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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 May 2024 (10.05.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/097573 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61P 1/16* (2006.01)
A61K 31/407 (2006.01) *A61P 3/04* (2006.01)

(21) International Application Number:
PCT/US2023/077834

(22) International Filing Date:
26 October 2023 (26.10.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/421,362 01 November 2022 (01.11.2022) US

(71) Applicant: **MERCK SHARP & DOHME LLC** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065 (US).

(72) Inventors: **LIM, Yeon-Hee**; 213 E. Grand Avenue, South San Francisco, California 94080 (US). **HUGELSHOFER, Cedric Lorenz**; 213 E. Grand Avenue, South San Francisco, California 94080 (US). **METWALLY, Essam**; 213 E. Grand Avenue, South San Francisco, California 94080 (US). **ROANE, James Patrick**; 213 E. Grand Avenue, South San Francisco, California 94080 (US). **SHOCKLEY, Samantha E.**; 213 E. Grand Avenue, South San Francisco, Georgia 94080 (US).

(74) Agent: **HARMAN, Kristi K.**; 126 East Lincoln Avenue, Rahway, New Jersey 07065 (US).

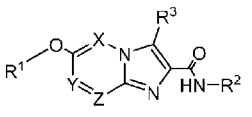
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, 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, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, 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, ME, 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 the identity of the inventor (Rule 4.17(i))*
— *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))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: PREPARATION OF IMIDAZOPYRIDINE AND IMIDAZOPYRIDAZINE DERIVATIVES AS NOVEL DIACYLGLYCERIDE O-ACYLTRANSFERASE 2 INHIBITORS



(I)

(57) Abstract: Provided are compounds of formula (I) and the pharmaceutically acceptable salts, esters, and prodrugs thereof, which are DGAT2 inhibitors. Also provided are methods of making compounds of Formula I, pharmaceutical compositions comprising compounds of Formula I, and methods of using these compounds to treat hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases such as chronic kidney diseases and heart failure and related diseases and conditions, comprising administering a compound of Formula I to a patient in need thereof.

WO 2024/097573 A1

PREPARATION OF IMIDAZOPYRIDINE AND IMIDAZOPYRIDAZINE DERIVATIVES AS NOVEL DIACYLGLYCERIDE O-ACYLTRANSFERASE 2 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This international application claims the benefit of priority to U.S. Provisional Application No. 63/421,362, filed November 1, 2022, the entirety of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present disclosure is directed to novel pharmaceutical compounds which inhibit diacylglyceride O-acyltransferase 2 ("DGAT2"), and may be useful for preventing, treating or acting as a reversing agent for hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases such as chronic kidney diseases and heart failure, and related diseases and conditions, as well as methods of making such compounds and pharmaceutical compositions comprising such a compound and a pharmaceutical carrier.

BACKGROUND

Triacylglycerols ("TGs") serve several functions in living organisms. One such function of TGs is in the storage of energy. TGs also play a role in the synthesis of membrane lipids. TG synthesis in cells may protect them from the potentially toxic effects of excess fatty acid ("FA"). In enterocytes and hepatocytes, TGs are synthesized for the assembly and secretion of lipoproteins which transport FA between tissues. TGs play a role in the skin's surface water barrier, and TGs in adipose tissue provide insulation for organisms.

The glycerol phosphate and the monoacylglycerol pathways are the major pathways for the biosynthesis of TG. However, the last step in the synthesis of TG involves the reaction of a fatty acyl-CoA and diacylglycerol ("DAG") to form TG. The reaction is catalyzed by acyl-CoA:diacylglycerol acyltransferase ("DGAT") enzymes. There have been identified two DGAT enzymes, DGAT1 and DGAT2. Although DGAT1 and DGAT2 catalyze the same reaction, they differ significantly at the level of DNA and protein sequences. DGAT2 can utilize endogenous fatty acid to synthesize TG in in vitro assays, whereas DGAT1 appears to be more dependent on exogenous fatty acid (Yen *et al.*, *J. Lipid Research,* 2008, 49, 2283). Inactivation of DGAT2 impaired cytosolic lipid droplet growth, whereas inactivation of DGAT1 exerts opposite effect. (Li *et al.*, *Arterioscler. Thromb. Vasc. Biol.* 2015, 35, 1080).

DGAT2 is an integral membrane protein of the endoplasmic reticulum and is expressed strongly in adipose tissue and the liver. DGAT2 appears to be the dominant DGAT enzyme controlling TG homeostasis *in vivo*. DGAT2 deficient mice survive for only a few hours after birth. On the other hand, DGAT1 deficient mice are viable (Yen *et al.*, *J. Lipid Research*, 2008, 49, 2283).

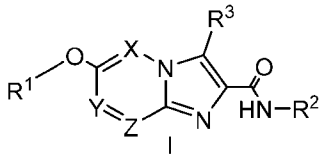
Despite this perinatal lethal phenotype, the metabolic role of DGAT2 has been mostly comprehended from effort exploiting anti-sense oligonucleotides (ASO) in rodents. In this setting, DGAT2 knockdown in *ob/ob* mice with a DGAT2 gene-specific ASO resulted in a dose dependent decrease in very low density lipoprotein ("VLDL") and a reduction in plasma TG, total cholesterol, and ApoB (Liu, *et al.*, *Biochim. Biophys Acta* 2008, 1781, 97). In the same study, DGAT2 antisense oligonucleotide treatment of *ob/ob* mice showed a decrease in weight gain, adipose weight and hepatic TG content. *Id.* In another study, antisense treatment of ob/ob mice improved hepatic steatosis and hyperlipidemia (Yu, *et al.*, *Hepatology*, 2005, 42, 362). Another study showed that diet-induced hepatic steatosis and insulin resistance was improved by knocking down DGAT2 in rats. These effects seem to be unique to inhibition of DGAT2, as ASO against DGAT1 did not lead to similar beneficial effects. Although the molecular mechanism behind these observations remains uncertain, the collective data suggest that suppression of DGAT2 is associated with reduced expression of lipogenic genes (SREBP1c, ACC1, SCD1, and mtGPAT) and increased expression of oxidative/thermogenic genes (CPT1, UCP2) (Choi *et al.*, *J. Bio. Chem.*, 2007, 282, 22678).

Inhibitors of DGAT2 are useful for treating disease related to the spectrum of metabolic syndrome such as hepatic steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases such as chronic kidney diseases and heart failure and related diseases and conditions.

DGAT2 inhibitor compounds are described in WO2022050749, WO2021133035, WO2021064590, WO2016036633, WO2016036636, WO2016036638, WO2018093696, WO2018093698, WO2013150416, US20150259323, WO2015077299, WO2017011276, WO2018033832, US201801628, and WO2003053363.

SUMMARY

The present disclosure is directed to compounds having structural Formula **I**:

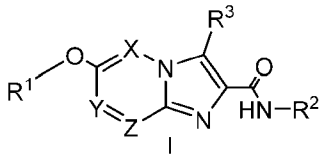


I

as well as pharmaceutically acceptable salts, esters, and prodrugs thereof, which are DGAT2 inhibitors. Also provided are methods of making compounds of Formula **I**, pharmaceutical compositions comprising compounds of Formula **I**, and methods of using these compounds to treat hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases such as chronic kidney diseases and heart failure and related diseases and conditions, comprising administering a compound of Formula **I** to a patient in need thereof.

DETAILED DESCRIPTION

The present disclosure is directed to compounds having structural Formula **I**:



I

or a pharmaceutically acceptable salt thereof wherein:

X, Y, and Z are independently selected from N and C(R^4);

R^1 is

(1) 6-membered aryl unsubstituted or substituted with 1, 2, or 3 R^5,

(2) 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(3) -(C_{1-6})alkyl-aryl, wherein the aryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(4) -(C_{1-6})alkyl-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from N, O and S, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(5) -(C_{1-3})haloalkyl, or

(6) -(C_{1-6})alkyl-O-(C_{1-6})alkyl optionally substituted with 1, 2, or 3 R^5;

R^2 is

(1) 4- to 7-membered heterocyclyl containing 1, 2 or 3 heteroatoms independently selected from N, O and S,

(2) phenyl,

(3) 5- or 6-membered heteroaryl containing 1, 2 or 3 heteroatoms independently selected from N, O, and S,

(4) -(C_{1-6})alkyl-heterocyclyl, wherein the heterocyclyl is a 4, 5- or 6-membered heterocyclyl containing 1, 2, or 3 heteroatoms independently selected from N, O and S,

(5) -(C_{1-6})alkyl-aryl,

(6) -(C_{3-6})cycloalkyl,

(7) -(C_{3-6})cyclic amine,

(8) -(C_{3-6})cycloalkyl-(C_{1-6})alkyl-SO_2(C_{1-6})alkyl, or

(9) 8-10-membered fused bicyclic heterocyclic ring comprising 1 or 2 heteroatoms independently selected from N, O and S and wherein the bicyclic ring is optionally independently substituted with one, two, or three halogens,

wherein each alkyl, aryl, cycloalkyl, heteroaryl, cyclic amine and heterocyclyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 R^6;

R^3 is

(1) hydrogen,

(2) halogen,

(3) hydroxy,

(4) (C_{1-6})alkyl,

(5) (C_{1-6})haloalkyl,

(6) (C_{1-6})alkylhydroxy,

(7) (C_{1-6})alkoxyl-,

(8) C(=O)NH_2,

(9) C(=O)OH, or

(10) O-(C_{1-6})alkyl;

when present, each R^4 is independently

(1) hydrogen,

(2) halogen,

(3) (C_{1-3})alkyl,

(4) C_{1-3}haloalkyl, or

(5) cyano;

when present, each R^5 is independently

(1) hydrogen,

(2) halogen,

(3) hydroxy,

(4) CN,

(5) C(O)OH,

(6) (C_{1-6})alkyl,

(7) (C_{1-6})haloalkyl,

(8) (C_{1-3})alkyl-OH,

(9) -OC_{1-6}alkyl,

(10) O-(C_{1-6})haloalkyl,

(11) SO_2(C_{1-6})alkyl,

(12) N(C_{1-6})alkyl,

(13) (C_{3-6})cycloalkyl,

(14) O-(C_{3-7})cycloalkyl,

(15) -OC_{1-6}alkyl-oxetanyl optionally substituted with halogen, or

(16) O-C_{1-6}alkyl-(C_{3-7})cycloalkyl optionally substituted with halogen;

when present, each R^6 is independently

(1) halogen,

(2) oxo,

(3) OH,

(4) C_{1-3}alkyl,

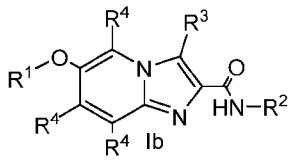
(5) C_{1-3}haloalkyl,

(6) C_{1-3}alkyl-CN,

(7) OC_{1-3}alkyl, or

(8) C(O)C_{1-3}haloalkyl.

In **Embodiment 2** of this disclosure are compounds of Formula I, or a pharmaceutically acceptable salt thereof, is the compound of formula Ib;



Ib

or a pharmaceutically acceptable salt thereof wherein:

R^1 is

(1) 6-membered aryl unsubstituted or substituted with 1, 2, or 3 R^5,

(2) 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(3) -(C_{1-6})alkyl-aryl, wherein the aryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(4) -(C_{1-6})alkyl-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1 nitrogen atom, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(5) -(C_{1-3})haloalkyl, or

(6) -(C_{1-6})alkyl-O-(C_{1-6})alkyl optionally substituted with 1, 2, or 3 R^5;

R^2 is

(1) 4- to 7-membered heterocyclyl containing 1, 2 or 3 heteroatoms independently selected from N, O and S,

(2) phenyl,

(3) 5- or 6-membered heteroaryl containing 1, 2 or 3 heteroatoms independently selected from N,

(4) -(C_{1-6})alkyl-heterocyclyl, wherein the heterocyclyl is a 4, 5 or 6-membered heterocyclyl containing 1 or 2 heteroatoms independently selected from S,

(5) -(C_{1-6})alkyl-aryl,

(6) -(C_{3-6})cycloalkyl,

(7) -(C_{3-6})cyclic amine,

(8) -(C_{3-6})cycloalkyl-(C_{1-6})alkyl-SO_2(C_{1-6})alkyl, or

(9) 10-membered fused bicyclic heterocyclic ring comprising 1 heteroatoms independently selected from N, O and S and wherein the bicyclic ring is optionally independently substituted with one, two, or three halogens,

wherein each alkyl, aryl, cycloalkyl, heteroaryl, cyclic amine and heterocyclyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 R^6;

R^3 is

(1) hydrogen,

(2) halogen,

(3) hydroxy,

(4) (C_{1-6})alkyl,

(6) (C_{1-6})haloalkyl,

(7) (C_{1-6})alkylhydroxy,

(8) (C_{1-6})alkoxyl-,

(9) C(=O)NH_2,

(10) C(=O)OH, or

(11) O-(C_{1-6})alkyl;

when present, each R^4 is independently

(1) hydrogen,

(2) halogen,

(3) (C_{1-3})alkyl,

(4) C_{1-3}haloalkyl, or

(5) cyano;

when present, each R^5 is independently

(1) hydrogen,

(2) halogen,

(3) hydroxy,

(4) CN,

(5) C(O)OH,

(6) (C_{1-6})alkyl,

(7) (C_{1-6})haloalkyl,

(8) (C_{1-3})alkyl-OH,

(9) -OC_{1-6}alkyl,

(10) O-(C_{1-6})haloalkyl,

(11) SO_2(C_{1-6})alkyl,

(12) N(C_{1-6})alkyl,

(13) (C_{3-6})cycloalkyl,

(14) O-(C_{3-7})cycloalkyl,

(15) -OC_{1-6}alkyl-oxetanyl optionally substituted with halogen, or

(16) O-C_{1-6}alkyl-(C_{3-7})cycloalkyl optionally substituted with halogen;

when present, each R^6 is independently

(1) halogen,

(2) oxo,

(3) OH,

(4) C_{1-3}alkyl,

(5) C_{1-3}haloalkyl,

(6) C_{1-3}alkyl-CN,

(7) OC_{1-3}alkyl, or

(8) C(O)C_{1-3}haloalkyl.

In **Embodiment 3** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-2 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein $R^1$is:

(1) 6-membered aryl unsubstituted or substituted with 1, 2, or 3 R^5,

(2) 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(3) -CH_2-aryl, wherein the aryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(4) -CH_2-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(5) -(C_{1-3})haloalkyl, or

(6) -(C_{1-6})alkyl-O-(C_{1-6})alkyl optionally substituted with 1, 2, or 3 R^5.

In **Embodiment 4** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-3 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein $R^1$is

(1) 6-membered aryl unsubstituted or substituted with -OC_{1-6}alkyl, or O-(C_{1-6})haloalkyl,

(2) 6-membered heteroaryl containing one or two nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, hydroxy, -O(C_{1-6})alkyl, (C_{1-6})alkyl, (C_{1-6})haloalkyl, O-(C_{1-6})haloalkyl, (C_{1-3})alkyl-OH, SO_2(C_{1-6})alkyl, N(C_{1-6})alkyl, (C_{3-6})cycloalkyl, O-(C_{3-7})cycloalkyl, CN, C(O)OH, O-C_{1-6}alkyl-(C_{3-7})cycloalkyl optionally substituted with halogen, and -OC_{1-6}alkyl-oxetanyl optionally substituted with halogen,

(3) -CH_2-aryl, wherein the aryl is substituted with one or two substituents independently selected from halogen, -OC_{1-3}alkyl, or -OC_{1-3}haloalkyl,

(4) -CH_2-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 substituents selected from halogen, C_{1-3}alkyl, C_{1-3}haloalkyl, -OC_{1-3}alkyl, and -OC_{1-3}haloalkyl,

(5) -(C_{1-3})haloalkyl, or

(6) -(C_{1-6})alkyl-O-(C_{1-6})alkyl.

In **Embodiment 5** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-4 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein $R^1$is

(1) 6-membered aryl unsubstituted or substituted with OCH_2CH_3, or OCH_2CF_3,

(2) 6-membered heteroaryl containing one or two nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from Cl, F, OH, CN, CH_3, CF_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_2OH$, $C(CH_3)_2F$, CF_3, $C(F)_2CH_2CH_3$, C(O)OH, OCH_2CH_3, OCH_2CF_3, OCH_2CHF_2, $OCH_2C(F)_2CH_3$, $OCH_2C(F)_2CH(F)_2$, $S(O)_2CH_3$, cyclopropyl, OCH_2-cyclopropyl, OCH_2-fluorocyclopropyl, O-cyclobutyl, OCH_2-oxetanyl-F and $N(CH_3)_2$;

(3) $-CH_2$-aryl, wherein the aryl is substituted with one or two substituents independently selected from F, OCH_2CH_3, and $OCHF_2$,

(4) $-CH_2$-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 substituents selected from OCH_2CHF_2, F, Cl, OCH_2CF_3, CH_3, CF_3 and OCH_2CH_3,

(5) $CH_2CH_2CF_3$, or

(6) $CH_2(CH_3)_2CH_2OCH_2CH_3$.

In **Embodiment 6** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein $R^1$is 6-membered aryl unsubstituted or substituted with $-OC_{1-6}$alkyl or $O-(C_{1-6})$haloalkyl.

In **Embodiment 7** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-6 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein $R^1$is 6-membered aryl unsubstituted or substituted with OCH_2CH_3, or OCH_2CF_3.

In **Embodiment 8** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is a 6-membered heteroaryl containing one or two nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, hydroxy, $-O(C_{1-6})$alkyl, (C_{1-6})alkyl, (C_{1-6})haloalkyl, $O-(C_{1-6})$haloalkyl, (C_{1-3})alkyl-OH, $SO_2(C_{1-6})$alkyl, $N(C_{1-6})$alkyl, (C_{3-6})cycloalkyl, $O-(C_{3-7})$cycloalkyl, $O-C_{1-6}$alkyl-(C_{3-7})cycloalkyl optionally substituted with halogen, CN, C(O)OH, and $-OC_{1-6}$alkyl-oxetanyl optionally substituted with halogen.

In **Embodiment 9** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5 or 8 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from Cl, F, OH, CN, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_2OH$, $C(CH_3)_2F$, CF_3, $C(F)_2CH_2CH_3$, C(O)OH, OCH_2CH_3,

OCH_2CF_3, OCH_2CHF_2, $OCH_2C(F)_2CH_3$, $OCH_2C(F)_2CH(F)_2$, $S(O)_2CH_3$, cyclopropyl, OCH_2-cyclopropyl, OCH_2-fluorocyclopropyl, O-cyclobutyl, OCH_2-oxetanyl-F and $N(CH_3)_2$.

In **Embodiment 10** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is -CH_2-aryl, wherein the aryl is substituted with one or two substituents independently selected from halogen, -OC_{1-3}alkyl, or -OC_{1-3}haloalkyl.

