroacetate salt (**2**) [from **C40**].*

Aqueous lithium hydroxide solution (2 M; 0.30 mL, 0.60 mmol) was added to a solution of **C40** (69 mg, 0.12 mmol) in a mixture of methanol (3 mL) and tetrahydrofuran (3 mL). After the reaction mixture had been stirred at 25 °C for 16 hours, aqueous lithium hydroxide solution (2 M; 0.30 mL, 0.60 mmol) was again added, and stirring was continued for an additional 20 hours. The reaction mixture was adjusted to pH 7 via addition of 1 M hydrochloric acid, and then concentrated *in vacuo* to remove methanol and tetrahydrofuran. The residue was adjusted to a pH of 5 to 6 by addition of trifluoroacetic acid and subsequently purified via reversed-phase HPLC (Column: Agela Durashell C18, 5 µm; Mobile phase A: 0.1% trifluoroacetic acid in water; Mobile phase B: acetonitrile; Gradient: 30% to 60% B) to afford **2** as a white solid. Yield: 22.9 mg, 33.6 µmol, 28%. LCMS *m/z* 567.0♦ $[M+H]^+$. ^1H NMR (400 MHz, methanol-d_4) δ 8.40 – 8.35 (m, 1H), 8.07 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.59 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.35 (dd, *J* = 10.2, 2.0 Hz, 1H), 7.31 (br dd, *J* = 8, 2 Hz, 1H), 7.22 (s, 1H), 6.87 (dd, *J* = 8.3, 8.0 Hz, 1H), 6.63 (br d, *J* = 8 Hz, 1H), 6.60 (br d, *J* = 8 Hz, 1H), 4.68 (s, 2H), 4.65 (t, *J* = 4.9 Hz, 2H), 3.76 (t, *J* = 4.8 Hz, 2H), 3.57 – 3.40 (m, 8H), 3.29 (s, 3H).

Example 3

*2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-imidazo[4,5-*b*]pyridine-6-carboxylic acid, trifluoroacetate salt (**3**)*



*Step 1. Synthesis of 4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine (**C13, free base**).*

To a solution of **P2** (300 mg, 0.670 mmol) in ethyl acetate (3.5 mL) was added *p*-toluenesulfonic acid monohydrate (318 mg, 1.67 mmol). The reaction mixture was stirred at 60 °C for 1 hour, whereupon it was basified by addition of saturated aqueous potassium carbonate solution (20 mL) and extracted with a mixture of dichloromethane and methanol (10:1, 3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to provide **C13, free base**, as a brown solid. Yield: 230 mg, 0.661 mmol, 99%.

*Step 2. Synthesis of 6-bromo-2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-imidazo[4,5-*b*]pyridine (**C41**).*

A suspension of **C13, free base** (130 mg, 0.374 mmol), **P13** (130 mg, 0.427 mmol), and potassium carbonate (172 mg, 1.24 mmol) in acetonitrile (2 mL) was stirred at 50 °C for 16 hours. The reaction mixture was then purified using preparative thin-layer chromatography (Eluent: ethyl acetate) to afford **C41** as a brown oil. Yield: 114 mg, 0.185 mmol, 49%. LCMS *m/z* 617.1 (bromine-chlorine isotope pattern observed) $[M+H]^+$.

*Step 3. Synthesis of methyl 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**C42**).*

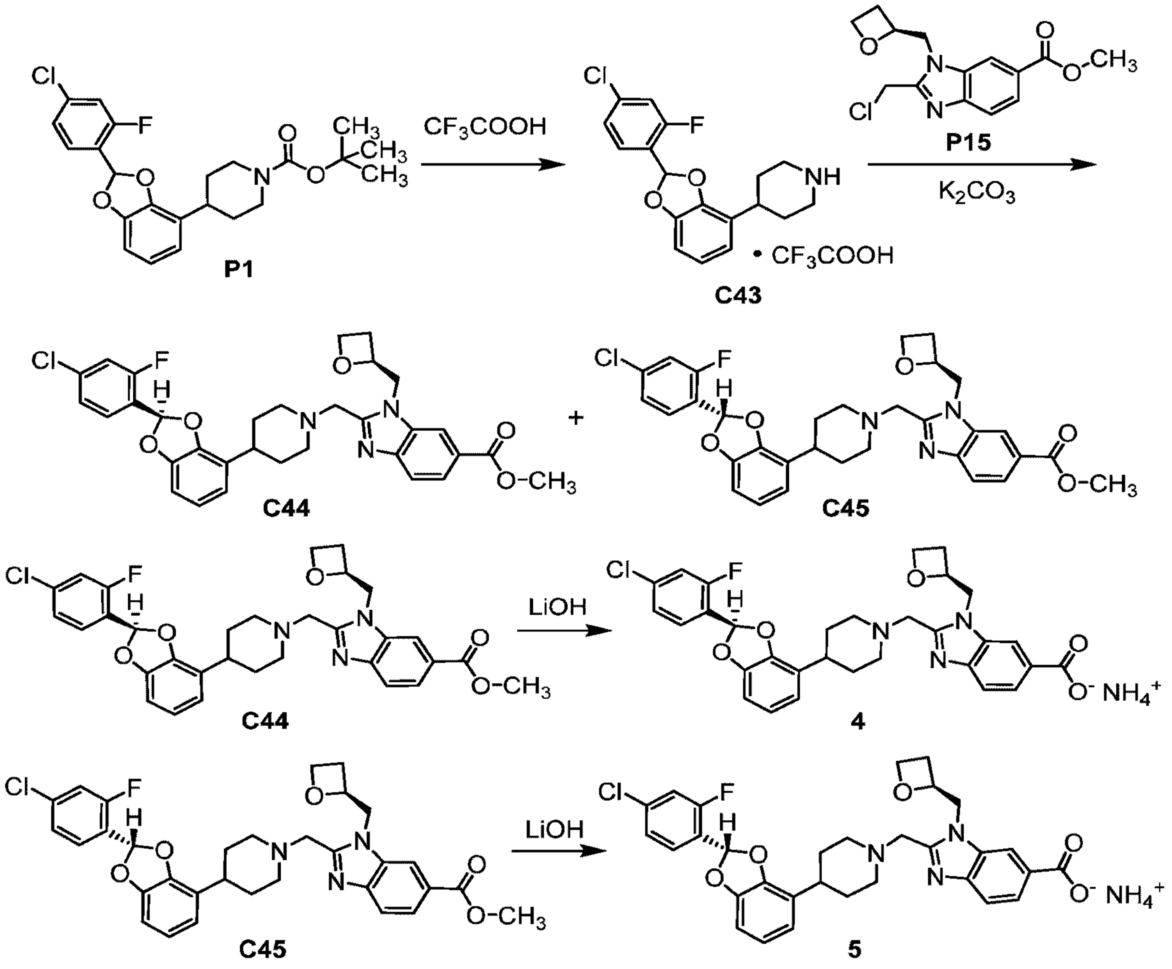
A solution of **C41** (114 mg, 0.185 mmol), 1,3-bis(diphenylphosphino)propane (15.3 mg, 37.1 µmol), palladium(II) acetate (8.3 mg, 37 µmol), and triethylamine (187 mg, 1.85 mmol) in a mixture of methanol (5 mL) and *N,N*-dimethylformamide (1 mL) was stirred at 80 °C under carbon monoxide (50 psi) for 16 hours. After the reaction mixture had been diluted with ethyl acetate (50 mL), it was washed with saturated aqueous sodium chloride solution (2 x 50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification using preparative thin-layer chromatography (Eluent: ethyl acetate) provided **C42** as a colorless oil. Yield: 60.0 mg, 0.101 mmol, 55%. LCMS *m/z* 617.2 (chlorine isotope pattern observed [M+Na$^+$].

*Step 4. Synthesis of 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-imidazo[4,5-*b*]pyridine-6-carboxylic acid, trifluoroacetate salt (**3**).*

To a solution of **C42** (60.0 mg, 0.101 mmol) in methanol (2.0 mL) was added aqueous sodium hydroxide solution (3 M; 1.0 mL, 3.0 mmol), and the reaction mixture was stirred at 20 °C for 2 hours. It was then adjusted to pH 7 by addition of 1 M hydrochloric acid, and extracted with a mixture of dichloromethane and methanol (10:1, 3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified using reversed-phase HPLC (Column: Boston Green ODS, 5 µm; Mobile phase A: 0.1% trifluoroacetic acid in water; Mobile phase B: acetonitrile; Gradient: 10% to 95% B) to afford **3** as a white solid. Yield: 29.6 mg, 42.6 µmol, 42%. LCMS *m/z* 581.0♦ [M+H]$^+$. ^{1}H NMR (400 MHz, methanol-d_4) δ 9.13 (d, *J* = 1.9 Hz, 1H), 8.74 (d, *J* = 1.9 Hz, 1H), 7.63 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.30 (dd, *J* = 10.9, 2.0 Hz, 1H), 7.24 (ddd, *J* = 8.4, 2.0, 0.7 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.82 – 6.77 (m, 2H), 4.98 – 4.89 (m, 2H, assumed; largely obscured by water peak), 4.64 (t, *J* = 4.8 Hz, 2H), 4.04 – 3.92 (br m, 2H), 3.75 (dd, *J* = 5.4, 4.2 Hz, 2H), 3.51 – 3.39 (m, 2H), 3.31 (s, 3H), 3.19 – 3.06 (m, 1H), 2.41 – 2.24 (m, 2H), 2.24 – 2.12 (m, 2H), 2.06 (d, *J* = 1.0 Hz, 3H).

Examples 4 and 5

*Ammonium 2-({4-[(2*R*)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**4**) and Ammonium 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**5**)*



*Step 1. Synthesis of 4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidine, trifluoroacetate salt (**C43**).*

To a solution of **P1** (300 mg, 0.691 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1.3 mL). The reaction mixture was stirred at 29 °C for 2 hours, whereupon it was concentrated *in vacuo* to afford **C43** as a brown oil, which was used directly in the following step.

*Step 2. Synthesis of methyl 2-({4-[(2*R*)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**C44**) and methyl 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**C45**).*

To a solution of **C43** (from the previous step, ≤0.691 mmol) in acetonitrile (10 mL) was added **P15** (204 mg, 0.692 mmol), followed by potassium carbonate (956 mg, 6.92 mmol). The reaction mixture was stirred at 29 °C for 16 hours, whereupon it was filtered; the filtrate was concentrated *in vacuo* to give a residue, which was purified by preparative thin-layer chromatography (Eluent: 2:1 petroleum ether / ethyl acetate) to provide a mixture of the diastereomeric products as a yellow gum (178 mg). Separation into the two products was carried out via SFC [Column: Chiral Technologies ChiralCel OD, 5 µm; Mobile phase: 55:45 carbon dioxide / (methanol containing 0.1% ammonium hydroxide)]. The first-eluting diastereomer, obtained as a yellow oil, was designated as **C44**. Yield: 44.3 mg, 74.8 µmol, 11% over 2 steps. LCMS *m/z* 592.1♦ $[M+H]^+$. Retention time 4.26 minutes (Column: Chiral Technologies ChiralCel OD-3, 4.6 x 100 mm, 3 µm; Mobile phase A: carbon dioxide; Mobile phase B: methanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 4.5 minutes, then held at 40% B for 2.5 minutes; Flow rate: 2.8 mL/minute).

The second-eluting diastereomer was subjected to a second purification via SFC [Column: Chiral Technologies ChiralCel OD, 5 µm; Mobile phase: 3:2 carbon dioxide / (methanol containing 0.1% ammonium hydroxide)], providing the second-eluting diastereomer as a colorless oil, which was designated as **C45**. Yield: 38 mg, 64 µmol, 9% over 2 steps. LCMS *m/z* 592.1♦ $[M+H]^+$. Retention time 4.41 minutes (Analytical conditions identical to those used for **C44**).

The indicated absolute stereochemistries at the dioxolane were assigned via potency correlation of **5** with a sample of **5, free acid** synthesized from intermediate **C48**; the absolute stereochemistry of that intermediate was determined via single-crystal X-ray structure determination (see below) of **C49**, a hemisulfate salt of **C48**.

*Step 3. Synthesis of ammonium 2-({4-[(2*R*)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**4**).*

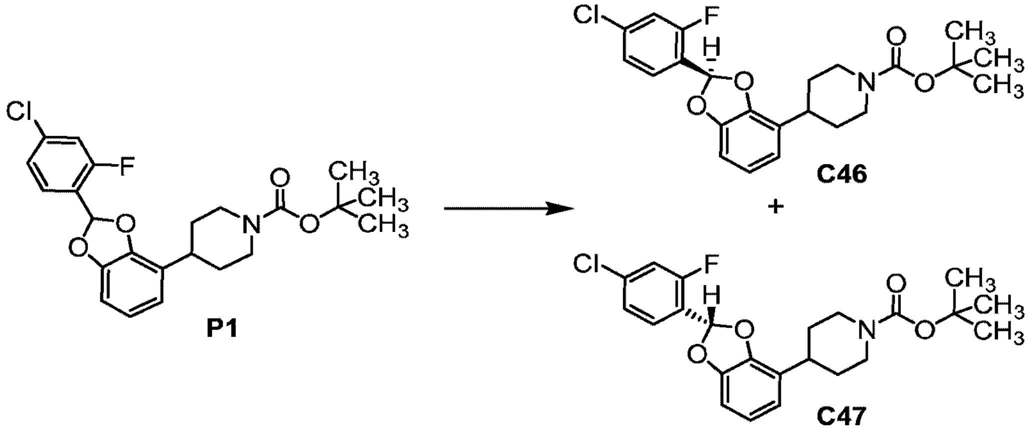
Aqueous lithium hydroxide solution (2 M; 0.80 mL, 1.6 mmol) was added to a solution of **C44** (44.3 mg, 74.8 µmol) in a mixture of methanol (1 mL) and tetrahydrofuran (1 mL), and the reaction mixture was stirred at 26 °C for 3 hours. It was then adjusted to pH 7 by addition of trifluoroacetic acid, and the resulting mixture was concentrated *in vacuo* and purified using reversed-phase HPLC (Column: Agela Durashell C18, 5 µm; Mobile phase A: 0.05% ammonium hydroxide in water; Mobile phase B: acetonitrile; Gradient: 30% to 50% B) to afford **4** as a white solid. Yield: 26.6 mg, 44.7 µmol, 60%. LCMS *m/z* 578.0♦ $[M+H]^+$. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.31 (d, *J* = 1.4 Hz, 1H), 7.96 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.57 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.34 (dd, *J* = 10.1, 2.0 Hz, 1H), 7.29 (br dd, *J* = 8.3, 2.0 Hz, 1H), 7.20 (s, 1H), 6.86 – 6.79 (m, 1H), 6.77 (br dd, component of ABC pattern, *J* = 7.9, 1.3 Hz, 1H), 6.73 (dd, component of ABC pattern, *J* = 7.5, 1.4 Hz, 1H), 5.29 – 5.18 (m, 1H), 4.9 – 4.78 (m, 1H, assumed; partially obscured by water peak), 4.68 (dd, *J* = 15.3, 2.7 Hz, 1H), 4.54 (td, *J* = 8.0, 5.9 Hz, 1H), 4.44 (dt, *J* = 9.2, 5.9 Hz, 1H), 4.02 (AB quartet, J_{AB} = 13.9 Hz, $\Delta\nu_{AB}$ = 49.0 Hz, 2H), 3.18 – 3.08 (m, 1H), 3.05 – 2.96 (m, 1H), 2.81 – 2.68 (m, 2H), 2.56 – 2.45 (m, 1H), 2.45 – 2.30 (m, 2H), 2.03 – 1.88 (m, 2H), 1.88 – 1.79 (m, 2H).

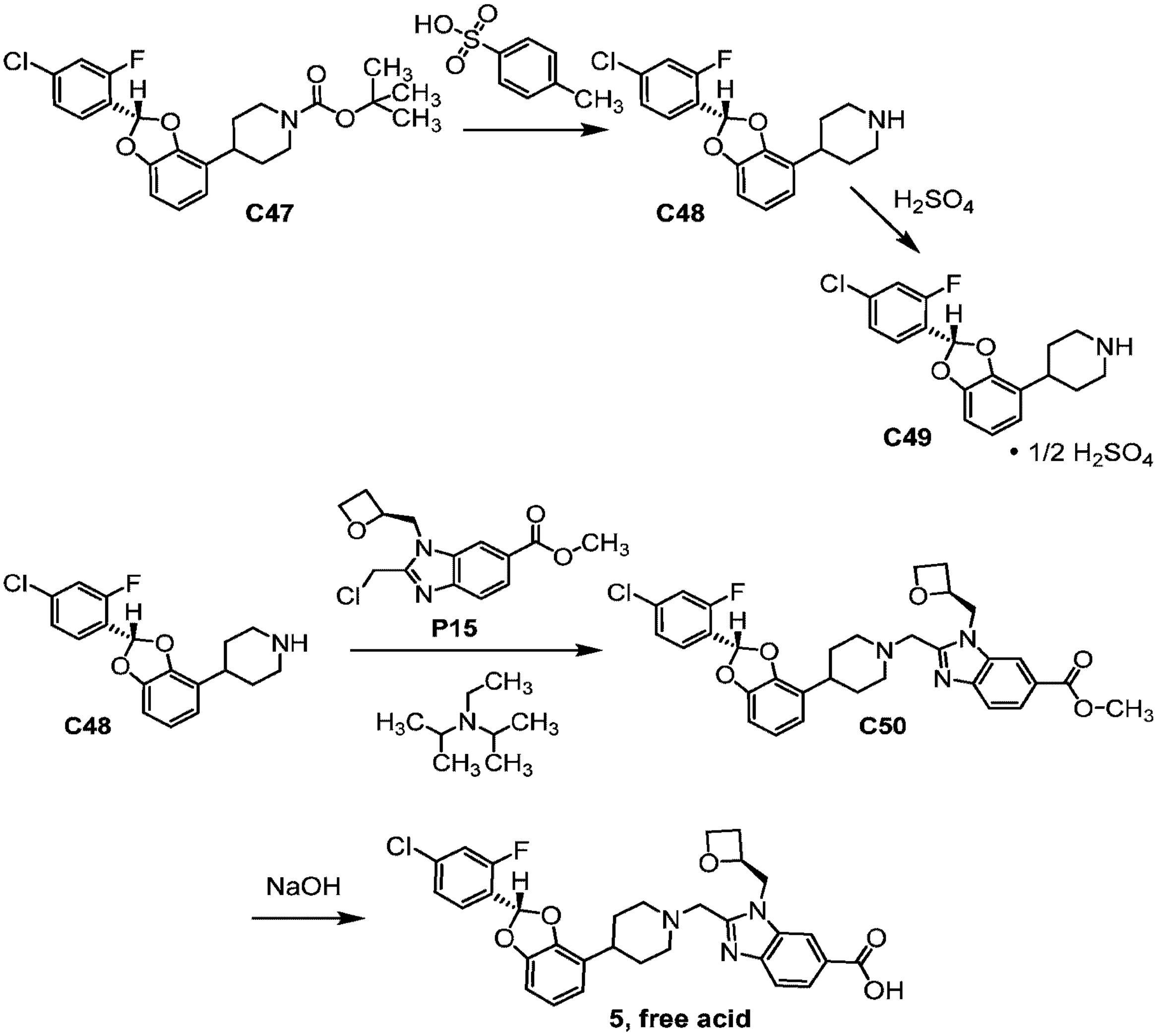
*Step 4. Synthesis of ammonium 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H-benzimidazole-6-carboxylate (**5**).*

Aqueous lithium hydroxide solution (2 M; 0.80 mL, 1.6 mmol) was added to a solution of **C45** (38 mg, 64 µmol) in a mixture of methanol (1 mL) and tetrahydrofuran (1 mL), and the reaction mixture was stirred at 24 °C for 2.5 hours. It was then adjusted to pH 7 by addition of 1 M hydrochloric acid, and the resulting mixture was concentrated *in vacuo* and purified using reversed-phase HPLC (Column: Agela Durashell C18, 5 µm; Mobile phase A: 0.05% ammonium hydroxide in water; Mobile phase B: acetonitrile; Gradient: 29% to 49% B), providing **5** as a white solid. Yield: 27.9 mg, 46.9 µmol, 73%. LCMS *m/z* 577.9♦ $[M+H]^+$. ^1H NMR (400 MHz, methanol-d_4) δ 8.32 (d, *J* = 1.4 Hz, 1H), 7.96 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.56 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.34 (dd, *J* = 10.2, 2.0 Hz, 1H), 7.29 (br dd, *J* = 8.3, 2.0 Hz, 1H), 7.20 (s, 1H), 6.85 – 6.80 (m, 1H), 6.77 (dd, component of ABC pattern, *J* = 8.0, 1.3 Hz, 1H), 6.73 (dd, component of ABC pattern, *J* = 7.5, 1.4 Hz, 1H), 5.30 – 5.20 (m, 1H), 4.9 – 4.79 (m, 1H, assumed; partially obscured by water peak), 4.68 (dd, *J* = 15.4, 2.7 Hz, 1H), 4.62 – 4.54 (m, 1H), 4.44 (dt, *J* = 9.2, 5.9 Hz, 1H), 4.02 (AB quartet, J_{AB} = 13.9 Hz, $\Delta\nu_{AB}$ = 44.6 Hz, 2H), 3.18 – 3.09 (m, 1H), 3.06 – 2.97 (m, 1H), 2.80 – 2.67 (m, 2H), 2.55 – 2.30 (m, 3H), 2.02 – 1.78 (m, 4H).

Alternate Synthesis of Example 5, free acid

*2-({4-[(2*S*)-2-(4-Chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H-benzimidazole-6-carboxylic acid (**5, free acid**)*





Step 1. Isolation of tert-*butyl 4-[(2*R*)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (**C46**) and* tert-*butyl 4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (**C47**).*

Separation of **P1** (10 g, 23 mmol) into its component enantiomers was carried out using reversed-phase HPLC [Column: Phenomenex Lux Amylose-1, 5 µm; Mobile phase: 9:1 carbon dioxide / (2-propanol containing 0.2% 1-aminopropan-2-ol)]. The first-eluting enantiomer was designated as **C46**, and the second-eluting enantiomer as **C47**; both were obtained as colorless oils. The absolute stereochemistries indicated for **C46** and **C47** were assigned based on a single-crystal X-ray structure determination carried out on **C49**, which was synthesized from **C47** (see below).

C46 Yield: 4.47 g, 10.3 mmol, 45%. Retention time: 3.98 minutes [Column: Phenomenex Lux Amylose-1, 4.6 x 250 mm, 5 µm; Mobile phase A: carbon dioxide; Mobile phase B: 2-propanol containing 0.2% 1-aminopropan-2-ol; Gradient: 5% B for 1.00 minute, then 5% to 60% B over 8.00 minutes; Flow rate: 3.0 mL/minute; Back pressure: 120 bar].

C47 Yield: 4.49 g, 10.3 mmol, 45%. Retention time: 4.32 minutes (Analytical SFC conditions identical to those used for **C46**).

*Step 2. Synthesis of 4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidine (**C48**).*

p-Toluenesulfonic acid monohydrate (566 mg, 2.98 mmol) was added to a solution of **C47** (1.12 g, 2.58 mmol) in ethyl acetate (26 mL). After the reaction mixture had been heated at 45 °C for 16 hours, it was concentrated *in vacuo*, dissolved in ethyl acetate, and washed with saturated aqueous sodium bicarbonate solution. The aqueous layers were extracted with ethyl acetate, and the combined organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure, affording **C48** as a foamy white solid (947 mg), LCMS *m/z* 334.0♦ $[M+H]^+$. A portion of this material, which still contained some *p*-toluenesulfonic acid, was used in the synthesis of **C50** below.

A second portion of the foamy white solid (440 mg) was dissolved in ethyl acetate (25 mL) and washed with saturated aqueous sodium bicarbonate solution (2 x 15 mL); the organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford **C48** (350 mg) as a colorless oil that no longer contained *p*-toluenesulfonic acid. Adjusted yield: 350 mg, 1.05 mmol, 88%. ^1H NMR (400 MHz, chloroform-*d*) δ 7.53 (dd, J = 8.4, 7.8 Hz, 1H), 7.22 – 7.13 (m, 3H), 6.87 – 6.80 (m, 1H), 6.79 – 6.71 (m, 2H), 3.23 – 3.14 (m, 2H), 2.86 – 2.69 (m, 3H), 1.90 – 1.68 (m, 4H).

*Step 3. Synthesis of 4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidine, hemisulfate salt (**C49**).*

A 0.1 M solution of **C48** (the colorless oil from above) in ethyl acetate was prepared and subjected to a salt screen. Only the sulfate salt formation is described here. A mixture of sulfuric acid (25 µmol) and the solution of substrate (0.1 M, 250 µL, 25 µmol) was heated to 45 °C for 1 hour, allowed to cool to room temperature, and stirred for 15 hours. The resulting suspension was treated with methanol (approximately 150 µL) until a solution formed; this was allowed to slowly evaporate overnight, until approximately 50 µL of solvent remained. One of the resulting crystals was analyzed by single-crystal X-ray structure determination, establishing the absolute stereochemistry as that shown.

*Single-crystal X-ray structural determination of **C49***

Single Crystal X-Ray Analysis

Data collection was performed on a Bruker D8 Venture diffractometer at room temperature. Data collection consisted of omega and phi scans.

The structure was solved by intrinsic phasing using SHELX software suite in the triclinic class space group *P*1. The structure was subsequently refined by the full-matrix least squares method. All non-hydrogen atoms were found and refined using anisotropic displacement parameters.

The hydrogen atoms located on nitrogen were found from the Fourier difference map and refined with distances restrained. The remaining hydrogen atoms were placed in calculated positions and were allowed to ride on their carrier atoms. The final refinement included isotropic displacement parameters for all hydrogen atoms.

The asymmetric unit is comprised of two molecules of protonated **C48**, one molecule of doubly deprotonated sulfuric acid, and one molecule full occupancy water. Thus, the structure is a hemisulfate salt and hemihydrate. The chlorofluorophenyl ring is disordered and modeled with occupancy of 60/40, with the ring flipped over two positions.

Analysis of the absolute structure using likelihood methods (Hooft, 2008) was performed using PLATON (Spek). The results indicate that the absolute structure has been correctly assigned; the method calculates that the probability that the structure is correct is 100.0. The Hooft parameter is reported as 0.061 with an esd of 0.004 and the Parson's parameter is reported as 0.063 with an esd of 0.005.

The final R-index was 3.1%. A final difference Fourier revealed no missing or misplaced electron density.

Pertinent crystal, data collection, and refinement information is summarized in Table E. Atomic coordinates, bond lengths, bond angles, and displacement parameters are listed in Tables F – H.

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Table E. Crystal data and structure refinement for **C49**.

Empirical formula	$C_{36}H_{38}Cl_2F_2N_2O_9S$	
Formula weight	783.64	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	$P1$	
Unit cell dimensions	a = 5.9095(2) Å	α = 86.5910(10)°
	b = 6.1712(2) Å	β = 89.3680(10)°
	c = 25.6096(8) Å	γ = 75.7680(10)°
Volume	903.68(5) $Å^3$	
Z	1	
Density (calculated)	1.440 Mg/m^3	
Absorption coefficient	2.743 mm^{-1}	
F(000)	408	
Crystal size	0.380 x 0.120 x 0.080 mm^3	
Theta range for data collection	3.458 to 72.096°	
Index ranges	$-7<=h<=7$, $-7<=k<=7$, $-31<=l<=31$	
Reflections collected	24619	
Independent reflections	6399 [R_{int} = 0.0323]]	
Completeness to theta = 67.679°	96.6%	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6399 / 9 / 495	
Goodness-of-fit on F^2	1.014	
Final R indices [$I>2\sigma(I)$]	$R1$ = 0.0305, $wR2$ = 0.0805	
R indices (all data)	$R1$ = 0.0310, $wR2$ = 0.0810	
Absolute structure parameter	0.058(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.167 and −0.184 e.$Å^{-3}$	

Table F. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **C49**. U(eq) is defined as one-third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	8968(1)	2512(1)	4774(1)	33(1)
Cl(1)	2534(3)	7001(5)	9863(1)	161(1)
F(1)	9192(9)	7761(7)	8721(2)	95(1)
C(1)	7533(7)	6719(7)	8821(1)	72(1)
C(2)	6041(9)	7355(8)	9230(2)	92(1)
C(3)	4428(8)	6206(10)	9350(2)	93(2)
C(4)	4276(8)	4392(9)	9082(2)	86(1)
C(5)	5801(7)	3784(7)	8678(1)	69(1)
C(6)	7444(6)	4930(5)	8533(1)	56(1)
Cl(1')	2534(3)	7001(5)	9863(1)	161(1)
F(1')	6045(13)	1811(12)	8450(3)	95(1)
C(1')	5801(7)	3784(7)	8678(1)	69(1)
C(2')	4276(8)	4392(9)	9082(2)	86(1)
C(3')	4428(8)	6206(10)	9350(2)	93(2)
C(4')	6041(9)	7355(8)	9230(2)	92(1)
C(5')	7533(7)	6719(7)	8821(1)	72(1)
C(6')	7444(6)	4930(5)	8533(1)	56(1)
Cl(2)	-2047(5)	12265(3)	154(1)	157(1)
F(2)	-2662(7)	5436(7)	1220(2)	92(1)
C(19)	-1591(6)	7059(7)	1154(1)	68(1)
C(20)	-2327(8)	8653(9)	752(2)	88(1)
C(21)	-1157(9)	10260(8)	665(2)	88(1)
C(22)	728(9)	10361(7)	964(2)	80(1)
C(23)	1431(6)	8731(6)	1364(1)	65(1)
C(24)	274(5)	7058(5)	1472(1)	54(1)
Cl(2')	-2047(5)	12265(3)	154(1)	157(1)
F(2')	3433(15)	8441(16)	1630(4)	92(1)
C(19')	1431(6)	8731(6)	1364(1)	65(1)
C(20')	728(9)	10361(7)	964(2)	80(1)
C(21')	-1157(9)	10260(8)	665(2)	88(1)
C(22')	-2327(8)	8653(9)	752(2)	88(1)
C(23')	-1591(6)	7059(7)	1154(1)	68(1)

C(24')	274(5)	7058(5)	1472(1)	54(1)
N(1)	4370(3)	2950(4)	5713(1)	41(1)
N(2)	4133(4)	8236(3)	4386(1)	42(1)
O(1)	10923(4)	2331(5)	8233(1)	77(1)
O(2)	7874(4)	3730(4)	7651(1)	64(1)
O(3)	1766(4)	6201(4)	2352(1)	64(1)
O(4)	2966(5)	3591(4)	1729(1)	75(1)
O(5)	9024(3)	2305(3)	4214(1)	50(1)
O(6)	7650(4)	989(3)	5024(1)	63(1)
O(7)	11358(3)	1934(4)	4982(1)	64(1)
O(8)	7789(3)	4827(3)	4909(1)	46(1)
O(1W)	10276(4)	6879(4)	5537(1)	54(1)
C(7)	9086(6)	4293(6)	8090(1)	63(1)
C(8)	9234(4)	1745(5)	7490(1)	44(1)
C(9)	11056(5)	930(6)	7834(1)	54(1)
C(10)	12654(5)	-1059(6)	7768(1)	62(1)
C(11)	12316(5)	-2213(6)	7338(1)	58(1)
C(12)	10459(4)	-1405(5)	6994(1)	47(1)
C(13)	8826(4)	623(4)	7066(1)	38(1)
C(14)	6762(4)	1637(4)	6711(1)	37(1)
C(15)	7243(4)	3516(4)	6343(1)	42(1)
C(16)	5126(4)	4639(4)	6009(1)	44(1)
C(17)	3883(5)	1105(5)	6056(1)	50(1)
C(18)	5997(4)	-38(4)	6386(1)	41(1)
C(25)	996(6)	5296(6)	1900(1)	60(1)
C(26)	3848(5)	4738(4)	2505(1)	45(1)
C(27)	4542(6)	3183(5)	2133(1)	52(1)
C(28)	6579(6)	1567(5)	2178(1)	56(1)
C(29)	7932(6)	1577(5)	2620(1)	56(1)
C(30)	7236(5)	3123(5)	2992(1)	51(1)
C(31)	5126(5)	4786(4)	2944(1)	42(1)
C(32)	4261(4)	6474(4)	3352(1)	39(1)
C(33)	6145(5)	7543(5)	3544(1)	51(1)
C(34)	5139(5)	9272(4)	3932(1)	50(1)
C(35)	2313(5)	7116(5)	4227(1)	49(1)
C(36)	3263(4)	5420(4)	3826(1)	42(1)

Table G. Bond lengths [Å] and angles [°] for **C49**.

S(1)-O(5)	1.4463(18)
S(1)-O(7)	1.4668(19)
S(1)-O(6)	1.475(2)
S(1)-O(8)	1.4863(18)
Cl(1)-C(3)	1.731(4)
F(1)-C(1)	1.314(6)
C(1)-C(6)	1.375(5)
C(1)-C(2)	1.374(6)
C(2)-C(3)	1.343(8)
C(2)-H(2)	0.9300
C(3)-C(4)	1.369(8)
C(4)-C(5)	1.373(6)
C(4)-H(4)	0.9300
C(5)-C(6)	1.370(5)
C(5)-H(5)	0.9300
C(6)-C(7)	1.493(5)
Cl(1')-C(3')	1.731(4)
F(1')-C(1')	1.357(8)
C(1')-C(6')	1.370(5)
C(1')-C(2')	1.373(6)
C(2')-C(3')	1.369(8)
C(2')-H(2')	0.9300
C(3')-C(4')	1.343(8)
C(4')-C(5')	1.374(6)
C(4')-H(4')	0.9300
C(5')-C(6')	1.375(5)
C(5')-H(5')	0.9300
C(6')-C(7)	1.493(5)
Cl(2)-C(21)	1.739(4)
F(2)-C(19)	1.312(5)
C(19)-C(24)	1.378(5)
C(19)-C(20)	1.378(6)
C(20)-C(21)	1.348(7)
C(20)-H(20)	0.9300

C(21)-C(22)	1.375(7)
C(22)-C(23)	1.384(6)
C(22)-H(22)	0.9300
C(23)-C(24)	1.385(5)
C(23)-H(23)	0.9300
C(24)-C(25)	1.485(5)
Cl(2')-C(21')	1.739(4)
F(2')-C(19')	1.340(9)
C(19')-C(20')	1.384(6)
C(19')-C(24')	1.385(5)
C(20')-C(21')	1.375(7)
C(20')-H(20')	0.9300
C(21')-C(22')	1.348(7)
C(22')-C(23')	1.378(6)
C(22')-H(22')	0.9300
C(23')-C(24')	1.378(5)
C(23')-H(23')	0.9300
C(24')-C(25)	1.485(5)
N(1)-C(17)	1.480(4)
N(1)-C(16)	1.480(3)
N(1)-H(1X)	0.95(2)
N(1)-H(1Y)	0.97(2)
N(2)-C(34)	1.483(4)
N(2)-C(35)	1.487(4)
N(2)-H(2X)	0.96(2)
N(2)-H(2Y)	0.99(2)
O(1)-C(9)	1.368(4)
O(1)-C(7)	1.445(4)
O(2)-C(8)	1.373(3)
O(2)-C(7)	1.443(3)
O(3)-C(26)	1.380(3)
O(3)-C(25)	1.440(3)
O(4)-C(27)	1.369(4)
O(4)-C(25)	1.447(4)
O(1W)-H(1WX)	0.93(2)
O(1W)-H(1WY)	0.94(2)
C(7)-H(7)	0.9800

C(8)-C(9)	1.374(4)
C(8)-C(13)	1.376(4)
C(9)-C(10)	1.370(5)
C(10)-C(11)	1.387(5)
C(10)-H(10)	0.9300
C(11)-C(12)	1.390(4)
C(11)-H(11)	0.9300
C(12)-C(13)	1.400(4)
C(12)-H(12)	0.9300
C(13)-C(14)	1.514(3)
C(14)-C(18)	1.518(3)
C(14)-C(15)	1.528(3)
C(14)-H(14)	0.9800
C(15)-C(16)	1.518(3)
C(15)-H(15A)	0.9700
C(15)-H(15B)	0.9700
C(16)-H(16A)	0.9700
C(16)-H(16B)	0.9700
C(17)-C(18)	1.513(4)
C(17)-H(17A)	0.9700
C(17)-H(17B)	0.9700
C(18)-H(18A)	0.9700
C(18)-H(18B)	0.9700
C(25)-H(25)	0.9800
C(26)-C(31)	1.367(4)
C(26)-C(27)	1.379(3)
C(27)-C(28)	1.363(4)
C(28)-C(29)	1.394(5)
C(28)-H(28)	0.9300
C(29)-C(30)	1.376(4)
C(29)-H(29)	0.9300
C(30)-C(31)	1.408(4)
C(30)-H(30)	0.9300
C(31)-C(32)	1.514(3)
C(32)-C(33)	1.527(4)
C(32)-C(36)	1.524(3)
C(32)-H(32)	0.9800

C(33)-C(34)	1.510(4)
C(33)-H(33A)	0.9700
C(33)-H(33B)	0.9700
C(34)-H(34A)	0.9700
C(34)-H(34B)	0.9700
C(35)-C(36)	1.515(3)
C(35)-H(35A)	0.9700
C(35)-H(35B)	0.9700
C(36)-H(36A)	0.9700
C(36)-H(36B)	0.9700
O(5)-S(1)-O(7)	109.68(13)
O(5)-S(1)-O(6)	109.65(13)
O(7)-S(1)-O(6)	109.45(15)
O(5)-S(1)-O(8)	111.22(11)
O(7)-S(1)-O(8)	109.11(11)
O(6)-S(1)-O(8)	107.69(11)
F(1)-C(1)-C(6)	118.6(4)
F(1)-C(1)-C(2)	119.1(4)
C(6)-C(1)-C(2)	122.1(4)
C(3)-C(2)-C(1)	118.9(4)
C(3)-C(2)-H(2)	120.5
C(1)-C(2)-H(2)	120.5
C(2)-C(3)-C(4)	121.6(4)
C(2)-C(3)-Cl(1)	119.3(4)
C(4)-C(3)-Cl(1)	119.1(5)
C(3)-C(4)-C(5)	118.2(5)
C(3)-C(4)-H(4)	120.9
C(5)-C(4)-H(4)	120.9
C(6)-C(5)-C(4)	122.4(4)
C(6)-C(5)-H(5)	118.8
C(4)-C(5)-H(5)	118.8
C(5)-C(6)-C(1)	116.7(3)
C(5)-C(6)-C(7)	122.7(3)
C(1)-C(6)-C(7)	120.6(3)
F(1')-C(1')-C(6')	114.7(4)
F(1')-C(1')-C(2')	122.1(5)
C(6')-C(1')-C(2')	122.4(4)

C(3')-C(2')-C(1')	118.2(5)
C(3')-C(2')-H(2')	120.9
C(1')-C(2')-H(2')	120.9
C(4')-C(3')-C(2')	121.6(4)
C(4')-C(3')-Cl(1')	119.3(4)
C(2')-C(3')-Cl(1')	119.1(5)
C(3')-C(4')-C(5')	118.9(4)
C(3')-C(4')-H(4')	120.5
C(5')-C(4')-H(4')	120.5
C(6')-C(5')-C(4')	122.1(4)
C(6')-C(5')-H(5')	118.9
C(4')-C(5')-H(5')	118.9
C(1')-C(6')-C(5')	116.7(3)
C(1')-C(6')-C(7)	122.7(3)
C(5')-C(6')-C(7)	120.6(3)
F(2)-C(19)-C(24)	119.3(4)
F(2)-C(19)-C(20)	118.1(4)
C(24)-C(19)-C(20)	122.5(4)
C(21)-C(20)-C(19)	118.4(4)
C(21)-C(20)-H(20)	120.8
C(19)-C(20)-H(20)	120.8
C(20)-C(21)-C(22)	122.4(4)
C(20)-C(21)-Cl(2)	118.9(4)
C(22)-C(21)-Cl(2)	118.7(4)
C(21)-C(22)-C(23)	117.8(4)
C(21)-C(22)-H(22)	121.1
C(23)-C(22)-H(22)	121.1
C(22)-C(23)-C(24)	122.0(4)
C(22)-C(23)-H(23)	119.0
C(24)-C(23)-H(23)	119.0
C(19)-C(24)-C(23)	116.8(3)
C(19)-C(24)-C(25)	120.3(3)
C(23)-C(24)-C(25)	122.9(3)
F(2')-C(19')-C(20')	123.5(5)
F(2')-C(19')-C(24')	113.9(5)
C(20')-C(19')-C(24')	122.0(4)
C(21')-C(20')-C(19')	117.8(4)