In **Embodiment 11** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5 or 10 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is -CH_2-aryl, wherein the aryl is a 6-membered aryl substituted with one or two substituents independently selected from F, OCH_2CH_3, and $OCHF_2$.

In **Embodiment 12** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is -CH_2-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 substituents selected from halogen, C_{1-3}alkyl, -OC_{1-3}alkyl, and -OC_{1-3}haloalkyl.

In **Embodiment 13** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5, 12 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is -CH_2-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 substituents selected from halogen, C_{1-3}alkyl, C_{1-3}haloalkyl, -OC_{1-3}alkyl, and -OC_{1-3}haloalkyl.

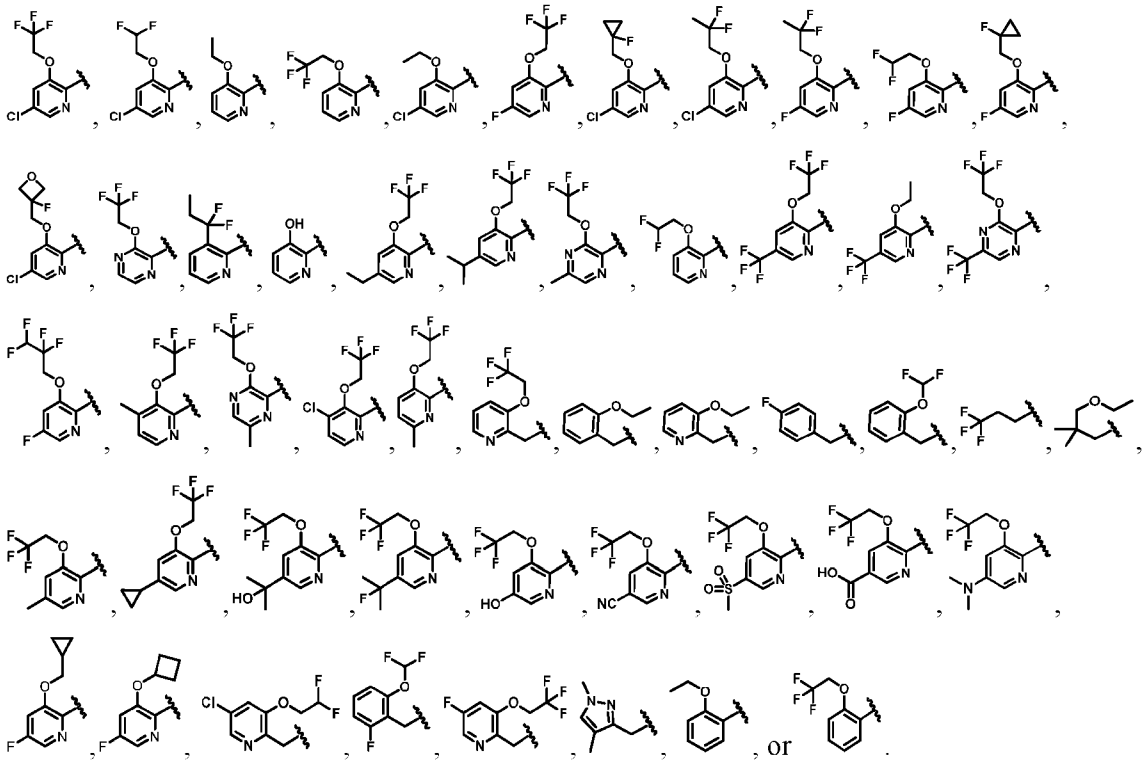
In **Embodiment 14** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5, 12-13 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is -CH_2-heteroaryl, wherein the heteroaryl is a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 substituents selected from OCH_2CHF_2, F, Cl, OCH_2CF_3, CH_3, CF_3, and OCH_2CH_3.

In **Embodiment 15** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is $CH_2CH_2CF_3$.

In **Embodiment 16** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is -(C_{1-6})alkyl-O-(C_{1-6})alkyl.

In **Embodiment 17** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5, 16 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is $CH_2(CH_3)_2CH_2OCH_2CH_3$.

In **Embodiment 18** of this disclosure are compounds of Formula I or Formula Ib, or any one of Embodiments 1-5, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is



In **Embodiment 19** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-18 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is

(1) 4- to 7-membered heterocyclyl containing 1, 2 or 3 heteroatoms independently selected from N, O and S,

(2) phenyl,

(3) 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms,

(4) -CH_2-heterocyclyl, wherein the heterocyclyl is a 4, 5- or 6-membered heterocyclyl containing 1, 2, or 3 sulfur atoms,

(5) -CH_2-aryl, wherein the aryl is a 6 membered aryl,

(6) -(C_{3-6})cycloalkyl,

(7) -(C_{3-6})cyclic amine,

(8) -(C_{3-6})cycloalkyl-CH_3-SO_2CH_3, or

(9) 10-membered fused bicyclic heterocyclic ring comprising 1 oxygen atom wherein the bicyclic ring is optionally independently substituted with one, two, or three halogens,

wherein each alkyl, aryl, cycloalkyl, heteroaryl, cyclic amine and heterocyclyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 R^6.

In **Embodiment 20** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-19 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is

(1) 4- to 7-membered heterocyclyl containing 1, 2 or 3 heteroatoms independently selected from N, O and S, optionally substituted with one, two, or three substituents independently selected from halogen, oxo, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{1-3}alkyl-CN, and C(O)C_{1-3}haloalkyl,

(2) phenyl,

(3) 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms optionally substituted with C_{1-3}alkyl,

(4) -CH_2-heterocyclyl, wherein the heterocyclyl is a 4 or 6 -membered heterocyclyl containing 1, 2, or 3 sulfur atoms, optionally substituted with one, two, three, four or five substituents independently selected from oxo, and C_{1-3}alkyl,

(5) -CH_2-aryl, wherein the aryl is a 6 membered aryl,

(6) -(C_{3-6})cycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3}alkyl, C_{1-3}haloalkyl, OC_{1-3}alkyl, and OH,

(7) -(C_{3-6})cyclic amine optionally substituted with one, two, or three substituents independently selected from oxo,

(8) -(C_4)cycloalkyl-CH_3-SO_2CH_3, or

(9) chromane optionally substituted with one, two, or three halogen,

wherein each alkyl, aryl, cycloalkyl, heteroaryl, cyclic amine and heterocyclyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 R^6.

In **Embodiment 21** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-20 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is

(1) 4- to 7-membered heterocyclyl containing 1, 2 or 3 heteroatoms independently selected from N, O and S, optionally substituted with one, two, three, four or five

substituents independently selected from halogen, oxo, CH_3, CH_2CF_3, $CH(CH_3)_2$, CH_2CH_3, CH_2CN, $C(O)CF_3$, and $(CH_3)_2$,

(2) phenyl,

(3) 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms optionally substituted with CH_3,

(4) -CH_2-heterocyclyl, wherein the heterocyclyl is a 4 or 6-membered heterocyclyl containing 1 sulfur atom optionally substituted with one, two, or three substituents independently selected from oxo and CH_3,

(5) -CH_2-aryl, wherein the aryl is a 6 membered aryl,

(6) -(C_{3-6})cycloalkyl optionally substituted with one, two, or three substituents independently selected from F, CH_3, CF_3, OH, F_2 and OCH_3,

(7) -(C_{3-6})cyclic amine optionally substituted with oxo,

(8) -(C_4)cycloalkyl-CH_3-SO_2CH_3. or

(9) chromane substituted independently with halogens.

In **Embodiment 22** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a 4- to 7-membered heterocyclyl containing 1 heteroatom selected from sulfur, nitrogen and oxygen, and optionally substituted with one, two, three, four or five substituents independently selected from halogen, oxo, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{1-3}alkyl-CN, and $C(O)C_{1-3}$haloalkyl.

In **Embodiment 23** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-22 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a 4- to 7-membered heterocyclyl containing 1 heteroatom selected from sulfur, nitrogen and oxygen, and optionally substituted with one, two, three, four or five substituents independently selected from halogen, oxo, CH_3, CH_2CF_3, $CH(CH_3)_2$, CH_2CH_3, CH_2CN, $C(O)CF_3$, and $(CH_3)_2$.

In **Embodiment 24** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-23 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a 4- to 7-membered heterocyclyl containing 1 sulfur atom, and optionally substituted with one, two, three, four or five substituents independently selected from oxo, CH_3, CH_2CF_3, $CH(CH_3)_2$, CH_2CH_3, CH_2CN and $(CH_3)_2$.

In **Embodiment 25** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-23 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a 4- to 7-membered heterocyclyl containing 1 nitrogen atom, and

optionally substituted with one, two or three substituents independently selected from CH_3, CH_2CN, and $C(O)CF_3$.

In **Embodiment 26** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-23 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a 4- to 7-membered heterocyclyl containing 1 oxygen atom, and optionally substituted with one, two, three, four or five substituents independently selected from CH_3, $(CH_3)_2$ and CH_2CF_3.

In **Embodiment 27** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is phenyl.

In **Embodiment 28** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms optionally substituted with CH_3.

In **Embodiment 29** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a $-CH_2$-heterocyclyl, wherein the heterocyclyl is a 4 or 6-membered heterocyclyl containing 1 sulfur atom optionally substituted with one, two, or three substituents independently selected from oxo and C_{1-3}alkyl.

In **Embodiment 30** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21, 29 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a $-CH_2$-heterocyclyl, wherein the heterocyclyl is a 4 or 6-membered heterocyclyl containing 1 sulfur atom optionally substituted with one, two, or three substituents independently selected from oxo and CH_3.

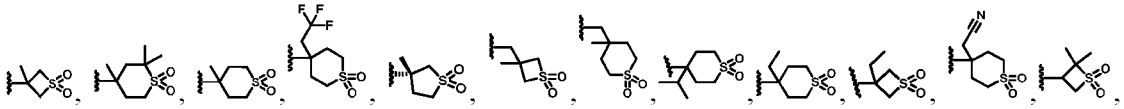
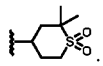
In **Embodiment 31** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is CH_2-6 membered aryl.

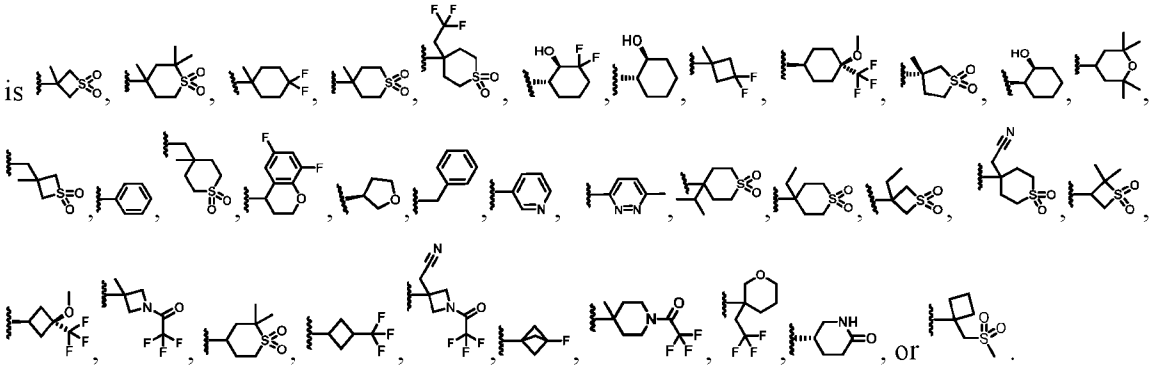
In **Embodiment 32** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a $-(C_{3-6})$cycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3}alkyl, C_{1-3}haloalkyl, OC_{1-3}alkyl, and OH.

In **Embodiment 33** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21, 32 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a $-(C_{3-6})$cycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, oxo, CH_3, CH_2CF_3, $CH(CH_3)_2$, CH_2CH_3, CH_2CN, $C(O)CF_3$, and $(CH_3)_2$.

In **Embodiment 34** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a -(C_{3-6})cyclic amine substituted with oxo.

In **Embodiment 35** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is -(C_4)cycloalkyl-CH_3-SO_2CH_3.

In **Embodiment 36** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  , or  .

In **Embodiment 37** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-21 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

In **Embodiment 38** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-37 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is hydrogen, halogen, C_{1-6}alkyl, OH, C(O)OH, $C(O)NH_2$, OC_{1-6}alkyl, C_{1-6}haloalkyl, or C_{1-6}alkyl-OH.

In **Embodiment 39** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-38 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is hydrogen, halogen, C_{1-3}alkyl, OH, C(O)OH, $C(O)NH_2$, OC_{1-3}alkyl, C_{1-3}haloalkyl, or C_{1-3}alkyl-OH.

In **Embodiment 40** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-39 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is hydrogen, Cl, F, CH_3, $CH(CH_3)_2$, CH_2CH_3, OH, C(O)OH, $C(O)NH_2$, OCH_3, CF_3, or CH_2OH.

In **Embodiment 41** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-40 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is hydrogen or CH_3.

In **Embodiment 42** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-41 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is hydrogen.

In **Embodiment 43** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-41 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is CH_3.

In **Embodiment 44** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-43 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein when present, each R^4 is independently selected from hydrogen, halogen, C_{1-3}alkyl, C_{1-3}haloalkyl and CN.

In **Embodiment 45** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-44 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein when present, each R^4 is independently selected from hydrogen, CH_3, F, Cl, $CH(CH_3)_2$, CF_3, CH_2CH_3 and CN.

In **Embodiment 46** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-43 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein when present, each R^4 is independently selected from hydrogen, halogen and CH_3.

In **Embodiment 47** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-44 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein when present, each R^4 is independently selected from hydrogen, Cl, F and CH_3.

In **Embodiment 48** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-47 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein when present, each R^4 is independently selected from hydrogen and CH_3.

In **Embodiment 49** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-47 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein when present, each R^4 is independently selected from hydrogen, F and Cl.

In **Embodiment 50** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-3, 19-49 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein when present, each $R^5$is hydrogen, halogen, hydroxy, CN, C(O)OH,

(C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{1-3})alkyl-OH, -OC_{1-6}alkyl, O-(C_{1-6})haloalkyl, $SO_2(C_{1-6})$alkyl, $N(C_{1-6})$alkyl, (C_{3-6})cycloalkyl, O-(C_{3-7})cycloalkyl, -OC_{1-6}alkyl-oxetanyl optionally substituted with halogen and O-C_{1-6}alkyl-(C_{3-7})cycloalkyl optionally substituted with halogen.

In **Embodiment 51** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-3, 19-50 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein when present, each $R^5$is hydrogen, Cl, F, OH, CN, CH_3, CF_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_2OH$, $C(CH_3)_2F$, CF_3, $C(F)_2CH_2CH_3$, C(O)OH, OCH_2CH_3, $OCHF_2$, OCH_2CF_3, OCH_2CHF_2, $OCH_2C(F)_2CH_3$, $OCH_2C(F)_2CH(F)_2$, $S(O)_2CH_3$, cyclopropyl, OCH_2-cyclopropyl, OCH_2-fluorocyclopropyl, O-cyclobutyl, OCH_2-oxetanyl-F and $N(CH_3)_2$. In **Embodiment 52** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-20, 38-51 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein when present, each R^6 is independently selected from halogen, oxo, OH, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{1-3}alkyl-CN, OC_{1-3}alkyl, and $C(O)C_{1-3}$haloalkyl.

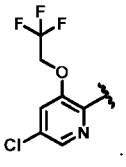
In **Embodiment 53** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-20, 38-52 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein when present, each R^6 is independently selected from halogen, oxo, CH_3, CF_3, OH, CH_2CF_3, $CH(CH_3)_2$, CH_2CH_3, OCH_3, CH_2CN, $C(O)CF_3$, and $(CH_3)_2$.

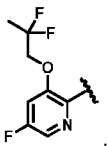
In **Embodiment 54** of this disclosure are compounds of Formula I, or Embodiments 1, 3-53 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is $C(R^4)$, Y is $C(R^4)$, and Z is $C(R^4)$.

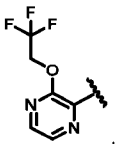
In **Embodiment 55** of this disclosure are compounds of Formula I, or Embodiments 1, 3-53 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is N, Y is $C(R^4)$, and Z is $C(R^4)$.

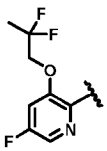
In **Embodiment 56** of this disclosure are compounds of Formula I, or Embodiments 1, 3-53 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is $C(R^4)$, Y is N, and Z is $C(R^4)$.

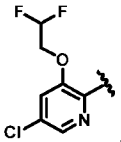
In **Embodiment 57** of this disclosure are compounds of Formula I, or Embodiments 1, 3-53 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is $C(R^4)$, Y is $C(R^4)$, and Z is N.

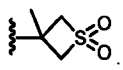
In **Embodiment 58** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5, 8-9, 19-57 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is  .

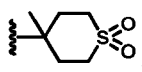
In **Embodiment 59** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 11-5, 8-9, 19-57 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is  .

In **Embodiment 60** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5, 8-9, 19-57 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is  .

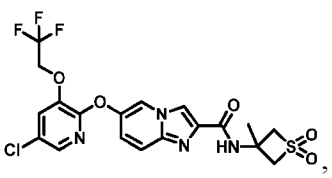
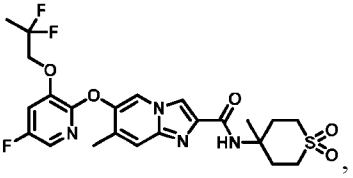
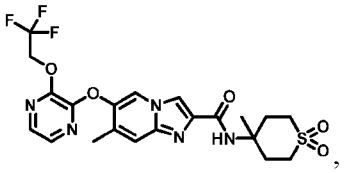
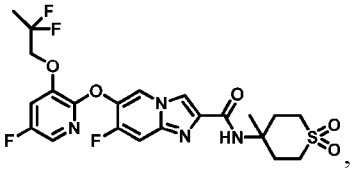
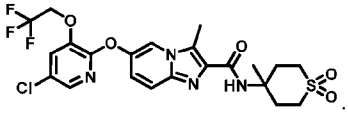
In **Embodiment 61** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5, 8-9, 19-57 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is  .

In **Embodiment 62** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-5, 8-9, 19-57 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is  .

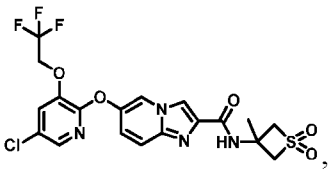
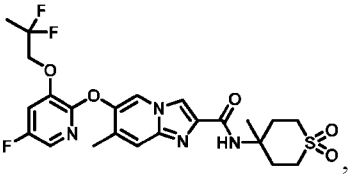
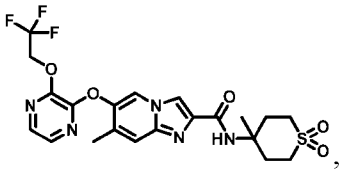
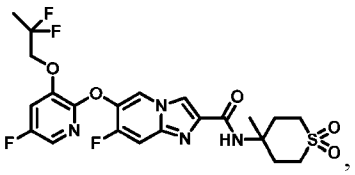
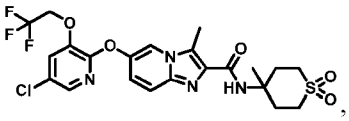
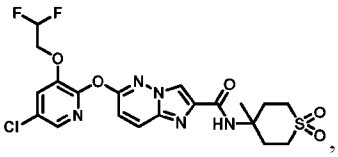
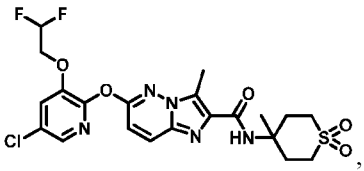
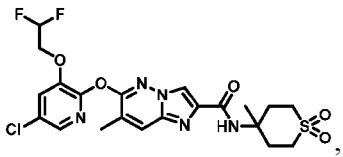
In **Embodiment 63** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-24, 36-62 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

In **Embodiment 64** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-24, 36-62 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

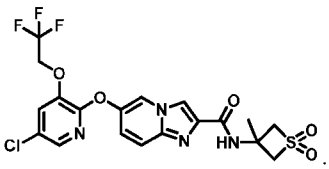
In **Embodiment 65** the present disclosure is a compound selected from:

 ,  ,  ,  , or  .

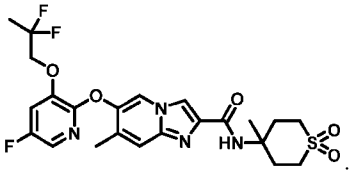
In **Embodiment 66,** the present disclosure is a compound selected from:

 ,  ,  ,  ,  ,  ,  ,  , or a pharmaceutically acceptable salt thereof.

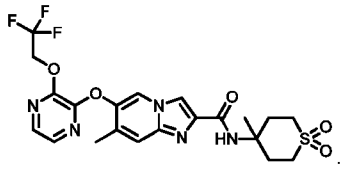
Embodiment 67 is a compound, or a pharmaceutically acceptable salt thereof, which is

 .

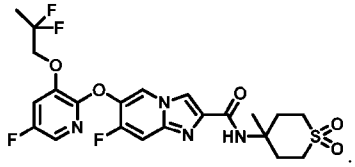
Embodiment 68 is a compound, or a pharmaceutically acceptable salt thereof, which is

 .

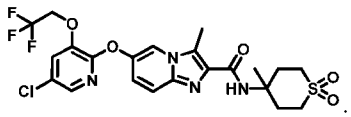
Embodiment 69 is a compound, or a pharmaceutically acceptable salt thereof, which is



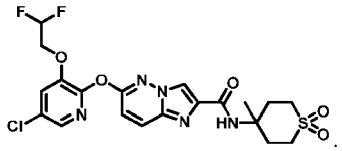
Embodiment 70 is a compound, or a pharmaceutically acceptable salt thereof, which is



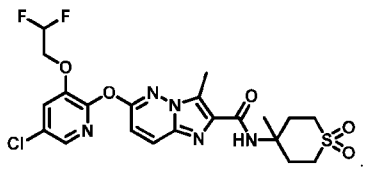
Embodiment 71 is a compound, or a pharmaceutically acceptable salt thereof, which is



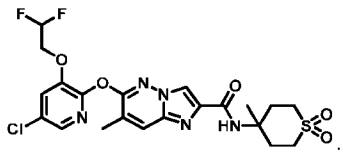
Embodiment 72 is a compound, or a pharmaceutically acceptable salt thereof, which is



Embodiment 73 is a compound, or a pharmaceutically acceptable salt thereof, which is



Embodiment 74 is a compound, or a pharmaceutically acceptable salt thereof, which is



In **Embodiment 75**, the compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, is:

6-[[5-Chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(2,2,4-trimethyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(4,4-difluoro-1-methyl-cyclohexyl)-6-[(3-ethoxy-2-pyridyl)oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[1,1-dioxo-4-(2,2,2-trifluoroethyl)thian-4-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

8-fluoro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(5-chloro-3-ethoxy-2-pyridyl)oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[1,1-dioxo-4-(2,2,2-trifluoroethyl)thian-4-yl]-7-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

7-chloro-6-[5-chloro-3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-8-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

N-[(1*S*,2*R*)-3,3-difluoro-2-hydroxy-cyclohexyl]-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

7-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyrazin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide,

7-fluoro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(1*S*,2*S*)-2-hydroxycyclohexyl]imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(3,3-difluoro-1-methyl-cyclobutyl)-6-[(3-ethoxy-2-pyridyl)oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

8-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3,3-difluoro-1-methyl-cyclobutyl)-7-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[4-methoxy-4-(trifluoromethyl)cyclohexyl]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-8-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3,3-difluoro-1-methyl-cyclobutyl)-5-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(3*S*)-3-methyl-1,1-dioxo-thiolan-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,

5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(1*R*,2*S*)-2-hydroxycyclohexyl]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(2,2,6,6-tetramethyltetrahydropyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

5-fluoro-N-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-a]pyridine-2-carboxamide,

6-[[3-(2,2-difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-5,7-dimethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-[(3-fluorooxetan-3-yl)methoxy]-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[(3-methyl-1,1-dioxo-thietan-3-yl)methyl]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

8-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-phenyl-imidazo[1,2-*a*]pyridine-2-carboxamide;2,2,2-trifluoroacetate,

6-[3-(2,2-difluoroethoxy)pyrazin-2-yl]oxy-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-((3-(2,2-difluoropropoxy)-5-fluoropyridin-2-yl)oxy)-7-fluoro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

7-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[(4-methyl-1,1-dioxo-thian-4-yl)methyl]imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(6,8-difluorochroman-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(3*S*)-tetrahydrofuran-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,

N-benzyl-6-[(3-ethoxy-2-pyridyl)oxy]imidazo[1,2-*a*]pyridine-2-carboxamide

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(3-pyridyl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-isopropyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-8-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(6-methylpyridazin-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

6-[[3-(1,1-difluoropropyl)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-ethyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-hydroxy-2-pyridyl)oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-[1,1-dioxo-4-(2,2,2-trifluoroethyl)thian-4-yl]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3,3-difluoro-1-methyl-cyclobutyl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(2,2,4-trimethyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-isopropyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-ethyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-ethyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(5-chloro-3-ethoxy-2-pyridyl)oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3-ethyl-1,1-dioxo-thietan-3-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(5-chloro-3-ethoxy-2-pyridyl)oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-isopropyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-[4-(cyanomethyl)-1,1-dioxo-thian-4-yl]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(4-ethyl-1,1-dioxo-thian-4-yl)-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[5-methyl-3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-ethyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(2,2-dimethyl-1,1-dioxo-thietan-3-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-[3-methoxy-3-(trifluoromethyl)cyclobutyl]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-[3-methyl-1-(2,2,2-trifluoroacetyl)azetidin-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(4,4-difluoro-1-methyl-cyclohexyl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[3-methyl-1-(2,2,2-trifluoroacetyl)azetidin-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-isopropyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,
3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-5-(trifluoromethyl)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(2,2-dimethyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-ethoxy-5-(trifluoromethyl)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)-6-[5-methyl-3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-[3-(trifluoromethyl)cyclobutyl]imidazo[1,2-*a*]pyridine-2-carboxamide,
N-[3-(cyanomethyl)-1-(2,2,2-trifluoroacetyl)azetidin-3-yl]-6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(2,2,4-trimethyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[(3*R*)-3-methyl-1,1-dioxo-thiolan-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[4-methyl-1-(2,2,2-trifluoroacetyl)-4-piperidyl]imidazo[1,2-*a*]pyridine-2-carboxamide,
3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)-6-[3-(2,2,2-trifluoroethoxy)-5-(trifluoromethyl)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,3,3-tetrafluoropropoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
N-(2,2-dimethyl-1,1-dioxo-thian-4-yl)-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(4-ethyl-1,1-dioxo-thian-4-yl)-3-methyl-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[4-methyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[6-methyl-3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[4-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[(3-methyl-1,1-dioxo-thietan-3-yl)methyl]imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[6-methyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[3-(2,2,2-trifluoroethyl)tetrahydropyran-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-[(3*S*)-6-oxo-3-piperidyl]-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-3-ethyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

3-ethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

3-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

8-fluoro-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

7-fluoro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-fluoro-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-fluoro-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

7-fluoro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

7-fluoro-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]methoxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[(2-ethoxyphenyl)methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[(3-ethoxy-2-pyridyl)methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[(4-fluorophenyl)methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[2-(difluoromethoxy)phenyl]methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-(3,3,3-trifluoropropoxy)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-(3-ethoxy-2,2-dimethyl-propoxy)-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3-chloro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
3-hydroxy-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
2-((4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)carbamoyl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-3-carboxylic acid
*N*2-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2,3-dicarboxamide,
3-methoxy-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methoxy-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridin-1-ium-2-carboxamide;2,2,2-trifluoroacetate,
N-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3-(hydroxymethyl)-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[5-chloro-3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-7-cyano-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3,5-dichloro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

3,5-dichloro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

3-chloro-6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-3-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[5-methyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-cyclopropyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-(1-hydroxy-1-methyl-ethyl)-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-(1-fluoro-1-methyl-ethyl)-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-hydroxy-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-cyano-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[5-methylsulfonyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[3-methyl-2-[(4-methyl-1,1-dioxo-thian-4-yl)carbamoyl]imidazo[1,2-*a*]pyridine-6-yl]oxy-5-(2,2,2-trifluoroethoxy)pyridine-3-carboxylic acid,

6-[5-(dimethylamino)-3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridin-1-ium-2-carboxamide,

6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-Chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-Fluoro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[3-(2,2-Difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[3-(Cyclopropylmethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[3-(Cyclobutoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-Chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[3-(2,2-Difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-((1*S*,2*R*)-3,3-difluoro-2-hydroxycyclohexyl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-N-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-b]pyridazine-2-carboxamide,

6-[[5-Chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-[1-(methylsulfonylmethyl)cyclobutyl]imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-Fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

N-(4-Methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-7-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-7-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3,7-dimethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3,7-dimethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-8-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-8-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

N-((1*S*,2*R*)-3,3-difluoro-2-hydroxycyclohexyl)-6-((3-(2,2-difluoroethoxy)-5-fluoropyridin-2-yl)oxy)-8-methylimidazo[1,2-*b*]pyridazine-2-carboxamide,

3,7-dichloro-6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

3-chloro-6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

3,7-dichloro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*b*]pyridazine-2-carboxamide,

3-chloro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*b*]pyridazine-2-carboxamide,

3,7-dichloro-6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[2-(Difluoromethoxy)-6-fluoro-phenyl]methoxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-Fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]methoxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

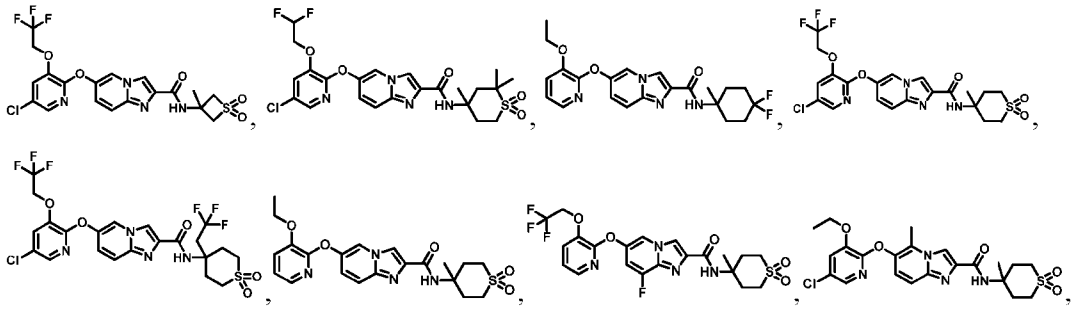
6-((1,4-dimethyl-1*H*-pyrazol-3-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

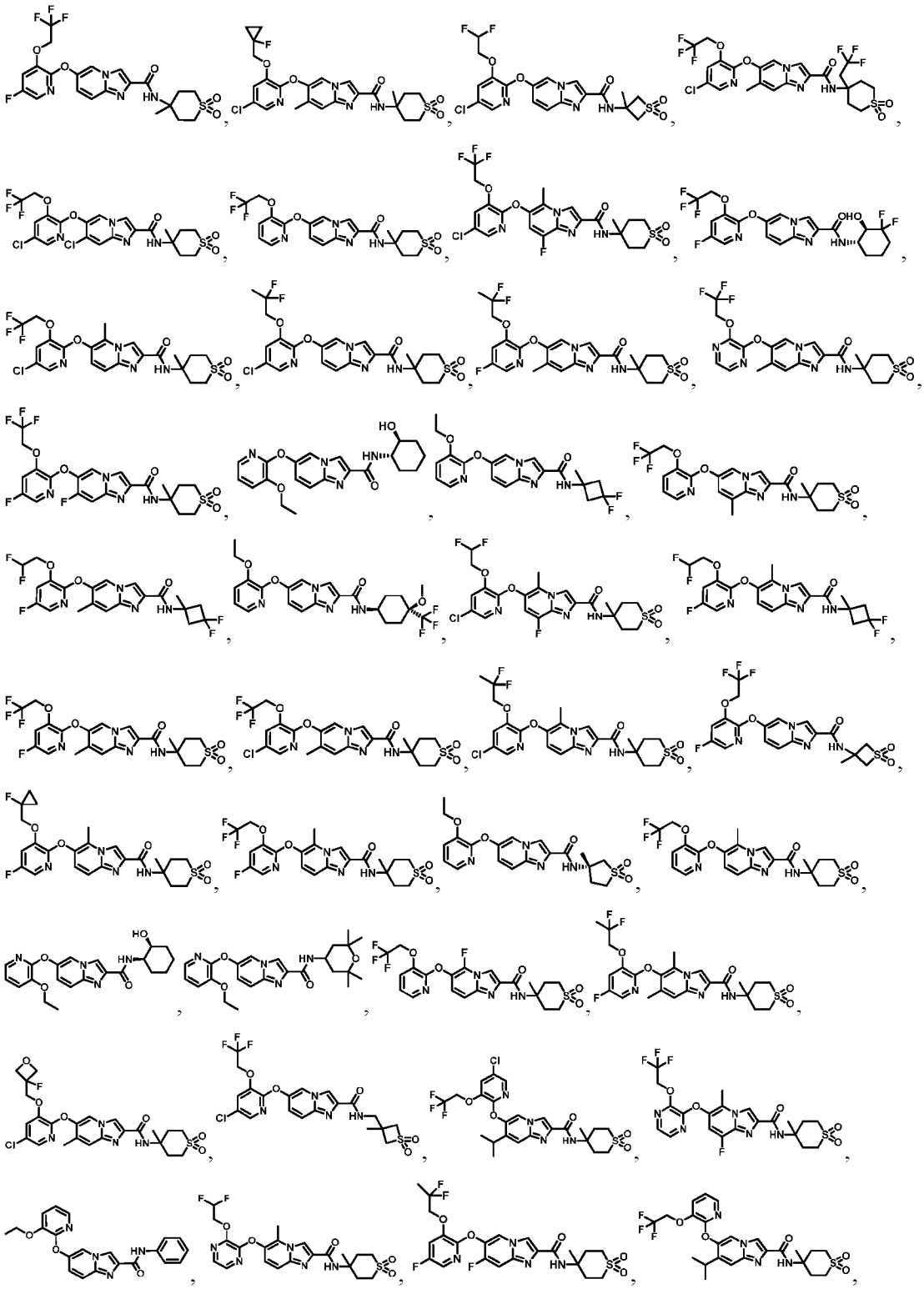
(*S*)-6-(2-ethoxyphenoxy)-*N*-(tetrahydrofuran-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

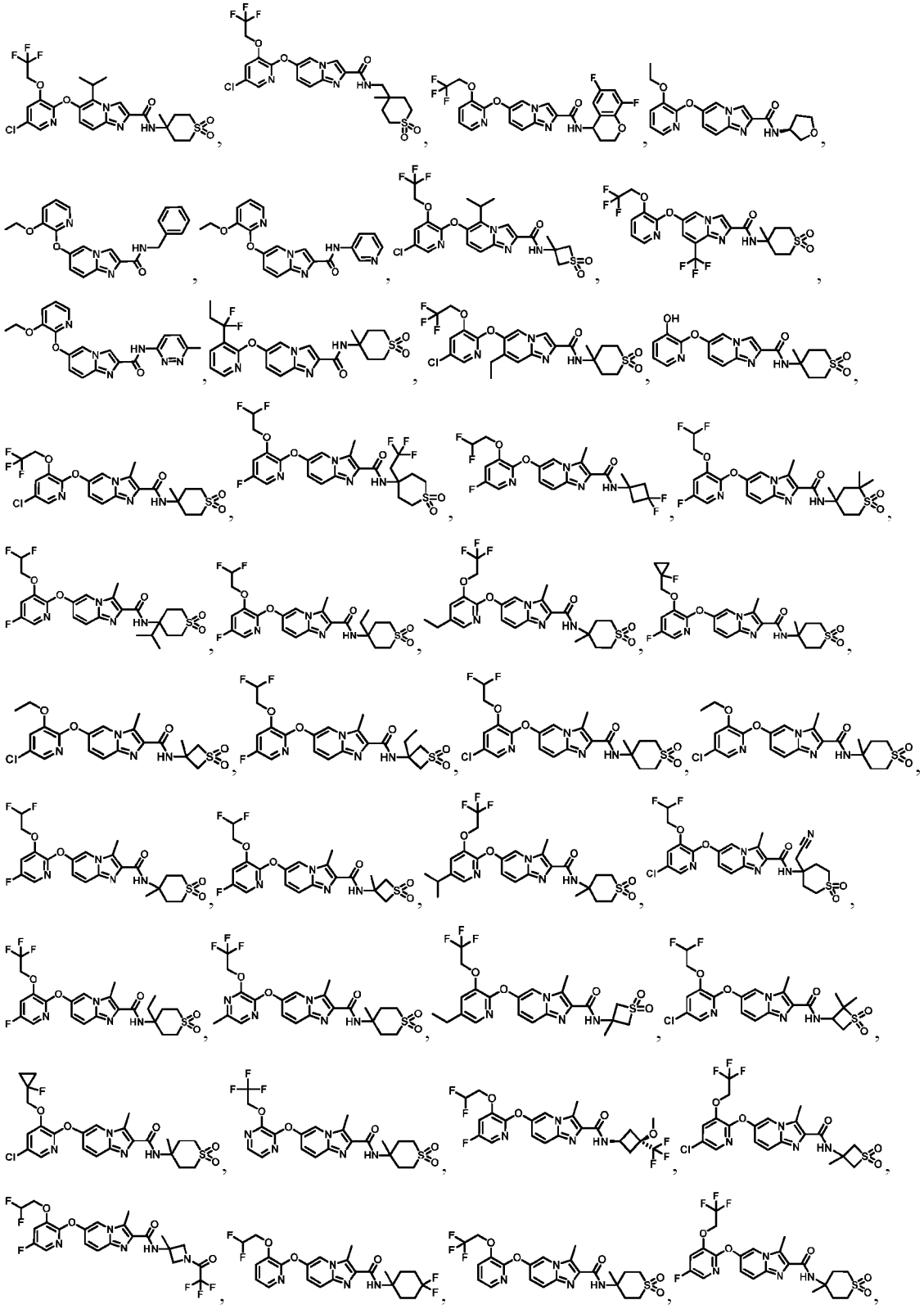
6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyrazine-2-carboxamide, or