C(21')-C(20')-H(20')	121.1
C(19')-C(20')-H(20')	121.1
C(22')-C(21')-C(20')	122.4(4)
C(22')-C(21')-Cl(2')	118.9(4)
C(20')-C(21')-Cl(2')	118.7(4)
C(21')-C(22')-C(23')	118.4(4)
C(21')-C(22')-H(22')	120.8
C(23')-C(22')-H(22')	120.8
C(24')-C(23')-C(22')	122.5(4)
C(24')-C(23')-H(23')	118.7
C(22')-C(23')-H(23')	118.7
C(23')-C(24')-C(19')	116.8(3)
C(23')-C(24')-C(25)	120.3(3)
C(19')-C(24')-C(25)	122.9(3)
C(17)-N(1)-C(16)	112.6(2)
C(17)-N(1)-H(1X)	110.7(19)
C(16)-N(1)-H(1X)	108(2)
C(17)-N(1)-H(1Y)	108(2)
C(16)-N(1)-H(1Y)	112.4(19)
H(1X)-N(1)-H(1Y)	105(3)
C(34)-N(2)-C(35)	112.2(2)
C(34)-N(2)-H(2X)	109.7(19)
C(35)-N(2)-H(2X)	109.7(19)
C(34)-N(2)-H(2Y)	107.7(19)
C(35)-N(2)-H(2Y)	110.8(19)
H(2X)-N(2)-H(2Y)	107(3)
C(9)-O(1)-C(7)	106.0(2)
C(8)-O(2)-C(7)	105.9(2)
C(26)-O(3)-C(25)	105.9(2)
C(27)-O(4)-C(25)	105.7(2)
H(1WX)-O(1W)-H(1WY)	105(4)
O(2)-C(7)-O(1)	106.5(3)
O(2)-C(7)-C(6)	110.4(3)
O(1)-C(7)-C(6)	111.2(3)
O(2)-C(7)-C(6')	110.4(3)
O(1)-C(7)-C(6')	111.2(3)
O(2)-C(7)-H(7)	109.6

O(1)-C(7)-H(7)	109.6
C(6)-C(7)-H(7)	109.6
C(9)-C(8)-O(2)	110.0(2)
C(9)-C(8)-C(13)	123.4(2)
O(2)-C(8)-C(13)	126.6(2)
O(1)-C(9)-C(10)	128.1(3)
O(1)-C(9)-C(8)	110.1(3)
C(10)-C(9)-C(8)	121.7(3)
C(9)-C(10)-C(11)	116.3(3)
C(9)-C(10)-H(10)	121.8
C(11)-C(10)-H(10)	121.8
C(10)-C(11)-C(12)	122.0(3)
C(10)-C(11)-H(11)	119.0
C(12)-C(11)-H(11)	119.0
C(11)-C(12)-C(13)	121.3(3)
C(11)-C(12)-H(12)	119.4
C(13)-C(12)-H(12)	119.4
C(8)-C(13)-C(12)	115.3(2)
C(8)-C(13)-C(14)	119.8(2)
C(12)-C(13)-C(14)	124.9(2)
C(13)-C(14)-C(18)	114.2(2)
C(13)-C(14)-C(15)	111.38(19)
C(18)-C(14)-C(15)	108.70(19)
C(13)-C(14)-H(14)	107.4
C(18)-C(14)-H(14)	107.4
C(15)-C(14)-H(14)	107.4
C(16)-C(15)-C(14)	111.7(2)
C(16)-C(15)-H(15A)	109.3
C(14)-C(15)-H(15A)	109.3
C(16)-C(15)-H(15B)	109.3
C(14)-C(15)-H(15B)	109.3
H(15A)-C(15)-H(15B)	107.9
N(1)-C(16)-C(15)	109.9(2)
N(1)-C(16)-H(16A)	109.7
C(15)-C(16)-H(16A)	109.7
N(1)-C(16)-H(16B)	109.7
C(15)-C(16)-H(16B)	109.7

H(16A)-C(16)-H(16B)	108.2
N(1)-C(17)-C(18)	110.94(19)
N(1)-C(17)-H(17A)	109.5
C(18)-C(17)-H(17A)	109.5
N(1)-C(17)-H(17B)	109.5
C(18)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	108.0
C(17)-C(18)-C(14)	110.6(2)
C(17)-C(18)-H(18A)	109.5
C(14)-C(18)-H(18A)	109.5
C(17)-C(18)-H(18B)	109.5
C(14)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	108.1
O(3)-C(25)-O(4)	106.6(2)
O(3)-C(25)-C(24')	111.0(3)
O(4)-C(25)-C(24')	109.4(3)
O(3)-C(25)-C(24)	111.0(3)
O(4)-C(25)-C(24)	109.4(3)
O(3)-C(25)-H(25)	109.9
O(4)-C(25)-H(25)	109.9
C(24)-C(25)-H(25)	109.9
C(31)-C(26)-C(27)	123.2(3)
C(31)-C(26)-O(3)	127.3(2)
C(27)-C(26)-O(3)	109.5(2)
C(28)-C(27)-O(4)	127.7(2)
C(28)-C(27)-C(26)	121.9(3)
O(4)-C(27)-C(26)	110.3(2)
C(27)-C(28)-C(29)	116.3(2)
C(27)-C(28)-H(28)	121.9
C(29)-C(28)-H(28)	121.9
C(30)-C(29)-C(28)	121.8(3)
C(30)-C(29)-H(29)	119.1
C(28)-C(29)-H(29)	119.1
C(29)-C(30)-C(31)	121.7(3)
C(29)-C(30)-H(30)	119.2
C(31)-C(30)-H(30)	119.2
C(26)-C(31)-C(30)	115.1(2)

C(26)-C(31)-C(32)	121.5(2)
C(30)-C(31)-C(32)	123.4(2)
C(31)-C(32)-C(33)	113.3(2)
C(31)-C(32)-C(36)	111.48(19)
C(33)-C(32)-C(36)	108.02(19)
C(31)-C(32)-H(32)	107.9
C(33)-C(32)-H(32)	107.9
C(36)-C(32)-H(32)	107.9
C(34)-C(33)-C(32)	110.5(2)
C(34)-C(33)-H(33A)	109.6
C(32)-C(33)-H(33A)	109.6
C(34)-C(33)-H(33B)	109.6
C(32)-C(33)-H(33B)	109.6
H(33A)-C(33)-H(33B)	108.1
N(2)-C(34)-C(33)	110.6(2)
N(2)-C(34)-H(34A)	109.5
C(33)-C(34)-H(34A)	109.5
N(2)-C(34)-H(34B)	109.5
C(33)-C(34)-H(34B)	109.5
H(34A)-C(34)-H(34B)	108.1
N(2)-C(35)-C(36)	110.71(19)
N(2)-C(35)-H(35A)	109.5
C(36)-C(35)-H(35A)	109.5
N(2)-C(35)-H(35B)	109.5
C(36)-C(35)-H(35B)	109.5
H(35A)-C(35)-H(35B)	108.1
C(35)-C(36)-C(32)	111.9(2)
C(35)-C(36)-H(36A)	109.2
C(32)-C(36)-H(36A)	109.2
C(35)-C(36)-H(36B)	109.2
C(32)-C(36)-H(36B)	109.2
H(36A)-C(36)-H(36B)	107.9

Symmetry transformations used to generate equivalent atoms.

Table H. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **C49**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	32(1)	32(1)	32(1)	-3(1)	-2(1)	-1(1)
Cl(1)	107(1)	258(2)	90(1)	-63(1)	19(1)	19(1)
F(1)	111(2)	91(2)	98(2)	-30(2)	6(2)	-46(2)
C(1)	81(2)	71(2)	60(2)	-20(2)	-16(2)	-6(2)
C(2)	100(3)	92(3)	74(3)	-42(2)	-16(2)	7(2)
C(3)	70(2)	134(4)	53(2)	-27(2)	-7(2)	19(3)
C(4)	71(2)	116(3)	67(2)	0(2)	-1(2)	-16(2)
C(5)	75(2)	70(2)	59(2)	-11(2)	-7(2)	-10(2)
C(6)	65(2)	54(2)	42(1)	-8(1)	-18(1)	-1(1)
Cl(1')	107(1)	258(2)	90(1)	-63(1)	19(1)	19(1)
F(1')	111(2)	91(2)	98(2)	-30(2)	6(2)	-46(2)
C(1')	75(2)	70(2)	59(2)	-11(2)	-7(2)	-10(2)
C(2')	71(2)	116(3)	67(2)	0(2)	-1(2)	-16(2)
C(3')	70(2)	134(4)	53(2)	-27(2)	-7(2)	19(3)
C(4')	100(3)	92(3)	74(3)	-42(2)	-16(2)	7(2)
C(5')	81(2)	71(2)	60(2)	-20(2)	-16(2)	-6(2)
C(6')	65(2)	54(2)	42(1)	-8(1)	-18(1)	-1(1)
Cl(2)	243(2)	110(1)	80(1)	12(1)	-39(1)	26(1)
F(2)	88(2)	106(2)	93(2)	-12(2)	-22(2)	-44(2)
C(19)	62(2)	77(2)	62(2)	-26(2)	-12(2)	-5(2)
C(20)	85(3)	98(3)	66(2)	-20(2)	-31(2)	10(2)
C(21)	117(3)	74(3)	51(2)	-11(2)	-10(2)	18(2)
C(22)	104(3)	70(2)	60(2)	-9(2)	8(2)	-8(2)
C(23)	58(2)	73(2)	60(2)	-13(2)	-3(1)	-6(2)
C(24)	50(2)	60(2)	47(2)	-23(1)	-4(1)	-2(1)
Cl(2')	243(2)	110(1)	80(1)	12(1)	-39(1)	26(1)
F(2')	88(2)	106(2)	93(2)	-12(2)	-22(2)	-44(2)
C(19')	58(2)	73(2)	60(2)	-13(2)	-3(1)	-6(2)
C(20')	104(3)	70(2)	60(2)	-9(2)	8(2)	-8(2)
C(21')	117(3)	74(3)	51(2)	-11(2)	-10(2)	18(2)
C(22')	85(3)	98(3)	66(2)	-20(2)	-31(2)	10(2)
C(23')	62(2)	77(2)	62(2)	-26(2)	-12(2)	-5(2)

C(24')	50(2)	60(2)	47(2)	-23(1)	-4(1)	-2(1)
N(1)	30(1)	59(1)	32(1)	-3(1)	-4(1)	-7(1)
N(2)	49(1)	38(1)	37(1)	-11(1)	-5(1)	0(1)
O(1)	58(1)	107(2)	55(1)	-23(1)	-26(1)	6(1)
O(2)	64(1)	66(1)	50(1)	-21(1)	-23(1)	12(1)
O(3)	66(1)	62(1)	52(1)	-27(1)	-19(1)	11(1)
O(4)	92(2)	64(1)	56(1)	-32(1)	-20(1)	10(1)
O(5)	62(1)	51(1)	34(1)	-5(1)	-2(1)	-9(1)
O(6)	76(1)	43(1)	70(1)	-4(1)	32(1)	-14(1)
O(7)	45(1)	68(1)	69(1)	-29(1)	-22(1)	13(1)
O(8)	45(1)	35(1)	53(1)	-9(1)	-4(1)	2(1)
O(1W)	56(1)	50(1)	51(1)	-3(1)	-12(1)	1(1)
C(7)	68(2)	73(2)	45(2)	-12(1)	-14(1)	-12(2)
C(8)	38(1)	51(1)	36(1)	-4(1)	-3(1)	0(1)
C(9)	42(1)	76(2)	39(1)	-1(1)	-9(1)	-4(1)
C(10)	38(1)	87(2)	48(2)	10(1)	-8(1)	6(1)
C(11)	45(1)	60(2)	55(2)	9(1)	2(1)	13(1)
C(12)	41(1)	46(1)	47(1)	0(1)	3(1)	0(1)
C(13)	34(1)	43(1)	34(1)	2(1)	-1(1)	-4(1)
C(14)	30(1)	44(1)	31(1)	-4(1)	-1(1)	0(1)
C(15)	41(1)	38(1)	45(1)	0(1)	-12(1)	-7(1)
C(16)	44(1)	43(1)	39(1)	-3(1)	-6(1)	4(1)
C(17)	39(1)	73(2)	42(1)	-1(1)	-3(1)	-23(1)
C(18)	41(1)	46(1)	39(1)	-4(1)	2(1)	-14(1)
C(25)	65(2)	62(2)	51(2)	-22(1)	-9(1)	-8(1)
C(26)	55(1)	37(1)	37(1)	-8(1)	1(1)	-2(1)
C(27)	72(2)	41(1)	39(1)	-9(1)	-2(1)	-6(1)
C(28)	79(2)	39(1)	43(1)	-10(1)	11(1)	1(1)
C(29)	62(2)	45(2)	48(2)	-2(1)	7(1)	8(1)
C(30)	58(2)	45(2)	42(1)	-1(1)	-1(1)	1(1)
C(31)	54(1)	34(1)	34(1)	-4(1)	2(1)	-4(1)
C(32)	50(1)	30(1)	33(1)	-4(1)	-6(1)	0(1)
C(33)	63(2)	45(1)	54(2)	-9(1)	17(1)	-28(1)
C(34)	59(2)	38(1)	58(2)	-9(1)	-1(1)	-22(1)
C(35)	46(1)	46(1)	56(2)	-17(1)	16(1)	-11(1)
C(36)	39(1)	36(1)	53(1)	-15(1)	12(1)	-13(1)

*Step 4. Synthesis of methyl 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**C50**).*

A solution of **C48** (500 mg of the foamy white solid from above, corrected for *p*-toluenesulfonic acid: 1.25 mmol) in acetonitrile (6 mL) was treated with *N,N*-diisopropylethylamine (0.68 mL, 3.9 mmol) and allowed to stir for 5 minutes at 45 °C. After addition of **P15** (319 mg, 1.08 mmol), stirring at 45 °C was continued for 7.25 hours, whereupon the reaction mixture was diluted with water (6 mL) and acetonitrile (2 mL) at 45 °C. The resulting heterogeneous mixture was allowed to cool to room temperature and stir for 72 hours. More water (5 mL) was added, and after a further 30 minutes of stirring, the solid was collected via filtration and washed with a mixture of acetonitrile and water (15:85, 3 x 5 mL), to afford **C50** as a white solid with a slight pink cast. Yield: 605 mg, 1.02 mmol, 82%. LCMS *m/z* 592.0♦ $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.17 (d, *J* = 1.6 Hz, 1H), 7.96 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.51 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.19 (br s, 1H), 7.18 – 7.14 (m, 2H), 6.85 – 6.79 (m, 1H), 6.76 – 6.71 (m, 2H), 5.26 – 5.18 (m, 1H), 4.73 (dd, component of ABX pattern, *J* = 15.3, 5.9 Hz, 1H), 4.67 (dd, component of ABX pattern, *J* = 15.3, 3.5 Hz, 1H), 4.63 – 4.55 (m, 1H), 4.38 (ddd, *J* = 9.1, 6.0, 5.9 Hz, 1H), 3.94 (s, 5H), 3.03 – 2.89 (m, 2H), 2.77 – 2.65 (m, 2H), 2.51 – 2.39 (m, 1H), 2.34 – 2.20 (m, 2H), 1.91 – 1.76 (m, 4H).

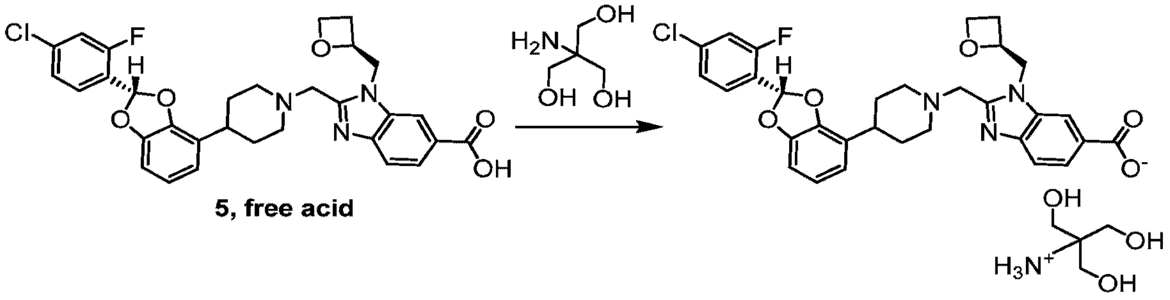
*Step 5. Synthesis of 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid (**5, free acid**).*

A suspension of **C50** (595 mg, 1.00 mmol) in methanol (10 mL) was heated to 45 °C and treated with aqueous sodium hydroxide solution (1 M; 2.01 mL, 2.01 mmol). After 21 hours at 45 °C, the reaction mixture was allowed to cool to room temperature; it was then treated with aqueous citric acid solution (1 M, 1 mL), which brought the pH to 5 to 6. Water (10 mL) was added, and the mixture was stirred for 1 hour, whereupon the solid was collected by filtration. It was washed with a mixture of methanol and water (1:10, 3 x 5 mL), to afford a solid (433 mg). A portion of this material (300 mg) was stirred with a mixture of heptane and ethyl acetate (1:3, 5 mL) at 40 °C for 1 hour; after cooling to room temperature with continued stirring, the solid was collected via filtration, and washed with a mixture of heptane and ethyl acetate (3:1, 3 x 3 mL) to afford **5, free acid**, as a white solid. Yield: 260 mg, 0.450 mmol, corresponding to 65% for the entire reaction. LCMS *m/z* 578.0♦ $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.75 (v br s, 1H), 8.26 (br s, 1H), 7.79 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.66 – 7.56 (m, 3H), 7.40 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.35 (s, 1H), 6.87 – 6.75 (m, 3H), 5.13 – 5.03 (m, 1H), 4.76 (dd, component of ABX pattern, *J* = 15.3, 7.2 Hz, 1H), 4.62 (dd, component of ABX pattern, *J* = 15.2, 2.8 Hz, 1H), 4.46 – 4.38 (m, 1H), 4.34 (ddd, *J* = 9.0, 5.9, 5.8 Hz, 1H), 3.84 (AB quartet, J_{AB} = 13.5 Hz, $\Delta\nu_{AB}$ = 67.7 Hz, 2H), 3.00 (br d, *J* = 11.2 Hz, 1H), 2.84 br (d, *J* = 11.3 Hz, 1H), 2.71 – 2.56 (m, 2H), 2.45 – 2.34 (m, 1H), 2.28 – 2.08 (m, 2H), 1.84 – 1.65 (m, 4H).

This material was determined to be of the same absolute configuration as **Example 5** above by comparison of its biological activity with that of both **4** and **5**: in Assay 2, this sample of **5, free acid** exhibited an EC_{50} of 25 nM (geometric mean of 3 replicates). The activity in Assay 2 for the ammonium salts of **Example 4** and **Example 5** were >20000 nM (2 replicates) and 20 nM (geometric mean of 3 replicates), respectively.

Synthesis of Example 5, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt

*1,3-Dihydroxy-2-(hydroxymethyl)propan-2-aminium 2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylate (**5, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt**).*



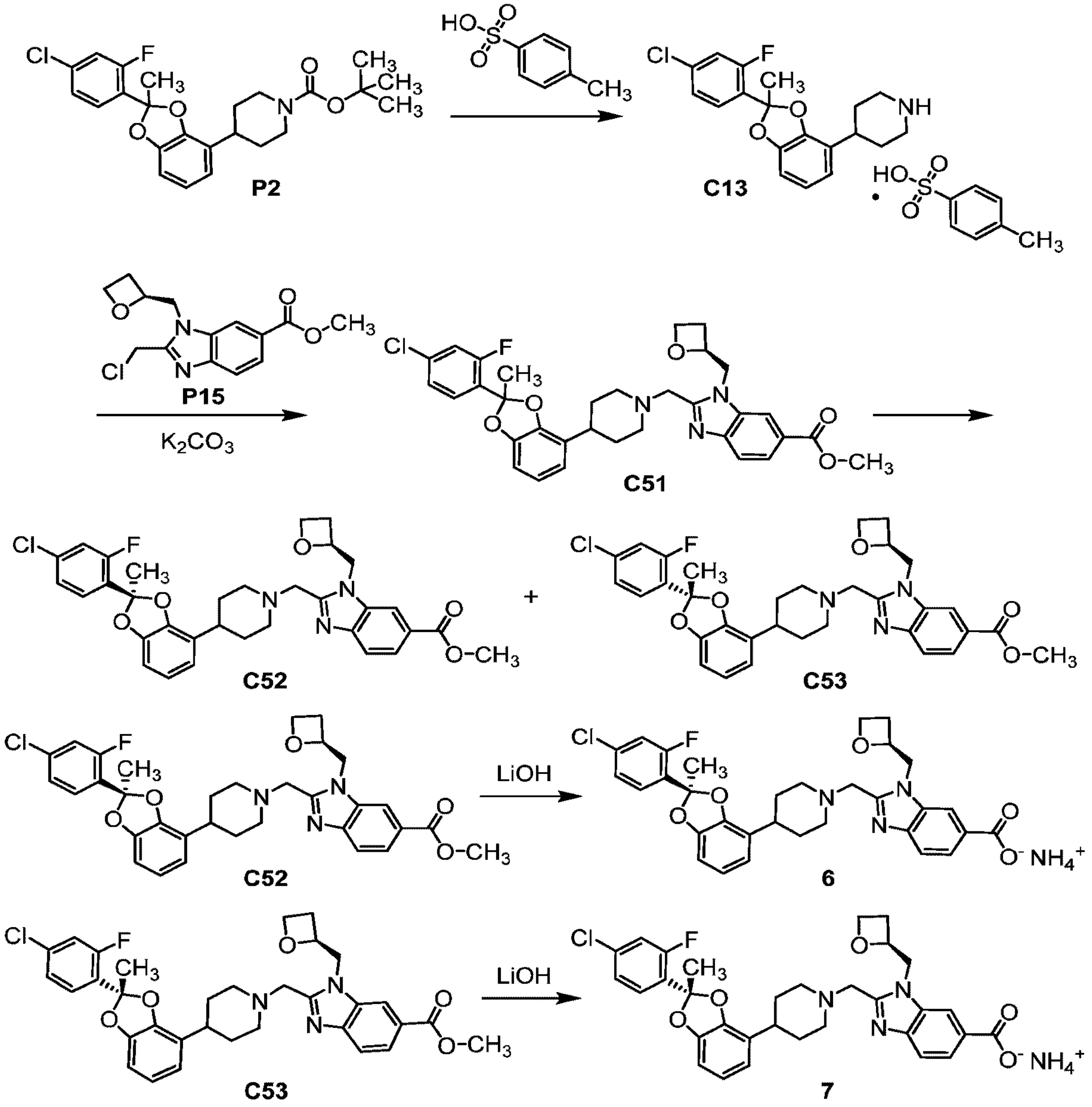
5, free acid

5, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt

A mixture of **5, free acid** (0.50 g, 0.86 mmol) in tetrahydrofuran (4 mL) was treated with an aqueous solution of 2-amino-2-(hydroxymethyl)propane-1,3-diol (Tris, 1.0 M; 0.5 mL, 1.0 mmol). After 20 hours, the mixture was concentrated *in vacuo* with ethanol (2 x 6 mL). The mixture was treated with ethanol (4 mL). After stirring for 48 hours, the solid was collected via filtration, washed with ethanol (2 x 10 mL) and dried under vacuum to afford **5, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt**, as a white solid. Yield: 410 mg, 0.586 mmol, 68%. ^1H NMR (600 MHz, DMSO-d_6), characteristic peaks: δ 8.19 (s, 1H), 7.78 (br d, *J* = 8.4 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.40 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.35 (s, 1H), 6.85 – 6.80 (m, 2H), 6.79 (dd, *J* = 6.9, 2.4 Hz, 1H), 5.11 – 5.05 (m, 1H), 4.73 (dd, *J* = 15.2, 7.2 Hz, 1H), 4.60 (dd, *J* = 15.3, 2.9 Hz, 1H), 4.45 – 4.39 (m, 1H), 4.34 (ddd, *J* = 9.0, 6.0, 5.8 Hz, 1H), 3.91 (d, *J* = 13.5 Hz, 1H), 3.74 (d, *J* = 13.5 Hz, 1H), 2.99 (br d, *J* = 11.1 Hz, 1H), 2.85 (br d, *J* = 11.3 Hz, 1H), 2.68 – 2.59 (m, 2H), 2.44 – 2.37 (m, 1H), 2.25 – 2.18 (m, 1H), 2.17 – 2.10 (m, 1H), 1.80 – 1.69 (m, 4H). mp = 168 °C to 178 °C.

Examples 6 and 7

*Ammonium 2-({4-[(2*R*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**6**) and Ammonium 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**7**)*



Step 1. Synthesis of 4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidine, p-*toluenesulfonate salt (**C13**).*

A solution of **P2** (150 mg, 0.335 mmol) and *p*-toluenesulfonic acid monohydrate (159 mg, 0.836 mmol) in ethyl acetate (2.0 mL) was stirred at 60 °C for 3.5 hours. The reaction mixture was concentrated *in vacuo* to afford **C13** as a brown oil, which was used directly in the following step. LCMS *m/z* 348.1♦ $[M+H]^+$.

*Step 2. Synthesis of methyl 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**C51**).*

To a suspension of **C13** (from the previous step; ≤0.335 mmol) and potassium carbonate (232 mg, 1.68 mmol) in acetonitrile (5.0 mL) was added **P15** (99.1 mg, 0.336 mmol). The reaction mixture was stirred at 60 °C for 10 hours, whereupon it was filtered, and the filtrate was concentrated *in vacuo*. After the residue (390 mg) had been combined with the material from a similar reaction carried out using **C13** (≤0.11 mmol), it was diluted with water (20 mL) and extracted with a mixture of dichloromethane and methanol (10:1, 3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated *in vacuo*, and subjected to preparative thin-layer chromatography (Eluent: 1:1 dichloromethane / methanol), providing **C51**, a mixture of diastereomers, as a colorless oil. Combined yield: 80.6 mg, 0.133 mmol, 30% over 2 steps. LCMS *m/z* 606.2♦ $[M+H]^+$.

*Step 3. Isolation of methyl 2-({4-[(2*R*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**C52**) and methyl 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**C53**).*

Separation of **C51** (180 mg, 0.297 mmol) into its component diastereomers was carried out via repeated SFC [Column: Chiral Technologies Chiralpak AD, 10 µm; Mobile phase: 65:35 carbon dioxide / (ethanol containing 0.1% ammonium hydroxide)]. The first-eluting diastereomer was designated as **C52**. Yield: 61.2 mg, 0.101 mmol, 34%. LCMS *m/z* 627.9♦ $[M+Na^+]$. Retention time: 5.03 minutes (Column: Chiral Technologies Chiralpak AD-3, 4.6 x 150 mm, 3 µm; Mobile phase A: carbon dioxide; Mobile phase B: ethanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 5.5 minutes, then held at 40% B for 3.0 minutes; Flow rate: 2.5 mL/minute).

The second-eluting diastereomer was designated as **C53**. Upon analysis, this material proved to be contaminated with the corresponding ethyl ester; it was taken into the hydrolysis step (to generate **7**) as this mixture. Yield: 40.0 mg, 66.0 µmol, 22%. LCMS *m/z* 606.0♦ $[M+H]^+$. Retention time: 5.19 minutes (Analytical conditions identical to those used for **C52**).

The indicated absolute stereochemistries at the dioxolane were assigned via potency correlation of **7** with a sample of **7, free acid** synthesized from intermediate **P3** (see below, *Alternate Synthesis of **Example 7, free acid***); the absolute stereochemistry of **P3** was established via single-crystal X-ray structure determination of **C8** (see above).

*Step 4. Synthesis of ammonium 2-({4-[(2*R*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**6**).*

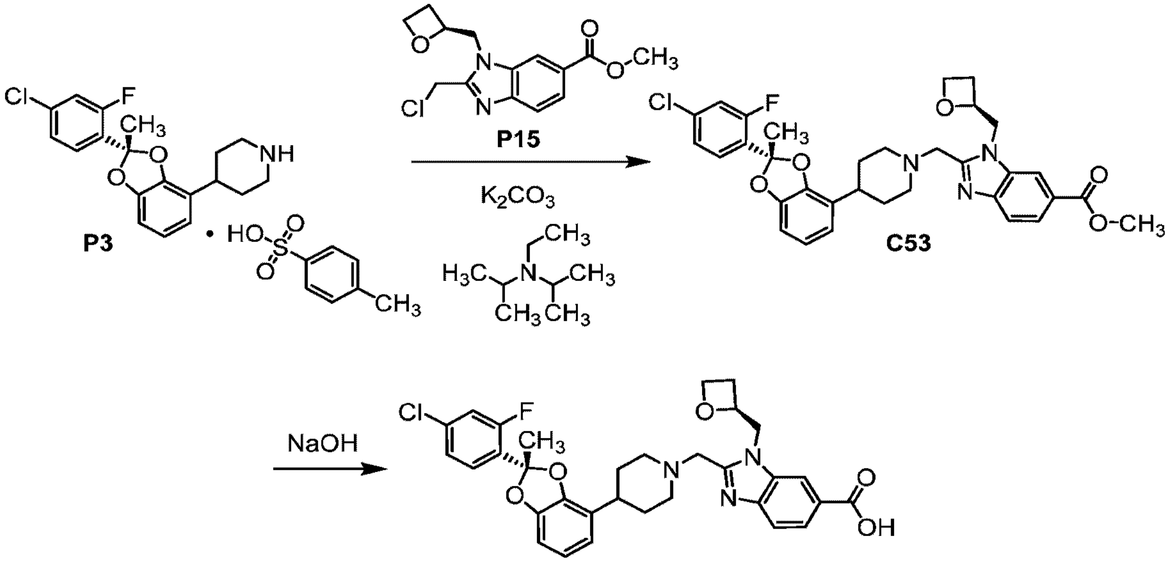
Aqueous lithium hydroxide solution (2 M; 0.990 mL, 1.98 mmol) was added to a solution of **C52** (60 mg, 99 µmol) in a mixture of methanol (1.0 mL) and tetrahydrofuran (1.0 mL), and the reaction mixture was stirred at 20 °C for 16 hours. Trifluoroacetic acid was added until the pH of the reaction mixture reached 7, whereupon it was concentrated *in vacuo*, and the residue was purified using reversed-phase HPLC (Column: Agela Durashell C18, 5 µm; Mobile phase A: 0.05% ammonium hydroxide in water; Mobile phase B: acetonitrile; Gradient: 29% to 49% B), affording **6** as a white solid. Yield: 14.4 mg. 23.6 µmol, 24%. LCMS *m/z* 592.0♦ $[M+H]^+$. ^1H NMR (400 MHz, methanol-d_4), characteristic peaks: δ 8.35 (d, *J* = 1.3 Hz, 1H), 7.97 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.58 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.28 (dd, *J* = 10.9, 2.0 Hz, 1H), 7.21 (br dd, *J* = 8.4, 1.9 Hz, 1H), 6.81 – 6.75 (m, 1H), 6.74 – 6.68 (m, 2H), 5.33 – 5.25 (m, 1H), 4.72 (dd, *J* = 15.4, 2.7 Hz, 1H), 4.49 (dt, *J* = 9.1, 6.0 Hz, 1H), 4.03 (AB quartet, J_{AB} = 13.9 Hz, $\Delta\nu_{AB}$ = 47.8 Hz, 2H), 3.14 (br d, *J* = 11 Hz, 1H), 3.02 (br d, *J* = 11.5 Hz, 1H), 2.88 – 2.78 (m, 1H), 2.77 – 2.68 (m, 1H), 2.60 – 2.50 (m, 1H), 2.47 – 2.32 (m, 2H), 2.03 (d, *J* = 1.1 Hz, 3H), 2.01 – 1.87 (m, 2H), 1.87 – 1.78 (br m, 2H).

*Step 5. Synthesis of ammonium 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**7**).*

Aqueous lithium hydroxide solution (2 M; 0.642 mL, 1.28 mmol) was added to a solution of **C53** (38.9 mg, 64.2 µmol) in a mixture of methanol (1.0 mL) and tetrahydrofuran (1.0 mL). After the reaction mixture had been stirred at 20 °C for 16 hours, it was adjusted to pH 7 by addition of trifluoroacetic acid, concentrated *in vacuo*, and purified using reversed-phase HPLC (Column: Agela Durashell C18, 5 µm; Mobile phase A: 0.05% ammonium hydroxide in water; Mobile phase B: acetonitrile; Gradient: 0% to 80% B), affording **7** as a white solid. Yield: 25.1 mg, 41.2 µmol, 64%. LCMS *m/z* 591.9♦ $[M+H]^+$. ^1H NMR (400 MHz, methanol-d_4), characteristic peaks: δ 8.34 (d, *J* = 1.5 Hz, 1H), 7.98 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.58 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.28 (dd, *J* = 10.9, 2.0 Hz, 1H), 7.20 (br dd, *J* = 8.4, 1.9 Hz, 1H), 6.81 – 6.74 (m, 1H), 6.74 – 6.67 (m, 2H), 5.33 – 5.23 (m, 1H), 4.73 (dd, *J* = 15.4, 2.7 Hz, 1H), 4.68 – 4.61 (m, 1H), 4.48 (dt, *J* = 9.1, 5.9 Hz, 1H), 4.05 (AB quartet, J_{AB} = 13.9 Hz, $\Delta\nu_{AB}$ = 44.1 Hz, 2H), 3.15 (br d, *J* = 11.7 Hz, 1H), 3.03 (br d, *J* = 11.6 Hz, 1H), 2.87 – 2.69 (m, 2H), 2.60 – 2.49 (m, 1H), 2.48 – 2.33 (m, 2H), 2.03 (br s, 3H), 2.01 – 1.77 (m, 4H).

Alternate Synthesis of Example 7, free acid

*2-({4-[(2S)-2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid (**7, free acid**)*



7, free acid

*Step 1. Synthesis of methyl 2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylate (**C53**).*

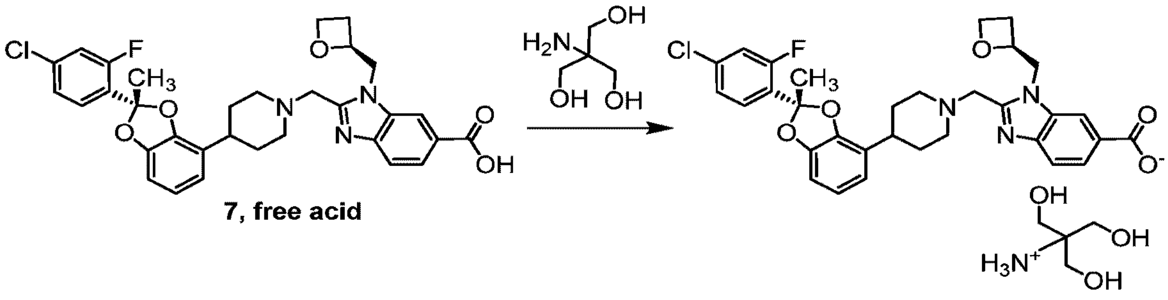
N,N-Diisopropylethylamine (15.1 mL, 86.9 mmol) was added to a mixture of **P3** (8.22 g, 15.8 mmol) in acetonitrile (185 mL); after stirring for 5 minutes, **P15** (4.57 g, 15.5 mmol) was added, and the reaction mixture was heated at 45 °C. After 4 hours, the reaction mixture was concentrated *in vacuo* to half of its original volume, and the resulting mixture was diluted with water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with water (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography (Gradient: 50% to 100% ethyl acetate in heptane) afforded **C53** as a white solid. Yield: 8.4 g, 13.9 mmol, 88%. LCMS *m/z* 606.1♦ $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.82 (br d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.33 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.80 – 6.76 (m, 2H), 6.76 – 6.72 (m, 1H), 5.14 – 5.07 (m, 1H), 4.81 (dd, *J* = 15.2, 7.2 Hz, 1H), 4.67 (dd, *J* = 15.3, 2.8 Hz, 1H), 4.51 – 4.44 (m, 1H), 4.37 (ddd, *J* = 8.9, 5.9, 5.9 Hz, 1H), 3.97 (d, *J* = 13.6 Hz, 1H), 3.87 (s, 3H), 3.78 (d, *J* = 13.5 Hz, 1H), 3.02 (br d, *J* = 11.1 Hz, 1H), 2.86 (br d, *J* = 11.3 Hz, 1H), 2.74 – 2.60 (m, 2H), 2.48 – 2.41 (m, 1H), 2.29 – 2.22 (m, 1H), 2.21 – 2.14 (m, 1H), 2.02 (s, 3H), 1.83 – 1.73 (m, 2H), 1.73 – 1.64 (m, 2H).

*Step 2. Synthesis of 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid* ***(7, free acid)****.*

A mixture of **C53** (8.40 g, 14.0 mmol) in methanol (135 mL) was heated to 45 °C, and treated with aqueous sodium hydroxide solution (1 M; 27.7 mL, 27.7 mmol). After 20 hours, the reaction mixture was concentrated *in vacuo* to half its original volume. The resulting mixture was diluted with water (100 mL), and aqueous citric acid solution (1 M, 15 mL) was used to adjust the pH to 5 to 6. The resultant solid was filtered, washed with water (2 x 15 mL), and transferred to a separatory funnel as a solution in ethyl acetate (50 mL); residual water was removed in this way. The organic layer was dried over magnesium sulfate, filtered, combined with four previously prepared batches from a similar procedure (amount of **C53** used in these reactions was 987 mg, 1.63 mmol; 1.15 g, 1.90 mmol; 8.57 g, 14.1 mmol; and 12.6 g, 20.8 mmol) and concentrated *in vacuo*. The resulting sticky solid was treated with 10% ethyl acetate in heptane (500 mL). After 4 hours, the solid was collected via filtration and washed with 10% ethyl acetate in heptane (2 x 25 mL) to afford **7, free acid,** as a white solid. Yield 29.4 g, 0.527 mmol, 74% for combined reactions. LCMS 592.2♦ [M+H]+. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.74 (br s, 1H), 8.28 (s, 1H), 7.80 (br d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.33 (dd, J = 8.4, 2.1 Hz, 1H), 6.81 – 6.76 (m, 2H), 6.76 – 6.72 (m, 1H), 5.14 – 5.07 (m, 1H), 4.79 (dd, J = 15.3, 7.3 Hz, 1H), 4.65 (dd, J = 15.2, 2.8 Hz, 1H), 4.51 – 4.45 (m, 1H), 4.38 (ddd, J = 9.0, 5.9, 5.9 Hz, 1H), 3.96 (br d, J = 13.6 Hz, 1H), 3.78 (br d, J = 13.5 Hz, 1H), 3.02 (br d, J = 11.1 Hz, 1H), 2.86 (br d, J = 11.1 Hz, 1H), 2.74 – 2.60 (m, 2H), 2.48 – 2.41 (m, 1H), 2.29 – 2.21 (m, 1H), 2.21 – 2.14 (m, 1H), 2.02 (s, 3H), 1.83 – 1.74 (m, 2H), 1.74 – 1.64 (m, 2H). This material was determined to be of the same absolute configuration as **Example 7** above by comparison of its biological activity with that of both **6** and **7**: in Assay 2, this sample of **7, free acid** exhibited an EC$_{50}$ of 4.3 nM (geometric mean of 3 replicates). The activity in Assay 2 for the ammonium salts of **Example 6** and **Example 7** were 2400 nM (geometric mean of 5 replicates) and 2.9 nM (geometric mean of 8 replicates), respectively.