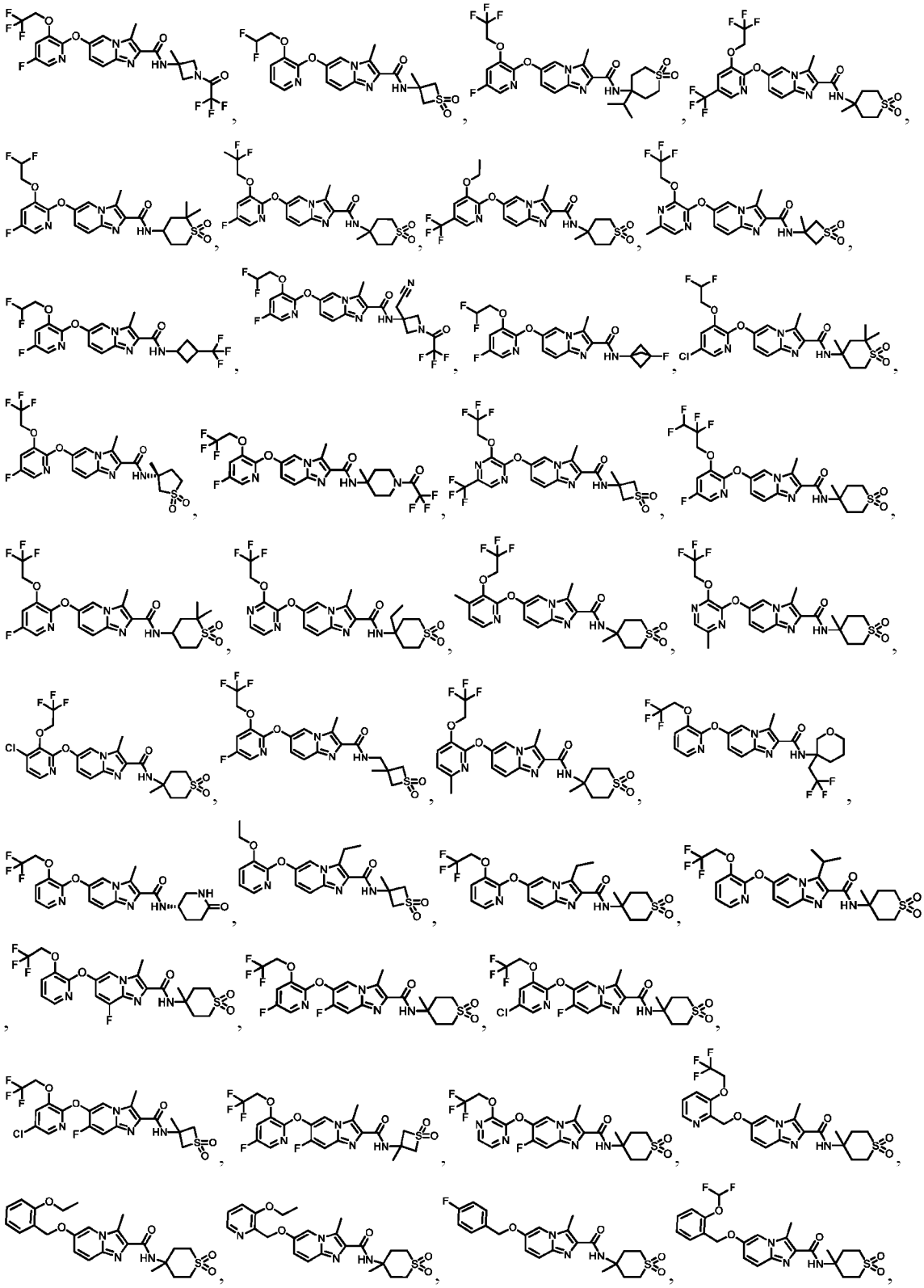
6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyrimidine-2-carboxamide.

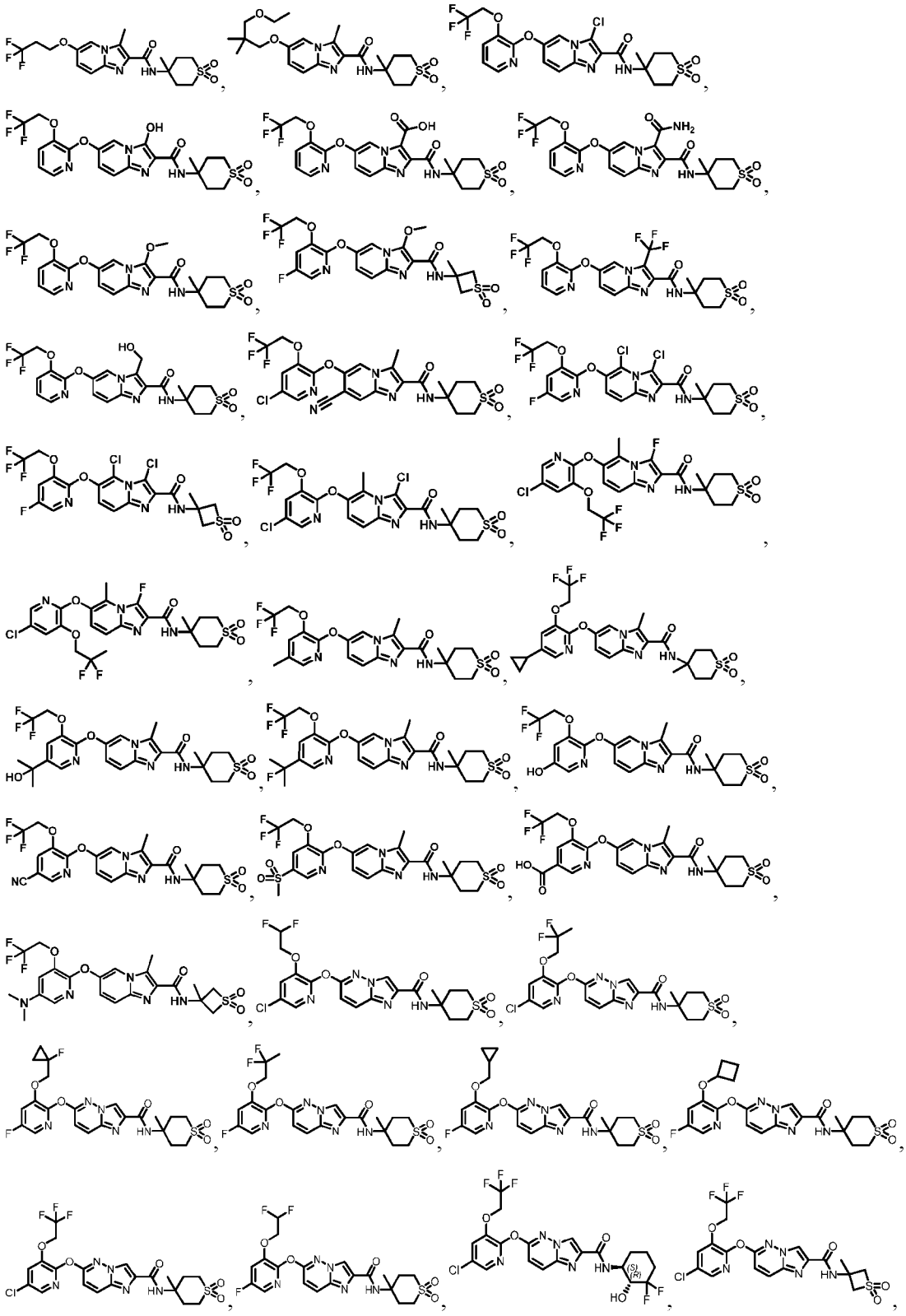
In **Embodiment 76**, the compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, is:

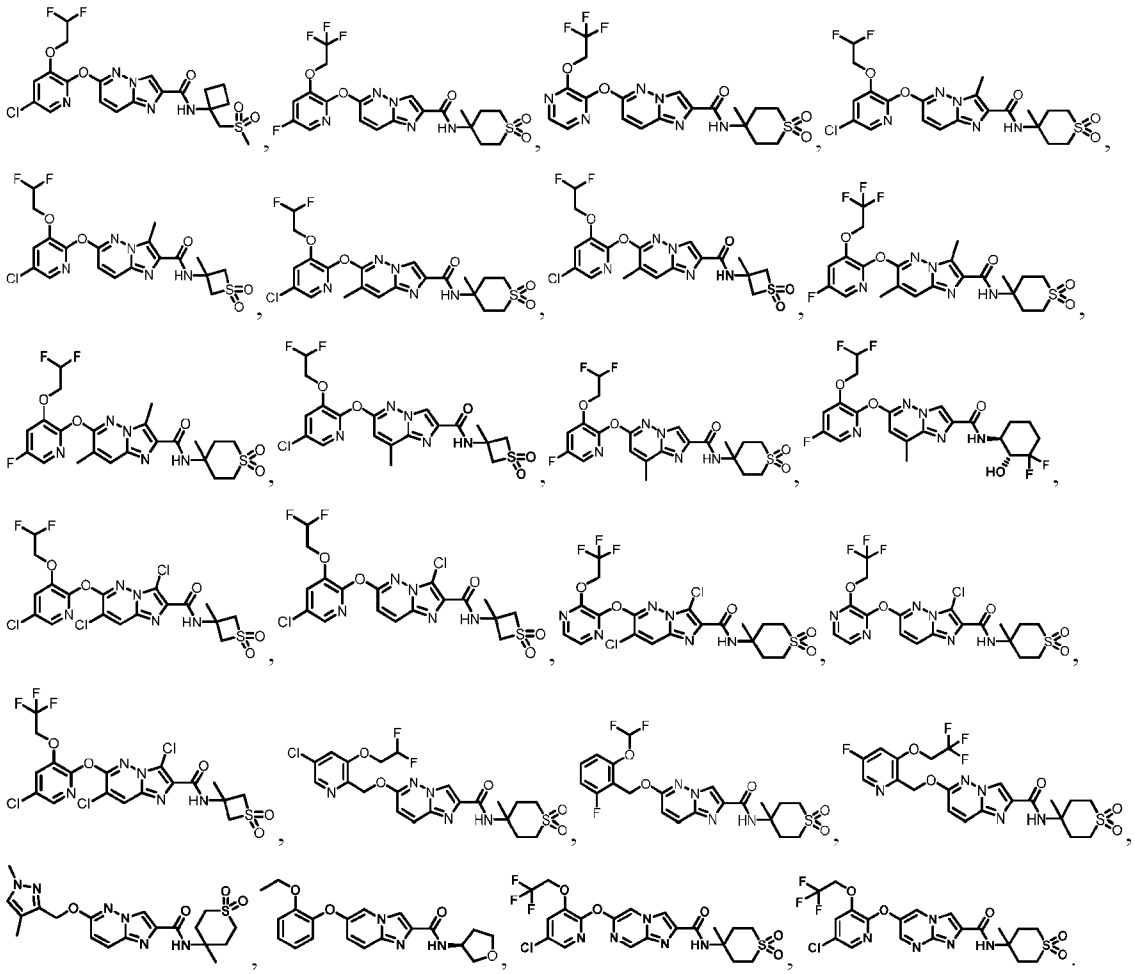












The present disclosure includes the pharmaceutically acceptable salts of the compounds defined therein.

In one embodiment, the present disclosure is a composition comprising an effective amount of at least one compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof.

The disclosure also provides a pharmaceutical composition comprising an effective amount of at least one compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The disclosure also provides a pharmaceutical composition comprising an effective amount of at least one compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, and an effective amount of at least one other pharmaceutically active ingredient (such as, for example, a chemotherapeutic agent).

The disclosure also provides a pharmaceutical composition comprising an effective amount of at least one compound of Formula I or Formula Ib, or a pharmaceutically acceptable

salt thereof, and an effective amount of at least one other pharmaceutically active ingredient (such as, for example, a chemotherapeutic agent), and a pharmaceutically acceptable carrier.

In one embodiment, the present disclosure provides a composition for treating hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases such as chronic kidney diseases or heart failure comprising an acceptable carrier and a compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof.

In one embodiment, the present disclosure provides a composition for treating hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases such as chronic kidney diseases or heart failure, comprising a compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof.

In one embodiment, the present disclosure provides a composition for treating hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases such as chronic kidney diseases or heart failure, comprising a compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In one embodiment, the present disclosure provides a method of treating hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases such as chronic kidney diseases or heart failure in a subject in need of such treatment, comprising administering to said subject a therapeutically effective amount of at least one compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof.

In one embodiment, the present disclosure provides a method of treating hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases such as chronic kidney diseases or heart failure in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of at least one compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The methods of the disclosure include the administration of a pharmaceutical composition comprising at least one compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the present disclosure includes a method of treating NASH and/or fibrosis, comprising administering to a patient in need thereof a compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present disclosure includes a method of treating NASH and/or fibrosis, comprising administering to a patient in need thereof a compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

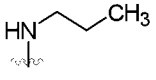
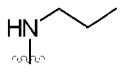
In another embodiment, the present disclosure includes a method of treating NASH and/or fibrosis, comprising administering to a patient in need thereof a composition comprising a compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present disclosure includes a method of treating NASH and/or fibrosis, comprising administering to a patient in need thereof a composition comprising a compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the present disclosure provides for the use of a compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating NASH and/or fibrosis.

In another embodiment, the present disclosure includes the use of a compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of NASH and/or fibrosis.

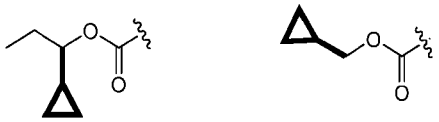
"**Alkyl**" means branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms when noted. If no number is specified, 1-6 carbon atoms are intended for linear and 3-7 carbon atoms for branched alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, *sec*- and *tert*-butyl, pentyl, hexyl, octyl, nonyl, and the like. For example, the term "$C_{1\text{-}6}$alkyl" includes all of "$C_{1\text{-}4}$alkyl" defined as follows, plus the linear or branched chain alkyl groups, including all possible isomers, having 5 or 6 carbon atoms. "$C_{1\text{-}6}$alkyl" means linear or branched chain alkyl groups, including all possible isomers, having 1, 2, 3, 4, 5 or 6 carbon atoms, and includes each of the alkyl groups within $C_{1\text{-}6}$alkyl including each of the hexyl and pentyl isomers as well as n-, iso-, sec- and tert-butyl (butyl, i-butyl, s-butyl, t-butyl, collectively "C_4alkyl"; Bu = butyl), n- and i-propyl (propyl, i-propyl, collectively "C_3alkyl"; Pr = propyl), ethyl (Et) and methyl (Me). Commonly used abbreviations for alkyl groups are used throughout the specification, e.g., methyl may be represented by conventional abbreviations including "Me" or CH_3 or a symbol that is an

extended bond as the terminal group, e.g., "ʢ—", ethyl may be represented by "Et" or CH_2CH_3, propyl may be represented by "Pr" or $CH_2CH_2CH_3$, butyl may be represented by "Bu" or $CH_2CH_2CH_2CH_3$, etc. For example, the structures  and  have equivalent meanings. If no number is specified, 1-6 carbon atoms are intended for linear or branched alkyl groups.

"**Alkoxy**" refers to an alkyl group linked to oxygen. Examples of alkoxy groups include methoxy, ethoxy, propoxy and the like.

"**Aryl**" refers to an aromatic monocyclic or multicyclic ring moiety comprising 6 to 14 ring carbon atoms. In one embodiment, an aryl group contains from about 6 to 10 ring carbon atoms. Monocyclic aryl rings include, but are not limited to, phenyl. Multicyclic rings include, but are not limited to, naphthyl and bicyclic rings, for example an 8-10 membered fused bicyclic heterocyclic ring. Aryl groups may be optionally substituted with one or more substituents as defined herein. Bonding can be through any of the carbon atoms of any ring.

"**Halogen**" or "Halo" includes fluorine, chlorine, bromine and iodine.

"**Cycloalkyl**" refers to a non-aromatic mono-or multicyclic ring system comprising about 3 to 10 ring carbon atoms. If no number of atoms is specified, 3-10 carbon atoms are intended. Cycloalkyl may also be fused, forming 1-3 carbocyclic rings. Non-limiting examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term $C_{1\text{-}6}$cycloalkyl" refers to a cycloalkyl group having 1 to 6 ring carbon atoms. The term $C_{3\text{-}6}$cycloalkyl" refers to a cycloalkyl group having 3 to 6 ring carbon atoms. Thus, for example, "$C_{3\text{-}6}$ cycloalkyl" includes each of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. A cycloalkyl group is unsubstituted or substituted with one or more ring system substituents which may be the same or different, and are as defined within. When cycloalkyl is a substituent on an alkyl group, the cycloalkyl substituent can be bonded to any available carbon in the alkyl group. The following are illustrations of -$C_{3\text{-}6}$cycloalkyl substituents on an alkyl group wherein the substituent is cyclopropyl in bold: 

"**Haloalkyl**" refers to an alkyl group as defined within, wherein one or more of the alkyl group's hydrogen atoms has been replaced with a halogen. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. Non-limiting examples of haloalkyl groups include CH_2F, CHF_2, CF_3, CH_2CF_3, CH_2CHF_2, CF_2CF_3, $CF_2CH_2CH_3$,CF_2CHF_2, -$C(CH_3)_2F$, CH_2Cl and CCl_3. The term "$C_{1\text{-}6}$haloalkyl" or "halo$C_{1\text{-}6}$alkyl"refers to a haloalkyl group having from 1 to 6 carbons.