Synthesis of Example 7, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt

*1,3-Dihydroxy-2-(hydroxymethyl)propan-2-aminium 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate* ***(7, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt)****.*



7, free acid

7, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt

A mixture of **7, free acid** (2.00 g, 3.38 mmol) in tetrahydrofuran (16 mL) was treated with an aqueous solution of 2-amino-2-(hydroxymethyl)propane-1,3-diol (Tris,1.0 M; 3.55 mL, 3.55 mmol). After 18 hours, the reaction mixture was concentrated *in vacuo* and treated with ethanol (30 mL). After this mixture had been stirred for 23 hours, the solid was collected via filtration and washed with ethyl acetate (2 x 10 mL) to afford **7, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt** as a white solid. Yield: 1.41 g, 1.98 mmol, 59%. LCMS *m/z* 592.3♦ $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6), characteristic peaks: δ 8.20 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.59 – 7.52 (m, 3H), 7.33 (br d, *J* = 8.5 Hz, 1H), 6.81 – 6.72 (m, 3H), 5.14 – 5.07 (m, 1H), 4.76 (dd, *J* = 15.2, 7.2 Hz, 1H), 4.63 (br d, *J* = 15.4 Hz, 1H), 4.50 – 4.44 (m, 1H), 4.37 (ddd, *J* = 8.9, 5.9, 5.9 Hz, 1H), 3.94 (d, *J* = 13.4 Hz, 1H), 3.76 (d, *J* = 13.4 Hz, 1H), 3.01 (br d, *J* = 11.1 Hz, 1H), 2.86 (br d, *J* = 11.2 Hz, 1H), 2.73 – 2.60 (m, 2H), 2.5 – 2.41 (m, 1H), 2.27 – 2.20 (m, 1H), 2.20 – 2.13 (m, 1H), 2.02 (s, 3H), 1.83 – 1.64 (m, 4H). mp = 175 °C to 180 °C.

Acquisition of Powder X-ray Diffraction (PXRD) Data for Form I of Example 7, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt

The white solid of the tris salt of Example 7 was submitted for PXRD analysis and found to be a crystalline material (which is designated as Form I of this *anhydrous crystal form).* Powder X-ray diffraction analysis was conducted using a Bruker AXS D8 Endeavor diffractometer equipped with a Cu radiation source. The divergence slit was set at 15 mm continuous illumination. Diffracted radiation was detected by a PSD-Lynx Eye detector, with the detector PSD opening set at 2.99 degrees. The X-ray tube voltage and amperage were set to 40 kV and 40 mA respectively. Data was collected at the Cu wavelength (CuK_{α} = 1.5418 λ) in the Theta-Theta goniometer from 3.0 to 40.0 degrees 2-Theta using a step size of 0.01 degrees and a step time of 1.0 second. The antiscatter screen was set to a fixed distance of 1.5 mm. Samples were rotated during data collection. Samples were prepared by placing them in a silicon low background sample holder and rotated during collection. Data were collected using Bruker DIFFRAC Plus software and analysis was performed by EVA diffract plus software. The PXRD data file was not processed prior to peak searching. Using the peak search algorithm in the EVA software, peaks selected with a threshold value of 1 were used to make preliminary peak assignments. To ensure validity, adjustments were manually made; the output of automated assignments was visually checked, and peak positions were adjusted to the peak maximum. Peaks with relative intensity of ≥ 3% were generally chosen. Typically, the peaks which were not resolved or were consistent with noise were not selected. A typical error associated with the peak position from PXRD stated in USP up to +/- 0.2° 2-Theta (USP-941). One diffraction pattern was consistently observed and is provided in Figure 24. A list of diffraction peaks expressed in terms of the degree 2θ and relative intensities with a relative intensity of ≥ 3.0% is provided above in Table X1.

Table X1

Angle (2theta)	Relative Intensity (%)
3.7	74.3
7.3	83.3
8.1	12.5
8.5	6.5
10.1	6.6
13.6	3.5
14.7	49.8
15.2	7.9
15.5	28.7
15.9	18.3
16.9	60.8
17.4	26.3
17.7	11.4
17.9	13.5
18.9	75.4
19.7	18.7
20.2	100.0
20.9	24.8
21.5	14.8
22.2	31.7
22.9	10.1
23.5	34.6
23.7	8.2

24.4	6.5
24.9	8.7
25.2	6.4
25.9	14.7
26.4	48.6
26.7	12.5
27.5	15.8
27.9	6.1
28.3	10.5
29.5	15.5
29.8	12.6
30.2	12.1
30.9	3.4
31.7	16.4
33.3	17.2
34.0	14.9
35.8	4.8
37.5	3.2
38.6	5.3

One embodiment provides a crystal form of anhydrous tris salt of 2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid. In some further embodiments, the crystal form of anhydrous (anhydrate) tris salt of 2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid is designated as "Form I" that is characterized according to its unique solid state signatures with respect to, for example, powder X-ray diffraction (PXRD), described herein (such as substantially as depicted in Figure 24). In some embodiments, Form I exhibits a powder X-ray diffraction pattern comprising at least two characteristic peaks, in terms of 2θ, selected from at 3.7 ± 0.2°; 7.3 ± 0.2°; 8.5 ± 0.2°; 10.1± 0.2°; 14.7± 0.2°; and 16.9± 0.2°. In some embodiments, Form I exhibits a powder X-ray diffraction pattern comprising at least three characteristic peaks, in terms of 2θ, selected from at 3.7 ± 0.2°; 7.3 ± 0.2°; 8.5 ± 0.2°; 10.1± 0.2°; 14.7± 0.2°; and 16.9± 0.2°. In some embodiments, Form I exhibits a powder X-ray diffraction pattern comprising at least four characteristic peaks, in terms of 2θ, selected from at 3.7 ± 0.2°; 7.3 ± 0.2°; 8.5 ± 0.2°; 10.1± 0.2°; 14.7± 0.2°; and 16.9± 0.2°. In some embodiments, Form I exhibits a powder X-ray diffraction pattern comprising at least five characteristic peaks, in terms of 2θ, selected from at 3.7 ± 0.2°; 7.3 ± 0.2°; 8.5 ± 0.2°; 10.1± 0.2°; 14.7± 0.2°; and 16.9± 0.2°.

In some embodiments, Form I exhibits a powder X-ray diffraction pattern comprising characteristic peaks, in terms of 2θ, at 3.7 ± 0.2° and 7.3 ± 0.2°.

In some embodiments, Form I exhibits a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 3.7 ± 0.2°; 7.3 ± 0.2°; and 14.7 ± 0.2°. In some futher embodiments, Form I exhibits the X-ray powder diffraction pattern further comprises at least one peak, in terms of 2θ, selected from at 8.5± 0.2°; 10.1± 0.2°; and 16.9± 0.2°.

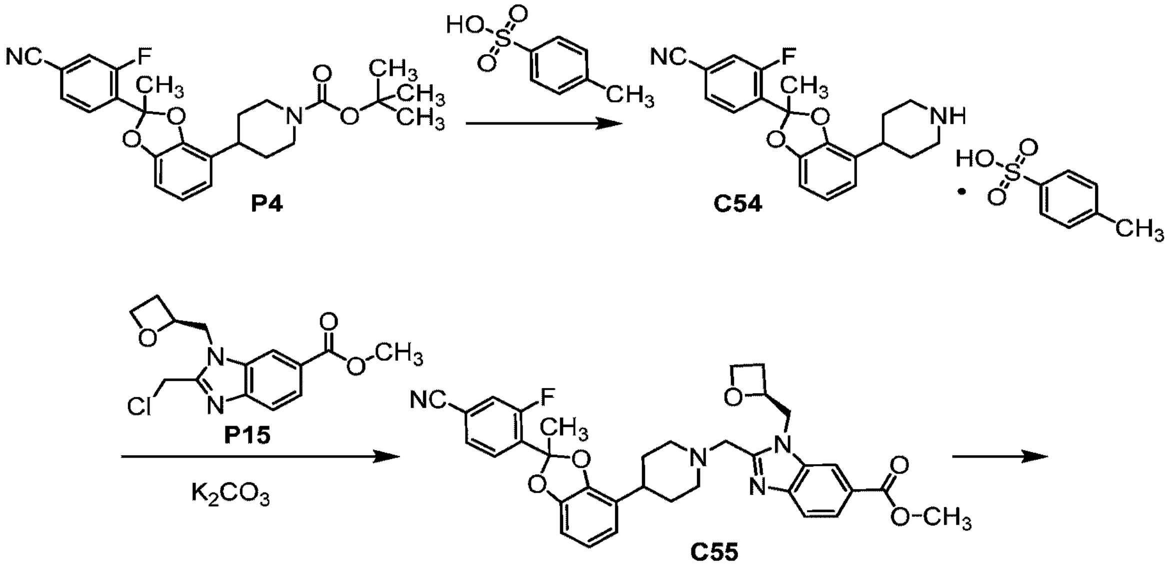
In some embodiments, Form I exhibits a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 3.7 ± 0.2°; 7.3 ± 0.2°; 14.7 ± 0.2°; and 16.9± 0.2°.

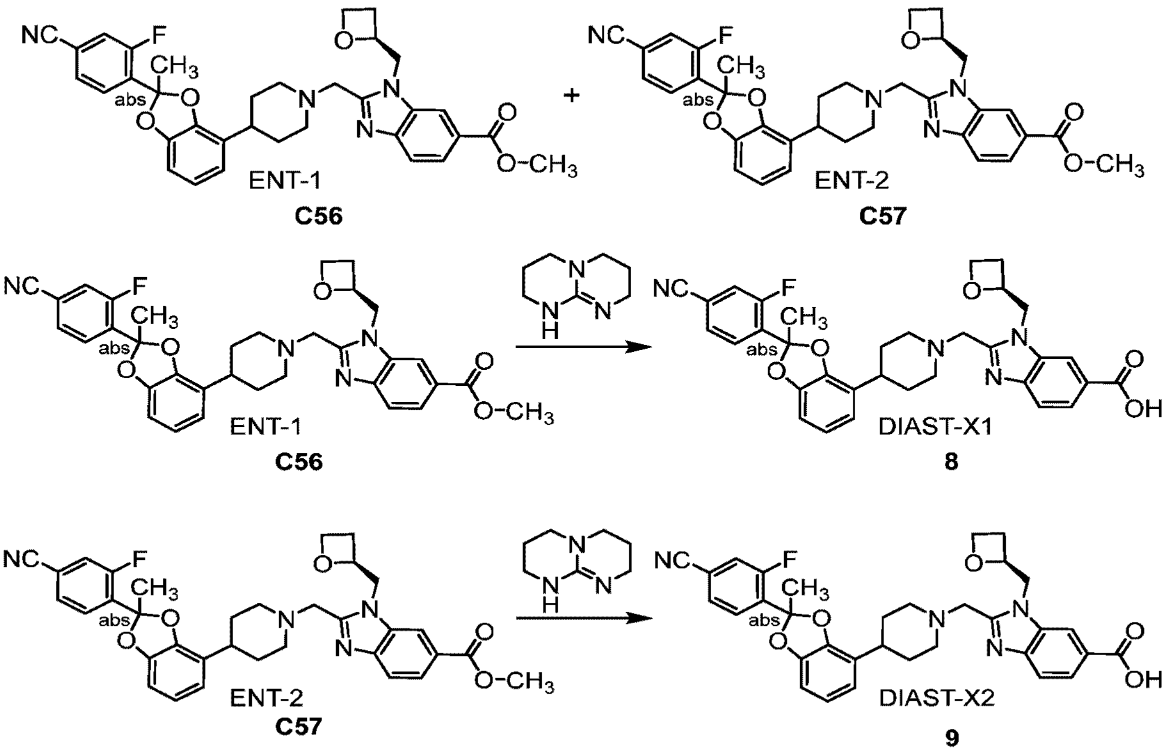
In some embodiments, Form I exhibits a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 3.7 ± 0.2°; 7.3 ± 0.2°; 8.5 ± 0.2°; 10.1± 0.2°; 14.7± 0.2°; and 16.9± 0.2°.

In some embodiments, Form I exhibits a powder X-ray diffraction pattern substantially as shown in Figure 24. A list of diffraction peaks expressed in terms of the degree 2θ and relative intensities with a relative intensity of ≥ 3.0% is provided above in Table X1.

Examples 8 and 9

*2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid, DIAST-X1 (**8**) [from **C56**]; and 2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid, DIAST-X2 (**9**) [from **C57**]*





*Step 1. Synthesis of 3-fluoro-4-[2-methyl-4-(piperidin-4-yl)-1,3-benzodioxol-2-yl]benzonitrile, p-toluenesulfonate salt (**C54**).*

To a solution of **P4** (161 mg, 0.367 mmol) in ethyl acetate (8 mL) was added *p*-toluenesulfonic acid (158 mg, 0.919 mmol), and the reaction mixture was stirred at 65 °C for 16 hours. Removal of solvent *in vacuo* provided **C54** as a dark yellow gum; this material was taken directly into the next step.

*Step 2. Synthesis of methyl 2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate (**C55**).*

To a solution of **C54** (from the previous step; ≤0.367 mmol) in acetonitrile (3.7 mL) was added potassium carbonate (219 mg, 1.58 mmol), followed by **P15** (115 mg, 0.390 mmol). The reaction mixture was stirred at 50 °C for 20 hours, whereupon it was diluted with ethyl acetate (10 mL) and filtered. The filter cake was washed with ethyl acetate (3 x 10 mL), and the combined filtrates were concentrated *in vacuo*. Silica gel chromatography (Gradient: 0% to 100% ethyl acetate in petroleum ether) afforded **C55** as a dark yellow oil. Yield: 191.0 mg, 0.320 mmol, 87% over 2 steps. LCMS *m/z* 619.1 [M+Na$^+$].

*Step 3. Isolation of methyl 2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate, ENT-1*

*(**C56**) and methyl 2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate, ENT-2 (**C57**).*

Separation of **C55** (191 mg, 0.320 mmol) into its component stereoisomers at the dioxolane was carried out via SFC [Column: Chiral Technologies ChiralCel OD, 5 µm; Mobile phase: 3:2 carbon dioxide / 2-propanol]. The first-eluting isomer, obtained as a white gum, was designated as ENT-1 (**C56**). Yield: 114 mg; this material contained residual ethanol. LCMS *m/z* 597.1 $[M+H]^+$. Retention time 4.40 minutes (Column: Chiral Technologies ChiralCel OD-3, 4.6 x 100 mm, 3 µm; Mobile phase A: carbon dioxide; Mobile phase B: 2-propanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 4.5 minutes, then held at 40% B for 2.5 minutes; Flow rate: 2.8 mL/minute).

The second-eluting isomer was repurified using SFC [Column: Chiral Technologies ChiralCel OD, 5 µm; Mobile phase: 55:45 carbon dioxide / (2-propanol containing 0.1% ammonium hydroxide)], to afford a colorless gum that was designated as ENT-2 (**C57**). Yield: 50 mg, 83.8 µmol, 26%. LCMS *m/z* 597.1 $[M+H]^+$. Retention time 4.74 minutes (Analytical conditions identical to those used for **C56**).

*Step 4. Synthesis of 2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid, DIAST-X1 (**8**) [from **C56**].*

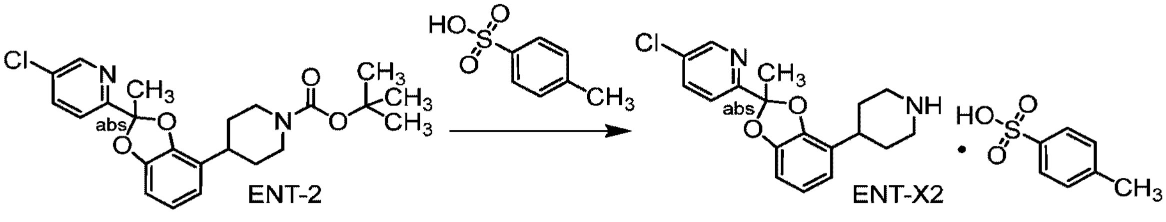
A solution of **C56** (114 mg, 0.191 mmol) in acetonitrile (10 mL) was treated with an aqueous solution of 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine (0.97 M, 394 µL, 0.382 mmol), and the reaction mixture was stirred at room temperature for 23 hours. More of the aqueous solution of 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine (0.97 M, 394 µL, 0.382 mmol) was added, and stirring was continued for 6 hours, whereupon the pH was carefully adjusted to 7 to 8 by addition of 1 M hydrochloric acid. After removal of volatiles *in vacuo*, purification was carried out using reversed-phase HPLC (Column: Agela Durashell C18, 5 µm; Mobile phase A: 0.05% ammonium hydroxide in water; Mobile phase B: acetonitrile; Gradient: 30% to 50% B) to provide **8** as a white solid. Yield: 22.2 mg, 38.1 µmol, 20%. LCMS *m/z* 583.3 $[M+H]^+$. ^{1}H NMR (400 MHz, methanol-d_4): δ 8.19 (d, *J* = 1.4 Hz, 1H), 7.94 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.77 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.64 (dd, *J* = 10.6, 1.6 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.81 – 6.75 (m, 1H), 6.75 – 6.68 (m, 2H), 5.34 – 5.25 (m, 1H), 4.73 (dd, *J* = 15.3, 3.0 Hz, 1H), 4.67 – 4.59 (m, 1H), 4.49 (dt, *J* = 9.2, 6.0 Hz, 1H), 3.96 (AB quartet, J_{AB} = 13.7 Hz, $\Delta\nu_{AB}$ = 41.2 Hz, 2H), 3.06 (br d, *J* = 11 Hz, 1H), 2.95 (br d, *J* = 11 Hz, 1H), 2.87 – 2.76 (m, 1H), 2.71 (tt, *J* = 12.0, 3.9 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.36 – 2.21 (m, 2H), 2.06 (s, 3H), 1.95 – 1.72 (m, 4H).

*Step 5. Synthesis of 2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid, DIAST-X2 (**9**) [from **C57**].*

A solution of **C57** (50 mg, 84 µmol) in acetonitrile (10 mL) was treated with an aqueous solution of 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine (0.97 M; 173 µL, 0.168 mmol). The reaction was stirred at room temperature (about 25 °C) for 16 hours, whereupon an additional quantity of an aqueous solution of 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine (0.97 M; 173 µL, 0.168 mmol) was added, and stirring was continued at 25 °C for 29 hours. The reaction mixture was then carefully adjusted to pH 7 to 8 by addition of 1 M hydrochloric acid; the resulting mixture was concentrated *in vacuo* and subjected to reversed-phase HPLC (Column: Xtimate™ C18, 5 µm; Mobile phase A: 0.05% ammonium hydroxide in water; Mobile phase B: acetonitrile; Gradient: 27% to 67% B), affording **9** as a white solid. Yield: 18.0 mg, 30.9 µmol, 37%. LCMS *m/z* 583.3 $[M+H]^+$. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.36 – 8.33 (m, 1H), 7.97 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.78 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.57 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.83 – 6.76 (m, 1H), 6.76 – 6.71 (m, 2H), 5.34 – 5.25 (m, 1H), 4.95 – 4.85 (m, 1H, assumed; partially obscured by water peak), 4.73 (dd, component of ABX pattern, *J* = 15.3, 2.7 Hz, 1H), 4.68 – 4.60 (m, 1H), 4.50 (dt, *J* = 9.2, 6.0 Hz, 1H), 4.02 (AB quartet, J_{AB} = 13.8 Hz, $\Delta\nu_{AB}$ = 48.2 Hz, 2H), 3.13 (br d, *J* = 11 Hz, 1H), 3.01 (br d, *J* = 11.5 Hz, 1H), 2.89 – 2.78 (m, 1H), 2.78 – 2.68 (m, 1H), 2.60 – 2.50 (m, 1H), 2.45 – 2.30 (m, 2H), 2.07 (br s, 3H), 2.00 – 1.86 (m, 2H), 1.83 (m, 2H).

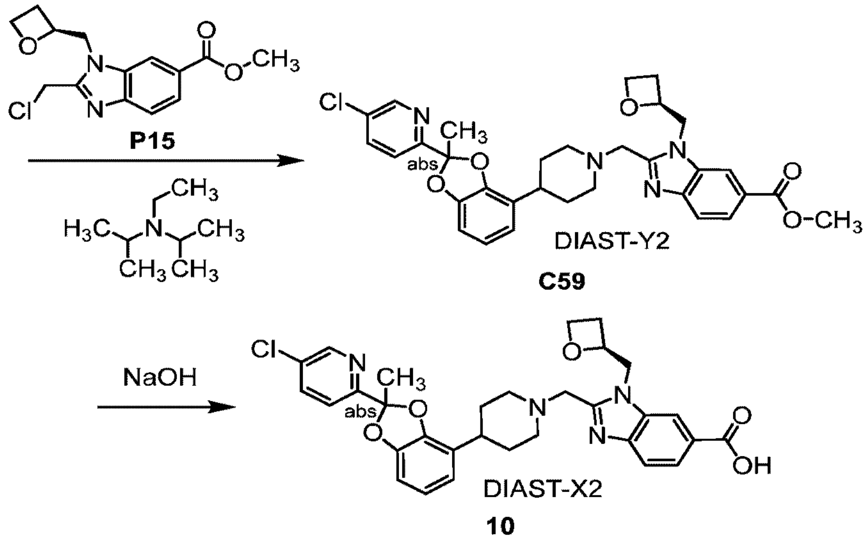
Example 10

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2 (10) [from P9]



P9

C58



Step 1. Synthesis of 5-chloro-2-[2-methyl-4-(piperidin-4-yl)-1,3-benzodioxol-2-yl]pyridine, ENT-X2, p*-toluenesulfonate salt (**C58**) [from **P9**].*

A solution of **P9** (228 mg, 0.529 mmol) in ethyl acetate (2.7 mL) was treated with *p*-toluenesulfonic acid monohydrate (116 mg, 0.610 mmol), and the reaction mixture was heated at 50 °C for 16 hours. It was then allowed to stir at room temperature overnight, whereupon the precipitate was collected via filtration and rinsed with a mixture of ethyl acetate and heptane (1:1, 2 x 20 mL) to provide **C58** as a white solid. Yield: 227 mg, 0.451 mmol, 85%. LCMS *m/z* 331.0♦ $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.73 (d, *J* = 2.4 Hz, 1H), 8.61 – 8.46 (br m, 1H), 8.35 – 8.18 (br m, 1H), 8.02 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 7.8, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.89 – 6.81 (m, 2H), 6.72 (pentet, *J* = 4.0 Hz, 1H), 3.45 – 3.27 (m, 2H, assumed; partially obscured by water peak), 3.10 – 2.91 (m, 3H), 2.28 (s, 3H), 2.02 (s, 3H), 1.97 – 1.80 (m, 4H).

*Step 2. Synthesis of methyl 2-({4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate, DIAST-Y2 (**C59**) [from **P9**].*

N,N-Diisopropylethylamine (0.234 mL, 1.34 mmol) was added to a solution of **C58** (225 mg, 0.447 mmol) in acetonitrile (2.2 mL). After this mixture had been stirred for 5 minutes at 45 °C, **P15** (120 mg, 0.407 mmol) was added, and stirring was continued at 45 °C for 16 hours, whereupon **P15** (11 mg, 37 µmol) was again added. After an additional 3 hours of stirring, the reaction mixture was treated with water (2.5 mL) and allowed to cool to room temperature. More water (5 mL) was added, and the resulting slurry was stirred for 2 hours, whereupon the solid was collected via filtration and washed with a mixture of acetonitrile and water (15:85, 3 x 5 mL) to afford **C59** as an off-white solid (252 mg). This material contained some *N,N*-

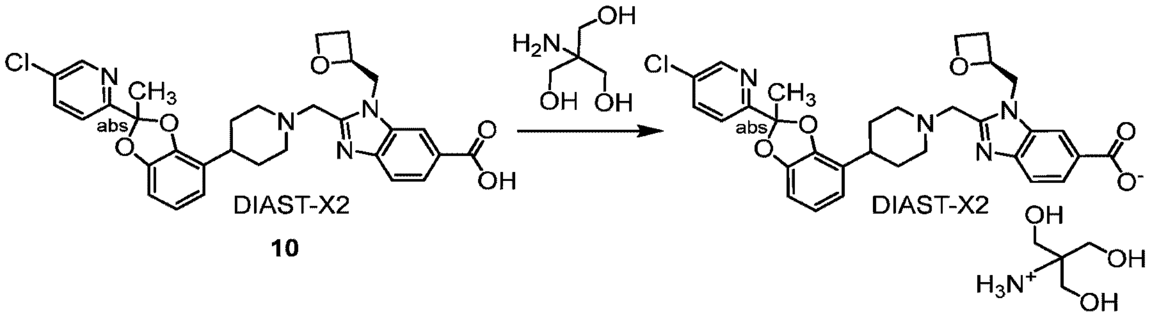
diisopropylethylamine by ^{1}H NMR analysis, and was taken directly to the following step. LCMS *m/z* 589.1♦ $[M+H]^+$. ^{1}H NMR (400 MHz, chloroform-*d*) 8.61 (d, *J* = 2.3 Hz, 1H), 8.18 (d, *J* = 1.5 Hz, 1H), 7.96 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.67 (dd, component of ABX pattern, *J* = 8.4, 2.4 Hz, 1H), 7.59 – 7.51 (m, 1H), 6.82 – 6.75 (m, 1H), 6.74 – 6.66 (m, 2H), 5.28 – 5.19 (m, 1H), 4.75 (dd, component of ABX pattern, *J* = 15.3, 6.0 Hz, 1H), 4.68 (dd, component of ABX pattern, *J* = 15.3, 3.4 Hz, 1H), 4.67 – 4.58 (m, 1H), 4.41 (ddd, *J* = 9.1, 5.9, 5.9 Hz, 1H), 3.95 (s, 2H), 3.95 (s, 3H), 3.07 – 2.89 (m, 2H), 2.81 – 2.69 (m, 2H), 2.53 – 2.41 (m, 1H), 2.37 – 2.22 (m, 2H), 2.05 (s, 3H), 1.93 – 1.74 (m, 4H).

*Step 3. Synthesis of 2-({4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid, DIAST-X2 **(10)** [from **P9**].*

A suspension of **C59** (from the previous step; 250 mg, ≤0.407 mmol) in methanol (2 mL) was heated to 40 °C, whereupon aqueous sodium hydroxide solution (1 M; 0.81 mL, 0.81 mmol) was added. After 17 hours, the reaction mixture was allowed to cool to room temperature, and the pH was adjusted to 5 to 6 with 1 M aqueous citric acid solution. The resulting mixture was diluted with water (2 mL), stirred for 2 hours, and extracted with ethyl acetate (3 x 5 mL); the combined organic layers were washed with saturated aqueous sodium chloride solution (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a foamy solid. This material was taken up in a mixture of ethyl acetate and heptane (1:1, 4 mL), heated to 50 °C, and then allowed to cool and stir overnight. Filtration afforded **10** as a white solid. Yield: 179 mg, 0.311 mmol, 76% over 2 steps. LCMS *m/z* 575.1♦ $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (br s, 1H), 8.71 (d, *J* = 2.5 Hz, 1H), 8.27 (d, *J* = 1.5 Hz, 1H), 8.00 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.80 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 6.83 – 6.72 (m, 3H), 5.14 – 5.06 (m, 1H), 4.77 (dd, component of ABX pattern, *J* = 15.2, 7.2 Hz, 1H), 4.63 (dd, component of ABX pattern, *J* = 15.2, 2.8 Hz, 1H), 4.50 – 4.42 (m, 1H), 4.37 (ddd, *J* = 9.0, 5.9, 5.9 Hz, 1H), 3.85 (AB quartet, J_{AB} = 13.6 Hz, $\Delta\nu_{AB}$ = 71.5 Hz, 2H), 3.01 (br d, *J* = 11.2 Hz, 1H), 2.85 (br d, *J* = 11.2 Hz, 1H), 2.74 – 2.57 (m, 2H), 2.47 – 2.38 (m, 1H), 2.29 – 2.10 (m, 2H), 2.01 (s, 3H), 1.81 – 1.64 (m, 4H).

Synthesis of Example 10, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt

*Synthesis of 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium 2-({4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylate, DIAST-X2 (**10, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt**) [from **P9**].*



10, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt

A mixture of **10** (1.54 g, 2.68 mmol) in tetrahydrofuran (10 mL) was treated with an aqueous solution of 2-amino-2-(hydroxymethyl)propane-1,3-diol (Tris, 1.0 M; 2.81 mL, 2.81 mmol). After 24 hours, the reaction mixture was concentrated *in vacuo* with ethanol (2 x 50 mL). The residue was treated with ethanol (15 mL). After stirring for 20 hours, the solid was collected via filtration and washed with cold ethanol (5 mL) to afford **10, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt** as a white solid. Yield: 1.41 g, 2.03 mmol, 76%. LCMS *m/z* 575.3♦ $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ 8.71 (d, *J* = 2.5 Hz, 1H), 8.21 (br s, 1H), 8.00 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.79 (br d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 6.82 – 6.73 (m, 3H), 5.13 – 5.07 (m, 1H), 4.74 (dd, *J* = 15.3, 7.2 Hz, 1H), 4.61 (dd, *J* = 15.3, 2.9 Hz, 1H), 4.49 – 4.43 (m, 1H), 4.37 (ddd, *J* = 9.0, 5.9, 5.9 Hz, 1H), 3.93 (d, *J* = 13.6 Hz, 1H), 3.75 (d, *J* = 13.5 Hz, 1H), 3.01 (br d, *J* = 11.3 Hz, 1H), 2.86 (br d, *J* = 11.4 Hz, 1H), 2.73 – 2.59 (m, 2H), 2.48 – 2.37 (m, 1H), 2.27 – 2.20 (m, 1H), 2.19 – 2.12 (m, 1H), 2.01 (s, 3H), 1.82 – 1.66 (m, 4H). mp = 184 °C to 190 °C.

Acquisition of Powder X-ray Diffraction (PXRD) Data for Form A of Example 10, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt (also known as Form A of anhydrous tris salt of compound Example 10)

The white solid of the tris salt of Example 10 was submitted for PXRD analysis and found to be a crystalline material (which is designated as Form A). Powder X-ray diffraction analysis was conducted using a Bruker AXS D8 Endeavor diffractometer equipped with a Cu radiation source. The divergence slit was set at 15 mm continuous illumination. Diffracted radiation was detected by a PSD-Lynx Eye detector, with the detector PSD opening set at 2.99 degrees. The X-ray tube voltage and amperage were set to 40 kV and 40 mA respectively. Data was collected at the Cu wavelength (CuK_{α} = 1.5418 λ) in the Theta-Theta goniometer from 3.0 to 40.0 degrees 2-Theta using a step size of 0.01 degrees and a step time of 1.0 second. The antiscatter screen was set to a fixed distance of 1.5 mm. Samples were rotated during data collection. Samples were prepared by placing them in a silicon low background sample holder and rotated during collection. Data were collected using Bruker DIFFRAC Plus software and analysis was performed by EVA diffract plus software. The PXRD data file was not processed prior to peak searching. Using the peak search algorithm in the EVA software, peaks selected with a threshold value of 1 were used to make preliminary peak assignments. To ensure validity, adjustments were manually made; the output of automated assignments was visually checked, and peak positions were adjusted to the peak maximum. Peaks with relative intensity of ≥ 3% were generally chosen. Typically, the peaks which were not resolved or were consistent with noise were not selected. A typical error associated with the peak position from PXRD stated in USP up to +/- 0.2° 2-Theta (USP-941). One diffraction pattern was consistently observed and is provided in Figure 25. A list of diffraction peaks expressed in terms of the degree 2θ and relative intensities with a relative intensity of ≥ 3.0% is provided above in Table X2.

Table X2

Angle (2 theta)	**Relative Intensity (%)**
3.9	18.4
7.7	36.3
8.1	10.4
8.7	3.4
10.2	4.1
14.6	5.8
15.2	30.1
15.7	45.5
16.0	31.3
16.8	8.7
17.6	86.0
19.2	46.6
19.5	25.4
19.8	31.4
20.2	25.0
21.1	100.0
21.4	40.2
22.2	37.0
23.0	19.8
24.3	43.0
25.0	9.9

26.0	15.8
27.3	35.3
28.2	14.1
29.3	19.7
29.8	11.7
31.6	9.3
32.8	6.0
34.0	14.4
34.5	12.1
35.4	3.0
36.5	4.1

One embodiment provides a crystal form of anhydrous tris salt of 2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2. In some further embodiments, the crystal form of anhydrous (anhydrate) tris salt of 2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2, is designated as “Form A” that is characterized according to its unique solid state signatures with respect to, for example, powder X-ray diffraction (PXRD), described herein (such as substantially as depicted in Figure 25). In some embodiments, Form A exhibits a powder X-ray diffraction pattern comprising at least two characteristic peaks, in terms of 2θ, selected from at 7.7 ± 0.2°; 15.2 ± 0.2°; 15.7± 0.2°; and 17.6± 0.2°. In some embodiments, Form A exhibits a powder X-ray diffraction pattern comprising at least three characteristic peaks, in terms of 2θ, selected from at 7.7 ± 0.2°; 15.2 ± 0.2°; 15.7± 0.2°; and 17.6± 0.2°. In some embodiments, Form A exhibits a powder X-ray diffraction pattern comprising characteristic peaks, in terms of 2θ, selected from at 7.7 ± 0.2°; 15.2 ± 0.2°; 15.7± 0.2°; and 17.6± 0.2°.

In some embodiments, Form I exhibits a powder X-ray diffraction pattern comprising characteristic peaks, in terms of 2θ, at 7.7 ± 0.2° and 17.6 ± 0.2°.

In some embodiments, Form A exhibits a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 7.7 ± 0.2°; 15.2 ± 0.2°; and 17.6 ± 0.2°.

In some embodiments, Form I exhibits a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 7.7 ± 0.2°; 15.2 ± 0.2°; and 15.7 ± 0.2°.

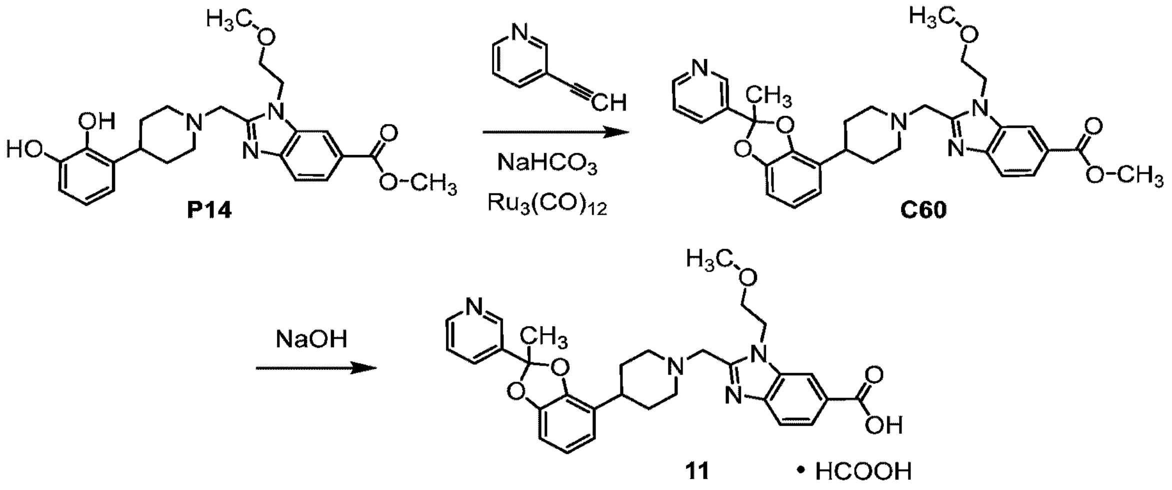
In some embodiments, Form I exhibits a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 7.7 ± 0.2°; 15.2 ± 0.2°; 15.7± 0.2°; and 17.6± 0.2°.

In some embodiments, Form A exhibits a powder X-ray diffraction pattern substantially as shown in Figure 25. A list of diffraction peaks expressed in terms of the degree 2θ and relative intensities with a relative intensity of ≥ 3.0% is provided above in Table X2.

As is well known in the art of powder diffraction, the relative intensities of the peaks (reflections) can vary, depending upon the sample preparation technique, the sample mounting procedure and the particular instrument employed. Moreover, instrument variation and other factors can affect the 2-theta values. Therefore, the XRPD peak assignments can vary by plus or minus about 0.2°.

Example 11

*1-(2-Methoxyethyl)-2-({4-[2-methyl-2-(pyridin-3-yl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt (**11**)*



This entire synthetic sequence was carried out in library format.

*Step 1. Synthesis of methyl 1-(2-methoxyethyl)-2-({4-[2-methyl-2-(pyridin-3-yl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylate (**C60**).*

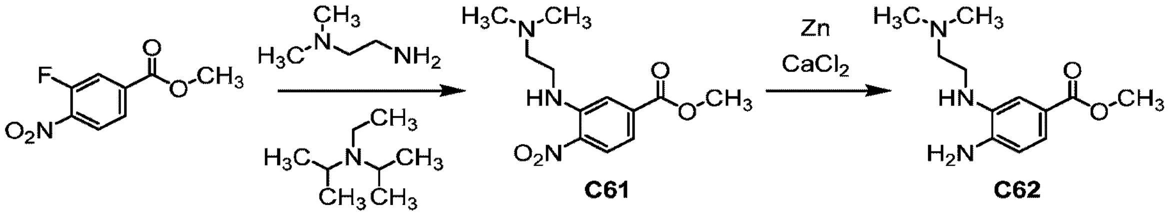
A mixture of **P14** (44 mg, 100 μmol) and 3-ethynylpyridine (21 mg, 200 μmol) in toluene (800 μL) was treated with sodium bicarbonate (100 μmol), followed by triruthenium dodecacarbonyl (6 mg, 9 μmol). The reaction vial was then capped and shaken at 120 °C for 16 hours. Removal of solvent using a Speedvac® concentrator provided **C60**, which was taken directly into the following step.