"**Haloalkoxy**," "haloalkyl-O" and derivatives such as "halo(C_{1-6})alkoxy" are used interchangeably and refer to halo substituted alkyl groups linked through the oxygen atom. Haloalkoxy include mono- substituted as well as multiple halo substituted alkoxy groups. For example, trifluoromethoxy, chloromethoxy, and bromomethoxy are included as well as OCH_2CF_3, OCH_2CHF_2, OCF_2CF_3, $OCH_2CF_2CH_3$, $OCH_2CF_2CHF_2$, $OCHF_2$, and OCF_2CHF_2.

"**Heterocyclyl**," "heterocycle" or "heterocyclic" refers to monocyclic ring structures in which one or more atoms in the ring, the heteroatom(s), is an element other than carbon. Heteroatoms are typically O, S or N atoms. A heterocycle containing more than one heteroatom may contain different heteroatoms. Bicyclic ring moieties include fused, spirocyclic and bridged bicyclic rings and may comprise one or more heteroatoms in either of the rings. The ring attached to the remainder of the molecule may or may not contain a heteroatom. Either ring of a bicyclic heterocycle may be saturated, partially unsaturated or unsaturated. The heterocycle may be attached to the rest of the molecule via a ring carbon atom, a ring oxygen atom or a ring nitrogen atom. Examples of heterocyclyl groups include: piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, azetidinyl, oxiranyl, or aziridinyl, and the like.

"**Bicyclic heterocyclyl**," "bicyclic heterocycle" or "bicyclic heterocyclic" refers to a heterocyclic ring fused to another ring system. The fusion may be bridged or unbridged.

Except where noted, the term "**heteroaryl**", as used herein, represents a stable monocyclic, bicyclic or tricyclic ring of up to 10 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydroindolyl, dihydroquinolinyl, methylenedioxybenzene, benzothiazolyl, benzothienyl, quinolinyl, isoquinolinyl, oxazolyl, and tetra-hydroquinoline.

"**Oxo**" means an oxygen linked to an atom by a double bond. An example of an oxo group is a double bonded oxygen in a ketone, sulfoxide, sulfone, sulfate, or double bonded oxygen fused to nonaromatic cycloalkyl or heteroalkyl.

"**Hydroxyalkyl**" or "**hydroxy(C_{1-3})alkyl-**" means an alkyl group having one or more hydrogen atoms replaced by hydroxyl (-OH) groups. An example of a hydroxyalkyl is CH_2OH, $C(CH_3)_2OH$, CH_2CH_2OH, or $CH(OH)CH_3$.

"**Cyanoalkyl**" means an alkyl group having one or more hydrogen atoms replaced by cyano (-CN) groups.

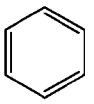
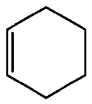
The term "**composition**" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "**at least one**" means one or more than one. The meaning of "at least one" with reference to the number of compounds of the disclosure is independent of the meaning with reference to the number of chemotherapeutic agents.

The term "**chemotherapeutic agent**" means a drug (medicament or pharmaceutically active ingredient) for treating cancer (i.e., an antineoplastic agent).

The term "**effective amount**" means a "therapeutically effective amount". The term "therapeutically effective amount" means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "**treating cancer**" or "**treatment of cancer**" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, and also refers to an effect that results in the inhibition of growth and/or metastasis of the cancer.

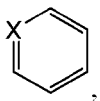
Except where noted herein, the term "**carbocycle**" (and variations thereof such as "carbocyclic" or "carbocyclyl") as used herein, unless otherwise indicated, refers to a C_3 to C_6 monocyclic ring, e.g., C_{3-6} monocyclic carbocycle. The carbocycle may be attached to the rest of the molecule at any carbon atom which results in a stable compound. Saturated carbocyclic rings include, for example, "cycloalkyl" rings, e.g., cyclopropyl, cyclobutyl, etc. Unsaturated carbocyclic rings include, for example   .

A "**stable**" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject).

The compounds of the present disclosure are limited to stable compounds embraced by Formula I or Formula Ib and its embodiments. For example, certain moieties as defined in Formula I or Formula Ib, may be unsubstituted or substituted, and the latter is intended to encompass substitution patterns (i.e., number and kind of substituents) that are chemically possible for the moiety and that result in a stable compound.

The term "**substituted**" means that one or more hydrogens on the designated atom is replaced with a selected from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure result. By optionally substituted, it is meant that compounds containing the specified optional substituent(s) as well as compounds that do not contain the optional substituent(s).

The wavy line , as used herein, indicates a point of attachment to the rest of the compound, for example,  .

Where ring atoms are represented by variables such as "X", e.g.,  , the variables are defined by indicating the atom located at the variable ring position without depicting the ring bonds associated with the atom. For example, when X in the above ring is nitrogen, the definition will show "N" and will not depict the bonds associated with it, e.g., will not show "=N-". Likewise, when X is a carbon atom that is substituted with bromide, the definition will show "C-Br" and will not depict the bonds associated with it, e.g., will not show  .

The disclosure also includes derivatives of the compound of Formula I or Formula Ib, acting as prodrugs and solvates. Any pharmaceutically acceptable pro-drug modification of a compound of Formula I or Formula Ib which results in conversion in vivo to a compound within the scope of the Formula I or Formula Ib is also within the scope of the disclosure. Prodrugs, following administration to the patient, are converted in the body by normal metabolic or chemical processes, such as through hydrolysis in the blood, to the compound of Formula I or

Formula Ib. Such prodrugs include those that demonstrate enhanced bioavailability, tissue specificity, and/or cellular delivery, to improve drug absorption of the compound of I. The effect of such prodrugs may result from modification of physicochemical properties such as lipophilicity, molecular weight, charge, and other physicochemical properties that determine the permeation properties of the drug.

For example, esters can optionally be made by esterification of an available carboxylic acid group or by formation of an ester on an available hydroxy group in a compound. Similarly, labile amides can be made. Pharmaceutically acceptable esters or amides of the compounds of Formula I or Formula Ib may be prepared to act as pro-drugs which can be hydrolyzed back to an acid (or -COO^- depending on the pH of the fluid or tissue where conversion takes place) or hydroxy form particularly in vivo and as such are encompassed within the scope of the invention. Included are those esters and acyl groups known in the art for modifying the solubility or hydrolysis characteristics for use as sustained-release or prodrug formulations. Examples of pharmaceutically acceptable pro-drug modifications include, but are not limited to, -C_{1-6}alkyl esters and –C_{1-6}alkyl substituted with phenyl esters.

"Celite®" (Fluka) diatomite is diatomaceous earth, and can be referred to as "celite".

When any variable (e.g., R^1 etc.) occurs more than one time in any constituent or in Formula I or Formula Ib or other generic Formula herein, its definition on each occurrence is independent of its definition at every other occurrence. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. In choosing compounds of Formula I or Formula Ib, one of ordinary skill in the art will recognize that the various substituents, i.e., R^1 etc., are to be chosen in conformity with well-known principles of chemical structure connectivity and stability. Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (e.g., aryl, a heteroaryl ring, or a saturated heterocyclic ring) provided such ring substitution is chemically allowed and results in a stable compound.

It should be noted that, if a discrepancy between the chemical name and structure exists, the structure is understood to dominate.

Compounds of structural Formula I or Formula Ib may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereoisomeric mixtures and individual diastereoisomers. Centers of asymmetry that are present in the compounds of Formula I or Formula Ib can all independently of one another have S configuration or R configuration. When bonds to the chiral carbon are depicted as straight lines in the structural Formulas herein, it is understood that both the (R) and (S) configurations of the

chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the Formulas. Similarly, when a compound name is recited without a chiral designation for a chiral carbon, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence individual enantiomers and mixtures thereof, are embraced by the name. The production of specific stereoisomers or mixtures thereof may be identified in the Examples where such stereoisomers or mixtures were obtained, but this in no way limits the inclusion of all stereoisomers and mixtures thereof from being within the scope of the disclosure.

The compounds of this disclosure include all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, enantiomers are a subject of the invention in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism the invention includes both the cis form and the trans form as well as mixtures of these forms in all ratios. The present disclosure is meant to comprehend all such stereo-isomeric forms of the compounds of structural Formula I or Formula Ib.

Compounds of structural Formula I or Formula Ib may be separated into their individual diastereoisomers by, for example, fractional crystallization from a suitable solvent, for example MeOH or EtOAc or a mixture thereof, or via chiral chromatography using an optically active stationary phase. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at an intermediate step during the synthesis of a compound of Formula I or Formula Ib, or it can be done on a final racemic product. Absolute stereochemistry may be determined by X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. Alternatively, any stereoisomer or isomers of a compound of Formula I or Formula Ib may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known absolute configuration. The present disclosure of Formula I and Formula Ib includes all such isomers, as well as salts, solvates (including hydrates) and solvated salts of such racemates, enantiomers, diastereomers and tautomers and mixtures thereof.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereoisomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is

often the formation of salts using an enantiomerically pure acid or base. The diasteromeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

For compounds of Formula I or Formula Ib described herein which contain olefinic double bonds, unless specified otherwise, they are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of Formula I or Formula Ib .

In the compounds of structural Formula I or Formula Ib, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominately found in nature. The present invention as described and claimed herein is meant to include all suitable isotopic variations of the compounds of structural Formula I or Formula Ib, and embodiments thereof. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H, also denoted herein as D). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within structural Formula I or Formula Ib, can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

It will be understood that the compounds of structural Formula I or Formula Ib may be prepared as pharmaceutically acceptable salts or as salts that are not pharmaceutically acceptable when they are used as precursors to the free compounds or their pharmaceutically acceptable salts or in other synthetic manipulations. The compounds of the present invention, including the compounds of the Examples, may also include all salts of the compounds of Formula I or Formula Ib, which, owing to low physiological compatibility, are not directly suitable for use in

pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of physiologically acceptable salts.

The compounds of Formula I or Formula Ib may be administered in the form of a pharmaceutically acceptable salt. The term "**pharmaceutically acceptable salt**" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids.

Salts of basic compounds encompassed within the term "pharmaceutically acceptable salt" refer to non-toxic salts of the compounds of Formula I or Formula Ib which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts of basic compounds of the Formula I or Formula Ib include, but are not limited to, the following: acetate, ascorbate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, camphorate, camphorsulfonate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, methanesulfonate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, propionate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, thiocyanate, tosylate, triethiodide, valerate and the like. Furthermore, where the compounds of Formula I or Formula Ib carry an acidic moiety, suitable pharmaceutically acceptable salts thereof include, but are not limited to, salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, zinc, and the like. In one embodiment, the salts of acidic compounds are as follows, the ammonium, calcium, magnesium, potassium, and sodium salts.

With basic reagents such as hydroxides, carbonates, hydrogencarbonates, alkoxides and ammonia, organic bases or alternatively basic amino acids the compounds of the Formula I or Formula Ib, form stable alkali metal, alkaline earth metal or optionally substituted ammonium salts.

Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, cyclic amines, dicyclohexyl amines and basic ion-exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine,

isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. Also included are the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

The preparation of pharmacologically acceptable salts from compounds of the Formula I and Ib, capable of salt formation, including their stereoisomeric forms, is carried out known methods, for example, by mixing a compound of Formula I or Formula Ib with an equivalent amount and a solution containing a desired acid, base, or the like, and then collecting the desired salt by filtering the salt or distilling off the solvent. The compounds of the Formula I and Formula Ib and salts thereof may form solvates with a solvent such as water, ethanol, or glycerol. The compounds of Formula I and Formula Ib may form an acid addition salt and a salt with a base at the same time according to the type of substituent of the side chain.

If the compounds of Formula I or Formula Ib simultaneously contain acidic and basic groups in the molecule, the disclosure also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). Salts can be obtained from the compounds of Formula I or Formula Ib by customary methods which are known to the person skilled in the art, for example by combination with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange from other salts.

Disclosed are compounds of structural Formula I or Formula Ib, as well as salts thereof, particularly pharmaceutically acceptable salts, solvates of such compounds and solvated salt forms thereof, where such forms are possible unless specified otherwise.

Furthermore, compounds of Formula I and Formula Ib may exist in amorphous form and/or one or more crystalline forms, and as such all amorphous and crystalline forms and mixtures thereof of the compounds of Formula I or Formula Ib, including the Examples, are intended to be included within the scope of the present disclosure. In addition, some of the compounds of the instant disclosure may form solvates with water (i.e., a hydrate) or common organic solvents such as but not limited to EtOAc. Such solvates and hydrates, particularly the pharmaceutically acceptable solvates and hydrates, of the instant compounds are likewise encompassed within the scope of this disclosure, along with un-solvated and anhydrous forms.

Accordingly, the compounds within the generic structural formulas, embodiments and specific compounds described in the Examples and claimed herein encompass salts, all possible

stereoisomers and tautomers, physical forms (e.g., amorphous and crystalline forms), solvate and hydrate forms thereof and any combination of these forms, as well as the salts, pro-drug forms thereof, and salts of pro-drug forms thereof, where such forms are possible unless specified otherwise.

Also provided are medicaments containing at least one compound of the Formula I or Formula Ib, and/or of a pharmaceutically acceptable salt of the compound of the Formula I or Formula Ib and/or an optionally stereoisomeric form of the compound of the Formula I or Formula Ib, or a pharmaceutically acceptable salt of the stereoisomeric form of the compound of Formula I or Formula Ib, or a pharmaceutically acceptable solvate of the compound Formula I or Formula Ib, or a pharmaceutically acceptable salt of the pharmaceutically acceptable solvate of the compound of Formula I or Formula Ib, or a prodrug of the compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt or solvate of the prodrug of the compound of Formula I or Formula Ib, or a polymorphic form of the compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt, solvate or prodrug of the polymorphic form of the compound of Formula I or Formula Ib, together with a pharmaceutically acceptable vehicle, carrier, additive and/or other active substances and auxiliaries.

The medicaments desribed herein can be administered by oral, inhalative, rectal or transdermal administration or by subcutaneous, intraarticular, intraperitoneal or intravenous injection. Oral administration is preferred.

Also provided is a process for the production of a medicament, which comprises bringing at least one compound of the Formula I or Formula Ib, or a pharmaceutically acceptable salt, solvate, prodrug or polymorphic form thereof, into a suitable administration form using a pharmaceutically acceptable carrier and optionally further suitable active substances, additives or auxiliaries.

Provided herein are processes for the preparation of the compounds of Formula I or Formula Ib which are described in the following and by which the compounds of Formula I and Formula Ib and the pharmaceutically acceptable salts, solvates, prodrugs or polymorphic forms thereof are obtainable.

The terms "**therapeutically effective** (or efficacious) amount" and similar descriptions such as "an amount efficacious for treatment" are intended to mean that amount of a pharmaceutical drug that will alleviate the symptoms of the disorder, condition or disease being treated (i.e., disorder, condition or disease associated with DGAT2 activity) in an animal or human. The terms "prophylactically effective (or efficacious) amount" and similar descriptions such as "an amount efficacious for prevention" are intended to mean that amount of a

pharmaceutical drug that will prevent or reduce the symptoms or occurrence of the disorder, condition or disease being treated (i.e., disorder, condition or disease associated with DGAT2 activity) in an animal or human. The dosage regimen utilizing a compound of the instant Formula I or Formula Ib or a pharmaceutically acceptable salt, solvate, prodrugs or polymorphic form thereof is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the potency of the compound chosen to be administered; the route of administration; and the renal and hepatic function of the patient. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amount needed to prevent, counter, or arrest the progress of the condition. It is understood that a specific daily dosage amount can simultaneously be both a therapeutically effective amount, e.g., for treatment of hepatic steatosis, diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, and a prophylactically effective amount, e.g., for treatment of NASH.

Disorders, conditions and diseases which can be treated or prevented by inhibiting DGAT2 by using the compounds of Formula I or Formula Ib are, for example, diseases such as non-alcoholic steatohepatitis (NASH), hepatic fibrosis, hyperlipidemia, type I diabetes, type II diabetes mellitus, cognitive decline, dementia, coronary heart disease, ischemic stroke, restenosis, peripheral vascular disease, intermittent claudication, myocardial infarction, dyslipidemia, post-prandial lipemia, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, hypertriglyceridemia, insulin resistance, impaired glucose tolerance, erectile dysfunction, skin and connective tissue disorders, hyper-apo B lipoproteinemia, non-alcoholic fatty liver disease, cardiorenal diseases such as chronic kidney diseases and heart failure, and related diseases and conditions.

The compounds of Formula I or Formula Ib and their pharmaceutically acceptable salts, solvates, prodrugs and polymorphic forms can be administered to animals, preferably to mammals, and in particular to humans, as pharmaceuticals by themselves, in mixtures with one another or in the form of pharmaceutical preparations. The compounds of Formula I or Formula Ib and their pharmaceutically acceptable salts, solvates, prodrugs and polymorphic forms can be administered to animals, including dogs and cats, as pharmaceuticals by themselves, in mixtures

with one another or in the form of pharmaceutical preparations. The term "patient" includes animals, preferably mammals and especially humans, who use the instant active agents for the prevention or treatment of a medical condition. Administering of the drug to the patient includes both self-administration and administration to the patient by another person. The patient may need, or desire, treatment for an existing disease or medical condition, or may be in need of or desire prophylactic treatment to prevent or reduce the risk of occurrence of said disease or medical condition. As used herein, a patient "in need" of treatment of an existing condition or of prophylactic treatment encompasses both a determination of need by a medical professional as well as the desire of a patient for such treatment.

Furthermore, provided herein are pharmaceutical preparations (or pharmaceutical compositions) which comprise as active component a therapeutically effective dose of at least one compound of Formula I or Formula Ib and/or a pharmaceutically acceptable salt, solvate, prodrug, or polymorphic form thereof and a customary pharmaceutically acceptable carrier, i.e., one or more pharmaceutically acceptable carrier substances and/or additives.

Thus, an aspect of the present disclosure is, for example, said compound and its pharmaceutically acceptable salts for use as a pharmaceutical, pharmaceutical preparations which comprise as active component a therapeutically effective dose of said compound and/or a pharmaceutically acceptable salt thereof and a customary pharmaceutically acceptable carrier, and the uses of said compound and/or a pharmaceutically acceptable salt thereof in the therapy or prophylaxis of the above mentioned syndromes as well as their use for preparing medicaments for these purposes.

The pharmaceuticals described herein can be administered orally, for example in the form of pills, tablets, lacquered tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the form of suppositories. Administration can also be carried out parenterally, for example subcutaneously, intramuscularly or intravenously in the form of solutions for injection or infusion. Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, tinctures, sprays or transdermal therapeutic systems, or the inhalative administration in the form of nasal sprays or aerosol mixtures, or, for example, microcapsules, implants or rods. The preferred administration form depends, for example, on the disease to be treated and on its severity.

For the production of pills, tablets, sugar-coated tablets and hard gelatin capsules it is possible to use, for example, lactose, starch, for example maize starch, or starch derivatives, talc, stearic acid or its salts, etc. Carriers for soft gelatin capsules and suppositories are, for example,

fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carriers for the preparation of solutions, for example of solutions for injection, or of emulsions or syrups are, for example, water, physiologically sodium chloride solution, alcohols such as ethanol, glycerol, polyols, sucrose, invert sugar, glucose, mannitol, vegetable oils, etc. It is also possible to lyophilize the compounds of Formula I or Formula Ib and their pharmaceutically acceptable salts, solvates, solvates, and prodrugs thereof and to use the resulting lyophilisates, for example, for preparing preparations for injection or infusion. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid.

Suitable solid or galenical preparation forms are, for example, granules, powders, coated tablets, tablets, (micro)capsules, suppositories, syrups, juices, suspensions, emulsions, drops or injectable solutions and preparations having prolonged release of active substance, in whose preparation customary excipients such as vehicles, disintegrants, binders, coating agents, swelling agents, glidants or lubricants, flavorings, sweeteners and solubilizers are used. Frequently used auxiliaries which may be mentioned are magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, lactose, gelatin, starch, cellulose and its derivatives, animal and plant oils such as cod liver oil, sunflower, peanut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and mono- or polyhydric alcohols such as glycerol.

Besides the active compounds and carriers, the pharmaceutical preparations can also contain customary additives, for example fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, dispersants, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants.

The dosage of the active compound of Formula I or Formula Ib and/or of a pharmaceutically acceptable salt, solvate, prodrug or polymorphic form thereof to be administered depends on the individual case and is, as is customary, to be adapted to the individual circumstances to achieve an optimum effect. Thus, it depends on the nature and the severity of the disorder, condition or disease to be treated, and also on the sex, age, weight and individual responsiveness of the human or animal to be treated, on the efficacy and duration of action of the compounds used, on whether the therapy is acute or chronic or prophylactic, or on whether other active compounds are administered in addition to compounds of Formula I or Formula Ib.

Combination Agents

The compounds of Formula I and Formula Ib, their salt, solvates, prodrugs and polymorphic forms thereof can be administered alone or in combination with one or more additional therapeutic agents disclosed herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments the one or more compounds of Formula I or Formula Ib will be co-administered with other agents as described herein. When used in combination therapy, the compounds described herein are administered with the second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound of Formula I or Ib and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of Formula I or Ib and any of the agents described above can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound of Formula I or Ib can be administered just followed by any of the agents described above, or vice versa. In some embodiments of the separate administration protocol, a compound of Formula I or Ib and any of the agents described above are administered a few minutes apart, or a few hours apart, or a few days apart.

Contemplated within this disclosure is the treatment of the disease/conditions with a combination of pharmaceutically active compounds that may be administered separately. The disclosure further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of Formula I or Ib, and a second pharmaceutical compound. The kit comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet. Additional examples of containers include syringes, boxes, and bags. In some embodiments, the kit comprises directions for the use of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (*e.g.*, oral, parenteral; IV, transdermal and subcutaneous), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing health care professional.

One or more additional pharmacologically active agents may be administered in combination with a compound of Formula I or Formula Ib. An additional active agent (or agents) is intended to mean a pharmaceutically active agent (or agents) that is active in the body, including pro-drugs that convert to pharmaceutically active form after administration, which are different from the compound of Formula I or Formula Ib and also includes free-acid, free-base and pharmaceutically acceptable salts of said additional active agents. Generally, any suitable

additional active agent or agents, including but not limited to anti-hypertensive agents, anti-obetic, anti-inflammatory, anti-fibrotic, and anti-atherosclerotic agents such as a lipid modifying compound, anti-diabetic agents and/or anti-obesity agents may be used in any combination with the compound of Formula I or Formula Ib in a single dosage formulation (a fixed dose drug combination), or may be administered to the patient in one or more separate dosage formulations which allows for concurrent or sequential administration of the active agents (co-administration of the separate active agents).

Examples of additional active agents which may be employed include but are not limited to angiotensin converting enzyme inhibitors (e.g., alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, moveltipril, perindopril, quinapril, ramipril, spirapril, temocapril, or trandolapril), angiotensin II receptor antagonists (e.g., losartan i.e., COZAAR®, valsartan, candesartan, olmesartan, telmesartan and any of these drugs used in combination with hydrochlorothiazide such as HYZAAR®); neutral endopeptidase inhibitors (e.g., thiorphan and phosphoramidon), aldosterone antagonists, aldosterone synthase inhibitors, renin inhibitors (e.g., urea derivatives of di- and tri-peptides, amino acids and derivatives, amino acid chains linked by non-peptidic bonds, di- and tri-peptide derivatives, peptidyl amino diols and peptidyl beta-aminoacyl aminodiol carbamates; also, and small molecule renin inhibitors including diol sulfonamides and, N-morpholino derivatives, N-heterocyclic alcohols and pyrolimidazolones; also, pepstatin derivatives and fluoro- and chloro-derivatives of statone-containing peptides, enalkrein, remikiren, A 65317, terlakiren, ES 1005, ES 8891, SQ 34017, aliskiren, SPP600, SPP630 and SPP635), endothelin receptor antagonists, phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalfil and vardenafil), vasodilators, calcium channel blockers (e.g., amlodipine, nifedipine, veraparmil, diltiazem, gallopamil, niludipine, nimodipins, nicardipine), potassium channel activators (e.g., nicorandil, pinacidil, cromakalim, minoxidil, aprilkalim, loprazolam), diuretics (e.g., hydrochlorothiazide), sympatholitics, beta-adrenergic blocking drugs (e.g., propranolol, atenolol, bisoprolol, carvedilol, metoprolol, or metoprolol tartate), alpha adrenergic blocking drugs (e.g., doxazosin, prazosin or alpha methyldopa) central alpha adrenergic agonists, peripheral vasodilators (e.g., hydralazine); lipid lowering agents e.g., HMG-CoA reductase inhibitors such as simvastatin and lovastatin which are marketed as ZOCOR® and MEVACOR® in lactone pro-drug form and function as inhibitors after administration, and pharmaceutically acceptable salts of dihydroxy open ring acid HMG-CoA reductase inhibitors such as atorvastatin (particularly the calcium salt sold in LIPITOR®), rosuvastatin (particularly the calcium salt sold in CRESTOR®), pravastatin (particularly the sodium salt sold in PRAVACHOL®), fluvastatin (particularly the sodium salt sold in

LESCOL®), cerivastatin, and pitavastatin; a cholesterol absorption inhibitor such as ezetimibe (ZETIA®) and ezetimibe in combination with any other lipid lowering agents such as the HMG-CoA reductase inhibitors noted above and particularly with simvastatin (VYTORIN®) or with atorvastatin calcium; niacin in immediate-release or controlled release forms, and/or with an HMG-CoA reductase inhibitor; niacin receptor agonists such as acipimox and acifran, as well as niacin receptor partial agonists; anti-cholesterol agents such as PCSK9 inhibitors (alirocumab, evolocumab), Nexletol™ (bempedoic acid, ACL inhibitor), and Vascepa® (Icosapent ethyl); metabolic altering agents including insulin and insulin mimetics (e.g., insulin degludec, insulin glargine, insulin lispro), dipeptidyl peptidase-IV (DPP-4) inhibitors (e.g., sitagliptin, alogliptin, omarigliptin, linagliptin, vildagliptin); insulin sensitizers, including (i) β-klotho/FGFR1 activating monoclonal antibody (e.g., MK-3655), pan FGFR1-4/KLB modulators, FGF19 analogue (e.g., Aldafermin) (ii) PPARγ agonists, such as the glitazones (e.g., pioglitazone, AMG 131, mitoglitazone, lobeglitazone, rosiglitazone, and balaglitazone), and other PPAR ligands, including (1) PPARα/γ dual agonists (e.g.ZYH2, ZYH1, GFT505, chiglitazar, muraglitazar, aleglitazar, sodelglitazar, and naveglitazar); (2) PPARα agonists such as fenofibric acid derivatives (e.g., gemfibrozil, clofibrate, ciprofibrate, fenofibrate, bezafibrate), (3) selective PPARγ modulators (SPPARγM's), (e.g., such as those disclosed in WO 02/060388, WO 02/08188, WO 2004/019869, WO 2004/020409, WO 2004/020408, and WO 2004/066963); (4) PPARγ partial agonists, (5) PPAR α/δ dual agonists (e.g., Elafibranor); (iii) biguanides, such as metformin and its pharmaceutically acceptable salts, in particular, metformin hydrochloride, and extended-release formulations thereof, such as Glumetza™, Fortamet™, and GlucophageXR™; and (iv) protein tyrosine phosphatase-1B (PTP-1B) inhibitors (e.g., ISIS-113715 and TTP814); insulin or insulin analogs (e.g., insulin detemir, insulin glulisine, insulin degludec, insulin glargine, insulin lispro and inhalable formulations of each); leptin and leptin derivatives and agonists; amylin and amylin analogs (e.g., pramlintide); sulfonylurea and non-sulfonylurea insulin secretagogues (e.g., tolbutamide, glyburide, glipizide, glimepiride, mitiglinide, meglitinides, nateglinide and repaglinide); α-glucosidase inhibitors (e.g., acarbose, voglibose and miglitol); glucagon receptor antagonists (e.g., MK-3577, MK-0893, LY-2409021 and KT6-971); incretin mimetics, such as GLP-1, GLP-1 analogs, derivatives, and mimetics; and GLP-1 receptor agonists (e.g., dulaglutide, semaglutide, albiglutide, exenatide, liraglutide, lixisenatide, taspoglutide, CJC-1131, and BIM-51077, including intranasal, transdermal, and once-weekly formulations thereof), bile acid sequestering agents (e.g., colestilan, colestimide, colesevalam hydrochloride, colestipol, cholestyramine, and dialkylaminoalkyl derivatives of a cross-linked dextran), acyl CoA:cholesterol acyltransferase inhibitors, (e.g., avasimibe); antiobesity

compounds; agents intended for use in inflammatory conditions, such as aspirin, non-steroidal anti-inflammatory drugs or NSAIDs, glucocorticoids, and selective cyclooxygenase-2 or COX-2 inhibitors; glucokinase activators (GKAs) (e.g., AZD6370); inhibitors of 11β-hydroxysteroid dehydrogenase type 1, (e.g., such as those disclosed in U.S. Patent No. 6,730,690, and LY-2523199); CETP inhibitors (e.g., anacetrapib, torcetrapib, and evacetrapib); inhibitors of fructose 1,6-bisphosphatase, (e.g., such as those disclosed in U.S. Patent Nos. 6,054,587; 6,110,903; 6,284,748; 6,399,782; and 6,489,476); inhibitors of acetyl CoA carboxylase-1 or 2 (ACC1 or ACC2); AMP-activated Protein Kinase (AMPK) activators; other agonists of the G-protein-coupled receptors: (i) GPR-109, (ii) GPR-119 (e.g., MBX2982 and PSN821), and (iii) GPR-40 (e.g., TAK875); SSTR3 antagonists (e.g., such as those disclosed in WO 2009/001836); neuromedin U receptor agonists (e.g., such as those disclosed in WO 2009/042053, including, but not limited to, neuromedin S (NMS)); SCD modulators (e.g., Aramchol); GPR-105 antagonists (e.g., such as those disclosed in WO 2009/000087); glucose pathway modulators such as SGLT inhibitors (e.g., ASP1941, SGLT-3, SGLT-2 such as empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin, BI-10773, remogloflozin, TS-071, tofogliflozin, ipragliflozin, and LX-4211); dual SGLT-1/2 inhibitor (e.g., licogliflozin), Glucose-6-P dehydrogenase inhibitor (e.g., fluasterone) LAPS glucagon combo (e.g., HM14320), SGLT-1 inhibitor (e.g., SGL5213)); inhibitors of acyl coenzyme A carboxylase (ACC, MK-4074); inhibitors of diacylglycerol acyltransferase 1 and 2 (DGAT-1 and DGAT-2); inhibitors of fatty acid synthase; inhibitors of acyl coenzyme A:monoacylglycerol acyltransferase 1 and 2 (MGAT-1 and MGAT-2); agonists of the TGR5 receptor (also known as GPBAR1, BG37, GPCR19, GPR131, and M-BAR); ileal bile acid transporter inhibitors; bile acid modulators; PACAP, PACAP mimetics, and PACAP receptor 3 agonists; IL-1b antibodies, (e.g., XOMA052 and canakinumab); anti-fibrotic and/or anti-inflammatory agents (CCR2/CCR5 dual receptor antagonist (e.g., cenicriviroc); galectin 3 inhibitor (e.g., belapectin, GB-1107, GB-1211), siRNA against HSP 47 (e.g., BMS-986263); NSAID derived from pirfenidone (e.g., hydronidone), A3AR agonist (e.g., namodenoson, FM101); TGFTX4 (e.g., nitazoxanide); 5-lipoxygenase inhibitor (e.g., tipelukast), Bifunctional urate inhibitor (e.g., ACQT1127), adiponectin receptor agonist (e.g., ALY688), TNF receptor antagonist (e.g., atrosimab), Autotaxin inhibitor (e.g., BLD-0409, TJC 0265, TJC 0316), CCL24 blocking monoclonal antibody (e.g., CM101), IL-11 inhibitor (e.g., ENx 108A), LPA1 receptor antagonist (e.g., EPGN 696), Dual JAK1/2 inhibitor (e.g., EX 76545), GPR antagonist (e.g., GPR91 antagonist), Integrin av b1, avb3 and av b6 inhibitor (e.g., IDL 2965), NLRP3 antagonist (e.g., IFM-514), inflammasome inhibitors (e.g., JT194, JT349), Cell membrane permeability inhibitor (e.g., Larazotide), CCR5 antagonist (e.g., Ieronlimab), TNF inhibitor (e.g., LIVNate),

integrin avβ6 inhibitor (e.g., MORF beta6), NLRP inflammasome antagonists, siRNA (e.g., OLX 701), dual TFGβ/Hedgehog inhibitor (e.g., Oxy 200), GPR40 agonist/GPR84 antagonist (e.g., PBI-4547), neutrophil elastase inhibitor (e.g., PHP-303), integrin inhibitor (e.g., PLN-1474), TGFβ1 modulator (e.g.PRM-151), CCK receptor antagonist (e.g., proglumide), LOXL2 inhibitor (e.g., PXS-5338K, PXS-5382A), IL-11 inhibitors, MPYS protein inhibitor (e.g., cGAS/STING antagonists), kinase inhibiting RNase, membrane protein mAbs, tumor necrosis factor inhibitor, NRF2 activator (e.g., SCO 116), SSAO inhibitor (e.g., TERN 201), TRAIL2 agonist (e.g., TLY012), IL-6 receptor antagonist (e.g., TZLS 501), AOC3 inhibitor (e.g., UD-014), SSAO/VAP-1 inhibitor, TREM2); anti-oxidant (e.g., vitamin E); anti-inflammatory agents (e.g., norfloxacin, ciprofloxacin, ceftriaxone); coagulation modifiers (e.g., anti-coagulants, anti-platelet agents, pentoxifylline, vitamin K, DDAVP); dual GIP and GLP-1 receptor agonist (e.g., tirzepetide); dual GLP-1/GRA (e.g., cotadutide, ALT-801, DD 01, G49, PB-718); dual GLP-1 (e.g., CT 868); GLP-1/GRA/GIP triple agonist (e.g., HM15211); GRP120 stimulant/inflammasome modulator/PPAR□ dual agonist (e.g., KDT501); GLP-1/FGF21 (e.g., YH25724); GLP-1 agonist (e.g., Ozempic (semaglutide sc), XW 003); selective thyroid hormone receptor-β agonist (e.g., resmetirom); apoptosis modulators (JNK-1 inhibitor (e.g., CC-90001), Peroxidase inhibitor (e.g., AZM198), ASK-1 inhibitor (e.g., CS-17919, SRT 015)); erythropoietin-stimulating agents (erythropoietin receptor agonist (e.g., cibinetide)); immune modulators (TLR4 inhibitor (e.g., GBK-233), immunomodulatory polyclonal antibody (e.g., IMM-124E), TLR4 antagonist (e.g., JKB-122), CD3 monoclonal antibody (e.g., foralumab), TLR4 antagonist (e.g., JKB 133), TLR4 inhibitor (e.g., mosedipimod), Macrophage inhibitor via CD206 targeting (e.g., MT2002), TLR2/4 antagonist (e.g., VB-201, VB-703), immunomodulatory polyclonal antibody (e.g., IMM-124E)); incretin-based therapies (GLP-1 agonist (e.g., Ozempic (semaglutide sc), XW 003), GLP-1/glucagon dual receptor agonist (e.g., HM12525A), prandial insulin (e.g., ORMD 0801)); lipid modulators (AMPK Activator/ Glutathione transferase (e.g., oltipraz), THR-beta agonist (e.g., resmetirom, VK2809, MGL-3745, ALG-009, ASC41, CNPT-101101, TERN 501), IBAT inhibitor (e.g., elobixibat, CJ 14199), omega-6- fatty acid (e.g., epeleuton), FASN inhibitor (e.g., TVB2640, FT 4101, FT 8225), ANGPTL3 inhibitor (e.g., vupanorsen), PNPLA3 inhibitor (e.g., AZD2693), RAS domain kinase inhibitor (e.g., BioE1115), NTCP inhibitor (e.g., bulevirtide), P2Y13 receptor agonist (e.g., CER-209), omega-3 fatty acid, HSD17β13 inhibitor; metabolism modulators (FXR agonist (e.g., Ocaliva (obeticholic acid), IOT022), recombinant variant of FGF19 (e.g., aldafermin), bi-specific FGFR1/KLB antibody (e.g., BFKB8488A), mTOT modulator (e.g., MSDC-0602K), pegylated analog of FGF21 (e.g., pegbelfermin, BMS-986171), non-bile FXR agonist (e.g.,

cilofexor, EDP-305, EYP 001, tropifexor, MET409, AGN-242256, AGN-242266, EDP 297, HPG 1860, MET642, RDX023, TERN 101), ACC inhibitor (e.g., firsocostat, PF-05221304), ketohexokinase inhibitor (e.g., PF-06835919), AMPK activator (e.g., PXL770, MSTM 101, O304), bile acid modulator (e.g., Albiero), FGF21 analog (e.g., BIO89-100), MOTSc analog (e.g., CB4211), cyclophilin inhibitor (e.g., CRV 431), FGF19 (e.g., DEL 30), mitochondrial uncoupler (e.g., GEN 3026), FXR/GPCR dual agonist (e.g., INT-767), Cysteamine derivative (e.g., KB-GE-001), dual amylin and calcitonin receptor agonist (e.g., KBP-089), transient FXR agonist (e.g., M 1217), anti-beta-klotho (KLB)-FGFR1c receptor complex mAb (e.g., MK3655), GDF15 analog (e.g., NGM395), cyclophilin inhibitor (e.g., NV556), LXR modulator (e.g., PX 329, PX 655, PX 788), LXR inverse agonist (e.g., PX016), deuterated obeticholic acid (e.g., ZG 5216)); PPAR modulators (dual PPARα/γ agonist (e.g., elafibranor), PPAR pan agonist (e.g., lanifibranor), PPARα agonists (e.g., Parmodia), PPARγ agonist (e.g., CHS 131), MPC inhibitor (e.g., PXL065), PPAR δ/γ agonist (e.g.T3D 959)); RAAS mIMModulators (mineralocorticoid receptor antagonist (e.g., apararenone, eplerenone, spironolactone), angiotensin receptor blocker (e.g., losartan potassium)); neurotransmitter modulators (cannabinoid receptor modulator, CB1 receptor antagonist (e.g., CRB-4001, IM-102, nimacimab), TPH1 inhibitor (e.g., CU 02), GPR120 agonist (e.g., KBR2001), combination of cannabinoid and botanical anti-inflammatory compound (e.g., SCN 002)); PDE Modulator (PDE4 inhibitor (e.g., ART 648)); CYP2E1 inhibitor (e.g., SNP-610); cell therapies (e.g., HepaStem)and bromocriptine mesylate and rapid-release formulations thereof; or with other drugs beneficial for the prevention or the treatment of the above-mentioned diseases including nitroprusside and diazoxide the free-acid, free-base, and pharmaceutically acceptable salt forms of the above active agents where chemically possible.