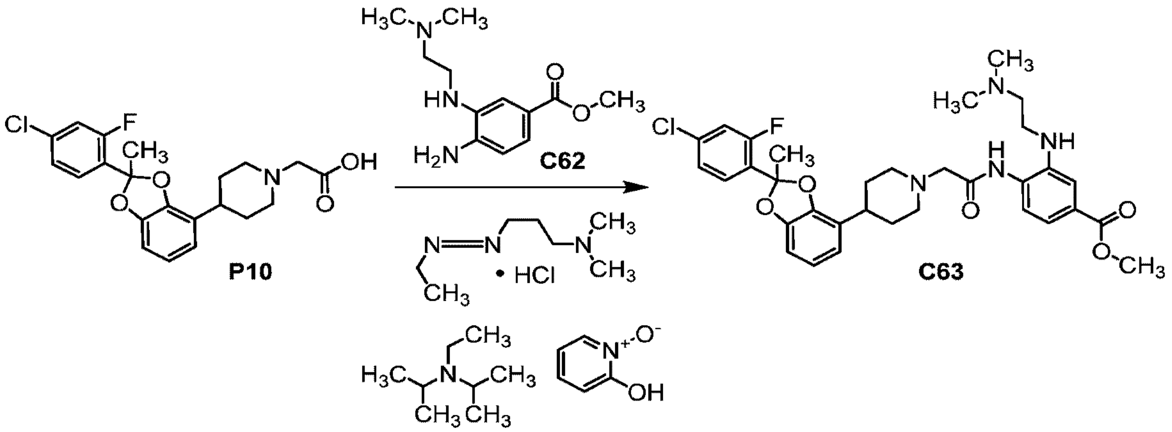
*Step 2. Synthesis of 1-(2-methoxyethyl)-2-({4-[2-methyl-2-(pyridin-3-yl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt (**11**).*

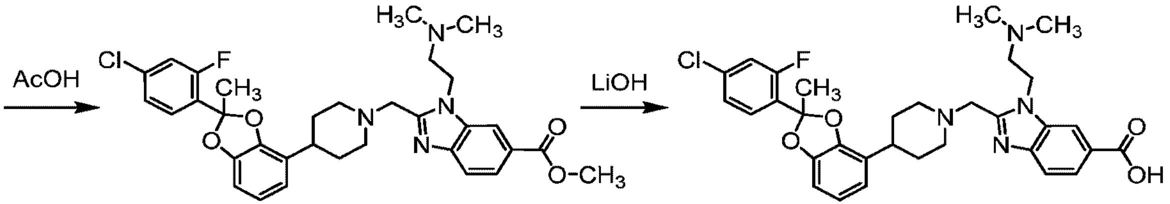
An aqueous solution of sodium hydroxide (1.0 M; 200 µL, 200 µmol) was added to a solution of **C60** (from the previous step, ≤100 µmol) in a mixture of methanol (400 µL) and tetrahydrofuran (400 µL). The reaction vial was capped and shaken at 80 °C for 16 hours, whereupon the reaction mixture was evaporated using a Speedvac® concentrator, and purified using reversed-phase HPLC (Column: Agela Durashell C18, 5 µm; Mobile phase A: 0.225% formic acid in water; Mobile phase B: acetonitrile; Gradient: 12% to 52% B) to afford **11**. Yield: 2.2 mg, 4.2 µmol, 4% over 2 steps. LCMS *m/z* 529 $[M+H]^+$. Retention time: 2.47 minutes (Column: Waters XBridge C18, 2.1 x 50 mm, 5 µm; Mobile phase A: 0.0375% trifluoroacetic acid in water; Mobile phase B: 0.01875% trifluoroacetic acid in acetonitrile; Gradient: 1% to 5% B over 0.6 minutes; 5% to 100% B over 3.4 minutes; Flow rate: 0.8 mL/minute).

Example 12

*2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(dimethylamino)ethyl]-1*H*-benzimidazole-6-carboxylic acid (**12**)*







C64 **12**

This entire synthetic sequence was carried out in library format.

*Step 1. Synthesis of methyl 3-{[2-(dimethylamino)ethyl]amino}-4-nitrobenzoate (**C61**).*

Methyl 3-fluoro-4-nitrobenzoate (0.2 M solution in *N,N*-dimethylformamide; 1 mL, 200 µmol) was treated with *N,N*-dimethylethane-1,2-diamine (18 mg, 200 µmol) and *N,N*-diisopropylethylamine (78 mg, 600 µmol). The reaction vial was then capped and shaken at 50 °C for 16 hours, whereupon the reaction mixture was evaporated using a Speedvac® concentrator to afford **C61**. This material was taken directly to the following step.

*Step 2. Synthesis of methyl 4-amino-3-{[2-(dimethylamino)ethyl]amino}benzoate (**C62**).*

Zinc dust was activated using dilute hydrochloric acid. Methanol (2 mL) was added to **C61** (from the previous step, ≤200 µmol), followed by an aqueous solution of calcium chloride (1.0 M; 200 µL, 200 µmol) and the activated zinc dust (130 mg, 2.0 mmol). The reaction vial was capped and shaken at 70 °C for 16 hours, whereupon the reaction mixture was filtered. The filtrate was concentrated using a Speedvac® concentrator, and the residue was taken up in water (2 mL) and then extracted with ethyl acetate (2 x 3 mL). The combined organic layers were evaporated using a Speedvac® concentrator to afford **C62** (estimated to be 150 µmol), which was used directly in the next step.

*Step 3. Synthesis of methyl 4-[({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}acetyl)amino]-3-{[2-(dimethylamino)ethyl]amino}benzoate (**C63**).*

Compound **P10** (41 mg, 100 µmol) was added to **C62** (from the previous step, approximately 150 µmol), and the mixture was treated with an *N,N*-dimethylacetamide solution of 2-hydroxypyridine 1-oxide and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.1 M in each; 1 mL, 100 µmol of each). *N,N*-Diisopropylethylamine (39 mg, 300 µmol) was then added, and the reaction vial was capped and shaken at 50 °C for 16 hours. The reaction mixture was then concentrated using a Speedvac® concentrator and purified using preparative thin-layer chromatography to provide **C63**, which was advanced directly to the following step.

*Step 4. Synthesis of methyl 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(dimethylamino)ethyl]-1*H*-benzimidazole-6-carboxylate (**C64**).*

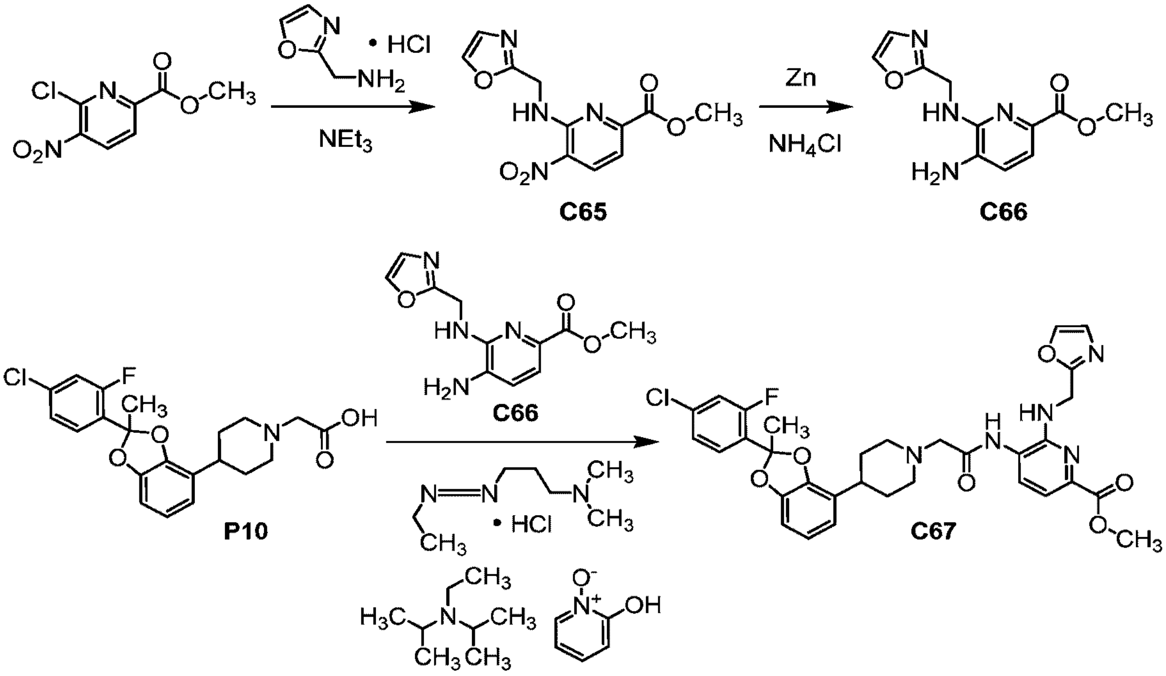
A mixture of acetic acid (500 µL) and **C63** (from the previous step, ≤100 µmol) was shaken in a capped vial at 150 °C for 2 hours, whereupon the reaction mixture was evaporated using a Speedvac® concentrator. The resulting **C64** was advanced directly to the following step.

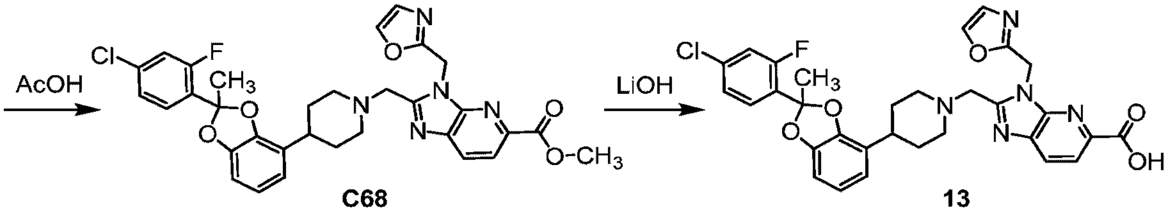
*Step 5. Synthesis of 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(dimethylamino)ethyl]-1*H*-benzimidazole-6-carboxylic acid (**12**).*

A solution of **C64** (from the previous step, ≤100 µmol) in ethanol (500 µL) was treated with an aqueous solution of lithium hydroxide (2.0 M; 500 µL, 1 mmol), and the reaction mixture was shaken at 50 °C for 2 hours in a sealed vial. After the pH of the mixture had been adjusted to 7 by addition of 1.0 M hydrochloric acid, the resulting mixture was concentrated using a Speedvac® concentrator, and then purified via reversed-phase HPLC [Column: Agela Durashell C18, 5 µm; Mobile phase A: ammonium hydroxide in water (pH 10); Mobile phase B: acetonitrile; Gradient: 25% to 65% B] to afford **12**. Yield: 7.0 mg, 12 µmol, 12% over 3 steps. LCMS *m/z* 593 $[M+H]^+$. Retention time: 2.45 minutes (Column: Waters XBridge C18, 2.1 x 50 mm, 5 µm; Mobile phase A: 0.0375% trifluoroacetic acid in water; Mobile phase B: 0.01875% trifluoroacetic acid in acetonitrile; Gradient: 10% to 100% B over 4.0 minutes; Flow rate: 0.8 mL/minute).

Example 13

*2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic acid (**13**)*





*Step 1. Synthesis of methyl 6-[(1,3-oxazol-2-ylmethyl)amino]-5-nitropyridine-2-carboxylate (**C65**).*

Triethylamine (532 mg, 5.26 mmol) was added to a suspension of 1-(1,3-oxazol-2-yl)methanamine, hydrochloride salt (236 mg, 1.75 mmol) and methyl 6-chloro-5-nitropyridine-2-carboxylate (386 mg, 1.78 mmol) in tetrahydrofuran (5 mL). After the reaction mixture had been stirred at 25 °C for 14 hours, it was poured into water (30 mL) and extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*; silica gel chromatography (Gradient: 0% to 5% methanol in dichloromethane) afforded **C65** as a yellow solid. Yield: 310 mg, 1.11 mmol, 63%. LCMS *m/z* 278.7 $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.69 – 8.61 (br m, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 0.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 1.0 Hz, 1H), 5.07 (d, *J* = 5.3 Hz, 2H), 3.97 (s, 3H).

The remainder of this synthetic sequence was carried out in library format.

*Step 2. Synthesis of methyl 5-amino-6-[(1,3-oxazol-2-ylmethyl)amino]pyridine-2-carboxylate (**C66**).*

Aqueous ammonium chloride solution (5.0 M; 400 µL, 2.0 mmol), followed by activated zinc (131 mg, 2.0 mmol), was added to a solution of **C65** (56 mg, 200 µmol) in methanol (2.0 mL). The reaction vial was then capped and shaken at 30 °C for 16 hours, whereupon the reaction mixture was filtered. The filtrate was concentrated using a Speedvac® concentrator, then mixed with water (1.0 mL) and extracted with dichloromethane (3 x 1.0 mL); the combined organic layers were evaporated using a Speedvac® concentrator to provide **C66**, which was taken directly into the following step.

*Step 3. Synthesis of methyl 5-[({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}acetyl)amino]-6-[(1,3-oxazol-2-ylmethyl)amino]pyridine-2-carboxylate (**C67**).*

A mixture of **P10** (81 mg, 200 µmol) and **C66** (from the previous step, ≤200 µmol) was mixed with *N*,*N*-dimethylacetamide and then treated with *N*,*N*-diisopropylethylamine (100 µL, 600 µmol). A solution containing 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride

(0.24 M) and 2-hydroxypyridine 1-oxide (0.1 M) in *N*,*N*-dimethylacetamide (1.0 mL, containing 240 µmol 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and 100 µmol 2-hydroxypyridine 1-oxide) was added, and the reaction vial was capped and shaken at 50 °C for 16 hours. Volatiles were then removed using a Speedvac® concentrator, and the residue was subjected to preparative thin-layer chromatography to afford **C67**, which was advanced directly to the next step.

*Step 4. Synthesis of methyl 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (**C68**).*

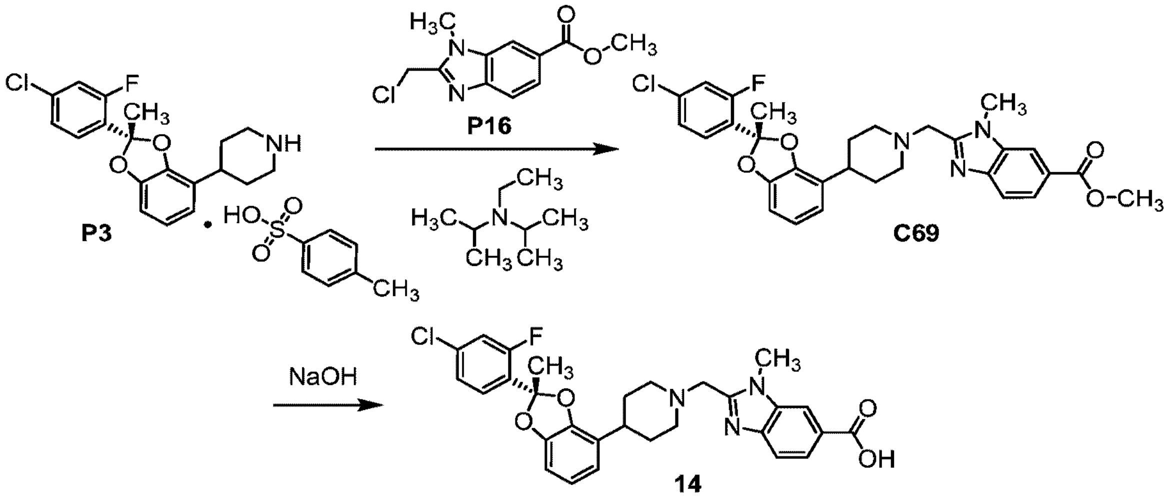
A mixture of acetic acid (1.0 mL) and **C67** (from the previous step, ≤200 µmol) was shaken at 150 °C for 2 hours, whereupon the reaction mixture was evaporated using a Speedvac® concentrator. The resulting **C68** was used directly in the following step.

*Step 5. Synthesis of 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic acid (**13**).*

Aqueous lithium hydroxide solution (2.0 M; 1.0 mL, 2.0 mmol) was added to a mixture of **C68** (from the previous step, ≤200 µmol) in tetrahydrofuran (1.0 mL). After addition of methanol (500 µL), the reaction vial was capped and shaken at 50 °C for 16 hours. After removal of volatiles using a Speedvac® concentrator, dimethyl sulfoxide (1.0 mL) was added, and the pH was adjusted to 7 to 8 with concentrated hydrochloric acid. The resulting mixture was purified using reversed-phase HPLC [Column: Agela Durashell C18, 5 µm; Mobile phase A: ammonium hydroxide in water (pH 10); Mobile phase B: acetonitrile; Gradient: 24% to 64% B] to afford **13**. Yield: 3.9 mg, 6.5 µmol, 3% over 4 steps. LCMS *m/z* 604 $[M+H]^+$. Retention time: 3.14 minutes (Column: Waters XBridge C18, 2.1 x 50 mm, 5 µm; Mobile phase A: 0.0375% trifluoroacetic acid in water; Mobile phase B: 0.01875% trifluoroacetic acid in acetonitrile; Gradient: 1% to 5% B over 0.6 minutes; 5% to 100% B over 3.4 minutes; Flow rate: 0.8 mL/minute).

Example 14

*2-({4-[(2*S*)-2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-methyl-1*H*-benzimidazole-6-carboxylic acid (**14**)*



*Step 1. Synthesis of methyl 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-methyl-1*H-benzimidazole-6-carboxylate (**C69**).*

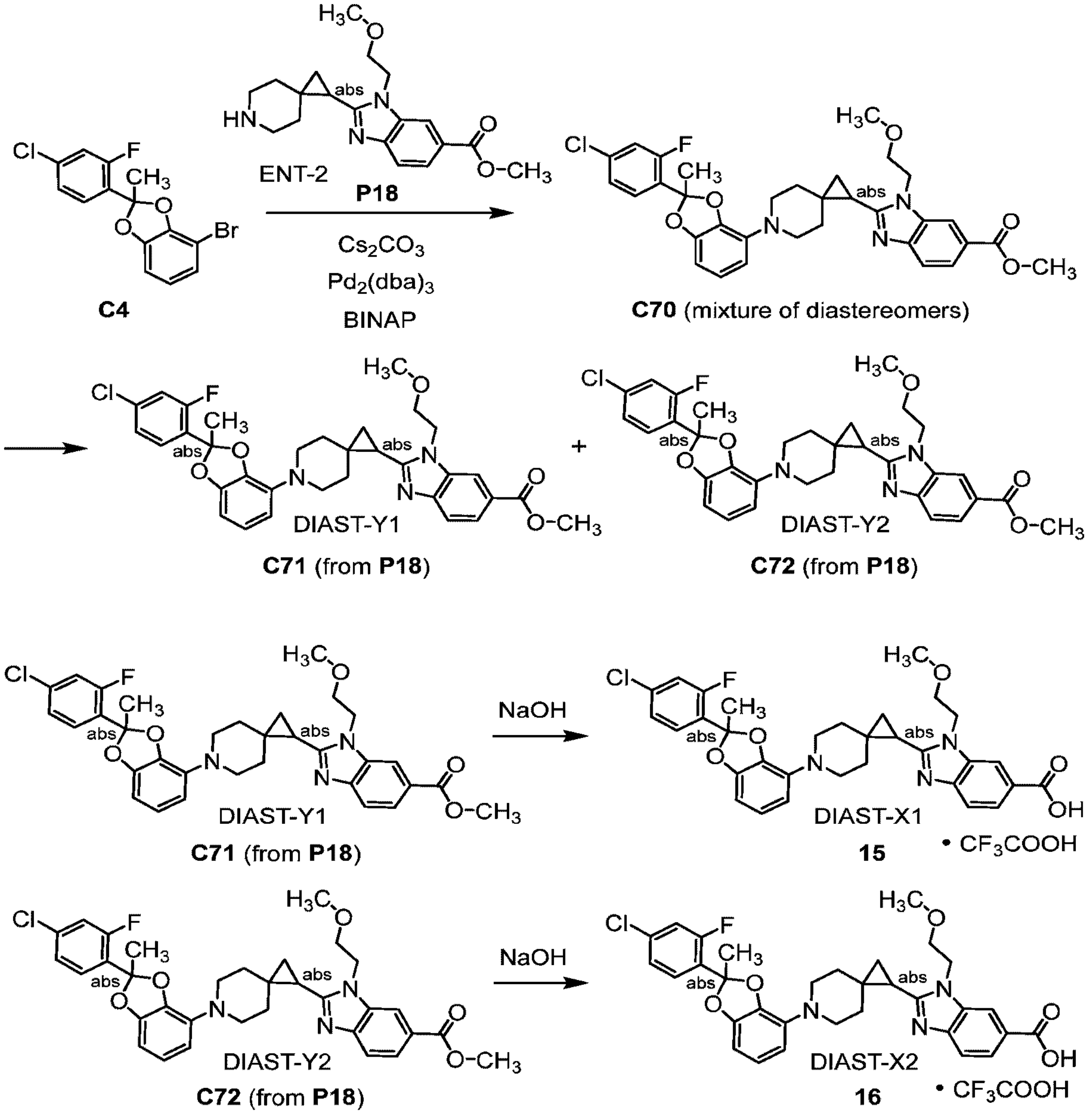
N,N-Diisopropylethylamine (683 µL, 3.92 mmol), was added to a mixture of **P3** (680 mg, 1.31 mmol) in acetonitrile (5.2 mL); this was allowed to stir for 5 minutes at 45 °C, whereupon **P16** (319 mg, 1.34 mmol) was added. Stirring was continued at 45 °C for 2.75 hours, and then water (6 mL) was added before allowing the reaction mixture to cool to room temperature and stir for 30 minutes. Solids were collected via filtration and washed with a mixture of acetonitrile and water (1:4, 3 x 5 mL) to afford **C69** as a white solid. Yield: 635 mg, 1.15 mmol, 88%. LCMS *m/z* 550.1♦ $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.15 – 8.12 (m, 1H), 7.97 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.50 (dd, *J* = 8.2, 8.2 Hz, 1H), 7.16 – 7.07 (m, 2H), 6.79 – 6.73 (m, 1H), 6.72 – 6.65 (m, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.88 (s, 2H), 3.04 – 2.93 (m, 2H), 2.76 – 2.66 (m, 1H), 2.37 – 2.25 (m, 2H), 2.04 (br s, 3H), 1.89 – 1.78 (m, 4H).

*Step 2. Synthesis of 2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-methyl-1*H-benzimidazole-6-carboxylic acid (**14**).*

A mixture of **C69** (600 mg, 1.09 mmol) in methanol (11 mL) was heated to 45 °C, and then treated with aqueous sodium hydroxide solution (1 M; 2.2 mL, 2.2 mmol). After 24 hours, the reaction mixture was adjusted to pH 5 to 6 via addition of aqueous citric acid (1 M; 1.1 mL), and then diluted with water (10 mL). The resulting mixture was allowed to cool to room temperature and stir for 1 hour, whereupon the precipitated solid was collected via filtration and washed with a mixture of methanol and water (1:4; 3 x 5 mL). This afforded **14** as a white solid. Yield: 535 mg, 0.998 mmol, 92%. LCMS *m/z* 536.1♦ $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, *J* = 1.5 Hz, 1H), 7.81 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.33 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.81 – 6.70 (m, 3H), 3.94 (s, 3H), 3.84 (s, 2H), 3.01 – 2.91 (m, 2H), 2.70 – 2.59 (m, 1H), 2.28 – 2.16 (m, 2H), 2.02 (s, 3H), 1.73 (m, 4H).

Examples 15 and 16

*2-{6-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-6-azaspiro[2.5]oct-1-yl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, DIAST-X1, trifluoroacetate salt (**15**) [from **P18** via **C71**]; and 2-{6-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-6-azaspiro[2.5]oct-1-yl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, DIAST-X2, trifluoroacetate salt (**16**) [from **P18** via **C72**]*



*Step 1. Synthesis of methyl 2-{6-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-6-azaspiro[2.5]oct-1-yl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate (**C70**) [from **P18**].*

A mixture of **P18** (240 mg, 0.699 mmol), **C4** (275 mg, 0.800 mmol), cesium carbonate (455 mg, 1.40 mmol), tris(dibenzylideneacetone)dipalladium(0) (40.0 mg, 43.7 µmol), and 1,1'-binaphthalene-2,2'-diylbis(diphenylphosphane) (BINAP; 52.2 mg, 83.8 µmol) in toluene (5 mL) was degassed with nitrogen for 5 minutes and then stirred at 90 °C for 16 hours. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*; preparative thin-layer chromatography (Eluent: 1:1 petroleum ether / ethyl acetate) afforded **C70**, a mixture of diastereomers, as a yellow oil. Yield: 165 mg, 0.272 mmol, 39%. LCMS *m/z* 628.1♦ [M+Na$^+$].

*Step 2. Isolation of methyl 2-{6-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-6-azaspiro[2.5]oct-1-yl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, DIAST-Y1 (**C71**) [from **P18**]; and methyl 2-{6-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-6-azaspiro[2.5]oct-1-yl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, DIAST-Y2 (**C72**) [from **P18**].*

Separation of the stereoisomers at the dioxolane in **C70** (165 mg, 0.272 mmol) was carried out using SFC [Column: Chiral Technologies Chiralpak AD, 10 µm; Mobile phase: 65:35 carbon dioxide / (ethanol containing 0.1% ammonium hydroxide)]. The first-eluting isomer was designated as DIAST-Y1 (**C71**), and the second-eluting isomer as DIAST-Y2 (**C72**); both were isolated as white solids.

C71 Yield: 55.0 mg, 90.7 µmol, 33%. LCMS *m/z* 605.9♦ [M+H]$^+$. Retention time 4.47 minutes (Column: Chiral Technologies Chiralpak AD-3, 4.6 x 100 mm, 3 µm; Mobile phase A: carbon dioxide; Mobile phase B: ethanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 4.5 minutes, then held at 40% B for 2.5 minutes; Flow rate: 2.8 mL/minute).

C72 Yield: 58.0 mg, 95.7 µmol, 35%. LCMS *m/z* 628.0♦ [M+Na$^+$]. Retention time 4.88 minutes (Analytical conditions identical to those used for **C71**).

*Step 3. Synthesis of 2-{6-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-6-azaspiro[2.5]oct-1-yl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, DIAST-X1, trifluoroacetate salt (**15**) [from **P18** via **C71**].*

To a solution of **C71** (55.0 mg, 90.7 µmol) in a mixture of methanol (2.0 mL) and tetrahydrofuran (1.0 mL) was added an aqueous solution of sodium hydroxide (3 M; 1.0 mL, 3.0 mmol). After the reaction mixture had been stirred at 20 °C for 2 hours, the pH was adjusted to 7 by addition of 1 M hydrochloric acid, and the resulting mixture was extracted with a mixture of dichloromethane and methanol (10:1, 3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo.* Reversed-phase HPLC (Column: Boston Green ODS, 5 µm; Mobile phase A: 0.1% trifluoroacetic acid in water; Mobile phase B: acetonitrile; Gradient: 10% to 95% B) provided **15** as a white solid. Yield: 35.8 mg, 50.7 µmol, 56%. LCMS *m/z* 592.3♦ [M+H]$^+$. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.46 (s, 1H), 8.21 (d, *J* = 8.6

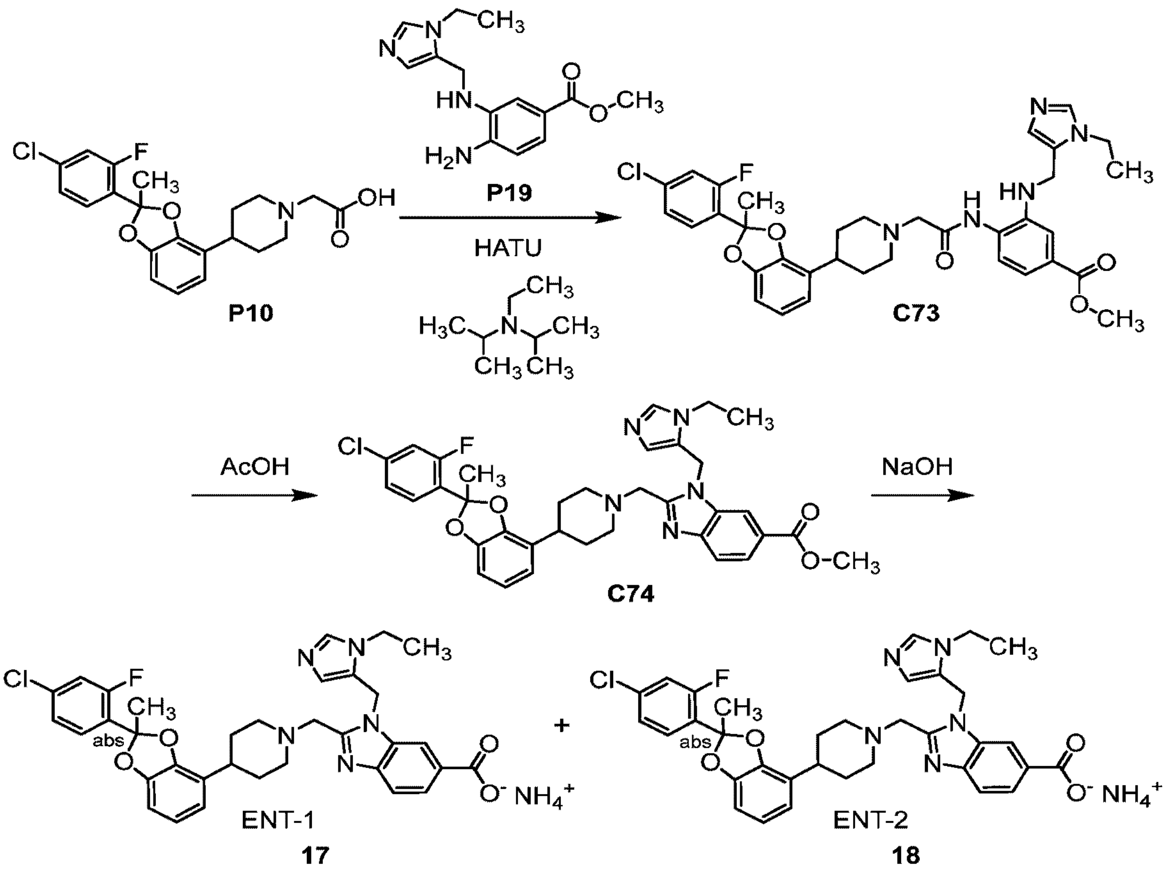
Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.54 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.76 (dd, *J* = 8.2, 8.1 Hz, 1H), 6.55 – 6.47 (m, 2H), 4.9 – 4.70 (m, 2H, assumed; partially obscured by water peak), 3.82 (t, *J* = 4.9 Hz, 2H), 3.66 – 3.56 (m, 1H), 3.50 – 3.41 (m, 1H), 3.19 – 3.09 (m, 1H), 3.15 (s, 3H), 3.08 – 2.99 (m, 1H), 2.63 – 2.57 (m, 1H), 2.27 – 2.17 (m, 1H), 2.01 (s, 3H), 1.76 – 1.66 (m, 2H), 1.62 – 1.50 (m, 2H), 1.35 – 1.26 (m, 1H).

*Step 4. Synthesis of 2-{6-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-6-azaspiro[2.5]oct-1-yl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, DIAST-X2, trifluoroacetate salt (**16**) [from **P18** via **C72**].*

To a solution of **C72** (58.0 mg, 95.7 µmol) in a mixture of methanol (2.0 mL) and tetrahydrofuran (1.0 mL) was added an aqueous solution of sodium hydroxide (3 M; 1.0 mL, 3.0 mmol). After the reaction mixture had been stirred at 20 °C for 2 hours, the pH was adjusted to 7 by addition of 1 M hydrochloric acid, and the resulting mixture was extracted with a mixture of dichloromethane and methanol (10:1, 3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Reversed-phase HPLC (Column: Boston Green ODS, 5 µm; Mobile phase A: 0.1% trifluoroacetic acid in water; Mobile phase B: acetonitrile; Gradient: 35% to 95% B) provided **16** as a white solid. Yield: 33.4 mg, 47.3 µmol, 49%. LCMS *m/z* 592.2♦ $[M+H]^+$. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.53 – 8.50 (m, 1H), 8.25 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.80 (br d, *J* = 8.6 Hz, 1H), 7.57 (dd, *J* = 8.4, 8.2 Hz, 1H), 7.25 (dd, *J* = 10.8, 2.0 Hz, 1H), 7.19 (br dd, *J* = 8.4, 2.1 Hz, 1H), 6.77 (dd, *J* = 8.2, 8.1 Hz, 1H), 6.55 – 6.50 (m, 2H), 4.9 – 4.72 (m, 2H, assumed; partially obscured by water peak), 3.93 – 3.80 (m, 2H), 3.68 – 3.58 (m, 1H), 3.41 – 3.3 (m, 1H, assumed; partially obscured by solvent peak), 3.25 (s, 3H), 3.22 – 3.12 (m, 1H), 3.07 – 2.97 (m, 1H), 2.67 (dd, *J* = 8.3, 5.8 Hz, 1H), 2.28 – 2.17 (m, 1H), 2.01 (d, *J* = 1.0 Hz, 3H), 1.86 – 1.71 (m, 2H), 1.69 – 1.56 (m, 2H), 1.36 – 1.26 (m, 1H).

Examples 17 and 18

*Ammonium 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-imidazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylate, ENT-1 (**17**) and Ammonium 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-imidazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylate, ENT-2 (**18**)*



*Step 1. Synthesis of methyl 4-[({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}acetyl)amino]-3-{[(1-ethyl-1*H*-imidazol-5-yl)methyl]amino}benzoate (**C73**).*

O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (566 mg, 1.49 mmol) was added to a mixture of **P19** (340 mg, 1.24 mmol) in *N,N*-dimethylformamide (10 mL), and the mixture was stirred at 25 °C for 10 minutes. A solution of **P10** (503 mg, 1.24 mmol) and *N,N*-diisopropylethylamine (615 µL, 3.53 mmol) in *N,N*-dimethylformamide (7.7 mL) was then added, and the reaction mixture was stirred at 25 °C for 16 hours, whereupon it was poured into water (10 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed sequentially with aqueous ammonium chloride solution (3 x 20 mL) and saturated aqueous sodium chloride solution (2 x 20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Upon purification using silica gel chromatography (Gradient: 0% to 5% methanol in ethyl acetate), **C73** was obtained as a pale brown gum. Yield: 316 mg, 0.477 mmol, 38%. LCMS *m/z* 662.2♦ $[M+H]^+$.

*Step 2. Synthesis of methyl 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-imidazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylate (**C74**).*

A solution of **C73** (316 mg, 0.477 mmol) in acetic acid (14 mL) was stirred at 55 °C for 16 hours. Solvent was removed under high vacuum, and the residue was purified using preparative thin-layer chromatography (Eluent: 10:1 dichloromethane / methanol) to afford **C74** as a colorless oil. Yield: 200 mg, 0.310 mmol, 65%. LCMS *m/z* 644.3♦ [M+H]$^+$.

*Step 3. Synthesis of ammonium 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-imidazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylate, ENT-1 (**17**) and ammonium 2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-imidazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylate, ENT-2 (**18**).*

A mixture of **C74** (150 mg, 0.233 mmol) and aqueous sodium hydroxide solution (2 M; 233 µL, 0.466 mmol) in a mixture of methanol (3 mL) and tetrahydrofuran (3 mL) was stirred at 45 °C for 16 hours. After the reaction mixture had been adjusted to pH 7 by addition of 1 M hydrochloric acid, it was concentrated *in vacuo* to afford a mixture of **17** and **18**. These enantiomers were separated via SFC [Column: Chiral Technologies ChiralCel OD, 10 µm; Mobile phase: 1:1 carbon dioxide / (ethanol containing 0.1% ammonium hydroxide)]. The first-eluting enantiomer was designated as ENT-1 (**17**), and the second-eluting enantiomer as ENT-2 (**18**); both were isolated as white solids.

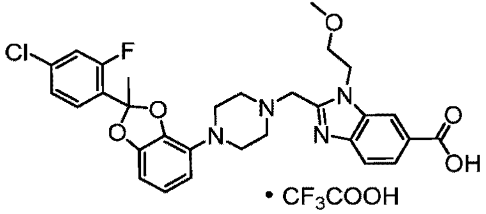
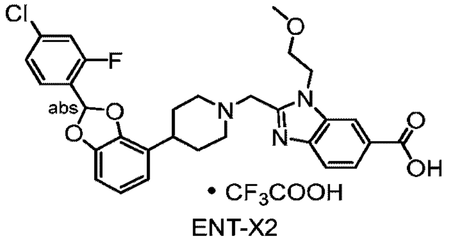
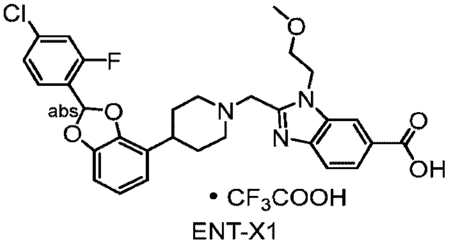
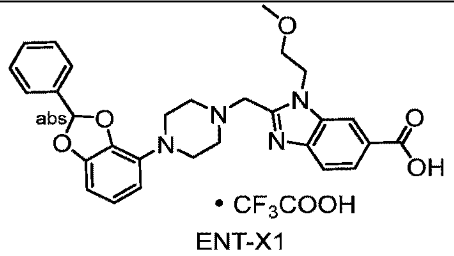
17 Yield: 45.0 mg, 69.5 µmol, 30%. LCMS *m/z* 630.3♦ [M+H]$^+$. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.15 (br s, 1H), 8.00 (br d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.56 (dd, J = 8.3, 8.3 Hz, 1H), 7.28 (dd, J = 10.9, 2.0 Hz, 1H), 7.21 (dd, J = 8.3, 2.1 Hz, 1H), 6.77 (dd, component of ABC pattern, J = 8.0, 7.7 Hz, 1H), 6.69 (dd, component of ABC pattern, J = 7.8, 1.2 Hz, 1H), 6.67 – 6.60 (m, 2H), 5.82 (s, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.89 (AB quartet, J_{AB} = 14.3 Hz, $\Delta\nu_{AB}$ = 6.9 Hz, 2H), 3.00 – 2.90 (m, 2H), 2.74 – 2.64 (m, 1H), 2.32 – 2.21 (m, 2H), 2.02 (s, 3H), 1.82 – 1.61 (m, 4H), 1.29 (t, J = 7.3 Hz, 3H). Retention time 5.66 minutes (Column: Chiral Technologies Chiralpak AD-3, 4.6 x 150 mm, 3 µm; Mobile phase A: carbon dioxide; Mobile phase B: methanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 5.5 minutes, then held at 40% B for 3.0 minutes; Flow rate: 2.5 mL/minute).

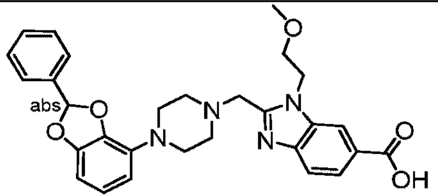
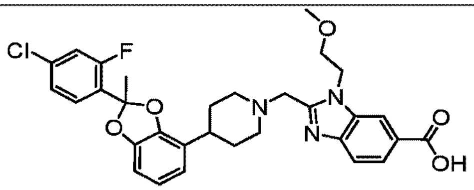
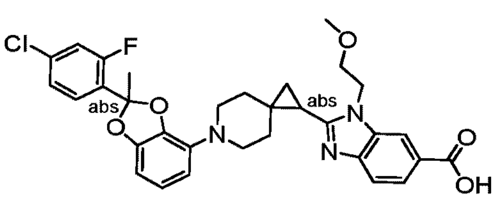
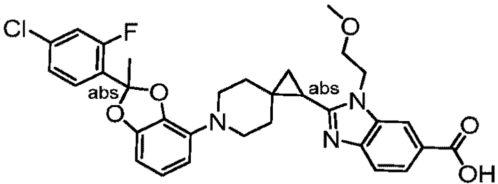
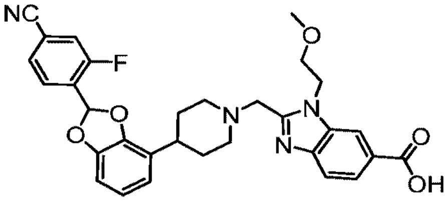
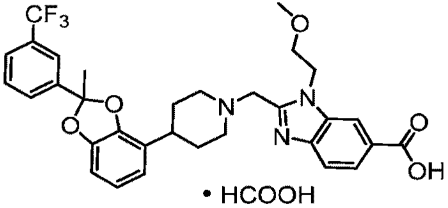
18 Yield: 32.8 mg, 50.7 µmol, 22%. LCMS *m/z* 630.3♦ [M+H]$^+$. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.15 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.81 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.56 (dd, J = 8.3, 8.3 Hz, 1H), 7.28 (dd, J = 10.9, 2.0 Hz, 1H), 7.21 (dd, J = 8.3, 2.0 Hz, 1H), 6.77 (dd, component of ABC pattern, J = 7.8, 7.8 Hz, 1H), 6.69 (dd, component of ABC pattern, J = 7.9, 1.2 Hz, 1H), 6.67 – 6.60 (m, 2H), 5.82 (s, 2H), 4.12 (q, J = 7.3 Hz, 2H), 3.89 (AB quartet, J_{AB} = 14.1 Hz, $\Delta\nu_{AB}$ = 7.4 Hz, 2H), 3.01 – 2.90 (m, 2H), 2.74 – 2.63 (m, 1H), 2.31 – 2.21 (m, 2H), 2.02 (s, 3H), 1.82

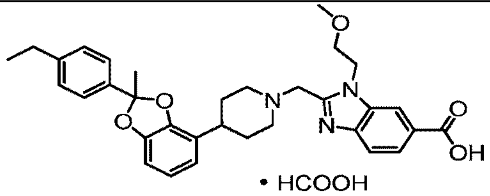
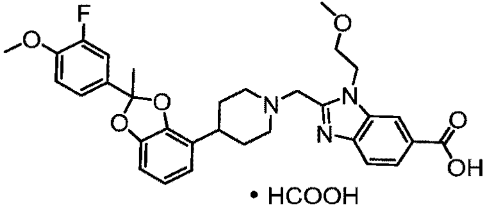
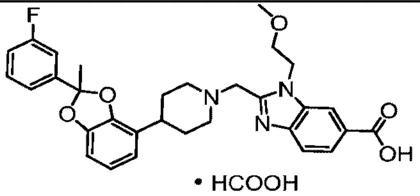
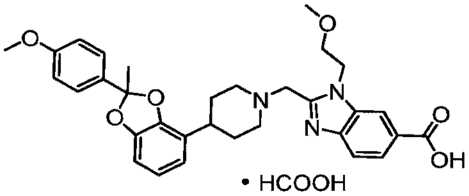
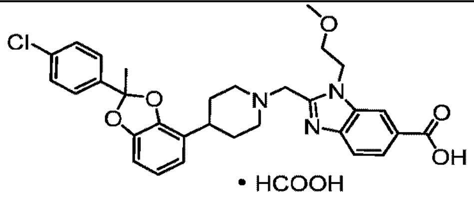
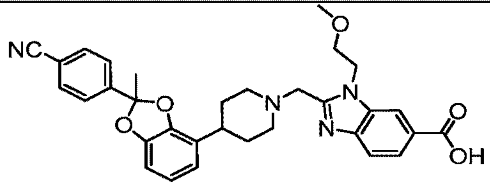
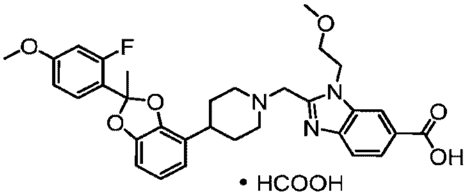
– 1.60 (m, 4H), 1.29 (t, *J* = 7.3 Hz, 3H). Retention time 5.34 minutes (Analytical SFC conditions identical to those used for **17**).