The present invention includes the pharmaceutically acceptable salts of the compounds defined herein, including the pharmaceutically acceptable salts of all structural formulas, embodiments and classes defined herein. Reference to the compounds of structural Formula I or Ib includes the compounds of other generic structural Formulas, such as Formulas and embodiments that fall within the scope of Formula I or Ib.

Dosages of the Compounds of Formula I or Ib

If the patient is responding, or is stable, after completion of the therapy cycle, the therapy cycle can be repeated according to the judgment of the skilled clinician. Upon completion of the therapy cycles, the patient can be continued on the compounds of the invention at the same dose that was administered in the treatment protocol. This maintenance dose can be continued until the patient progresses or can no longer tolerate the dose (in which case the dose can be reduced and the patient can be continued on the reduced dose).

Those skilled in the art will recognize that the actual dosages and protocols for administration employed in the methods disclosed herein may be varied according to the judgment of the skilled clinician. The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. A determination to vary the dosages and protocols for administration may be made after the skilled clinician considers such factors as the patient's age, condition and size, as well as the severity of the condition being treated and the response of the patient to the treatment.

The dosage regimen utilizing a compound of Formula I or Formula Ib ,or a pharmaceutically acceptable salt, solvate, prodrug or polymorphic form thereofis selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the potency of the compound chosen to be administered; the route of administration; and the renal and hepatic function of the patient. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amount needed to prevent, counter, or arrest the progress of the condition. It is understood that a specific daily dosage amount can simultaneously be both a therapeutically effective amount, *e.g.*, for treatment of an oncological condition, and a prophylactically effective amount, *e.g.*, for prevention of an oncological condition.

While individual needs vary, determination of optimal ranges of effective amounts of the compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt, solvate, prodrug or polymorphic form thereof is within the skill of the art. For administration to a human in the curative or prophylactic treatment of the conditions and disorders identified herein, for example, typical dosages of the compounds of Formula I or Formula Ib can be about 0.05 mg/kg/day to about 50 mg/kg/day, for example at least 0.05 mg/kg, at least 0.08 mg/kg, at least 0.1 mg/kg, at least 0.2 mg/kg, at least 0.3 mg/kg, at least 0.4 mg/kg, or at least 0.5 mg/kg, and preferably 50 mg/kg or less, 40 mg/kg or less, 30 mg/kg or less, 20 mg/kg or less, or 10 mg/kg or less, which can be about 2.5 mg/day (0.5 mg/kg x 5 kg) to about 5000 mg/day (50 mg/kg x 100 kg), for example. For example, dosages of the compounds can be about 0.1 mg/kg/day to about 50 mg/kg/day, about 0.05 mg/kg/day to about 10 mg/kg/day, about 0.05 mg/kg/day to about 5 mg/kg/day, about 0.05 mg/kg/day to about 3 mg/kg/day, about 0.07 mg/kg/day to about 3 mg/kg/day, about 0.09 mg/kg/day to about 3 mg/kg/day, about 0.05 mg/kg/day to about 0.1 mg/kg/day, about 0.1 mg/kg/day to about 1 mg/kg/day, about 1 mg/kg/day to about 10 mg/kg/day, about 1 mg/kg/day to about 5 mg/kg/day, about 1 mg/kg/day to about 3 mg/kg/day,

about 3 mg/day to about 500 mg/day, about 5 mg/day to about 250 mg/day, about 10 mg/day to about 100 mg/day, about 3 mg/day to about 10 mg/day, or about 100 mg/day to about 250 mg/day. Such doses may be administered in a single dose or may be divided into multiple doses.

Pharmaceutical Compositions

The compounds of Formula I or Formula Ib and their pharmaceutically acceptable salts, solvates, prodrugs and polymorphic forms thereof can be administered to animals, preferably to mammals, and in particular to humans, as pharmaceuticals by themselves, in mixtures with one another or in the form of pharmaceutical compositions. The term "subject" or "patient" includes animals, preferably mammals and especially humans, who use the instant active agents for the prevention or treatment of a medical condition.

Administering of the compound of Formula I or Formula Ib or a pharmaceutically acceptable salt, solvate, prodrug or polymorphic form thereof to the subject includes both self-administration and administration to the patient by another person. The subject may need, or desire, treatment for an existing disease or medical condition, or may be in need of or desire prophylactic treatment to prevent or reduce the risk of occurrence of said disease or medical condition. As used herein, a subject "in need" of treatment of an existing condition or of prophylactic treatment encompasses both a determination of need by a medical professional as well as the desire of a patient for such treatment.

If the patient is responding, or is stable, after completion of the therapy cycle, the therapy cycle can be repeated according to the judgment of the skilled clinician. Upon completion of the therapy cycles, the patient can be continued on the compounds of Formula I or Formula Ib or pharmaceutically acceptable salts, solvates, prodrugs or polymorphic forms thereofat the same dose that was administered in the treatment protocol. This maintenance dose can be continued until the patient progresses or can no longer tolerate the dose (in which case the dose can be reduced and the patient can be continued on the reduced dose).

Those skilled in the art will recognize that the actual dosages and protocols for administration employed in the methods described herein may be varied according to the judgment of the skilled clinician. The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. A determination to vary the dosages and protocols for administration may be made after the skilled clinician takes into

account such factors as the patient's age, condition and size, as well as the severity of the condition being treated and the response of the patient to the treatment.

The amount and frequency of administration of the compound of Formula I or Formula Ib, and any additional agents will be regulated according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the patient as well as severity of the condition being treated.

The compounds of Formula I or Formula Ib, and pharmaceutically acceptable salts, solvates, prodrugs or polymorphic forms thereof, are also useful in preparing a medicament that is useful in treating NASH and fibrosis.

The instant compounds are also useful in combination with therapeutic, chemotherapeutic and anti-cancer agents for the treatment of hepatic cellular carcinoma. Combinations of the presently disclosed compounds with therapeutic, chemotherapeutic and anti-cancer agents are within the scope of the disclosure. Examples of such agents can be found in Cancer Principles and Practice of Oncology by V.T. Devita and S. Hellman (editors), 9th edition (May 16, 2011), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such agents include the following: estrogen receptor modulators, programmed cell death protein 1 (PD-1) inhibitors, programmed death-ligand 1 (PD-L1) inhibitors, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, inhibitors of cell proliferation and survival signaling, bisphosphonates, aromatase inhibitors, siRNA therapeutics, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs) and agents that interfere with cell cycle checkpoints.

The chemotherapeutic agent can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent can be varied depending on the cancer being treated and the known effects of the chemotherapeutic agent on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents on the patient, and in view of the observed responses of the cancer to the administered therapeutic agents. The particular choice of chemotherapeutic agent will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

The determination of the order of administration, and the number of repetitions of administration of the chemotherapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the condition being treated and the condition of the patient.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a chemotherapeutic agent according to the individual patient's needs, as the treatment proceeds. All such modifications are within the scope of the present disclosure.

The agent can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the anti-cancer agent can be varied depending on the cancer being treated and the known effects of the anti-cancer agent on that disease.

The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

The particular choice of agent will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

The determination of the order of administration, and the number of repetitions of administration of the agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the cancer being treated and the condition of the patient.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of cancer-related symptoms (e.g., pain), inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

The compounds, compositions and methods provided herein are useful for the treatment of cancer. Cancers that may be treated by the compounds, compositions and methods disclosed

herein include, but are not limited to: Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma.

PD-1 inhibitors include pembrolizumab (lambrolizumab), nivolumab and MPDL3280A. PDL- inhibitors include atezolizumab, avelumab, and durvalumab.

Further provided is a method of treating hepatic cellular carcinoma in a human patient comprising administration of a compound of of Formula I or Formula Ib or a pharmaceutically acceptable salt, solvate, prodrug or polymorphic form thereof and a PD-1 antagonist to the patient. The compound of Formula I or Formula Ib and the PD-1 antagonist may be administered concurrently or sequentially.

In particular embodiments, the PD-1 antagonist is an anti-PD-1 antibody, or antigen binding fragment thereof. In alternative embodiments, the PD-1 antagonist is an anti-PD-L1 antibody, or antigen binding fragment thereof. In some embodiments, the PD-1 antagonist is pembrolizumab (KEYTRUDA™, Merck & Co., Inc., Rahway, NJ, USA), nivolumab (OPDIVO™, Bristol-Myers Squibb Company, Princeton, NJ, USA), cemiplimab (LIBTAYO™, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA), atezolizumab (TECENTRIQ™, Genentech, San Francisco, CA, USA), durvalumab (IMFINZI™, AstraZeneca Pharmaceuticals LP, Wilmington, DE), or avelumab (BAVENCIO™, Merck KGaA, Darmstadt, Germany).

In some embodiments, the PD-1 antagonist is pembrolizumab. In particular sub-embodiments, the method comprises administering 200 mg of pembrolizumab to the patient about every three weeks. In other sub-embodiments, the method comprises administering 400 mg of pembrolizumab to the patient about every six weeks.

In further sub-embodiments, the method comprises administering 2 mg/kg of pembrolizumab to the patient about every three weeks. In particular sub-embodiments, the patient is a pediatric patient.

In some embodiments, the PD-1 antagonist is nivolumab. In particular sub-embodiments, the method comprises administering 240 mg of nivolumab to the patient about every two weeks. In other sub-embodiments, the method comprises administering 480 mg of nivolumab to the patient about every four weeks.

In some embodiments, the PD-1 antagonist is cemiplimab. In particular embodiments, the method comprises administering 350 mg of cemiplimab to the patient about every 3 weeks.

In some embodiments, the PD-1 antagonist is atezolizumab. In particular sub-embodiments, the method comprises administering 1200 mg of atezolizumab to the patient about every three weeks.

In some embodiments, the PD-1 antagonist is durvalumab. In particular sub-embodiments, the method comprises administering 10 mg/kg of durvalumab to the patient about every two weeks.

In some embodiments, the PD-1 antagonist is avelumab. In particular sub-embodiments, the method comprises administering 800 mg of avelumab to the patient about every two weeks.

A compound of Formula I or Formula Ib, or a pharmaceutically acceptable salt thereof, may also be useful for treating cancer in combination with the following therapeutic agents: pembrolizumab (Keytruda®), abarelix (Plenaxis depot®); aldesleukin (Prokine®); Aldesleukin (Proleukin®); Alemtuzumabb (Campath®); alitretinoin (Panretin®); allopurinol (Zyloprim®); altretamine (Hexalen®); amifostine (Ethyol®); anastrozole (Arimidex®); arsenic trioxide (Trisenox®); asparaginase (Elspar®); azacitidine (Vidaza®); bevacuzimab (Avastin®); bexarotene capsules (Targretin®); bexarotene gel (Targretin®); bleomycin (Blenoxane®); bortezomib (Velcade®); busulfan intravenous (Busulfex®); busulfan oral (Myleran®); calusterone (Methosarb®); capecitabine (Xeloda®); carboplatin (Paraplatin®); carmustine (BCNU®, BiCNU®); carmustine (Gliadel®); carmustine with Polifeprosan 20 Implant (Gliadel Wafer®); celecoxib (Celebrex®); cetuximab (Erbitux®); chlorambucil (Leukeran®); cisplatin (Platinol®); cladribine (Leustatin®, 2-CdA®); clofarabine (Clolar®); cyclophosphamide (Cytoxan®, Neosar®); cyclophosphamide (Cytoxan Injection®); cyclophosphamide (Cytoxan Tablet®); cytarabine (Cytosar-U®); cytarabine liposomal (DepoCyt®); dacarbazine (DTIC-Dome®); dactinomycin, actinomycin D (Cosmegen®); Darbepoetin alfa (Aranesp®); daunorubicin liposomal (DanuoXome®); daunorubicin, daunomycin (Daunorubicin®); daunorubicin, daunomycin (Cerubidine®); Denileukin diftitox (Ontak®); dexrazoxane (Zinecard®); docetaxel (Taxotere®); doxorubicin (Adriamycin PFS®); doxorubicin (Adriamycin®, Rubex®); doxorubicin (Adriamycin PFS Injection®); doxorubicin liposomal (Doxil®); dromostanolone propionate (Dromostanolone®); dromostanolone propionate (Masterone injection®); Elliott's B Solution (Elliott's B Solution®); epirubicin (Ellence®); Epoetin alfa (epogen®); erlotinib (Tarceva®); estramustine (Emcyt®); etoposide phosphate (Etopophos®); etoposide, VP-16 (Vepesid®); exemestane (Aromasin®); Filgrastim (Neupogen®); floxuridine (intraarterial) (FUDR®); fludarabine (Fludara®); fluorouracil, 5-FU (Adrucil®); fulvestrant (Faslodex®); gefitinib (Iressa®); gemcitabine (Gemzar®); gemtuzumab ozogamicin (Mylotarg®); goserelin acetate (Zoladex Implant®); goserelin acetate (Zoladex®);

histrelin acetate (Histrelin implant®); hydroxyurea (Hydrea®); Ibritumomab Tiuxetan (Zevalin®); idarubicin (Idamycin®); ifosfamide (IFEX®); imatinib mesylate (Gleevec®); interferon alfa 2a (Roferon A®); Interferon alfa-2b (Intron A®); irinotecan (Camptosar®); lenalidomide (Revlimid®); letrozole (Femara®); leucovorin (Wellcovorin®, Leucovorin®); Leuprolide Acetate (Eligard®); levamisole (Ergamisol®); lomustine, CCNU (CeeBU®); meclorethamine, nitrogen mustard (Mustargen®); megestrol acetate (Megace®); melphalan, L-PAM (Alkeran®); mercaptopurine, 6-MP (Purinethol®); mesna (Mesnex®); mesna (Mesnex tabs®); methotrexate (Methotrexate®); methoxsalen (Uvadex®); mitomycin C (Mutamycin®); mitotane (Lysodren®); mitoxantrone (Novantrone®); nandrolone phenpropionate (Durabolin-50®); nelarabine (Arranon®); Nofetumomab (Verluma®); Oprelvekin (Neumega®); oxaliplatin (Eloxatin®); paclitaxel (Paxene®); paclitaxel (Taxol®); paclitaxel protein-bound particles (Abraxane®); palifermin (Kepivance®); pamidronate (Aredia®); pegademase (Adagen (Pegademase Bovine)®); pegaspargase (Oncaspar®); Pegfilgrastim (Neulasta®); pemetrexed disodium (Alimta®); pentostatin (Nipent®); pipobroman (Vercyte®); plicamycin, mithramycin (Mithracin®); porfimer sodium (Photofrin®); procarbazine (Matulane®); quinacrine (Atabrine®); Rasburicase (Elitek®); Rituximab (Rituxan®); Ridaforolimus; sargramostim (Leukine®); Sargramostim (Prokine®); sorafenib (Nexavar®); streptozocin (Zanosar®); sunitinib maleate (Sutent®); talc (Sclerosol®); tamoxifen (Nolvadex®); temozolomide (Temodar®); teniposide, VM-26 (Vumon®); testolactone (Teslac®); thioguanine, 6-TG (Thioguanine®); thiotepa (Thioplex®); topotecan (Hycamtin®); toremifene (Fareston®); Tositumomab (Bexxar®); Tositumomab/I-131 tositumomab (Bexxar®); Trastuzumab (Herceptin®); tretinoin, ATRA (Vesanoid®); Uracil Mustard (Uracil Mustard Capsules®); valrubicin (Valstar®); vinblastine (Velban®); vincristine (Oncovin®); vinorelbine (Navelbine®); vorinostat (Zolinza®) and zoledronate (Zometa®), or a pharmaceutically acceptable salt thereof.

Methods for Making the Compounds of Formula I and Formula Ib

The following examples are provided so that the disclosure might be more fully understood. Unless otherwise indicated, the starting materials are commercially available. They should not be construed as limiting the invention in any way.

Several methods for preparing the compounds of Formula I or Formula Ib are described in the following Schemes and Examples. Starting materials and intermediates are purchased, made from known procedures, or as otherwise illustrated. Some frequently applied routes to the

compounds of Formula I or Formula Ib are also described by the Schemes as follows. In some cases, the order of carrying out the steps of reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. For stereoisomers, enantiomer A refers to the faster/ earlier eluting enantiomer and enantiomer B refers to the slower/ later eluting enantiomer at the point of separation and this nomenclature is maintained through the remainder of a synthetic sequence for a given enantiomeric series regardless of the possibility that subsequent intermediates and final compounds may have the same or opposite orders of elution.