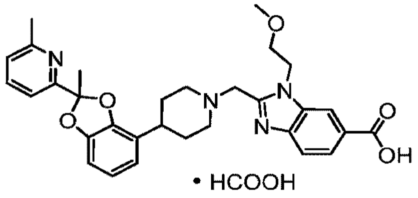
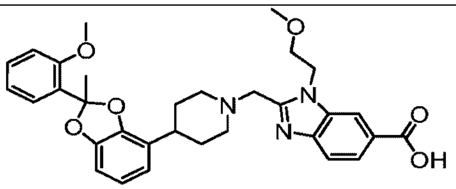
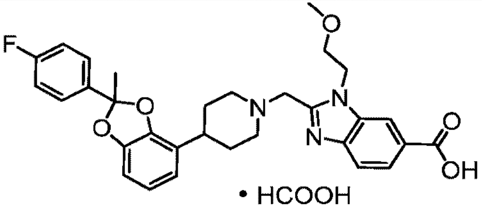
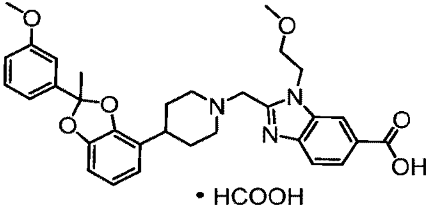
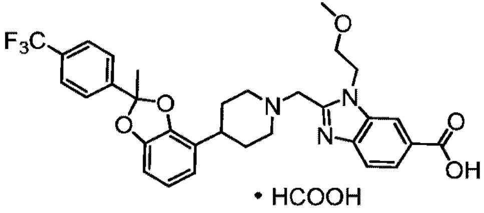
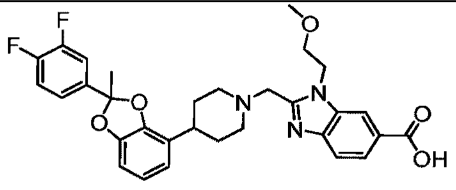
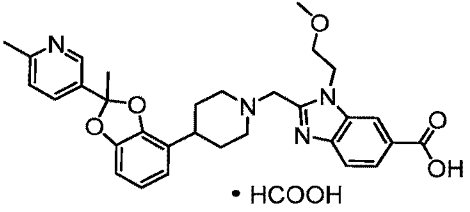
The compounds listed in Table 1 were prepared using procedures analogous to the examples identified in Table 2 using the appropriate intermediate(s) identified in Table 2. The compounds were purified using methods discussed herein. The final compounds may have been isolated as neutrals or acid or base salts.

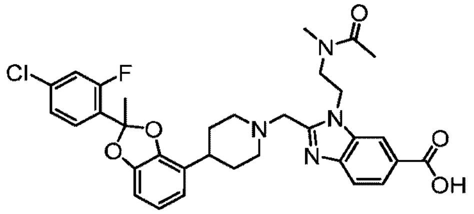
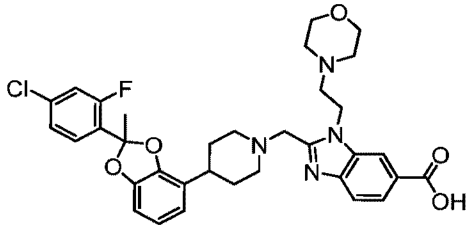
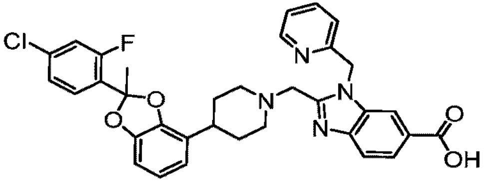
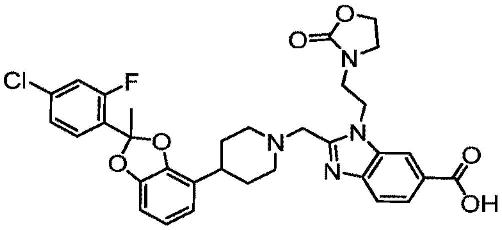
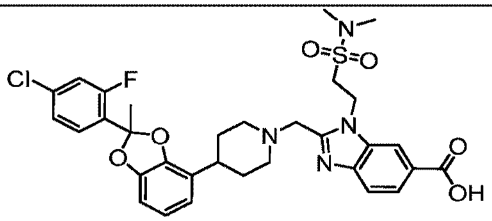
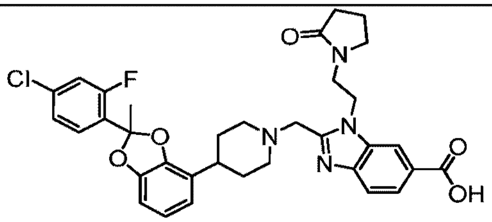
Table 1. Structure and IUPAC name for Examples 19 – 102

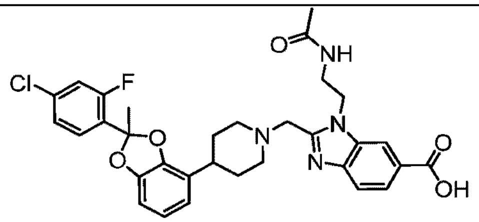
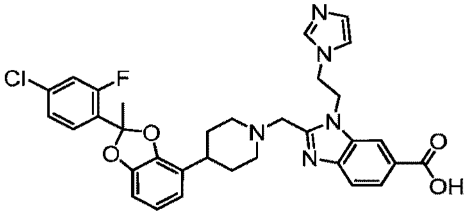
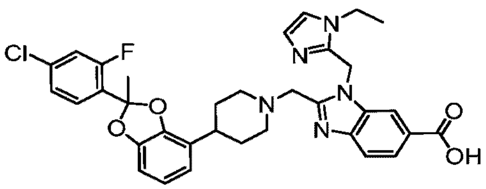
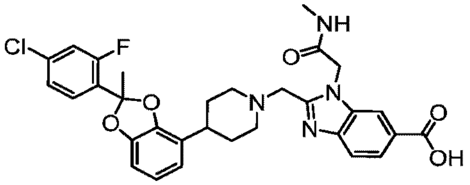
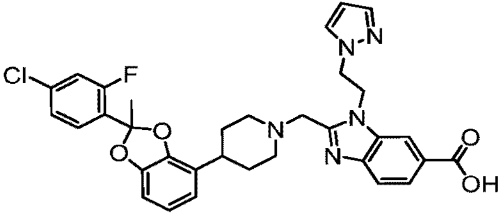
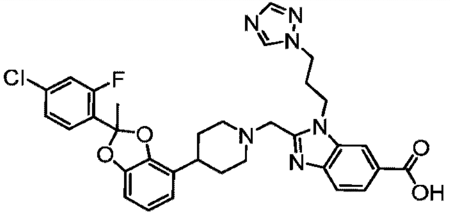
Ex. No.	Structure	IUPAC Name
19		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperazin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, trifluoroacetate salt
20		2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, ENT-X2, trifluoroacetate salt, [from **C77**; footnote 1 in Table 2]
21		2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, ENT-X1, trifluoroacetate salt, [from **C76**; footnote 1 in Table 2]
22		1-(2-methoxyethyl)-2-{[4-(2-phenyl-1,3-benzodioxol-4-yl)piperazin-1-yl]methyl}-1*H*-benzimidazole-6-carboxylic acid, ENT-X1, trifluoroacetate salt, [from **P5**]

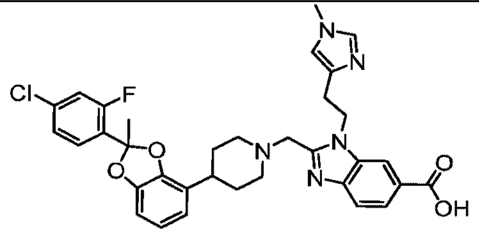
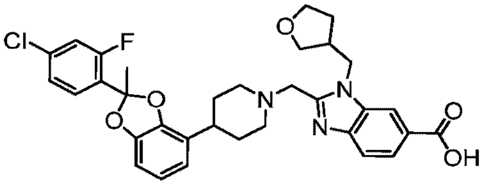
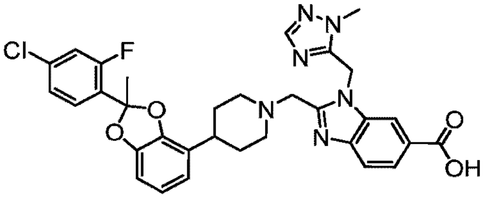
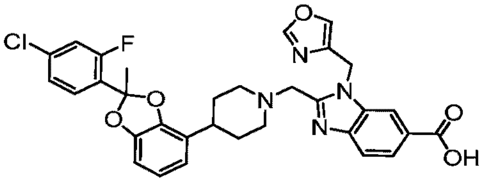
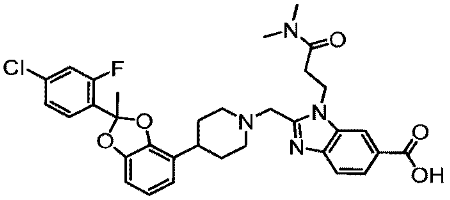
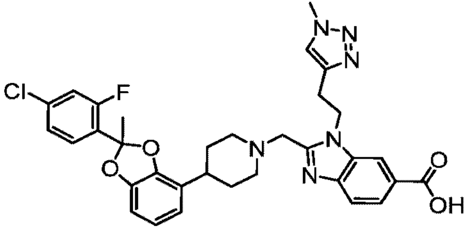
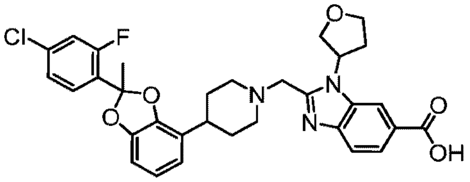
23	 • CF_3COOH ENT-X2	1-(2-methoxyethyl)-2-{[4-(2-phenyl-1,3-benzodioxol-4-yl)piperazin-1-yl]methyl}-1*H*-benzimidazole-6-carboxylic acid, ENT-X2, trifluoroacetate salt, [from **P6**]
24	 • CF_3COOH	2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, trifluoroacetate salt
25	 • CF_3COOH DIAST-Z2	2-{6-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-6-azaspiro[2.5]oct-1-yl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, DIAST-Z2, trifluoroacetate salt, [from **P17** via **C79**; footnote 2 in Table 2]
26	 • CF_3COOH DIAST-Z1	2-{6-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-6-azaspiro[2.5]oct-1-yl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, DIAST-Z1, trifluoroacetate salt, [from **P17** via **C78**; footnote 2 in Table 2]
27	 • CF_3COOH	2-({4-[2-(4-cyano-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, trifluoroacetate salt
28	 • HCOOH	1-(2-methoxyethyl)-2-[(4-{2-methyl-2-[3-(trifluoromethyl)phenyl]-1,3-benzodioxol-4-yl}piperidin-1-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid, formate salt

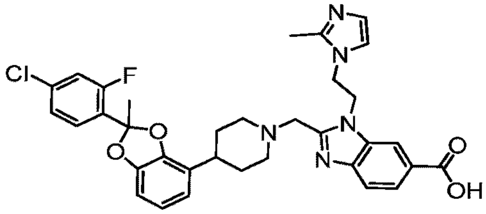
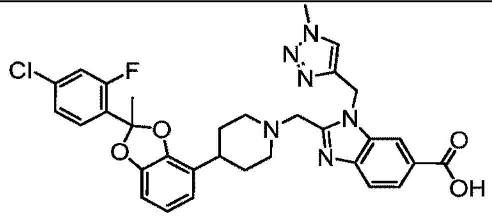
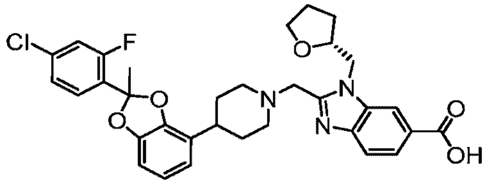
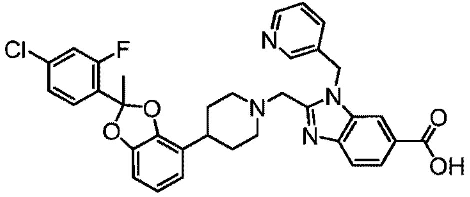
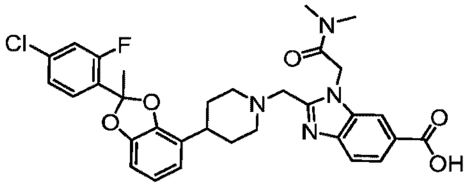
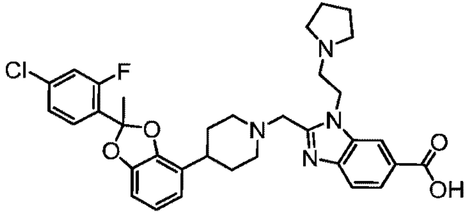
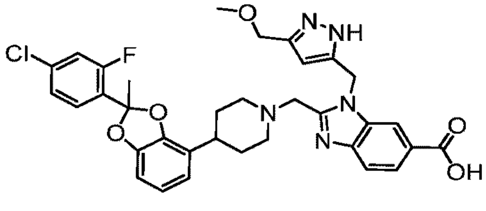
29		2-({4-[2-(4-ethylphenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
30		2-({4-[2-(3-fluoro-4-methoxyphenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
31		2-({4-[2-(3-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
32		1-(2-methoxyethyl)-2-({4-[2-(4-methoxyphenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
33		2-({4-[2-(4-chlorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
34		2-({4-[2-(4-cyanophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid
35		2-({4-[2-(2-fluoro-4-methoxyphenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt

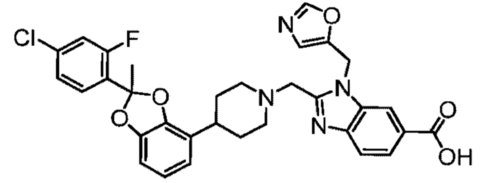
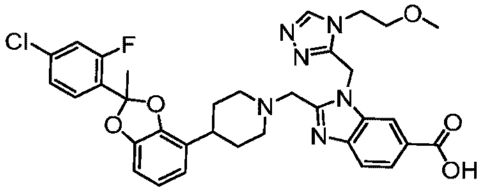
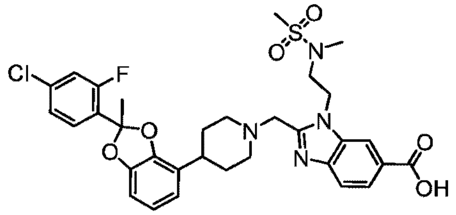
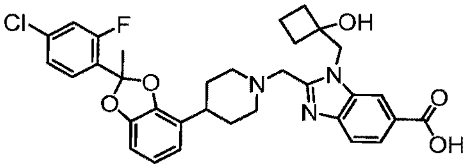
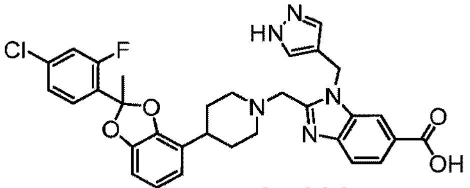
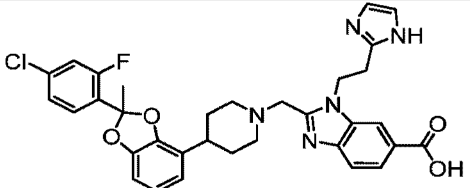
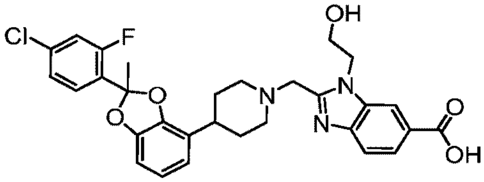
36		1-(2-methoxyethyl)-2-({4-[2-methyl-2-(6-methylpyridin-2-yl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
37		1-(2-methoxyethyl)-2-({4-[2-(2-methoxyphenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid
38		2-({4-[2-(4-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
39		1-(2-methoxyethyl)-2-({4-[2-(3-methoxyphenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
40		1-(2-methoxyethyl)-2-[(4-{2-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-benzodioxol-4-yl}piperidin-1-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid, formate salt
41		2-({4-[2-(3,4-difluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid
42		1-(2-methoxyethyl)-2-({4-[2-methyl-2-(6-methylpyridin-3-yl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt

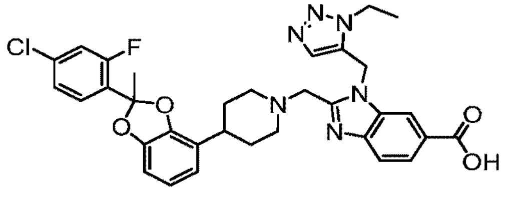
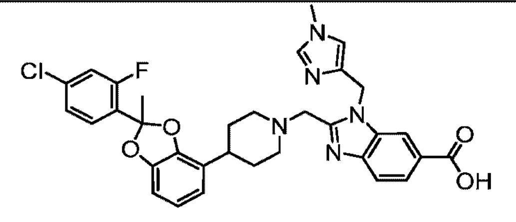
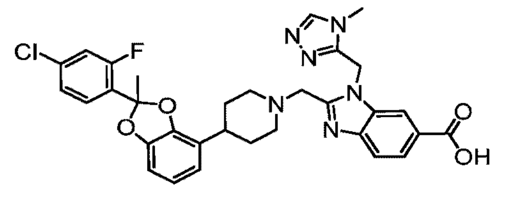
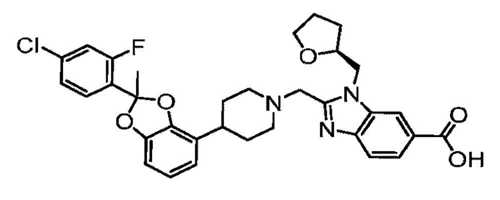
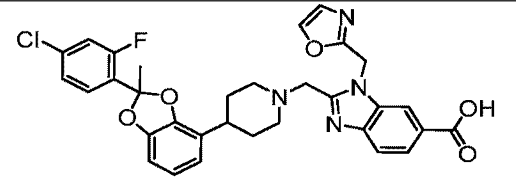
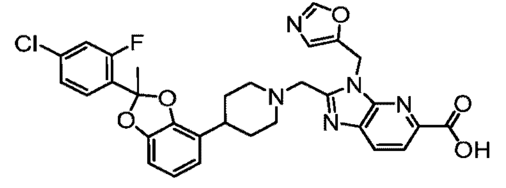
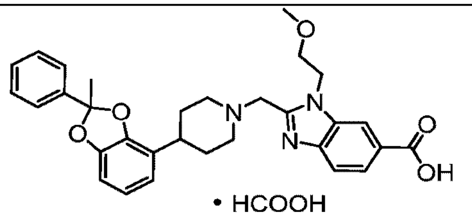
43		1-{2-[acetyl(methyl)amino]ethyl}-2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid
44		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(morpholin-4-yl)ethyl]-1*H*-benzimidazole-6-carboxylic acid
45		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid
46		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-1*H*-benzimidazole-6-carboxylic acid
47		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(dimethylsulfamoyl)ethyl]-1*H*-benzimidazole-6-carboxylic acid
48		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(2-oxopyrrolidin-1-yl)ethyl]-1*H*-benzimidazole-6-carboxylic acid

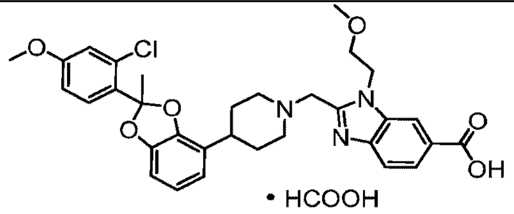
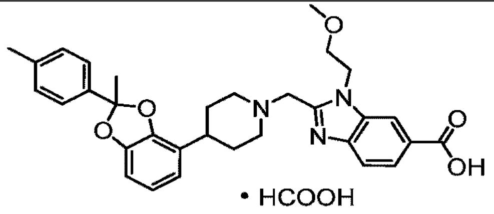
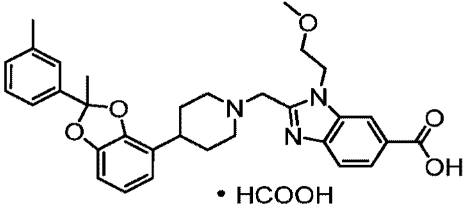
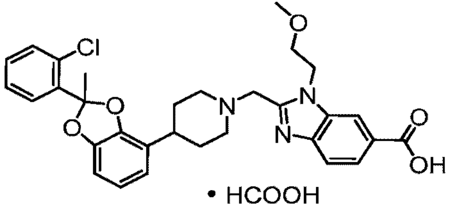
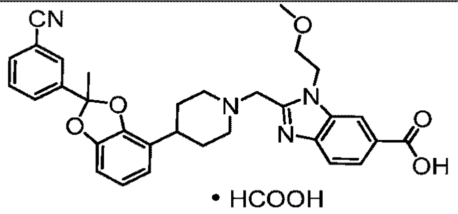
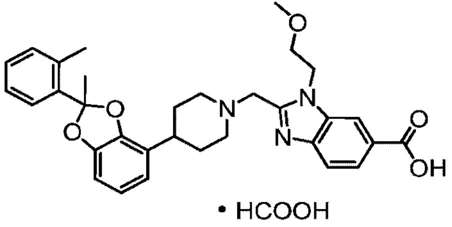
49		1-[2-(acetylamino)ethyl]-2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid
50		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(1*H*-imidazol-1-yl)ethyl]-1*H*-benzimidazole-6-carboxylic acid
51		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-imidazol-2-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid
52		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(methylamino)-2-oxoethyl]-1*H*-benzimidazole-6-carboxylic acid
53		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(1*H*-pyrazol-1-yl)ethyl]-1*H*-benzimidazole-6-carboxylic acid
54		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[3-(1*H*-1,2,4-triazol-1-yl)propyl]-1*H*-benzimidazole-6-carboxylic acid

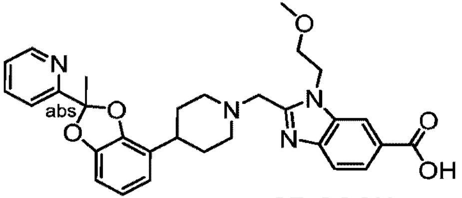
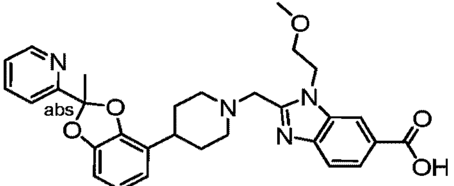
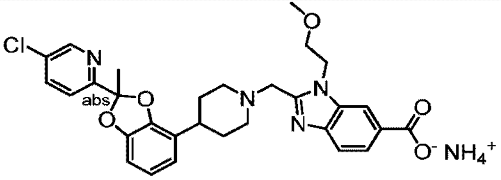
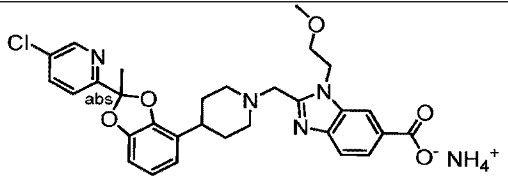
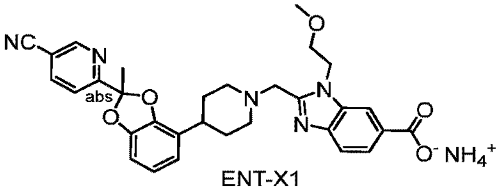
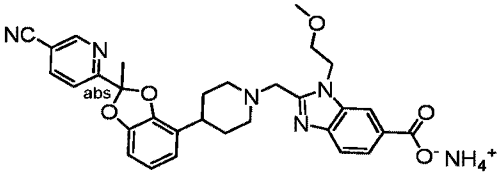
55		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]-1*H*-benzimidazole-6-carboxylic acid
56		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(tetrahydrofuran-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid
57		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-methyl-1*H*-1,2,4-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid
58		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid
59		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[3-(dimethylamino)-3-oxopropyl]-1*H*-benzimidazole-6-carboxylic acid
60		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(1-methyl-1*H*-1,2,3-triazol-4-yl)ethyl]-1*H*-benzimidazole-6-carboxylic acid
61		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(tetrahydrofuran-3-yl)-1*H*-benzimidazole-6-carboxylic acid

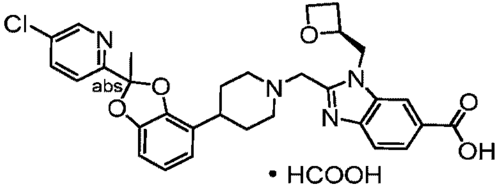
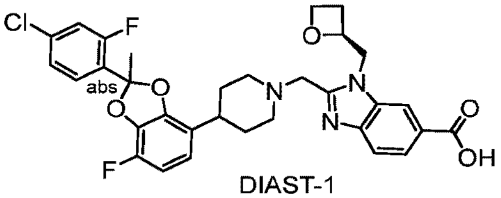
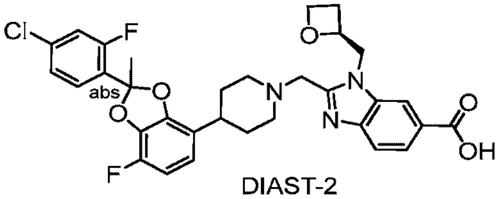
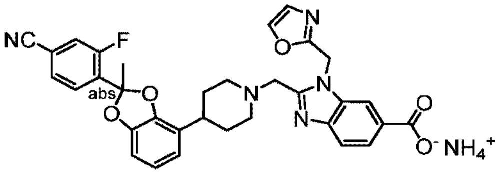
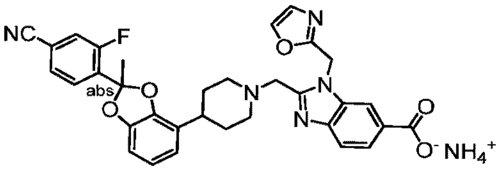
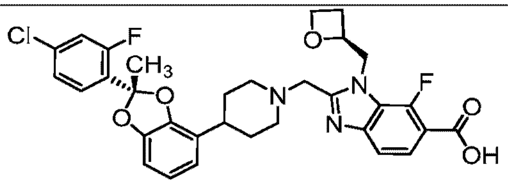
62		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(2-methyl-1*H*-imidazol-1-yl)ethyl]-1*H*-benzimidazole-6-carboxylic acid
63		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-methyl-1*H*-1,2,3-triazol-4-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid
64		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*R*)-tetrahydrofuran-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid
65		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid
66		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(dimethylamino)-2-oxoethyl]-1*H*-benzimidazole-6-carboxylic acid
67		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(pyrrolidin-1-yl)ethyl]-1*H*-benzimidazole-6-carboxylic acid
68		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-{[3-(methoxymethyl)-1*H*-pyrazol-5-yl]methyl}-1*H*-benzimidazole-6-carboxylic acid

69		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid
70		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-{[4-(2-methoxyethyl)-4*H*-1,2,4-triazol-3-yl]methyl}-1*H*-benzimidazole-6-carboxylic acid
71		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-{2-[methyl(methylsulfonyl)amino]ethyl}-1*H*-benzimidazole-6-carboxylic acid
72		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-hydroxycyclobutyl)methyl]-1*H*-benzimidazole-6-carboxylic acid
73	 • CF_3COOH	2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1*H*-pyrazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid, trifluoroacetate salt
74	 • CF_3COOH	2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[2-(1*H*-imidazol-2-yl)ethyl]-1*H*-benzimidazole-6-carboxylic acid, trifluoroacetate salt
75		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-hydroxyethyl)-1*H*-benzimidazole-6-carboxylic acid

76		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid
77		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-methyl-1*H*-imidazol-4-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid
78		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(4-methyl-4*H*-1,2,4-triazol-3-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid
79		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-tetrahydrofuran-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid
80		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid
81		2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-5-ylmethyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic acid
82		1-(2-methoxyethyl)-2-{[4-(2-methyl-2-phenyl-1,3-benzodioxol-4-yl)piperidin-1-yl]methyl}-1*H*-benzimidazole-6-carboxylic acid, formate salt

83		2-({4-[2-(2-chloro-4-methoxyphenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
84		1-(2-methoxyethyl)-2-({4-[2-methyl-2-(4-methylphenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
85		1-(2-methoxyethyl)-2-({4-[2-methyl-2-(3-methylphenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
86		2-({4-[2-(2-chlorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
87		2-({4-[2-(3-cyanophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt
88		1-(2-methoxyethyl)-2-({4-[2-methyl-2-(2-methylphenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid, formate salt

89	 • CF_3COOH ENT-X2	1-(2-methoxyethyl)-2-({4-[2-methyl-2-(pyridin-2-yl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid, ENT-X2, trifluoroacetate salt [from **C81**; footnote 7 in Table 2]
90	 • CF_3COOH ENT-X1	1-(2-methoxyethyl)-2-({4-[2-methyl-2-(pyridin-2-yl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylic acid, ENT-X1, trifluoroacetate salt [from **C80**; footnote 7 in Table 2]
91	 ENT-X1	ammonium 2-({4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, ENT-X1 [from **P8**]
92	 ENT-X2	ammonium 2-({4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, ENT-X2 [from **P9**]
93	 ENT-X1	ammonium 2-({4-[2-(5-cyanopyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, ENT-X1 [from **P8**]
94	 ENT-X2	ammonium 2-({4-[2-(5-cyanopyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate, ENT-X2 [from **P9**]

95	 • HCOOH DIAST-X1	2-({4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid, DIAST-X1 [from **P8**]
96	 DIAST-1	2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid, DIAST-1 [footnote 10 in Table 2]
97	 DIAST-2	2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid, DIAST-2 [footnote 10 in Table 2]
98	 ENT-X2	ammonium 2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylate, ENT-X2 [from **C83**; footnote 12 in Table 2]
99	 ENT-X1	ammonium 2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylate, ENT-X1 [from **C82**; footnote 12 in Table 2]
100	 • 1/2 citric acid	2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid, hemicitrate salt [from **P3**]

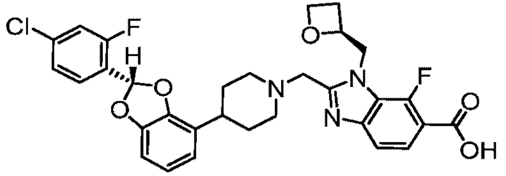
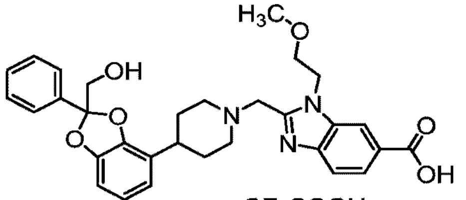
101	 • 1/2 citric acid	2-({4-[(2*S*)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid, hemicitrate salt [from **C48**]
102	 • CF_3COOH	2-({4-[2-(hydroxymethyl)-2-phenyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylic acid, trifluoroacetate salt

Table 2. Method of preparation and physicochemical data for Examples 19 – 102.

Ex. No.	Method	^{1}H NMR (400 MHz, methanol-d_4) δ; Mass spectrum, observed ion *m/z* $[M+H]^+$ or HPLC retention time; Mass spectrum *m/z* $[M+H]^+$ (unless otherwise indicated)
19	**Examples 15** and **16**; **C4**, **P12**	8.39 (br s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.60 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.28 (dd, *J* = 10.9, 2.1 Hz, 1H), 7.22 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.83 (dd, *J* = 8.1, 8.1 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 4.73 (s, 2H), 4.66 (t, *J* = 4.9 Hz, 2H), 3.77 (t, *J* = 4.8 Hz, 2H), 3.59 – 3.43 (m, 8H), 3.30 (s, 3H^^), 2.05 (s, 3H); 581.0
20	**Examples 4** and **5**[1]; **C43**, **P11**	8.34 – 8.31 (m, 1H), 8.03 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.60 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.36 (dd, *J* = 10.2, 1.9 Hz, 1H), 7.31 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.25 (s, 1H), 6.90 (dd, component of ABC pattern, *J* = 8.9, 6.6 Hz, 1H), 6.86 – 6.80 (m, 2H), 4.79 (s, 2H), 4.60 (br t, *J* = 4.8 Hz, 2H), 3.95 – 3.85 (m, 2H), 3.74 (dd, *J* = 5.3, 4.2 Hz, 2H), 3.44 – 3.33 (m, 2H), 3.28 (s, 3H), 3.15 – 3.05 (m, 1H), 2.37 – 2.12 (m, 4H); 566.0♦
21	**Examples 4** and **5**[1]; **C43**, **P11**	8.32 (dd, *J* = 1.6, 0.7 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.78 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.60 (dd, *J* = 8.1, 7.9 Hz, 1H), 7.36 (dd, *J* = 10.2, 2.0 Hz, 1H), 7.31 (br dd, *J* = 8.3, 1.8 Hz, 1H), 7.25 (s, 1H), 6.90 (dd, component of ABC pattern, *J* = 8.8, 6.7 Hz, 1H), 6.87 –

		6.80 (m, 2H), 4.79 (s, 2H), 4.60 (t, *J* = 4.8 Hz, 2H), 3.90 (br d, *J* = 12.3 Hz, 2H), 3.74 (dd, *J* = 5.3, 4.2 Hz, 2H), 3.38 (br dd, *J* = 12.6, 12.5 Hz, 2H), 3.28 (s, 3H), 3.10 (tt, *J* = 11.9, 4.0 Hz, 1H), 2.37 – 2.11 (m, 4H); 566.0♦
22	**Examples** **1** and **2**; **P12**, **P5**	8.37 (d, *J* = 1.5 Hz, 1H), 8.07 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.50 – 7.42 (m, 3H), 6.98 (s, 1H), 6.86 (dd, *J* = 8.1, 8.1 Hz, 1H), 6.61 (dd, *J* = 7.9, 0.9 Hz, 1H), 6.59 (dd, *J* = 8.4, 0.9 Hz, 1H), 4.73 (s, 2H), 4.64 (t, *J* = 4.8 Hz, 2H), 3.75 (dd, *J* = 5.4, 4.3 Hz, 2H), 3.61 – 3.44 (m, 8H), 3.28 (s, 3H); 515.1
23	**Examples** **1** and **2**; **P12**, **P6**	8.37 (br s, 1H), 8.07 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.51 – 7.42 (m, 3H), 6.98 (s, 1H), 6.86 (dd, *J* = 8.2, 8.1 Hz, 1H), 6.61 (br d, *J* = 8 Hz, 1H), 6.59 (br d, *J* = 8.5 Hz, 1H), 4.69 (s, 2H), 4.64 (t, *J* = 4.9 Hz, 2H), 3.75 (t, *J* = 4.9 Hz, 2H), 3.59 – 3.43 (m, 8H), 3.29 (s, 3H); 515.1
24	**Examples** **4** and **5**; **C13**, **P11**	8.33 (dd, *J* = 1.5, 0.6 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.79 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.62 (dd, *J* = 8.4, 8.3 Hz, 1H), 7.29 (dd, *J* = 10.9, 2.0 Hz, 1H), 7.22 (ddd, *J* = 8.4, 2.0, 0.7 Hz, 1H), 6.88 – 6.82 (m, 1H), 6.82 – 6.76 (m, 2H), 4.83 (s, 2H), 4.63 (t, *J* = 4.8 Hz, 2H), 3.98 – 3.88 (m, 2H), 3.75 (dd, *J* = 5.3, 4.2 Hz, 2H), 3.47 – 3.36 (m, 2H), 3.31 (s, 3H^^), 3.10 (tt, *J* = 12.0, 4.1 Hz, 1H), 2.36 – 2.10 (m, 4H), 2.05 (d, *J* = 1.0 Hz, 3H); 580.1♦
25	**Examples** **15** and **16**[2]; **C4**, **P17**	8.51 (dd, *J* = 1.5, 0.7 Hz, 1H), 8.25 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.79 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.57 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.25 (dd, *J* = 10.8, 2.0 Hz, 1H), 7.19 (ddd, *J* = 8.4, 2.0, 0.7 Hz, 1H), 6.80 – 6.73 (m, 1H), 6.55 – 6.50 (m, 2H), 4.9 – 4.73 (m, 2H^), 3.92 – 3.81 (m, 2H), 3.66 – 3.58 (m, 1H), 3.41 – 3.3 (m, 1H^^), 3.25 (s, 3H), 3.20 – 3.12 (m, 1H), 3.05 – 2.97 (m, 1H), 2.70 – 2.63 (m, 1H), 2.27 – 2.17 (m, 1H), 2.01 (d, *J* = 1.0 Hz, 3H), 1.84 – 1.71 (m, 2H), 1.67 – 1.58 (m, 2H),

		1.31 (br d, *J* = 13 Hz, 1H); 592.3♦
26	**Examples 15** and **16**[2]; **C4**, **P17**	8.53 – 8.50 (m, 1H), 8.26 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.55 (dd, *J* = 8.3, 8.2 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.77 (dd, *J* = 8.3, 7.9 Hz, 1H), 6.52 (br d, *J* = 8.3 Hz, 1H), 6.51 (br d, *J* = 7.7 Hz, 1H), 4.9 – 4.74 (m, 2H^), 3.83 (t, *J* = 4.8 Hz, 2H), 3.68 – 3.60 (m, 1H), 3.54 – 3.46 (m, 1H), 3.18 – 3.09 (m, 1H), 3.14 (s, 3H), 3.09 – 3.01 (m, 1H), 2.69 – 2.62 (m, 1H), 2.31 – 2.21 (m, 1H), 2.01 (br s, 3H), 1.78 – 1.69 (m, 2H), 1.63 – 1.52 (m, 2H), 1.33 – 1.25 (m, 1H); 592.3♦
27	**Examples 4** and **5**[3]; **P11**	8.32 (br s, 1H), 8.02 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.73 (br d, *J* = 10.0 Hz, 1H), 7.67 (br d, *J* = 8.0 Hz, 1H), 7.35 (s, 1H), 6.96 – 6.89 (m, 1H), 6.88 – 6.83 (m, 2H), 4.76 (s, 2H), 4.61 (t, *J* = 4.8 Hz, 2H), 3.87 (br d, *J* = 12.3 Hz, 2H), 3.74 (t, *J* = 4.8 Hz, 2H), 3.39 – 3.3 (m, 2H^^), 3.29 (s, 3H), 3.15 – 3.05 (m, 1H), 2.35 – 2.10 (m, 4H); 557.1
28	**Example 11**; **P14**	3.08 minutes[4]; 596
29	**Example 11**; **P14**	3.12 minutes[4]; 556
30	**Example 11**; **P14**	2.90 minutes[4]; 576
31	**Example 11**; **P14**	2.92 minutes[4]; 546
32	**Example 11**; **P14**	2.88 minutes[4]; 558
33	**Example 11**; **P14**	3.04 minutes[4]; 562
34	**Example 11**; **P14**	2.99 minutes[5]; 553
35	**Example 11**; **P14**	2.92 minutes[4]; 576
36	**Example 11**; **P14**	2.81 minutes[5]; 543
37	**Example**	2.90 minutes[4]; 558

	11; P14	
38	**Example 11; P14**	2.91 minutes[4]; 546
39	**Example 11; P14**	2.89 minutes[4]; 558
40	**Example 11; P14**	3.11 minutes[4]; 596
41	**Example 11; P14**	2.97 minutes[4]; 564
42	**Example 11; P14**	2.40 minutes[5]; 543
43	**Example 12; P10**	2.70 minutes[4]; 621
44	**Example 12; P10**	2.49 minutes[4]; 635
45	**Example 12; P10**	2.79 minutes[4]; 613
46	**Example 12; P10**	2.71 minutes[4]; 635
47	**Example 12; P10**	2.85 minutes[4]; 657
48	**Example 12; P10**	2.71 minutes[4]; 633
49	**Example 12; P10**	2.66 minutes[4]; 607
50	**Example 12; P10**	2.43 minutes[4]; 616
51	**Example 12; P10**	2.74 minutes[4]; 630
52	**Example 12; P10**	2.73 minutes[4]; 593
53	**Example 12; P10**	2.79 minutes[4]; 616
54	**Example 12; P10**	2.67 minutes[4]; 631

55	**Example 12; P10**	2.44 minutes[4]; 630
56	**Example 12; P10**	2.77 minutes[4]; 606
57	**Example 12; P10**	2.72 minutes[4]; 617
58	**Example 12; P10**	2.78 minutes[4]; 603
59	**Example 12; P10**	2.82 minutes[4]; 621
60	**Example 12; P10**	2.74 minutes[4]; 631
61	**Example 12; P10**	2.76 minutes[4]; 592
62	**Example 12; P10**	2.45 minutes[4]; 630
63	**Example 12; P10**	2.78 minutes[4]; 617
64	**Example 12; P10**	2.84 minutes[4]; 606
65	**Example 12; P10**	2.56 minutes[4]; 613
66	**Example 12; P10**	2.75 minutes[4]; 607
67	**Example 12; P10**	2.48 minutes[4]; 619
68	**Example 12; P10**	2.75 minutes[4]; 646
69	**Example 12; P10**	2.73 minutes[4]; 603
70	**Example 12; P10**	2.86 minutes[5]; 661
71	**Example 12; P10**	2.77 minutes[4]; 657

72	**Example 12; P10**	2.79 minutes[4]; 606
73	**Example 12; P10**	2.70 minutes[4]; 602
74	**Example 12; P10**	2.45 minutes[4]; 616
75	**Example 13; P10**	2.92 minutes[4]; 566
76	**Example 13; P10**	2.99 minutes[4]; 631
77	**Example 13; P10**	2.94 minutes[4]; 616
78	**Example 13; P10**	3.08 minutes[5]; 617
79	**Example 13; P10**	3.09 minutes[4]; 606
80	**Example 13; P10**	3.02 minutes[4]; 603
81	**Example 13; P10**	3.10 minutes[5]; 604
82	**Example 11; P14**	2.87 minutes[4]; 528
83	**Example 11; P14**	3.00 minutes[4]; 592
84	**Example 11; P14**	2.99 minutes[4]; 542
85	**Example 11; P14**	2.98 minutes[4]; 542
86	**Example 11; P14**	2.97 minutes[4]; 562
87	**Example 11; P14**	2.97 minutes[5]; 553
88	**Example 11; P14**	2.90 minutes[4]; 542

89	**Examples 4** and **5**[6,7]; **P11**	8.63 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 8.34 (dd, *J* = 1.6, 0.7 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.90 (ddd, *J* = 7.8, 7.8, 1.7 Hz, 1H), 7.80 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.74 (ddd, *J* = 7.9, 1.1, 1.0 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 6.88 – 6.83 (m, 1H), 6.83 – 6.76 (m, 2H), 4.83 (s, 2H), 4.63 (t, *J* = 4.8 Hz, 2H), 3.99 – 3.88 (m, 2H), 3.75 (dd, *J* = 5.3, 4.2 Hz, 2H), 3.45 – 3.34 (m, 2H), 3.31 (s, 3H), 3.15 – 3.03 (m, 1H), 2.41 – 2.20 (m, 2H), 2.19 – 2.08 (m, 2H), 2.05 (s, 3H); 529.3
90	**Examples 4** and **5**[6,7]; **P11**	8.63 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 8.34 (dd, *J* = 1.6, 0.7 Hz, 1H), 8.04 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.90 (ddd, *J* = 7.8, 7.8, 1.7 Hz, 1H), 7.80 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.73 (ddd, *J* = 8.0, 1.1, 1.0 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 6.88 – 6.83 (m, 1H), 6.83 – 6.75 (m, 2H), 4.83 (s, 2H), 4.63 (t, *J* = 4.9 Hz, 2H), 3.98 – 3.88 (m, 2H), 3.75 (t, *J* = 4.8 Hz, 2H), 3.44 – 3.34 (m, 2H), 3.32 (s, 3H^^), 3.15 – 3.03 (m, 1H), 2.40 – 2.19 (m, 2H), 2.18 – 2.08 (m, 2H), 2.05 (s, 3H); 529.3
91	**Examples 6** and **7**; **P8**, **P11**	8.59 (d, *J* = 2.4 Hz, 1H), 8.26 (d, *J* = 1.4 Hz, 1H), 7.96 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.87 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.68 – 7.61 (m, 2H), 6.83 – 6.75 (m, 1H), 6.75 – 6.67 (m, 2H), 4.67 (t, *J* = 5.2 Hz, 2H), 4.00 (s, 2H), 3.82 (t, *J* = 5.1 Hz, 2H), 3.29 (s, 3H), 3.13 – 3.05 (m, 2H), 2.81 – 2.70 (m, 1H), 2.45 – 2.34 (m, 2H), 2.01 (s, 3H), 1.98 – 1.77 (m, 4H); 563.3♦
92	**Examples 6** and **7**; **P9**, **P11**	8.59 (d, *J* = 2.3 Hz, 1H), 8.26 (d, *J* = 1.4 Hz, 1H), 7.96 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.87 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.68 – 7.62 (m, 2H), 6.82 – 6.76 (m, 1H), 6.74 – 6.68 (m, 2H), 4.67 (t, *J* = 5.2 Hz, 2H), 4.00 (s, 2H), 3.82 (t, *J* = 5.1 Hz, 2H), 3.29 (s, 3H), 3.13 – 3.04 (m, 2H), 2.76 (tt, *J* = 11.8, 4 Hz, 1H), 2.45 – 2.34 (m, 2H), 2.01 (s, 3H), 1.97 – 1.78 (m, 4H); 563.3♦
93	**Examples 8** and **9**[8]; **P8**, **P11**	8.97 (dd, *J* = 2.1, 0.9 Hz, 1H), 8.27 – 8.25 (m, 1H), 8.21 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.96 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.81 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.64 (d, *J* = 8.6

		Hz, 1H), 6.83 – 6.77 (m, 1H), 6.76 – 6.68 (m, 2H), 4.68 (t, J = 5.2 Hz, 2H), 3.95 (s, 2H), 3.83 (t, J = 5.2 Hz, 2H), 3.30 (s, 3H), 3.08 – 2.99 (m, 2H), 2.79 – 2.69 (m, 1H), 2.39 – 2.28 (m, 2H), 2.04 (s, 3H), 1.96 – 1.76 (m, 4H); 554.4
94	**Examples 8** and **9**[8]; **P9**, **P11**	8.97 (dd, J = 2.2, 0.9 Hz, 1H), 8.26 (br s, 1H), 8.21 (dd, J = 8.2, 2.1 Hz, 1H), 7.96 (dd, J = 8.4, 1.4 Hz, 1H), 7.81 (dd, J = 8.2, 0.9 Hz, 1H), 7.64 (br d, J = 8.5 Hz, 1H), 6.83 – 6.77 (m, 1H), 6.76 – 6.69 (m, 2H), 4.68 (t, J = 5.3 Hz, 2H), 3.95 (s, 2H), 3.83 (t, J = 5.2 Hz, 2H), 3.30 (s, 3H), 3.08 – 2.99 (m, 2H), 2.79 – 2.69 (m, 1H), 2.39 – 2.28 (m, 2H), 2.04 (s, 3H), 1.96 – 1.76 (m, 4H); 554.4
95	**Example 10**; **P8**, **P15**	8.61 (dd, J = 2.5, 0.7 Hz, 1H), 8.41 (s, 1H), 8.33 (dd, J = 1.6, 0.7 Hz, 1H), 7.97 (dd, J = 8.5, 1.5 Hz, 1H), 7.88 (dd, J = 8.5, 2.5 Hz, 1H), 7.66 (dd, J = 8.5, 0.6 Hz, 1H), 7.65 (dd, J = 8.5, 0.7 Hz, 1H), 6.82 – 6.77 (m, 1H), 6.76 – 6.69 (m, 2H), 5.32 – 5.24 (m, 1H), 4.9 – 4.83 (m, 1H^), 4.71 (dd, J = 15.4, 2.6 Hz, 1H), 4.65 – 4.58 (m, 1H), 4.48 (ddd, J = 9.2, 6.0, 5.9 Hz, 1H), 4.03 (AB quartet, J_{AB} = 13.9 Hz, $\Delta\nu_{AB}$ = 49.7 Hz, 2H), 3.18 – 3.11 (m, 1H), 3.06 – 2.98 (m, 1H), 2.87 – 2.69 (m, 2H), 2.60 – 2.49 (m, 1H), 2.46 – 2.31 (m, 2H), 2.02 (s, 3H), 1.98 – 1.79 (m, 4H); 574.9♦
96	**Examples 6** and **7**[9,10]; **P15**	7.01 minutes[11]; 610.5♦
97	**Examples 6** and **7**[9,10]; **P15**	7.89 minutes[11]; 610.5♦
98	**C54**[12]	8.25 – 8.23 (m, 1H), 8.00 (dd, J = 8.5, 1.5 Hz, 1H), 7.89 (d, J = 0.9 Hz, 1H), 7.76 (dd, J = 7.9, 7.6 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.64 (dd, J = 10.6, 1.5 Hz, 1H), 7.57 (dd, J = 8.0, 1.5 Hz, 1H), 7.14 (d, J = 0.9 Hz, 1H), 6.78 (dd, component of ABC pattern, J = 7.9, 7.8 Hz, 1H), 6.70 (dd, component of ABC pattern, J = 7.8,

		1.2 Hz, 1H), 6.66 (br d, component of ABC pattern, J = 7.9 Hz, 1H), 5.94 (AB quartet, J_{AB} = 17.2 Hz, $\Delta\nu_{AB}$ = 6.5 Hz, 2H), 3.96 (s, 2H), 3.02 – 2.92 (m, 2H), 2.74 – 2.63 (m, 1H), 2.31 – 2.21 (m, 2H), 2.05 (br s, 3H), 1.80 – 1.58 (m, 4H); 594.3
99	**C54**[12]	8.23 (d, J = 1.4 Hz, 1H), 8.00 (dd, J = 8.5, 1.5 Hz, 1H), 7.89 (d, J = 0.9 Hz, 1H), 7.76 (dd, J = 7.9, 7.6 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.64 (dd, J = 10.6, 1.5 Hz, 1H), 7.57 (dd, J = 8.1, 1.5 Hz, 1H), 7.14 (d, J = 0.9 Hz, 1H), 6.78 (dd, component of ABC pattern, J = 7.8, 7.8 Hz, 1H), 6.70 (dd, component of ABC pattern, J = 7.8, 1.2 Hz, 1H), 6.66 (br d, component of ABC pattern, J = 7.9 Hz, 1H), 5.94 (AB quartet, J_{AB} = 17.1 Hz, $\Delta\nu_{AB}$ = 6.6 Hz, 2H), 3.96 (s, 2H), 3.01 – 2.92 (m, 2H), 2.74 – 2.63 (m, 1H), 2.30 – 2.20 (m, 2H), 2.05 (br s, 3H), 1.80 – 1.58 (m, 4H); 594.3
100	**Example 7, free acid**[13]**; P3, C29**	characteristic peaks: 7.80 (dd, J = 8.5, 6.6 Hz, 1H), 7.59 (dd, J = 8.3, 8.3 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.28 (dd, J = 10.9, 2.0 Hz, 1H), 7.21 (br dd, J = 8.4, 2.0 Hz, 1H), 6.83 – 6.77 (m, 1H), 6.76 – 6.71 (m, 2H), 5.32 – 5.23 (m, 1H), 4.99 (dd, J = 15.5, 7.1 Hz, 1H), 4.79 (dd, J = 15.6, 2.8 Hz, 1H), 4.72 – 4.63 (m, 1H), 4.47 (ddd, J = 9.1, 6.0, 6.0 Hz, 1H), 4.31 (AB quartet, J_{AB} = 14.4 Hz, $\Delta\nu_{AB}$ = 33.3 Hz, 2H), 3.40 (br d, J = 11.9 Hz, 1H), 2.92 – 2.65 (m, 4H), 2.82 (AB quartet, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 37.5 Hz, 2H), 2.61 – 2.49 (m, 1H), 2.13 – 1.87 (m, 4H), 2.04 (s, 3H); 610.0♦
101	**Example 5, free acid**[13]**; C48, C29**	characteristic peaks: 7.79 (dd, J = 8.5, 6.6 Hz, 1H), 7.57 (dd, J = 8.0, 8.0 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.35 (dd, J = 10.2, 1.9 Hz, 1H), 7.30 (br d, J = 8.4 Hz, 1H), 7.22 (s, 1H), 6.88 – 6.82 (m, 1H), 6.82 – 6.74 (m, 2H), 5.30 – 5.21 (m, 1H), 4.95 (dd, J = 15.4, 7.1 Hz, 1H), 4.77 (br d, J = 15.1 Hz, 1H), 4.67 – 4.59 (m, 1H), 4.44 (ddd, J = 9.1, 5.9, 5.9 Hz, 1H), 4.28 (AB quartet, J_{AB} = 14.4 Hz, $\Delta\nu_{AB}$ = 31.7 Hz, 2H), 3.37 (br d, J = 12.3 Hz, 1H^^), 2.92 – 2.61 (m, 4H), 2.82 (AB quartet, J_{AB} =

		15.6 Hz, $\Delta\nu_{AB}$ = 37.1 Hz, 2H), 2.58 – 2.47 (m, 1H), 2.12 – 1.89 (m, 4H); 596.1♦
102	**Examples 4 and 5**[14]; **P11**	8.34 (dd, *J* = 1.6, 0.7 Hz, 1H), 8.04 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.80 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.46 – 7.36 (m, 3H), 6.84 – 6.76 (m, 2H), 6.74 (dd, *J* = 7.2, 2.0 Hz, 1H), 4.84 (s, 2H), 4.63 (t, *J* = 4.7 Hz, 2H), 4.01 – 3.91 (m, 4H), 3.76 (dd, *J* = 5.3, 4.2 Hz, 2H), 3.47 – 3.37 (m, 2H), 3.32 (s, 3H), 3.19 – 3.08 (m, 1H), 2.41 – 2.26 (m, 2H), 2.26 – 2.13 (m, 2H); 544.2

^area is assumed, peak is partially obscured by water peak

^^area is assumed, peak is partially obscured by solvent peak

♦chlorine isotope pattern observed

1. The racemic methyl ester [methyl 2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate] was separated into its component enantiomers via SFC [Column: Chiral Technologies ChiralCel OD-H, 5 µm; Mobile phase: 7:3 carbon dioxide / (2-propanol containing 0.1% ammonium hydroxide)]. The first-eluting enantiomer, ENT-1 (**C76**), was used in the synthesis of **Example 21**, and the second-eluting enantiomer, ENT-2 (**C77**), was converted to **Example 20**. **C76** retention time: 5.72 minutes (Column: Chiral Technologies Chiralpak OD-3, 4.6 x 150 mm, 3 µm; Mobile phase A: carbon dioxide; Mobile phase B: 2-propanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 5.5 minutes, then held at 40% B for 3.0 minutes; Flow rate: 2.5 mL/minute). **C77** retention time: 6.01 minutes (Analytical SFC conditions identical to those used for **C76**).

2. The methyl ester (methyl 2-{6-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]-6-azaspiro[2.5]oct-1-yl}-1-(2-methoxyethyl)-1*H*-benzimidazole-6-carboxylate) derived from coupling of **C4** and **P17** was separated into its component stereoisomers at the dioxolane via SFC [Column: Chiral Technologies Chiralpak AD, 10 µm; Mobile phase: 65:35 carbon dioxide / (ethanol containing 0.1% ammonium hydroxide)]. The first-eluting isomer, DIAST-1 (**C78**), was converted to **Example 26**; by examination of ^{1}H NMR data, this material was the enantiomer of **Example 15**. The second-eluting isomer, DIAST-2 (**C79**), was used in the synthesis of **Example 25**; by examination of ^{1}H NMR data, this material was the enantiomer of **Example 16**. **C78** retention time: 3.60 minutes (Column: Chiral Technologies Chiralpak AD-3, 4.6 x 100 mm, 3 µm; Mobile phase A: carbon dioxide; Mobile phase B: ethanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 4.5 minutes, then held at 40% B for 2.5 minutes; Flow rate: 2.8 mL/minute). **C79** retention time: 3.82 minutes (Analytical SFC conditions identical to those used for **C78**).

3. 4-(4-Bromo-1,3-benzodioxol-2-yl)-3-fluorobenzonitrile was prepared via treatment of 3-fluoro-4-formylbenzonitrile and 3-bromobenzene-1,2-diol with *p*-toluenesulfonic acid in toluene, with removal of water using a Dean-Stark apparatus. This material was then reacted with [1-(*tert*-butoxycarbonyl)piperidin-4-yl](iodo)zinc in the presence of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and copper(i) iodide, followed by ester cleavage using *p*-toluenesulfonic acid, to afford the requisite 3-fluoro-4-[4-(piperidin-4-yl)-1,3-benzodioxol-2-yl]benzonitrile.

4. Conditions for analytical HPLC. Column: Waters XBridge C18, 2.1 x 50 mm, 5 µm; Mobile phase A: 0.0375% trifluoroacetic acid in water; Mobile phase B: 0.01875% trifluoroacetic acid in acetonitrile; Gradient: 10% to 100% B over 4.0 minutes; Flow rate: 0.8 mL/minute.

5. Conditions for analytical HPLC. Column: Waters XBridge C18, 2.1 x 50 mm, 5 µm; Mobile phase A: 0.0375% trifluoroacetic acid in water; Mobile phase B: 0.01875% trifluoroacetic acid in acetonitrile; Gradient: 1% to 5% B over 0.6 minutes; 5% to 100% B over 3.4 minutes; Flow rate: 0.8 mL/minute.

6. *tert*-Butyl 4-[2-methyl-2-(pyridin-2-yl)-1,3-benzodioxol-4-yl]-3,6-dihydropyridine-1(2*H*)-carboxylate was synthesized from 3-bromobenzene-1,2-diol and 2-ethynylpyridine using the procedure described for synthesis of **C12** in **Preparation P7**. Subsequent hydrogenation over palladium on carbon, followed by treatment with hydrogen chloride in ethyl acetate, afforded the requisite 2-[2-methyl-4-(piperidin-4-yl)-1,3-benzodioxol-2-yl]pyridine, hydrochloride salt.

7. The racemic methyl ester [methyl 1-(2-methoxyethyl)-2-({4-[2-methyl-2-(pyridin-2-yl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1*H*-benzimidazole-6-carboxylate] was separated into its component enantiomers via SFC [Column: Chiral Technologies Chiralpak AD, 10 µm; Mobile phase: 65:35 carbon dioxide / (ethanol containing 0.1% ammonium hydroxide)]. The first-eluting enantiomer ENT-1 (**C80**) was used in the synthesis of **Example 90**, and the second-eluting enantiomer ENT-2 (**C81**) was converted to **Example 89**. **C80** retention time: 4.11 minutes (Column: Chiral Technologies Chiralpak AD-3, 4.6 x 100 mm, 3 µm; Mobile phase A: carbon dioxide; Mobile phase B: ethanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 4.5 minutes, then held at 40% B for 2.5 minutes; Flow rate: 2.8 mL/minute). **C81** retention time: 4.62 minutes (Analytical SFC conditions identical to those used for **C80**).

8. Conversion of **P8** and **P9** to the corresponding cyano-substituted derivatives was carried out using the method described for synthesis of **P4** from **P2** in **Preparation P4**.

9. Treatment of 1-(4-chloro-2-fluorophenyl)ethanone with trimethyl orthoformate and *p*-toluenesulfonic acid provided 4-chloro-1-(1,1-dimethoxyethyl)-2-fluorobenzene, which was reacted with 3-bromo-6-fluorobenzene-1,2-diol in the presence of *p*-toluenesulfonic acid to afford 4-bromo-2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxole. This material was converted to the requisite *tert*-butyl 4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-

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CLAIMS:

1. A combination comprising (1) a GLP-1R agonist, and (2) 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof, wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

2. A combination comprising (1) a GLP-1R agonist and (2) 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof, for use in a therapeutically effective amount for treating a disease or condition in a patient in need thereof, wherein:

the disease or condition is selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, obesity, and type 2 diabetes; and

the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

3. A combination comprising (1) a GLP-1R agonist and (2) 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or a pharmaceutically acceptable salt thereof, for use in a therapeutically effective amount for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity, or reducing the

medical consequences of nonalcoholic steatohepatitis in a patient, wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

4. The combination of claim 2, wherein the disease or condition is fatty liver.

5. The combination of claim 2, wherein the disease or condition is nonalcoholic fatty liver disease.

6. The combination of claim 2, wherein the disease or condition is nonalcoholic steatohepatitis.

7. The combination of claim 2, wherein the disease or condition is nonalcoholic steatohepatitis with liver fibrosis.

8. The combination of claim 2, wherein the disease or condition is nonalcoholic steatohepotitis with cirrhosis.

9. The combination of claim 2, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma.

10. The combination of claim 2, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with a metabolic-related disease.

11. The combination of any one of Claims 1 to 10, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

12. The combination of Claim 11, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

13. The combination of Claim 12, wherein the pharmaceutically acceptable salt is a tris salt.

14. The combination of any one of Claims 1 to 10, wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

15. The combination of Claim 14, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

16. The combination of Claim 15, wherein the pharmaceutically acceptable salt is a tris salt.

17. The combination of any one of Claims 1 to 16, wherein the 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or pharmaceutically acceptable salt thereof is 2-amino-2-(hydroxymethyl)propane-1,3-diol salt of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid.

18. The combination of Claim 17, wherein the 2-amino-2-(hydroxymethyl)propane-1,3-diol salt of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid is a crystal form.

19. The combination of Claim 18, wherein the ratio of 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and 2-amino-2-(hydroxymethyl)propane-1,3-diol in the crystal form is 1:1.

20. The combination of Claim 18 or 19, wherein the crystal form is an anhydrous crystal form.

21. The combination of Claim 20, wherein the anhydrous crystal form has a PXRD pattern comprising peaks at diffraction angles of 9.6, 10.7, and 11.3 2Θ, ± 0.2° 2Θ.

22. The combination of Claim 20 or 21, wherein the anhydrous crystal form has a Raman spectrum comprising peak shifts at 1511, 1561, and 1615 cm^{-1}, ± 2 cm^{-1}.

23. The combination of any one of Claims 20 to 22 wherein the anhydrous crystal form has a ^{13}C ssNMR spectrum comprising chemical shifts at 22.9, 146.2, and 161.9 ppm, ± 0.2 ppm.

24. The combination of Claim 23, wherein the anhydrous crystal form has an analytical parameter selected from the group consisting of a Raman spectrum comprising peak shifts at 1511 and 1615 cm^{-1}, ± 2 cm^{-1}, and a ^{13}C ssNMR spectrum comprising at least one chemical shift at 22.9, 146.2, or 161.9 ppm, ± 0.2 ppm.

25. The combination of claim 18 or 19, wherein the crystal form is a trihydrate crystal form.

26. The combination of Claim 25, wherein the trihydrate crystal form has a PXRD pattern comprising peaks at diffraction angles of 8.4, 9.0, and 10.5 2Θ, ± 0.2° 2Θ.

27. The combination of Claim 25 or 26, wherein the trihydrate crystal form has a Raman spectrum comprising peak shifts at 1507, 1557, and 1610 cm^{-1}, ± 2 cm^{-1}.

28. The combination of any one of claims 25 to 27, wherein the trihydrate crystal form has a ^{13}C ssNMR spectrum comprising chemical shifts at 19.2, 149.5, and 163.8 ppm, ± 0.2 ppm.

29. The combination of claim 28, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of

a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ,
a Raman spectrum comprising peak shifts at 1557 and 1610 cm^{-1}, ± 2 cm^{-1}, and
a ^{13}C ssNMR spectrum comprising at least one chemical shift at 19.2, 149.5, or 163.8 ppm, ± 0.2 ppm.

30. The combination of Claim 28, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ, and a Raman spectrum comprising at least one peak shift at 1507, 1557, or 1610 cm^{-1}, ± 2 cm^{-1}.

31. The combination of Claim 28, wherein the trihydrate crystal form has an analytical parameter selected from the group consisting of a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ, ± 0.2° 2Θ, and a ^{13}C ssNMR spectrum comprising at least one chemical shift at 19.2, 149.5, or 163.8 ppm, ± 0.2 ppm.

32. The combination of any one of Claims 2 to 31, wherein the GLP-1R agonist and the 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or salt thereof, are for administration simultaneously.

33. The combination of Claims 32, wherein the GLP-1R agonist and the 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or salt thereof are present in a same pharmaceutically composition, or wherein each of the GLP-1R agonist and the 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or salt thereof is present in a separate pharmaceutically composition, and wherein each of the compositions independently further comprises a pharmaceutically acceptable excipient.

34. The combination of any one of Claims 2 to 31, the GLP-1R agonist and the 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-

2-yl)benzoic acid or salt thereof are for administration sequentially and in any order, wherein each of the GLP-1R agonist and the 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid or salt thereof is present in a separate pharmaceutically composition, and wherein each of the compositions independently further comprises a pharmaceutically acceptable excipient.

35. The combination of any one of Claims 1 and 11 to 31, wherein the composition further comprises at least one other pharmaceutical agent.

36. The combination of any one of Claims 2 to 34, for use with at least one other pharmaceutical agent.

37. The combination of Claim 35 or Claim 36, wherein the at least one other pharmaceutical agent is selected from the group consisting of an acetyl-CoA carboxylase-(ACC) inhibitor, a diacylglycerol *O*-acyltransferase 1 (DGAT-1) inhibitor, monoacylglycerol O-acyltransferase inhibitors, a phosphodiesterase (PDE)-10 inhibitor, an AMPK activator, a sulfonylurea, a meglitinide, an α-amylase inhibitor, an α-glucoside hydrolase inhibitor, an α-glucosidase inhibitor, a PPARγ agonist, a PPAR α/γ agonist, a biguanide, a glucagon-like peptide 1 (GLP-1) modulator, liraglutide, albiglutide, exenatide, albiglutide, lixisenatide, dulaglutide, semaglutide, a protein tyrosine phosphatase-1B (PTP-1B) inhibitor, SIRT-1 activator, a dipeptidyl peptidease IV (DPP-IV) inhibitor, an insulin secreatagogue, a fatty acid oxidation inhibitor, an A2 antagonist, a c-jun amino-terminal kinase (JNK) inhibitor, glucokinase activators (GKa), insulin, an insulin mimetic, a glycogen phosphorylase inhibitor, a VPAC2 receptor agonist, SGLT2 inhibitors, a glucagon receptor modulator, GPR119 modulators, FGF21 derivatives or analogs, TGR5 receptor modulators, GPBAR1 receptor modulators, GPR40 agonists, GPR120 modulators, high affinity nicotinic acid receptor (HM74A) activators, SGLT1 inhibitors, inhibitors or modulators of carnitine palmitoyl transferase enzymes, inhibitors of fructose 1,6-diphosphatase, inhibitors of aldose reductase, mineralocorticoid receptor inhibitors, inhibitors of TORC2, inhibitors of CCR2 and/or CCR5, inhibitors of PKC isoforms, inhibitors of fatty acid synthetase, inhibitors of serine palmitoyl transferase, modulators of GPR81, GPR39, GPR43, GPR41, GPR105, Kv1.3, retinol binding protein 4, glucocorticoid receptor, somatostain receptors, inhibitors or modulators of PDHK2 or PDHK4, inhibitors of MAP4K4, modulators of IL1 family including IL1beta, HMG-CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, choesterol absorption inhibitors, PCSK9 modulators, cholesteryl ester transfer protein inhibitors and modulators of RXRalpha.

38. The combination of Claim 35 or Claim 36, wherein the at least one other pharmaceutical agent is selected from the group consisting of cysteamine or a pharmaceutically acceptable salt thereof, cystamine or a pharmaceutically acceptable salt thereof, an anti-oxidant compound, lecithin, vitamin B complex, a bile salt preparations, an antagonists of Cannabinoid-1 (CB1) receptor, an inverse agonists of Cannabinoid-1 (CB1) receptor, a peroxisome proliferator-activated receptor activity regulators, a benzothiazepine or benzothiepine compound, an RNA antisense construct to inhibit protein tyrosine phosphatase PTPRU, a heteroatom-linked substituted piperidine and derivatives thereof, an azacyclopentane derivative capable of inhibiting stearoyl-coenzyme alpha delta-9 desaturase, acylamide compound having secretagogue or inducer activity of adiponectin, a quaternary ammonium compound, Glatiramer acetate, pentraxin proteins, a HMG-CoA reductase inhibitor, n-acetyl cysteine, isoflavone compound, a macrolide antibiotic, a galectin inhibitor, an antibody, or any combination of thereof.

39. A combination comprising (1) a GLP-1R agonist and (2) [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof, wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

40. A combination comprising (1) GLP-1R agonist and (2) [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof, for use in a therapeutically effective amount for treating a disease or condition a patient in need thereof, wherein:

the disease or condition is selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, obesity, and type 2 diabetes; and

the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,
or pharmaceutically acceptable salt thereof.

41. A combination comprising (1) a GLP-1R agonist and (2) [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or a pharmaceutically acceptable salt thereof, for use in a therapeutically effective amount for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity, or reducing the medical consequences of nonalcoholic steatohepatitis in a patient, wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

42. The combination of claim 40, wherein the disease or condition is fatty liver.

43. The combination of claim 40, wherein the disease or condition is nonalcoholic fatty liver disease.

44. The combination of claim 40, wherein the disease or condition is nonalcoholic steatohepatitis.

45. The combination of claim 40, wherein the disease or condition is nonalcoholic steatohepatitis with liver fibrosis.

46. The combination of claim 40, wherein the disease or condition is nonalcoholic steatohepotitis with cirrhosis.

47. The combination of claim 40, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma.

48. The combination of claim 40, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with a metabolic-related disease.

49. The combination of any one of Claims 39 to 48, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

50. The combination of Claim 49, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

51. The combination of Claim 50, wherein the pharmaceutically acceptable salt is a tris salt.

52. The combination of any one of Claims 39 to 48, wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,
or a pharmaceutically acceptable salt thereof.

53. The combination of Claim 52, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

54. The combination of Claim 53, wherein the pharmaceutically acceptable salt is a tris salt.

55. The combination of any one of Claims 39 to 54 wherein the [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid or salt thereof is a crystal form of [(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid.

56. A combination comprising (1) GLP-1R agonist and (2) (S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof, wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

57. A combination comprising (1) a GLP-1R agonist and (2) (S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof, for use in a therapeutically effective amount for treating a disease or condition in a patient in need thereof, wherein:

the disease or condition is selected from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, obesity, and type 2 diabetes; and

the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

58. A combination comprising (1) GLP-1R agonist and (2) (S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or a pharmaceutically acceptable salt thereof, for use in a therapeutically effective amount for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity, or reducing the medical consequences of nonalcoholic steatohepatitis in a patient, wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,

or pharmaceutically acceptable salt thereof.

59. The combination of claim 58, wherein the disease or condition is fatty liver.

60. The combination of claim 58, wherein the disease or condition is nonalcoholic fatty liver disease.

61. The combination of claim 58, wherein the disease or condition is nonalcoholic steatohepatitis.

62. The combination of claim 58, wherein the disease or condition is nonalcoholic steatohepatitis with liver fibrosis.

63. The combination of claim 58, wherein the disease or condition is nonalcoholic steatohepotitis with cirrhosis.

64. The combination of claim 58, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma.

65. The combination of claim 58, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with a metabolic-related disease.

66. The combination of any one of Claims 56 to 65, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

67. The combination of Claim 66, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

68. The combination of Claim 67, wherein the pharmaceutically acceptable salt is a tris salt.

69. The combination of any one of Claims 56 to 65, wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

70. The combination of Claim 69, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

71. The combination of Claim 70, wherein the pharmaceutically acceptable salt is a tris salt.

72. The combination of any one of Claims 56 to 71 wherein the (S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide or salt thereof is a crystal form of (S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide.

73. A combination comprising (1) a GLP-1R agonist and (2) 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof, , wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,
or pharmaceutically acceptable salt thereof.

74. A combination comprising (1) GLP-1R agonist and (2) 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof, for use in a therapeutically effective amount for treating a disease or condition in a patient in need thereof, wherein:

the disease or condition selected is from fatty liver, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, nonalcoholic steatohepatitis with liver fibrosis, nonalcoholic steatohepotitis with cirrhosis, and nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma or with a metabolic-related disease, obesity, and type 2 diabetes; and

the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,
or pharmaceutically acceptable salt thereof.

75. A combination comprising (1) a GLP-1R agonist and (2) 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or a pharmaceutically acceptable salt thereof, for use in a therapeutically effective amount for reducing at least one point in severity of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis grading scoring systems, reducing the level of serum markers of nonalcoholic steatohepatitis activity, reducing nonalcoholic steatohepatitis disease activity, or reducing the medical consequences of nonalcoholic steatohepatitis in a patient, wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2; and

2-[(4-{6-[(4-Cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid,
or pharmaceutically acceptable salt thereof.

76. The combination of claim 74, wherein the disease or condition is fatty liver.

77. The combination of claim 74, wherein the disease or condition is nonalcoholic fatty liver disease.

78. The combination of claim 74, wherein the disease or condition is nonalcoholic steatohepatitis.

79. The combination of claim 74, wherein the disease or condition is nonalcoholic steatohepatitis with liver fibrosis.

80. The combination of claim 74, wherein the disease or condition is nonalcoholic steatohepotitis with cirrhosis.

81. The combination of claim 74, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with hepatocellular carcinoma.

82. The combination of claim 74, wherein the disease or condition is nonalcoholic steatohepatitis with cirrhosis and with a metabolic-related disease.

83. The combination of any one of Claims 73 to 82, wherein the GLP-1R agonist is 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof.

84. The combination of Claim 83, wherein the GLP-1R agonist is a pharmaceutically acceptable salt of 2-[(4-{6-[(4-cyano-2-fluorobenzyl)oxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid.

85. The combination of Claim 84, wherein the pharmaceutically acceptable salt is a tris salt.

86. The combination of any one of Claims 73 to 82, wherein the GLP-1R agonist is selected from:

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-4-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(pyridin-3-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-5-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1*H*-1,2,3-triazol-5-yl)methyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-7-fluoro-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2*S*)-oxetan-2-ylmethyl]-1*H*-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-(1,3-oxazol-2-ylmethyl)-1*H*-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-7-fluoro-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

87. The combination of Claim 86, wherein the GLP-1R agonist is selected from:

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[2-(4-Chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-3-(1,3-oxazol-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid;

2-({4-[2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6- carboxylic acid;

2-({4-[(2S)-2-(4-chloro-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(4-Cyano-2-fluorophenyl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid;

2-({4-[(2R)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid; and

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2,

or a pharmaceutically acceptable salt thereof.

88. The combination of Claim 87, wherein the pharmaceutically acceptable salt is a tris salt.

89. The combination of any one of Claims 56 to 71 wherein the 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid or salt thereof is 2-[(1R,3R,5S)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy)phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid.

FIG. 1

PXRD pattern of crystalline Form 1 of Example DGAT2i Compound

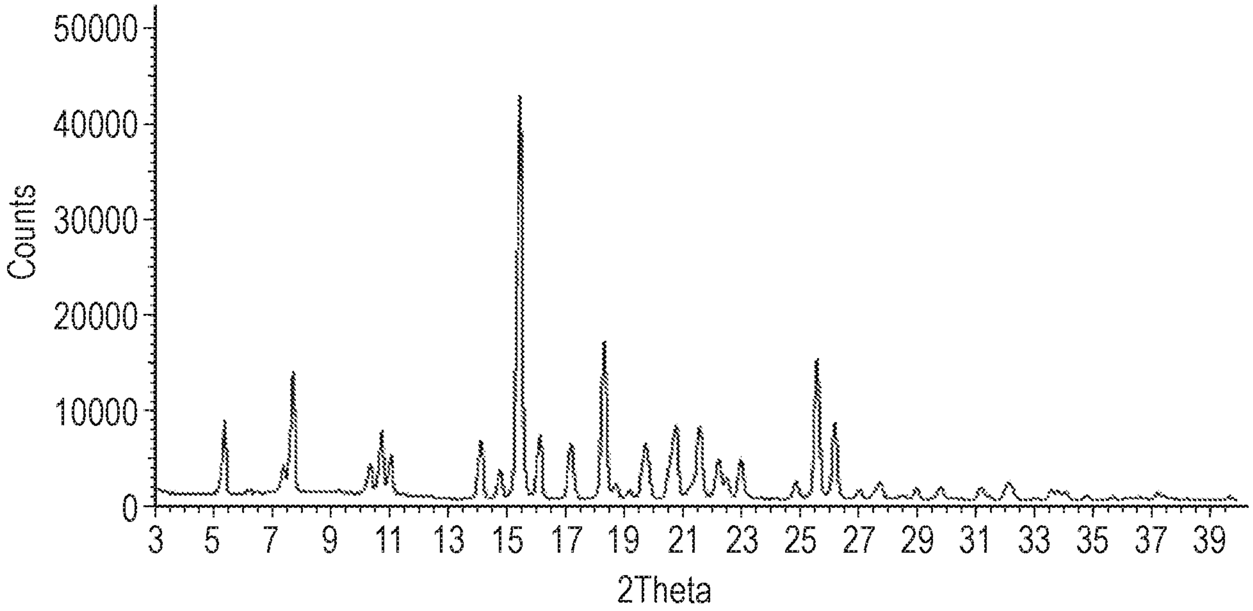


FIG. 2

PXRD pattern of crystalline Form 2 of Example DGAT2i Compound

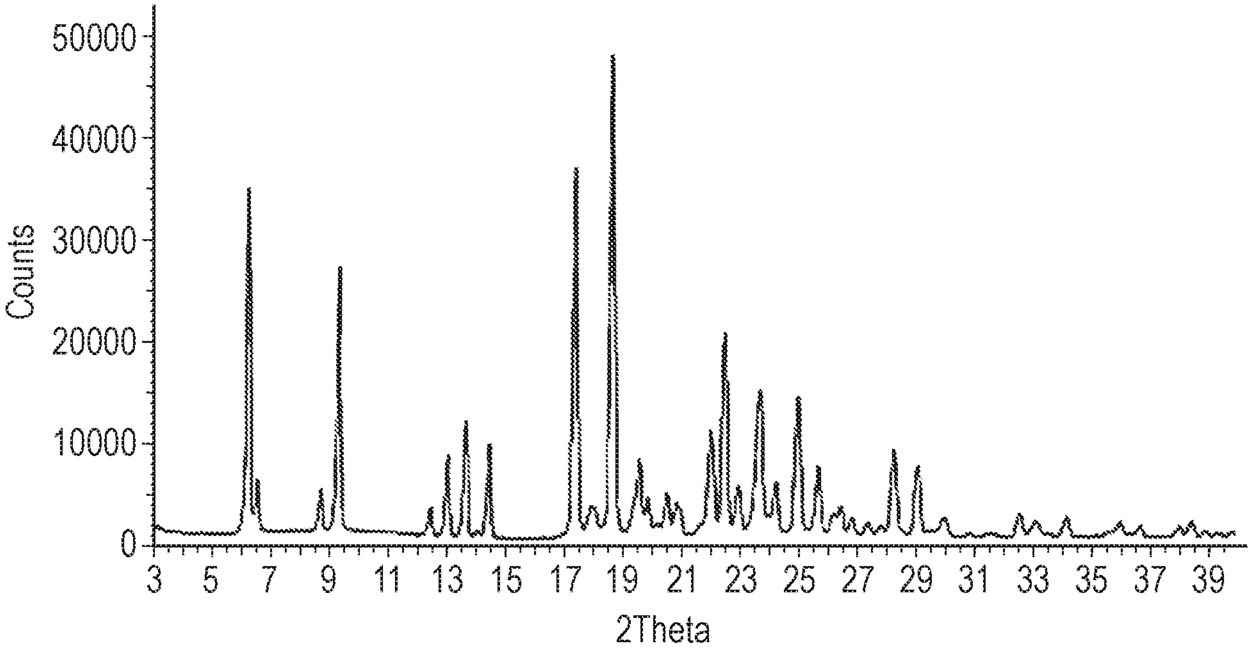


FIG. 3

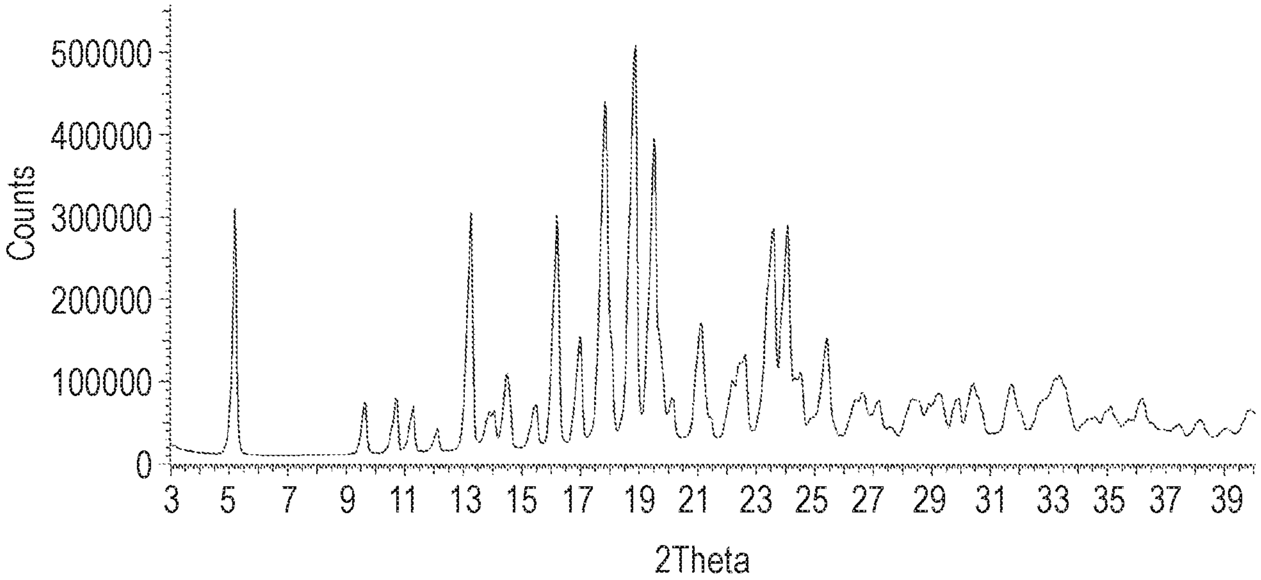

500000
400000
300000
200000
100000
0
Counts
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
2Theta

FIG. 4

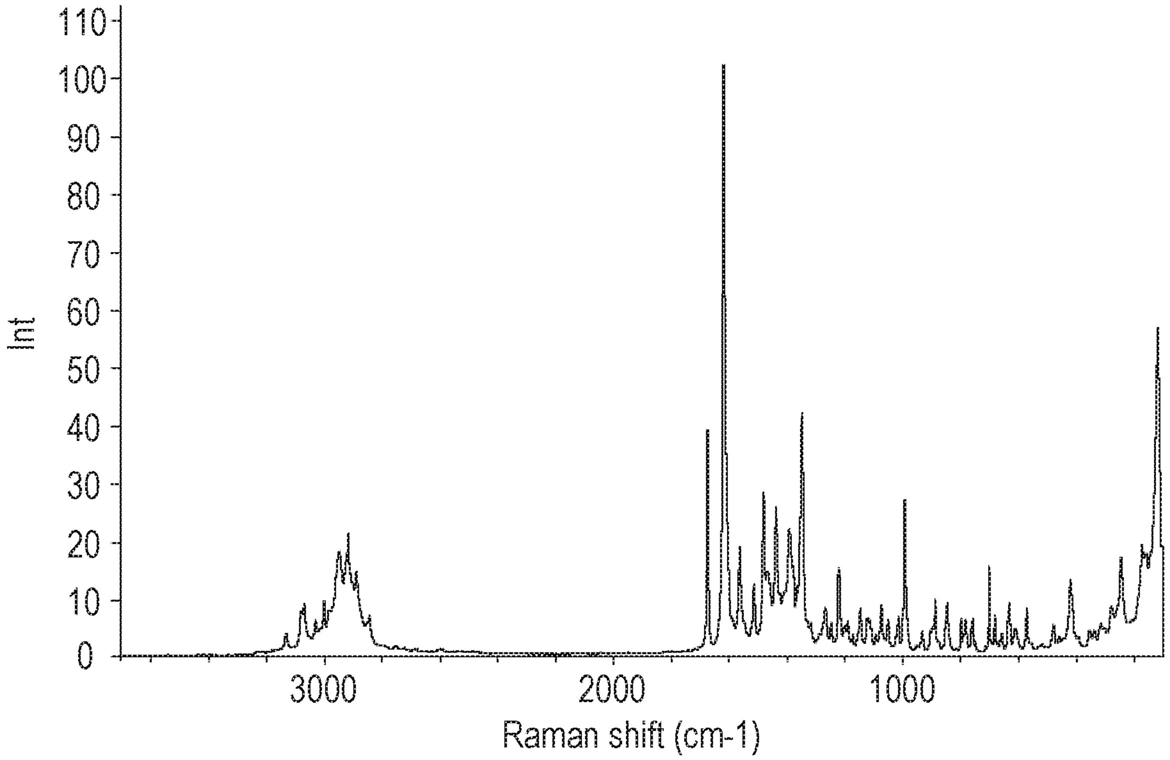

110
100
90
80
70
60
50
40
30
20
10
0
Int
3000
2000
1000
Raman shift (cm-1)

FIG. 5

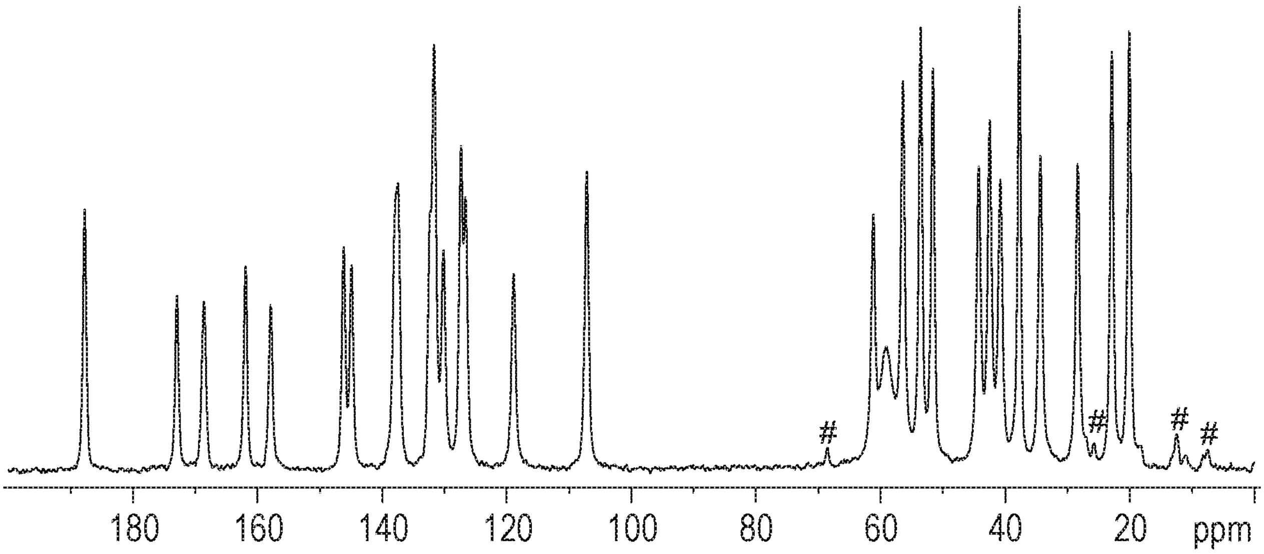


FIG. 6

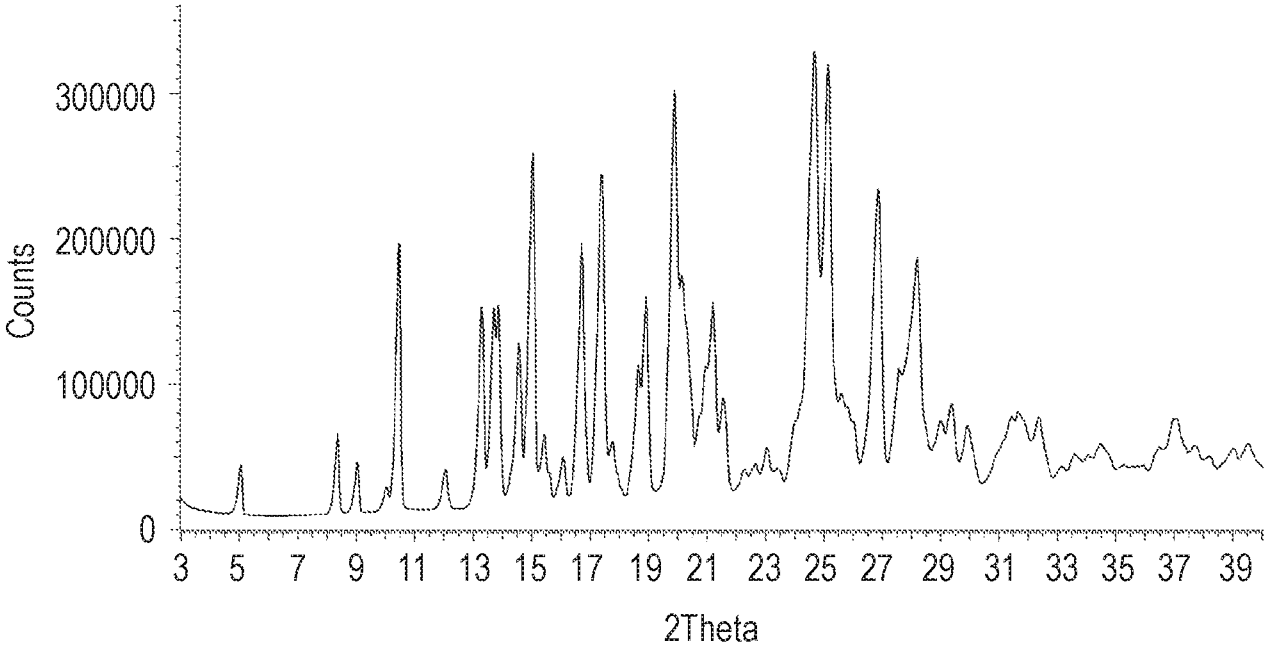

Counts
300000
200000
100000
0
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
2Theta

FIG. 7

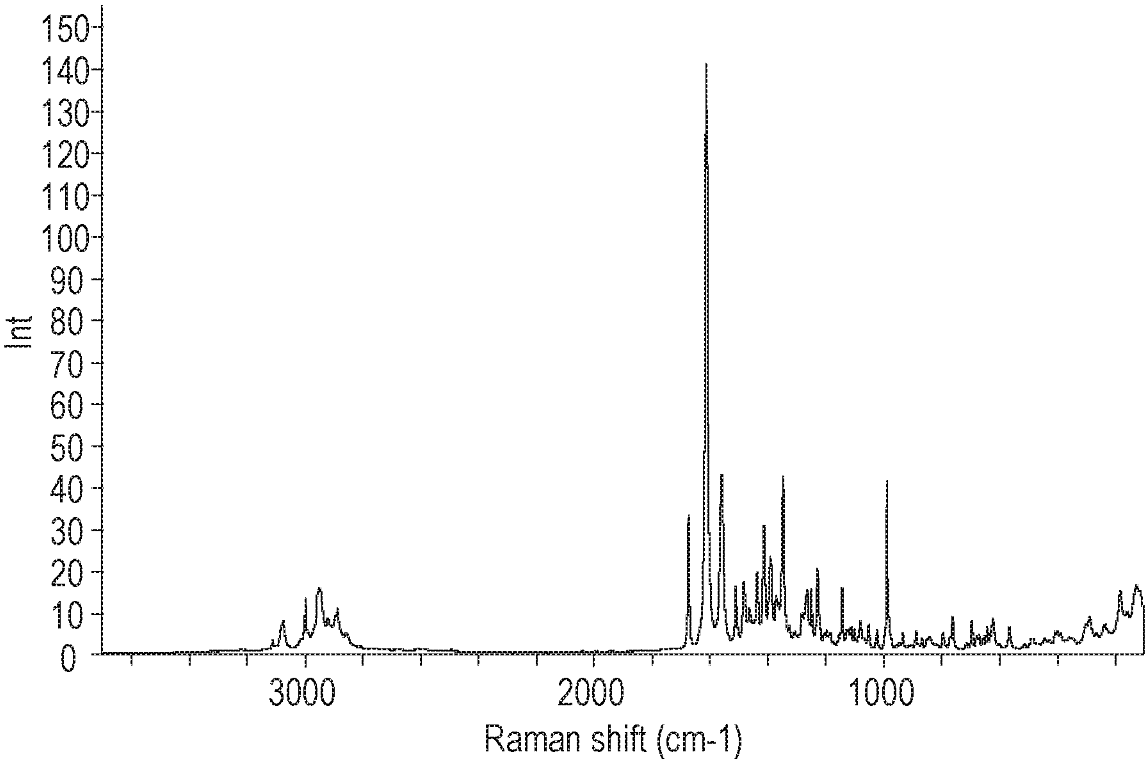

Int
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
3000
2000
1000
Raman shift (cm-1)

FIG. 8

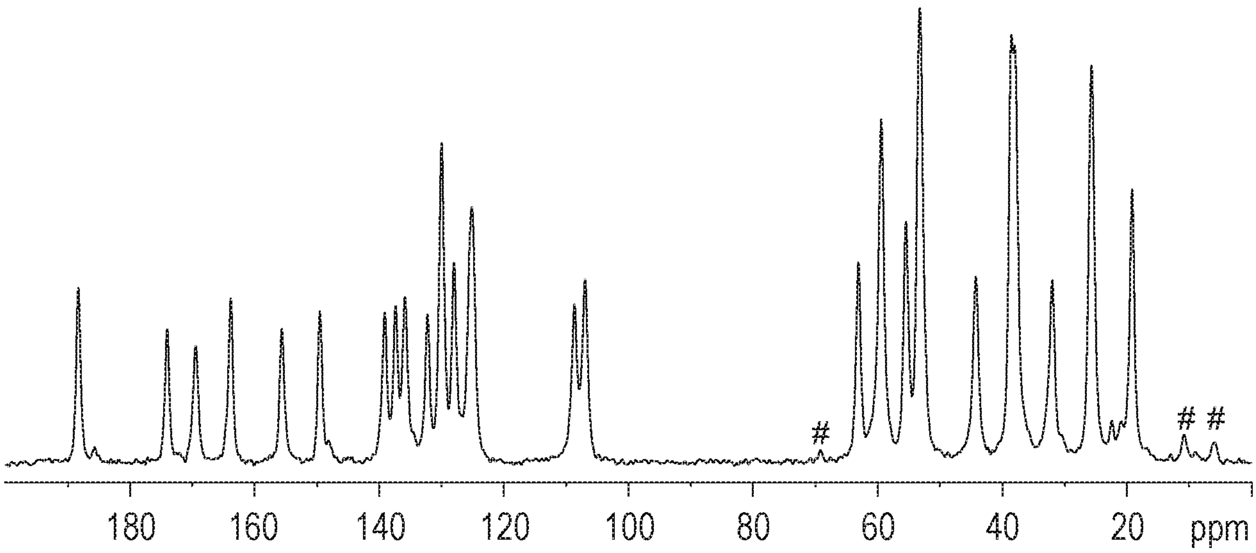


FIG. 9

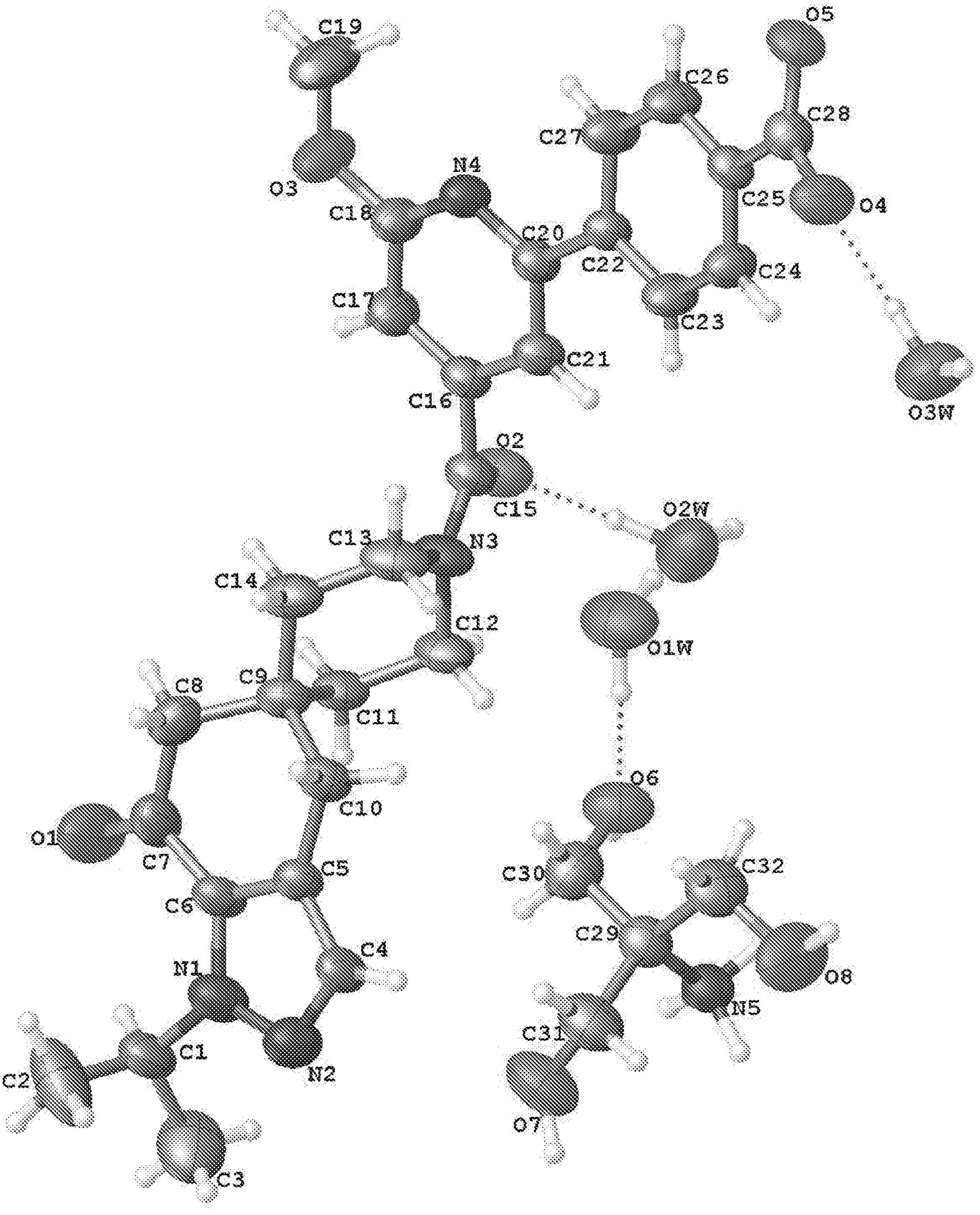

C19
O5
C26
C28
C27
N4
O3
C18
C25
O4
C20
C22
C24
C17
C23
C21
O3W
C16
O2
C15
O2W
C13
N3
C14
C12
O1W
C8
C9
C11
C10
O6
O1
C7
C5
C30
C32
C6
C29
C4
O8
N1
N5
C31
C1
C2
N2
O7
C3

FIG. 10

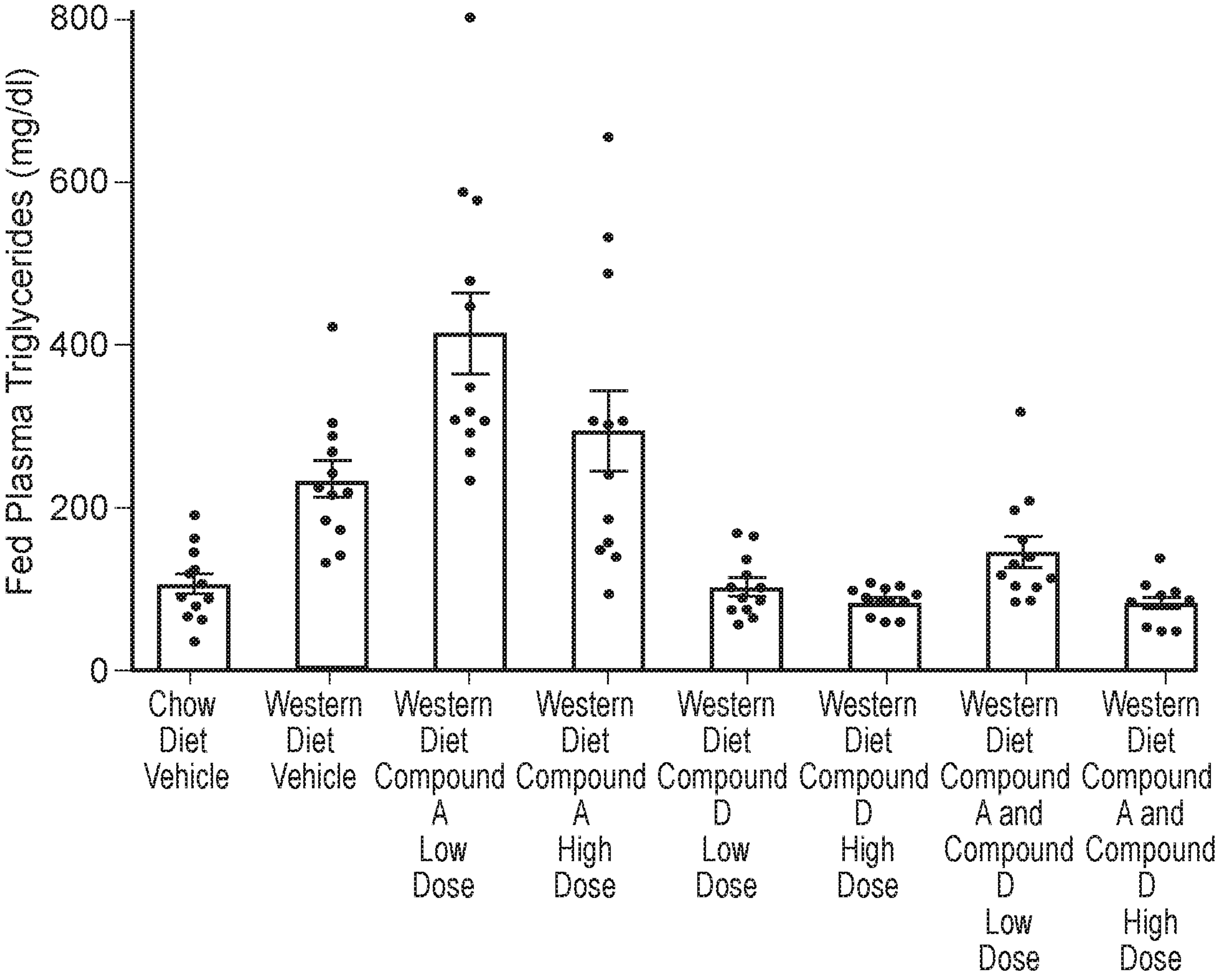

Fed Plasma Triglycerides (mg/dl)
800
600
400
200
0
Chow Diet Vehicle
Western Diet Vehicle
Western Diet Compound A Low Dose
Western Diet Compound A High Dose
Western Diet Compound D Low Dose
Western Diet Compound D High Dose
Western Diet Compound A and Compound D Low Dose
Western Diet Compound A and Compound D High Dose

FIG. 11

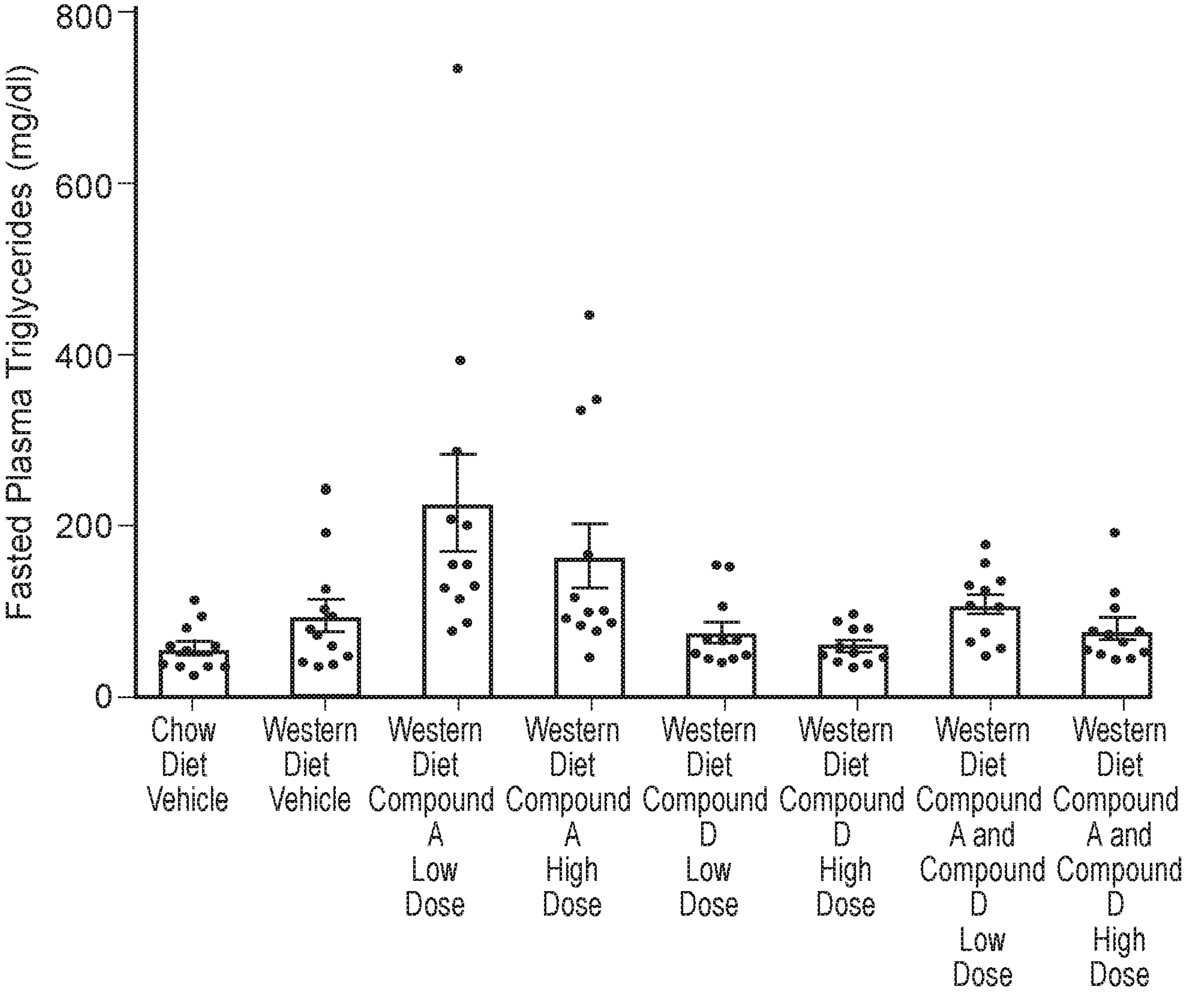

Fasted Plasma Triglycerides (mg/dl)
800
600
400
200
0
Chow Diet Vehicle
Western Diet Vehicle
Western Diet Compound A Low Dose
Western Diet Compound A High Dose
Western Diet Compound D Low Dose
Western Diet Compound D High Dose
Western Diet Compound A and Compound D Low Dose
Western Diet Compound A and Compound D High Dose

FIG. 12

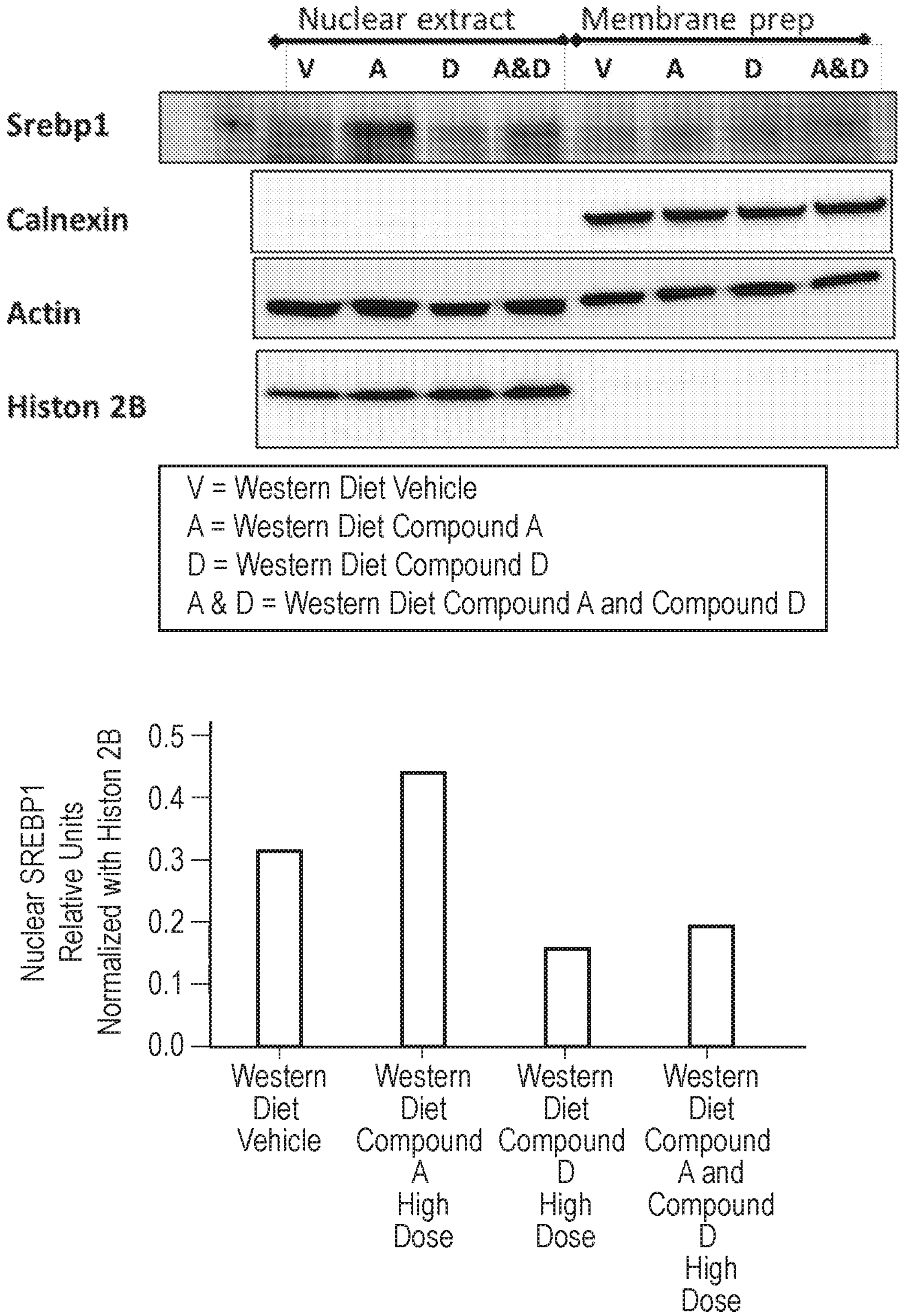

Nuclear extract
Membrane prep
V
A
D
A&D
V
A
D
A&D
Srebp1
Calnexin
Actin
Histon 2B
V = Western Diet Vehicle
A = Western Diet Compound A
D = Western Diet Compound D
A & D = Western Diet Compound A and Compound D
Nuclear SREBP1 Relative Units Normalized with Histon 2B
0.5
0.4
0.3
0.2
0.1
0.0
Western Diet Vehicle
Western Diet Compound A High Dose
Western Diet Compound D High Dose
Western Diet Compound A and Compound D High Dose

FIG. 13

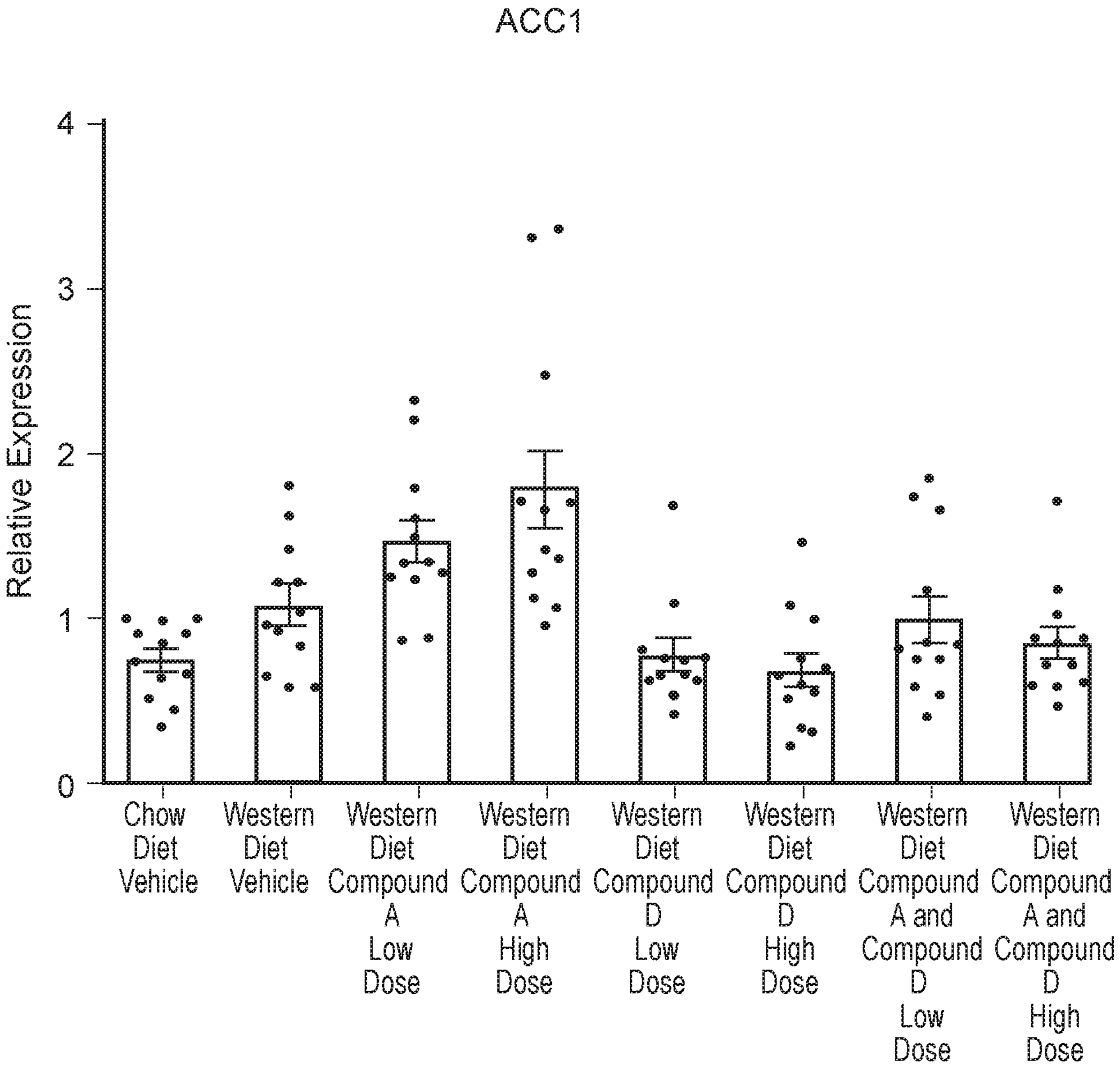

ACC1
Relative Expression
0
1
2
3
4
Chow Diet Vehicle
Western Diet Vehicle
Western Diet Compound A Low Dose
Western Diet Compound A High Dose
Western Diet Compound D Low Dose
Western Diet Compound D High Dose
Western Diet Compound A and Compound D Low Dose
Western Diet Compound A and Compound D High Dose

FIG. 14

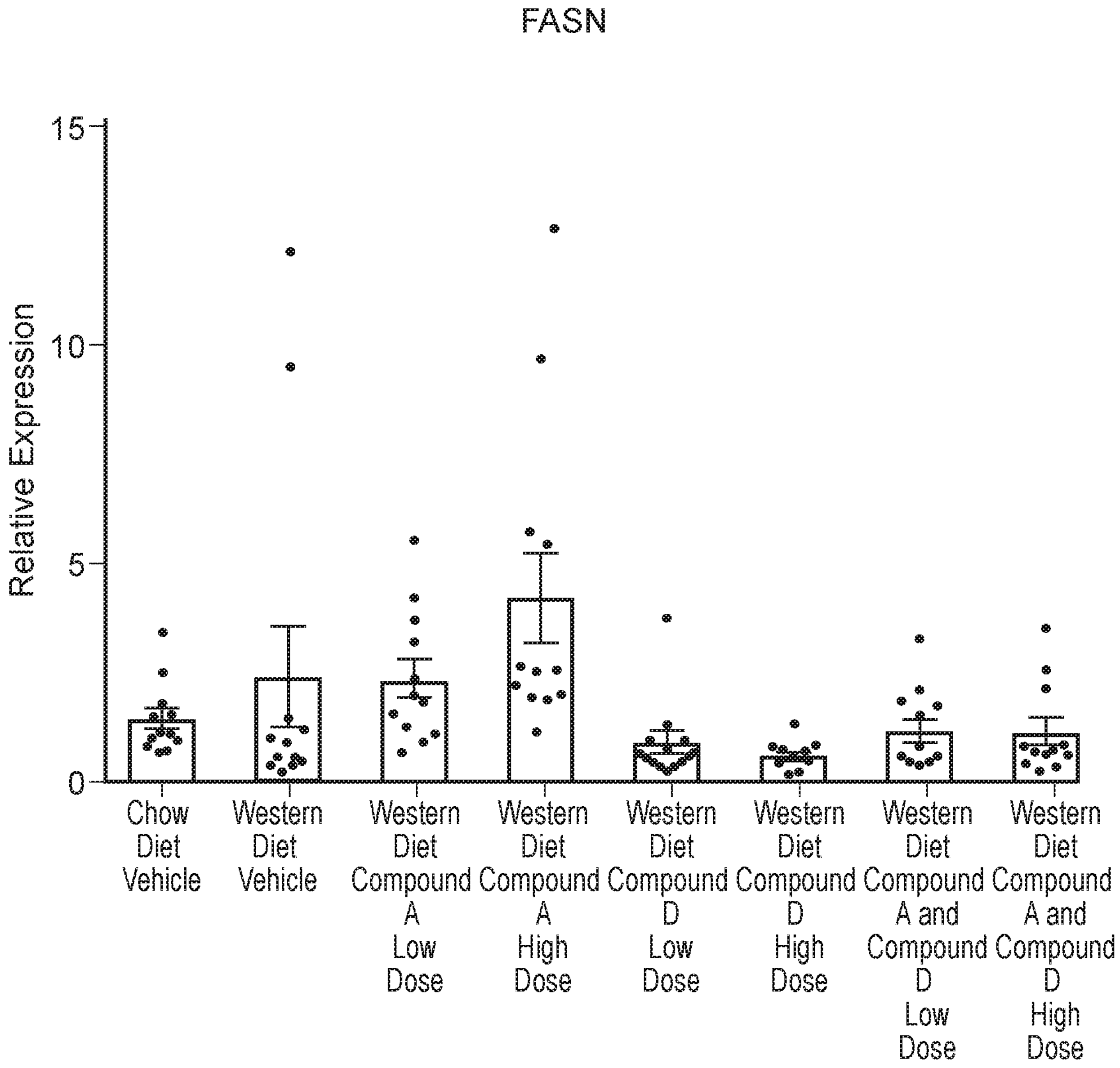

FASN
Relative Expression
15
10
5
0
Chow Diet Vehicle
Western Diet Vehicle
Western Diet Compound A Low Dose
Western Diet Compound A High Dose
Western Diet Compound D Low Dose
Western Diet Compound D High Dose
Western Diet Compound A and Compound D Low Dose
Western Diet Compound A and Compound D High Dose

FIG. 15

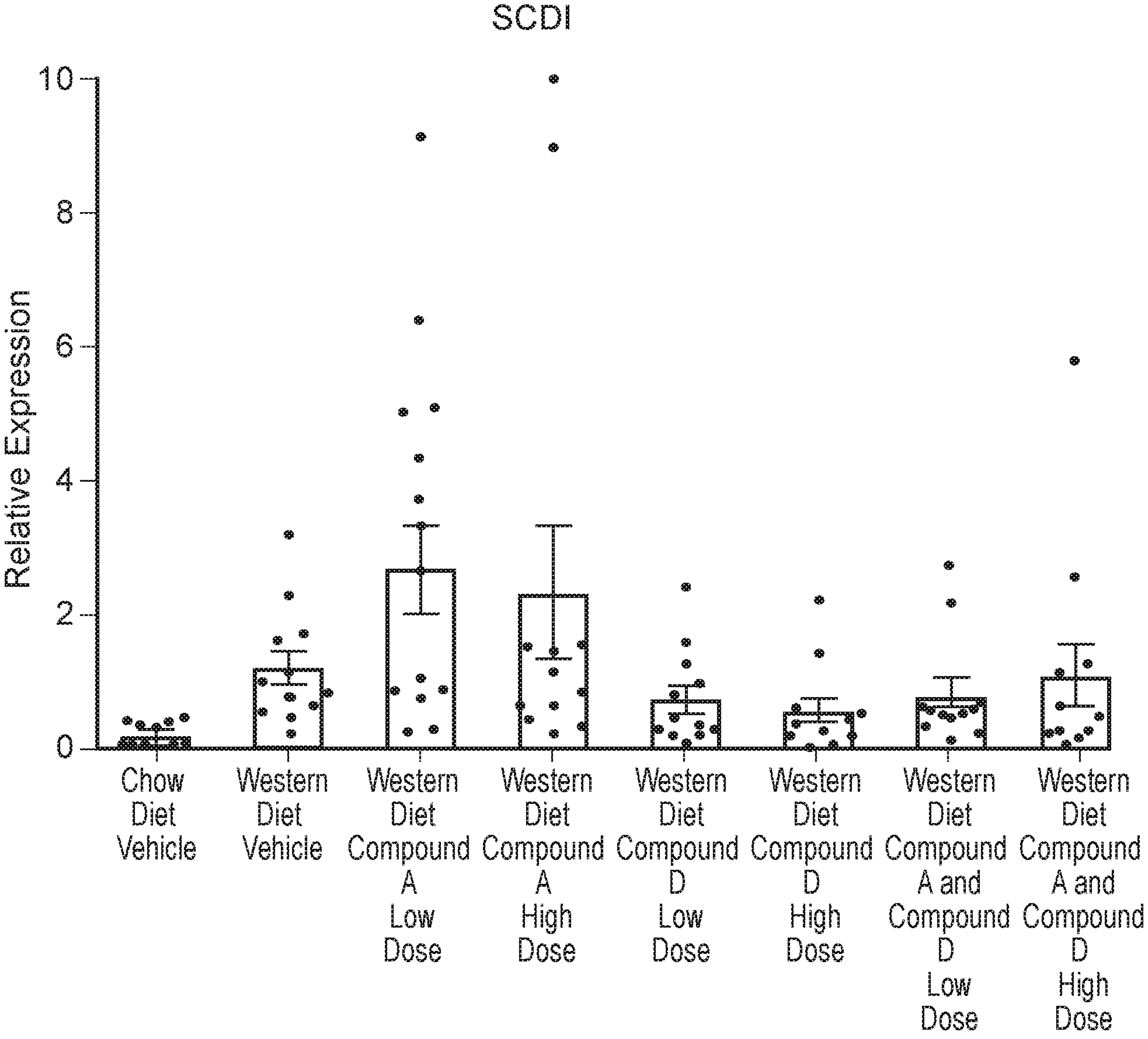

SCDI
Relative Expression
0
2
4
6
8
10
Chow Diet Vehicle
Western Diet Vehicle
Western Diet Compound A Low Dose
Western Diet Compound A High Dose
Western Diet Compound D Low Dose
Western Diet Compound D High Dose
Western Diet Compound A and Compound D Low Dose
Western Diet Compound A and Compound D High Dose

FIG. 16

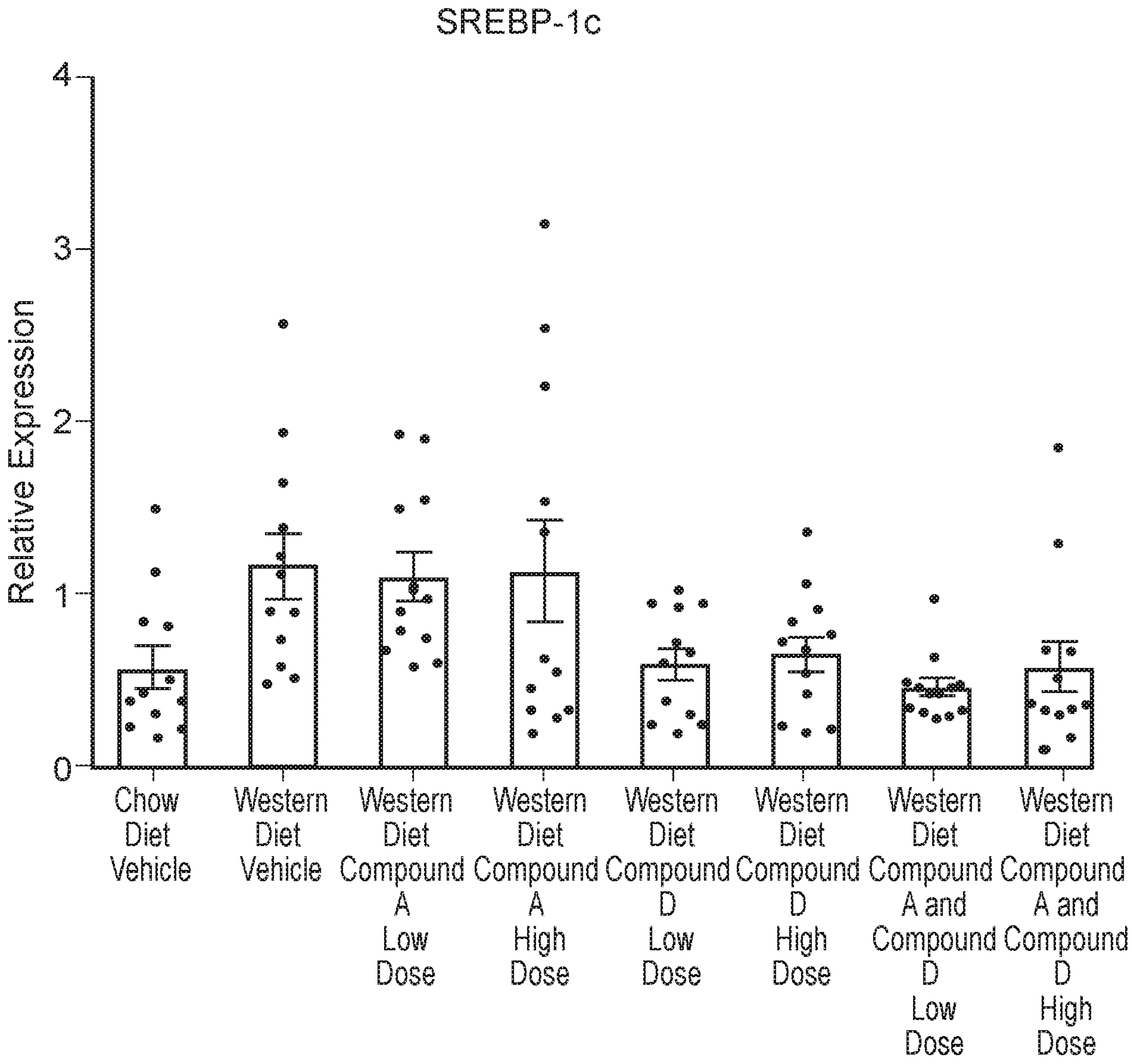

SREBP-1c
Relative Expression
4
3
2
1
0
Chow Diet Vehicle
Western Diet Vehicle
Western Diet Compound A Low Dose
Western Diet Compound A High Dose
Western Diet Compound D Low Dose
Western Diet Compound D High Dose
Western Diet Compound A and Compound D Low Dose
Western Diet Compound A and Compound D High Dose

FIG. 17

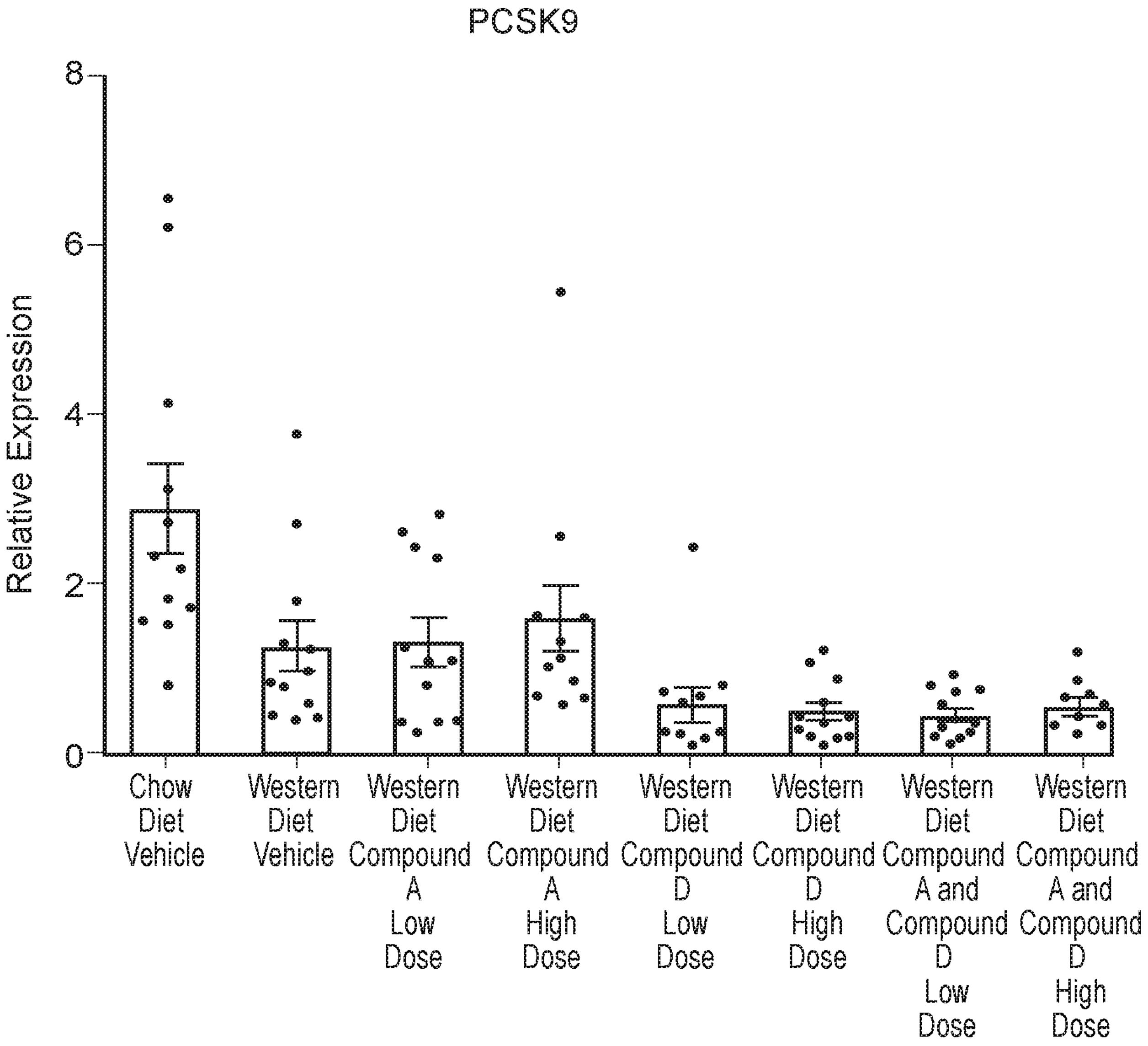

PCSK9
Relative Expression
8
6
4
2
0
Chow Diet Vehicle
Western Diet Vehicle
Western Diet Compound A Low Dose
Western Diet Compound A High Dose
Western Diet Compound D Low Dose
Western Diet Compound D High Dose
Western Diet Compound A and Compound D Low Dose
Western Diet Compound A and Compound D High Dose

FIG. 18

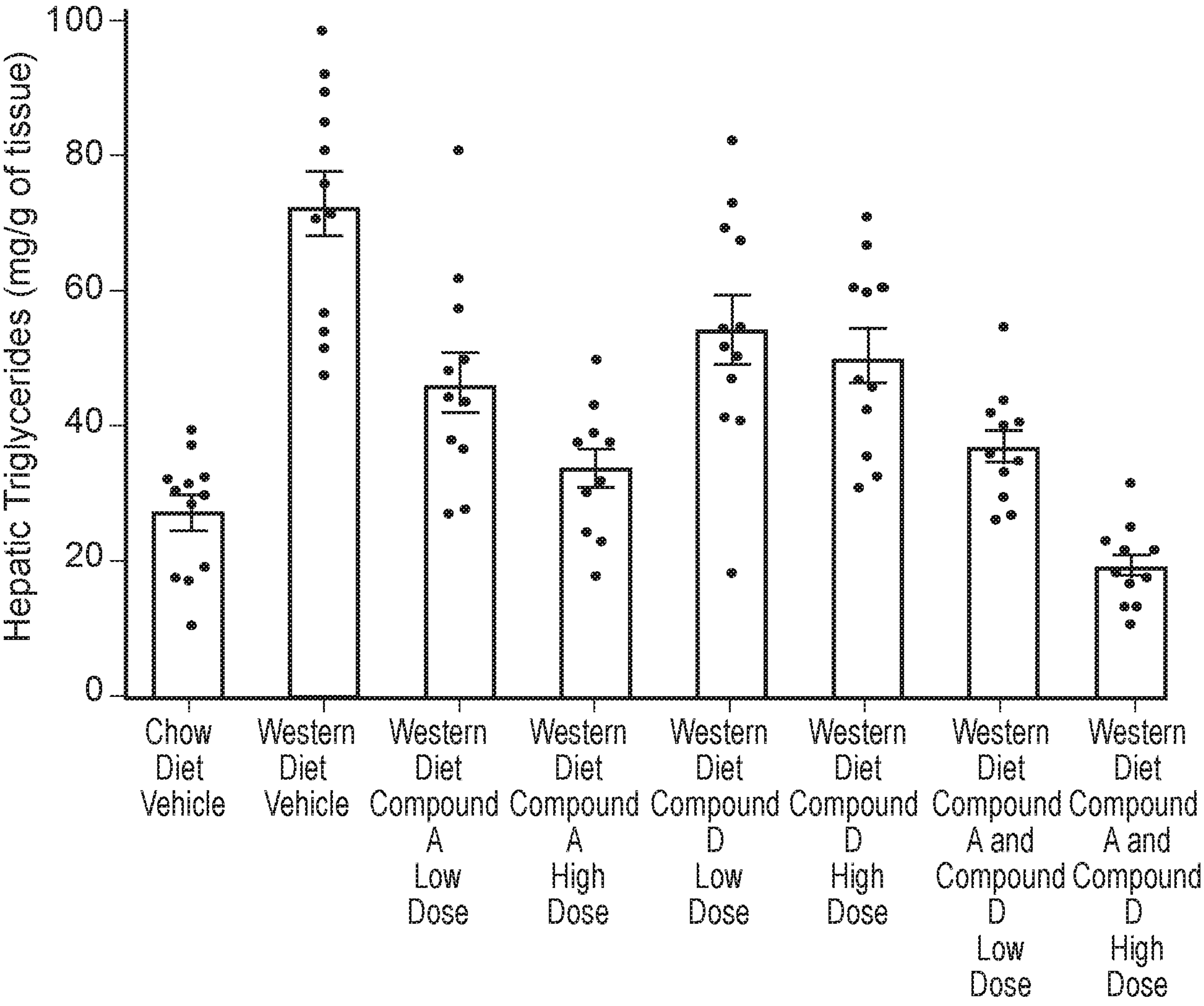

Hepatic Triglycerides (mg/g of tissue)
100
80
60
40
20
0
Chow Diet Vehicle
Western Diet Vehicle
Western Diet Compound A Low Dose
Western Diet Compound A High Dose
Western Diet Compound D Low Dose
Western Diet Compound D High Dose
Western Diet Compound A and Compound D Low Dose
Western Diet Compound A and Compound D High Dose

FIG. 19

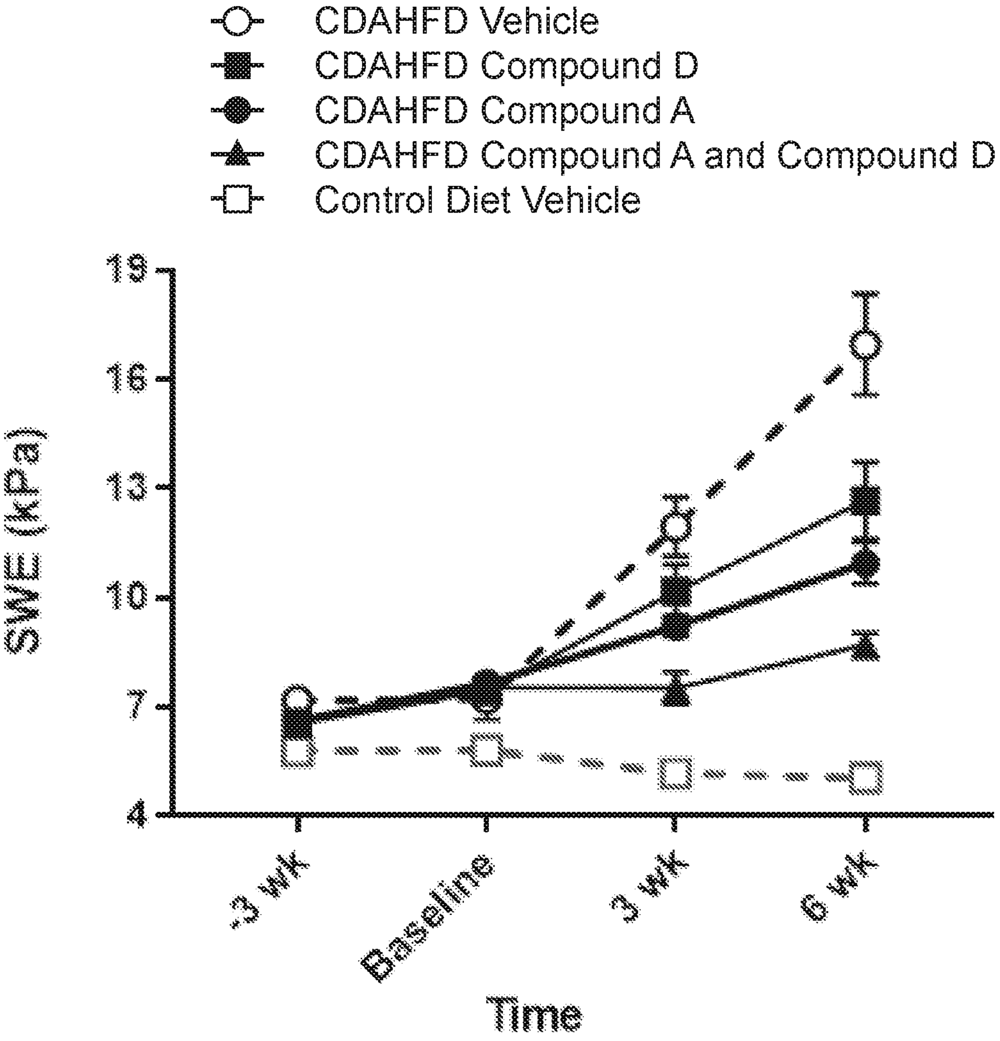

CDAHFD Vehicle
CDAHFD Compound D
CDAHFD Compound A
CDAHFD Compound A and Compound D
Control Diet Vehicle
SWE (kPa)
19
16
13
10
7
4
-3 wk
Baseline
3 wk
6 wk
Time

FIG. 20

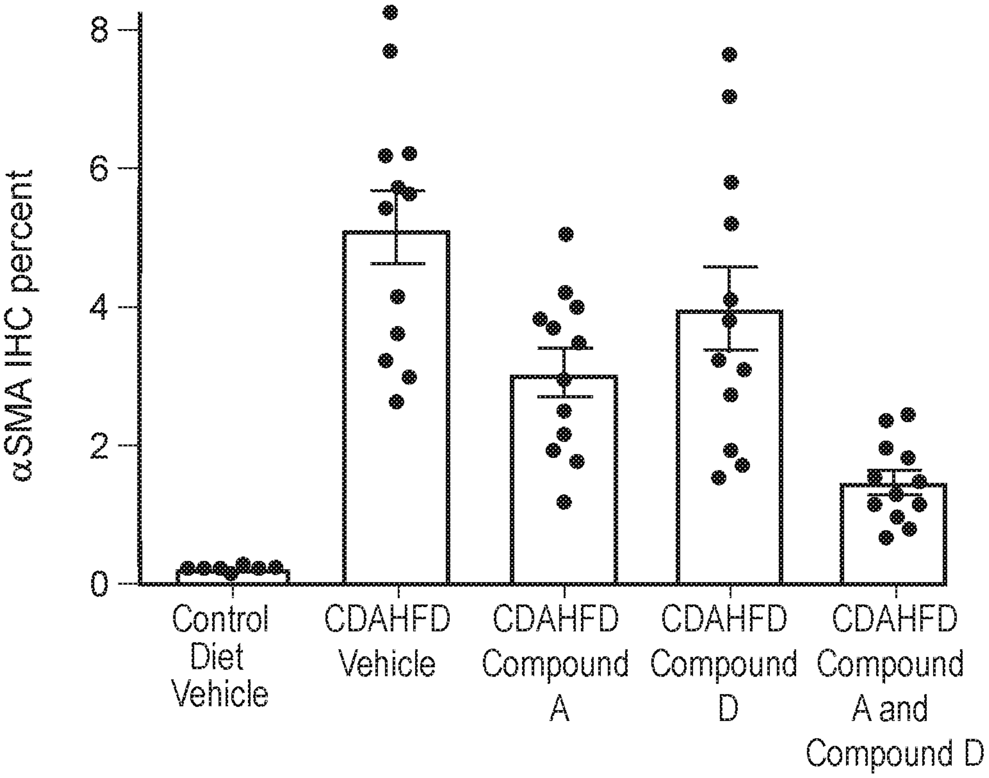

αSMA IHC percent
0
2
4
6
8
Control Diet Vehicle
CDAHFD Vehicle
CDAHFD Compound A
CDAHFD Compound D
CDAHFD Compound A and Compound D

FIG. 21

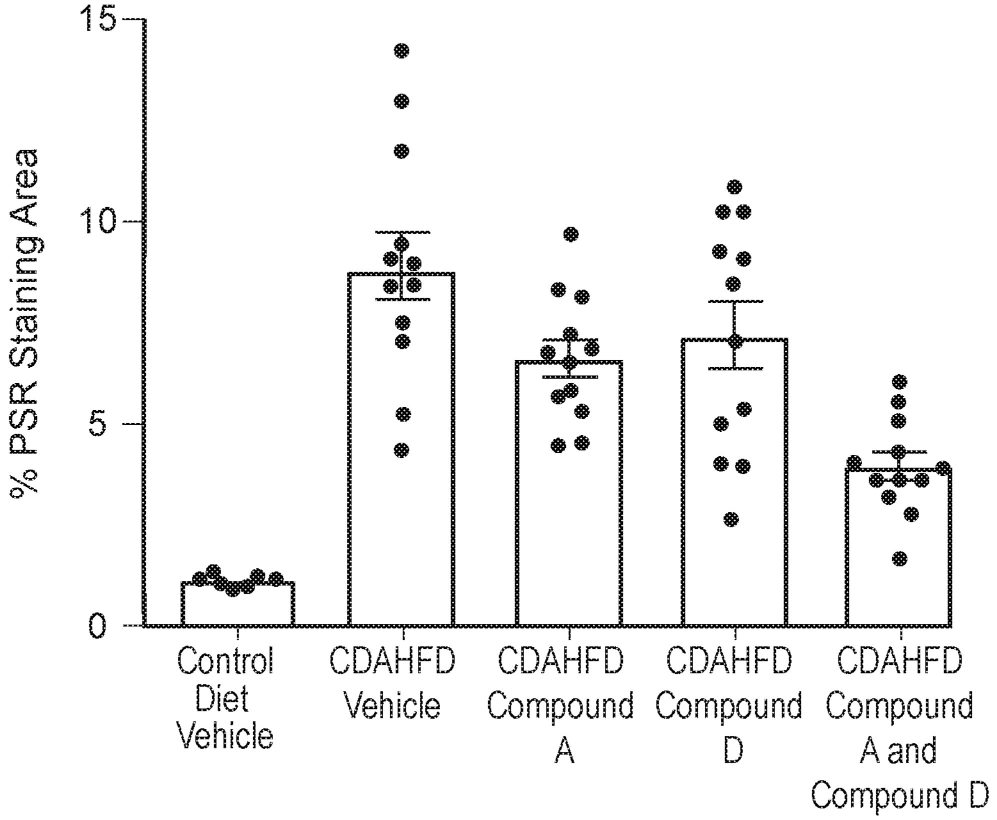

% PSR Staining Area
15
10
5
0
Control Diet Vehicle
CDAHFD Vehicle
CDAHFD Compound A
CDAHFD Compound D
CDAHFD Compound A and Compound D

FIG. 22

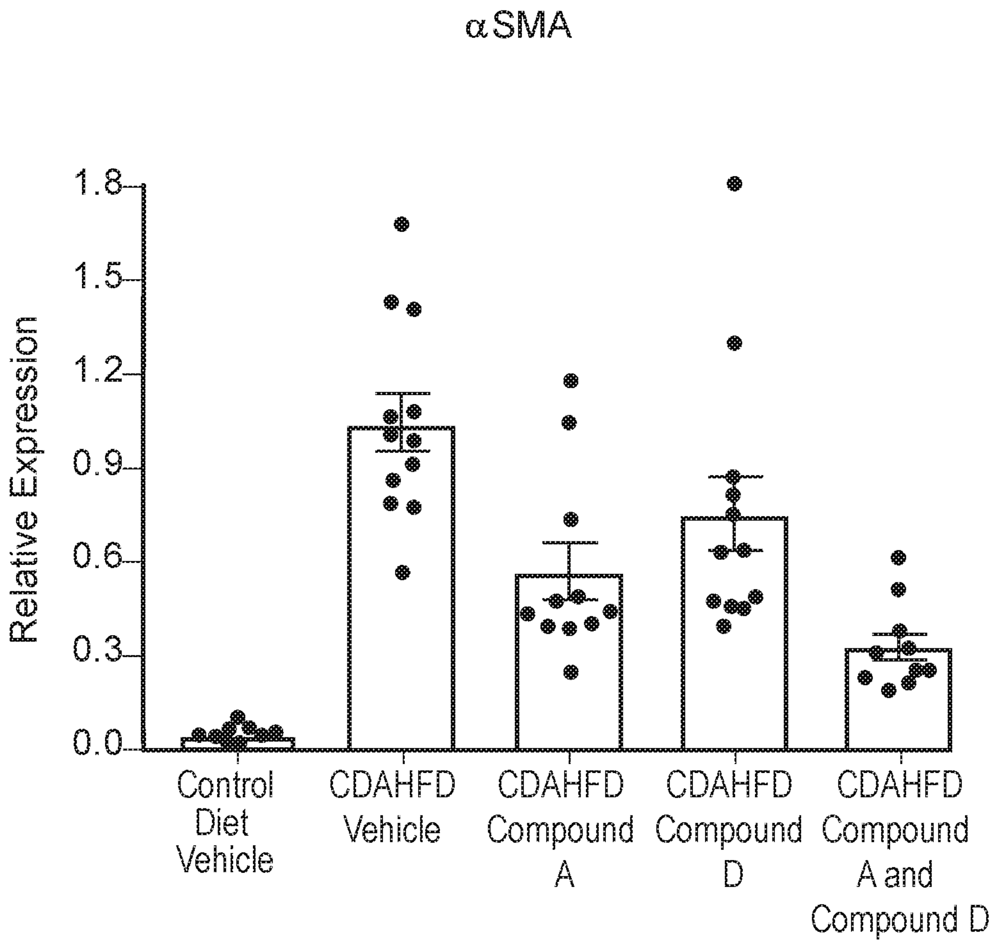

αSMA
Relative Expression
1.8
1.5
1.2
0.9
0.6
0.3
0.0
Control Diet Vehicle
CDAHFD Vehicle
CDAHFD Compound A
CDAHFD Compound D
CDAHFD Compound A and Compound D

FIG. 23

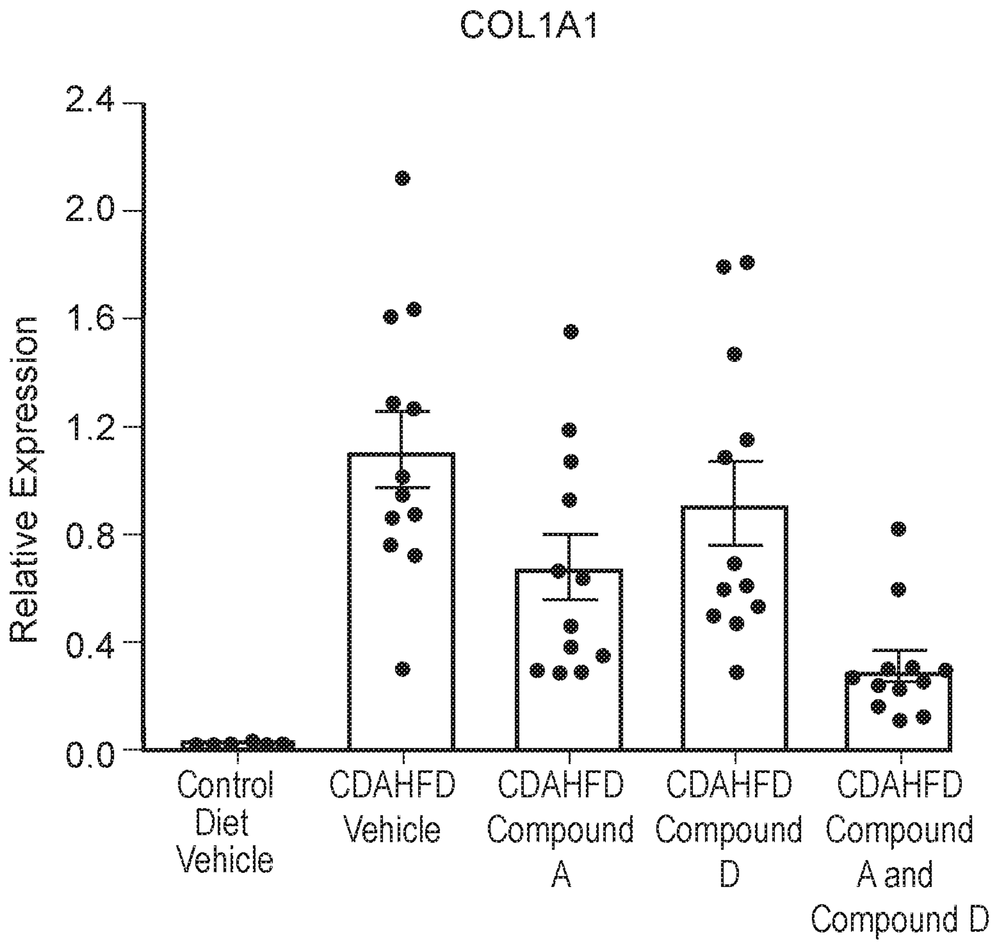

COL1A1
Relative Expression
2.4
2.0
1.6
1.2
0.8
0.4
0.0
Control Diet Vehicle
CDAHFD Vehicle
CDAHFD Compound A
CDAHFD Compound D
CDAHFD Compound A and Compound D

FIG. 24

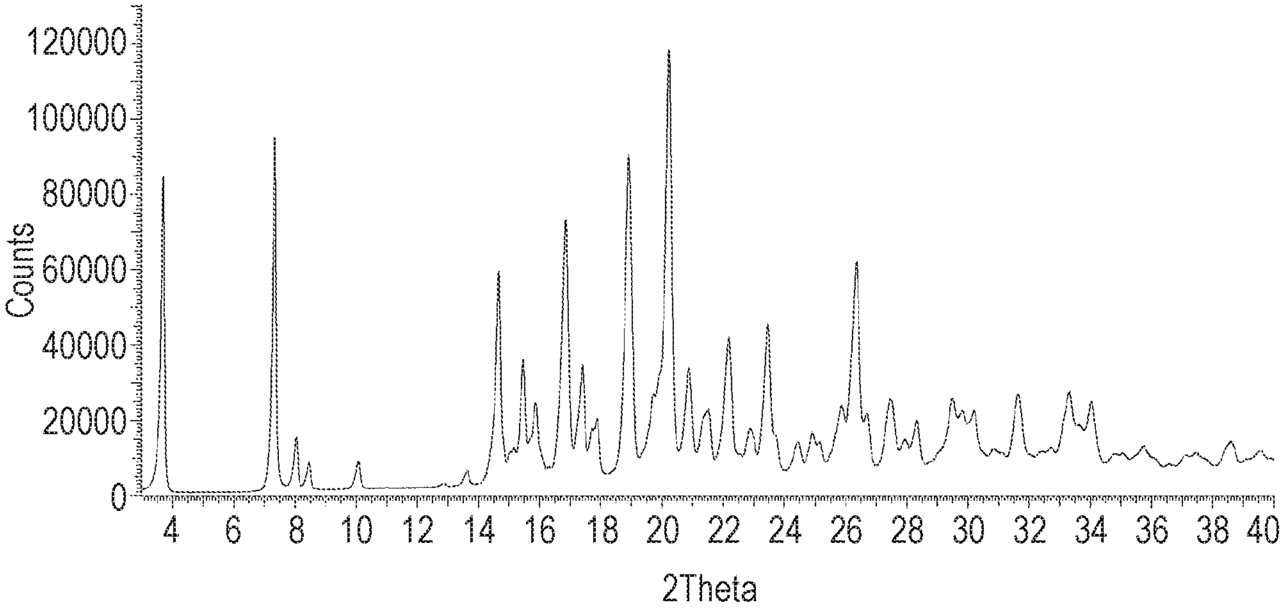
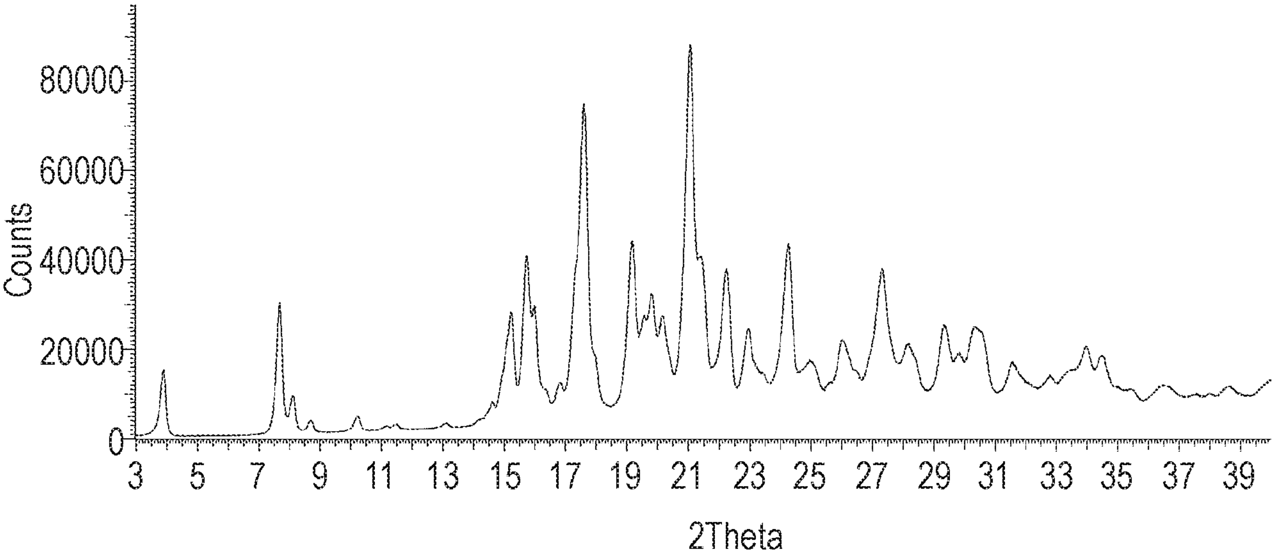

Counts
120000
100000
80000
60000
40000
20000
0
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
2Theta

FIG. 25


Counts
80000
60000
40000
20000
0
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
2Theta