List of Abbreviations:

ACN = acetonitrile

aq. = aqueous

°C = degrees Celcius

CatAXium A Pd G2 = Chloro[(di(1-adamantyl)-N-butylphosphine)-2-(2-aminobiphenyl)]palladium(II)

DAST = Diethylaminosulfur trifluoride

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCPP = 2,3 dichlorophenylpiperazine

DMF = dimethylformamide

DCM = dichloromethane

DCE = 1,2-dichloroethane

DIPEA = *N,N*-diisopropylethylamine

DMSO = dimethyl sulfoxide

Et = ethyl

EtOAc = ethyl acetate

FA = formic acid

RP HPLC = Reverse Phase High Pressure Liquid Chromatography

H or hrs = hour or hours

HATU = 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid-hexafluorophosphate

HCl = hydrogen chloride

HOAc = acetic acid

HPLC = High Pressure Liquid Chromatography

LCMS or LC/MS = liquid chromatography mass spectrometry

Me = methyl

*m*CPBA = meta-chloroperoxybenzoic acid

$MgSO_4$= magnesium sulfate

MTBE = methyl *tert*-butyl ether

RT or rt = room temperature

NBS = *N*-bromosuccinimide

NCS = *N*-Chlorosuccinimide

NIS = *N*-Iodosuccinimide

NMR = nuclear magnetic resonance

PE or pet. ether = petroleum ether

$Pd(OAc)_2$ = Palladium(II) acetate

$PdCl_2$(dppf) = bis(diphenylphosphino)ferrocene]dichloropalladium(II)

PyBroP = Bromotripyrrolidinophosphonium hexafluorophosphate

TBAF = Tetra-n-butylammonium fluoride

THF = tetrahydrofuran

TFA = trifluoroacetic acid

TFAA = trifluoroacetic anhydride

TLC = thin layer chromatography

PhMe = toluene

wt. % = percentage by weight

x g = times gravity

% w/v = percentage in weight of the former agent relative to the volume of the latter agent.

Sat. = saturated

Soln. = solution

LCMS conditions: column: ACQUITY UPLC-QDa BEH C18, 1.7mm, 2.1 x 50mm.

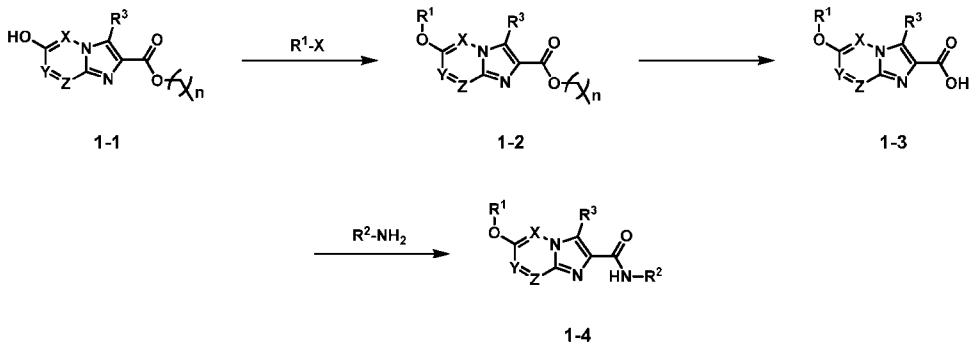
Solvent system: A: Water 0.1% FA, B: ACN 0.1% FA

Gradient condition: 10-90% B, in 1.7 min, total run time 2.4 min

GENERAL SYNTHETIC SCHEMES

In addition to the specific examples set forth that follow, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. In some cases, the order of carrying out the steps of the reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present disclosure.

General Scheme 1

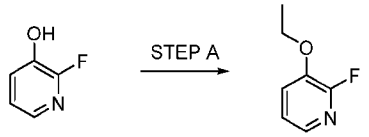


1-1 1-2 1-3 1-4

Compounds of the formula 1-4 were prepared from 1-1 with R^1-X via SN2, SNAr or copper-mediated C-O coupling. Saponification of 1-2 provided the corresponding carboxylic acid (1-3) and subsequent amide coupling with the appropriate amines (R^2-NH_2) provided compounds of formula (1-4) as described by the general scheme. The order of steps for some examples may be varied to facilitate the syntheses.

INTERMEDIATES

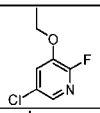
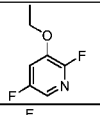
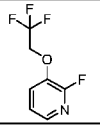
Intermediate 1: 3-Ethoxy-2-fluoropyridine

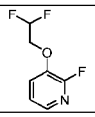
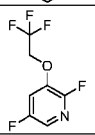
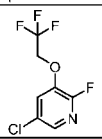
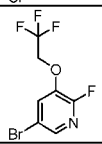
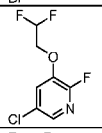
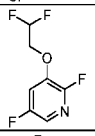
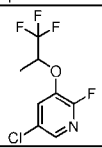
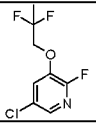
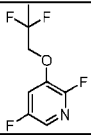
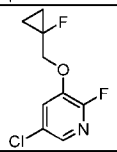
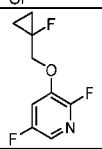
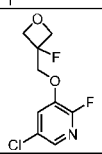


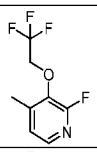
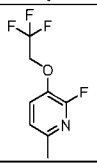
INT-1

At RT, to a stirred solution of 2-fluoropyrid-3-ol (5.0 g, 44 mmol) and K_2CO_3 (9.8 g, 71 mmol) in DMF (45 mL) was added iodoethane (6.4 mL, 80 mmol), and the reaction mixture was stirred at 80 °C for 5 h. The reaction mixture was cooled to RT, diluted with water, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-10% EtOAc/PE) to afford the title compound. LC/MS = 142 [M+H].

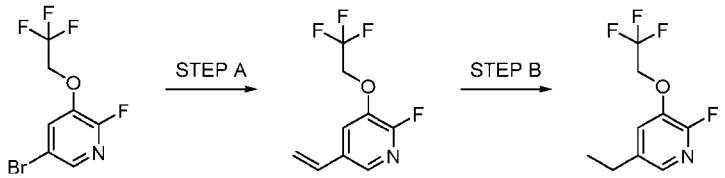
By using procedures similar to those described in Intermediate 1 with appropriate reagents, the following intermediates were synthesized. These intermediates were characterized by LC/MS.

Intermediate	Structure	Name	LC/MS [M+H]
Int-2		5-chloro-3-ethoxy-2-fluoropyridine	177
Int-3		3-ethoxy-2,5-difluoropyridine	160
Int-4		2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine	196

Int-5		3-(2,2-difluoroethoxy)-2-fluoropyridine	178
Int-6		2,5-difluoro-3-(2,2,2-trifluoroethoxy)pyridine	214
Int-7		5-chloro-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine	229
Int-8		5-bromo-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine	274
Int-9		5-chloro-3-(2,2-difluoroethoxy)-2-fluoropyridine	213
Int-10		3-(2,2-difluoroethoxy)-2,5-difluoropyridine	196
Int-11		5-chloro-2-fluoro-3-((1,1,1-trifluoropropan-2-yl)oxy)pyridine	244
Int-12		5-chloro-3-(2,2-difluoropropoxy)-2-fluoropyridine	227
Int-13		3-(2,2-difluoropropoxy)-2,5-difluoropyridine	210
Int-14		5-chloro-2-fluoro-3-((1-fluorocyclopropyl)methoxy)pyridine	221
Int-15		2,5-difluoro-3-((1-fluorocyclopropyl)methoxy)pyridine	204
Int-16		5-chloro-2-fluoro-3-((3-fluorooxetan-3-yl)methoxy)pyridine	236

Int-17		2-fluoro-4-methyl-3-(2,2,2-trifluoroethoxy)pyridine	210
Int-18		2-fluoro-6-methyl-3-(2,2,2-trifluoroethoxy)pyridine	210

Intermediate 19: 5-Ethyl-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine



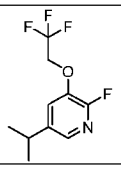
STEP A: 2-Fluoro-3-(2,2,2-trifluoroethoxy)-5-vinylpyridine

At RT, to a stirred solution of 5-bromo-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine (500.0 mg, 1.83 mmol), K_2CO_3 (757 mg, 5.47 mmol), and $PdCl_2(dppf)$ (107 mg, 0.146 mmol) in 1,4-dioxane (730.0 µl) and water (183 µl) was added 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (365 mg, 2.37 mmol). The resulting mixture was stirred at 100 °C for 1 h. The reaction mixture was cooled to RT, filtered through a pad of celite, washing with EtOAc, and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 222 [M+H]

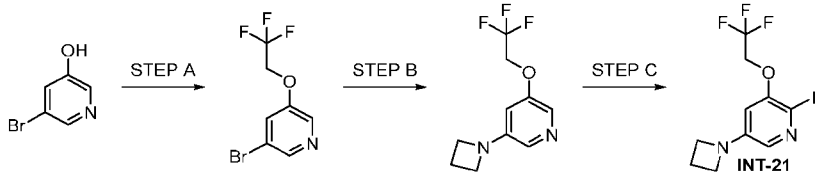
STEP B: 5-Ethyl-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine

At RT under an N_2 atmosphere, $Pd(OH)_2$-C (73.3 mg, 104.0 µmol) was added to a stirred solution of 2-fluoro-3-(2,2,2-trifluoroethoxy)-5-vinylpyridine (330.0 mg, 1.49 mmol) in MeOH (7.46 mL). Triethylsilane (715 µl, 4.48 mmol) was then added dropwise. The reaction mixture was sparged with N_2, then was filtered through a pad of celite, washing with MeOH, and the filtrate was concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 224 [M+H]

By using procedures similar to those described in Intermediate 19 with appropriate reagents, the following intermediate was synthesized. This intermediate was characterized by LC/MS.

Intermediate	Structure	Name	LC/MS [M+H]
Int-20		2-Fluoro-5-isopropyl-3-(2,2,2-trifluoroethoxy)pyridine	238

Intermediate 21: 5-(Azetidin-1-yl)-2-iodo-3-(2,2,2-trifluoroethoxy)pyridine



STEP A: 3-Bromo-5-(2,2,2-trifluoroethoxy)pyridine

At RT, to a stirred solution of 5-bromopyridin-3-ol (1.50 g, 8.62 mmol) and K_2CO_3 (1.55 g, 11.2 mmol) in DMF (30.0 ml) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (2.40 g, 10.4 mmol). The resulting mixture was stirred at RT for 12 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (20% EtOAc/PE) to give the title compound. LC/MS = 256 [M+H]

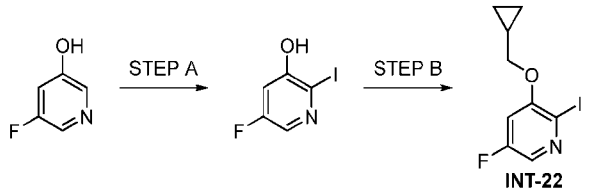
STEP B: 3-(Azetidin-1-yl)-5-(2,2,2-trifluoroethoxy)pyridine

At RT under an N_2 atmosphere, azetidine hydrochloride (128 mg, 1.37 mmol) was added to a stirred solution of 3-bromo-5-(2,2,2-trifluoroethoxy)pyridine (350.0 mg, 1.37 mmol), Cs_2CO_3 (1.16 g, 3.55 mmol), $Pd_2(dba)_3$ (125 mg, 137 µmol), and XantPhos (79.0 mg, 137 µmol) in 1,4-dioxane (20.0 mL). The resulting solution was stirred at 120 °C for 12 h, then the reaction mixture was filtered through a pad of celite, washing with EtOAc, and the filtrate was concentrated in vacuo. The crude material was purified by flash column chromatography on silica (17% EtOAc/PE) to give the title compound. LC/MS = 233 [M+H]

STEP C: 5-(Azetidin-1-yl)-2-iodo-3-(2,2,2-trifluoroethoxy)pyridine

At RT, to a stirred solution of 3-(azetidin-1-yl)-5-(2,2,2-trifluoroethoxy)pyridine (80.0 mg, 345 µmol) in ACN (4.00 mL) was added NIS (81.0 mg, 362 µmol). The resulting mixture was stirred at RT for 12 h then directly purified by preparatory thin layer chromatography on silica (25% EtOAc/PE) to give the title compound. LC/MS = 359 [M+H]

Intermediate 22: 3-(Cyclopropylmethoxy)-5-fluoro-2-iodopyridine



INT-22

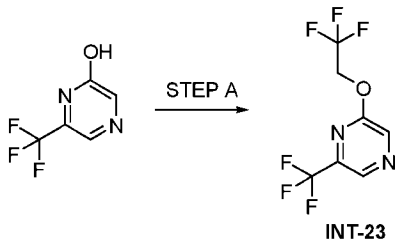
STEP A: 5-Fluoro-2-iodopyridin-3-ol

At RT, to a stirred solution of 5-fluoropyridin-3-ol (3.50 g, 30.9 mmol) in water (50.0 mL) was added Na_2CO_3 (6.56 g, 61.9 mmol) and KI (6.17 g, 37.1 mmol) followed by a solution of iodine (7.85 g, 30.9 mmol) in water (20.0 mL) dropwise. The resulting mixture was stirred at RT for 2 h then the pH value was adjusted to 5-6 using 4M aqueous HCl. The resulting precipitate was collected by filtration and dried in vacuo. The crude material was purified by preparative HPLC to give the title compound. LC/MS = 239 [M+H].

STEP B: 3-(Cyclopropylmethoxy)-5-fluoro-2-iodopyridine

At RT, to a stirred solution of 5-fluoro-2-iodopyridin-3-ol (0.800 g, 3.35 mmol) in DMF (3.00 mL) was added K_2CO_3 (694 mg, 5.02 mmol) and (bromomethyl)cyclopropane (678 mg, 5.02 mmol). The resulting solution was stirred at 80 °C for 12 h. The mixture was diluted with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to give the title compound. LC/MS 294 [M+H].

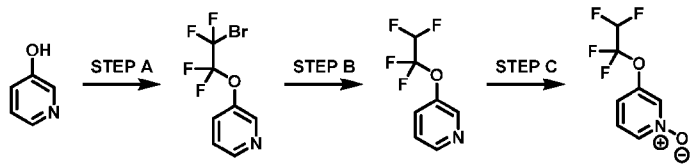
Intermediate 23: 2-(2,2,2-Trifluoroethoxy)-6-(trifluoromethyl)pyrazine



INT-23

At RT, to a stirred solution of 2-chloro-6-(trifluoromethyl)pyrazine (2.00 g, 11.0 mmol) and Cs_2CO_3 (4.28 g, 13.2 mmol) in DMF (11.0 mL) was added 2,2,2-trifluoroethan-1-ol (860 µL, 12.1 mmol). The resulting solution was stirred at 50 °C for 2 h. The mixture was then filtered through a pad of celite, and the filtrate was directly purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to give the title compound. LC/MS = 247 [M+H].

Intermediate 24: 3-(1,1,2,2-Tetrafluoroethoxy)pyridine 1-oxide



INT-24

STEP A: 3-(2-Bromo-1,1,2,2-tetrafluoroethoxy)pyridine

At RT, to a stirred solution of pyridin-3-ol (0.500 g, 5.26 mmol) and Cs_2CO_3 (3.43 g, 10.5 mmol) in DMF (26.3 ml) was added 1,3-dibromo-1,1,2,2,3,3-hexafluoropropane (750 µL, 5.26 mmol). The resulting mixture was stirred at RT for 18 h. The mixture was diluted with water and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound. LC/MS = 275 [M+H].

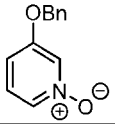
STEP B: 3-(1,1,2,2-Tetrafluoroethoxy)pyridine

At RT, to a stirred solution of 3-(2-bromo-1,1,2,2-tetrafluoroethoxy)pyridine (1.44 g, 5.26 mmol) in HOAc (5.26 mL) was added zinc (1.03 g, 15.8 mmol). The resulting mixture was stirred at 50 °C for 1 h. The reaction mixture was diluted with water, neutralized with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with DCM. The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound. LC/MS = 196 [M+H].

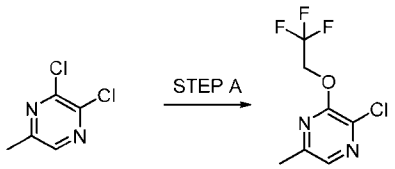
STEP C: 3-(1,1,2,2-Tetrafluoroethoxy)pyridine 1-oxide

At RT, to a stirred solution of 3-(1,1,2,2-tetrafluoroethoxy)pyridine (1.03 g, 5.26 mmol) in DCM (11.1 mL) was added *m*CPBA (1.09 g, 6.31 mmol). The resulting mixture was stirred at RT for 18 h. The reaction mixture was diluted with water, neutralized with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with DCM. The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-10% MeOH/DCM) to give the title compound. LC/MS = 212 [M+H].

By using procedures similar to those described in Intermediate 24 with appropriate reagents, the following intermediate was synthesized. This intermediate was characterized by LC/MS.

Intermediate	Structure	Name	LC/MS [M+H]
Int-25		3-(Benzyloxy)pyridine 1-oxide	202

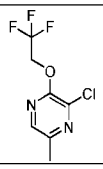
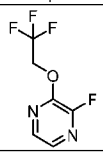
Intermediate 26: 2-Chloro-5-methyl-3-(2,2,2-trifluoroethoxy)pyrazine



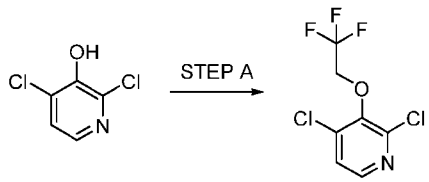
INT-26

At RT, to a stirred solution of 2,3-dichloro-5-methylpyrazine (1.00 g, 6.13 mmol) and Cs_2CO_3 (2.40 g, 7.36 mmol) in DMF (6.13 mL) was added 2,2,2-trifluoroethan-1-ol (0.526 ml, 7.36 mmol). After 15 min, the resulting mixture was stirred at 50 °C for 45 min then filtered over a pad of celite, washing with EtOAc, and concentrated in vacuo to afford the title compound. LC/MS = 227 [M+H].

By using procedures similar to those described in Intermediate 26 with appropriate reagents, the following intermediates were synthesized. These intermediates were characterized by LC/MS.

Intermediate	Structure	Name	LC/MS [M+H]
Int-27		3-Chloro-5-methyl-2-(2,2,2-trifluoroethoxy)pyrazine	227
Int-28		2-Fluoro-3-(2,2,2-trifluoroethoxy)pyrazine	197

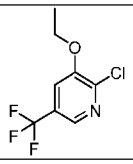
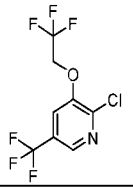
Intermediate 29: 2,4-Dichloro-3-(2,2,2-trifluoroethoxy)pyridine



INT-29

At RT, to a stirred solution of 2,4-dichloropyridin-3-ol (330 mg, 2.01 mmol) and K_2CO_3 (556 mg, 4.02 mmol) in DMF (2.00 mL) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (350 µl, 2.42 mmol). After 10 min, the resulting mixture was stirred at 50 °C for 45 min then filtered over a pad of celite, washing with EtOAc, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to give the title compound. LC/MS = 246 [M+H].

By using procedures similar to those described in Intermediate 29 with appropriate reagents, the following intermediates were synthesized. These intermediates were characterized by LC/MS.

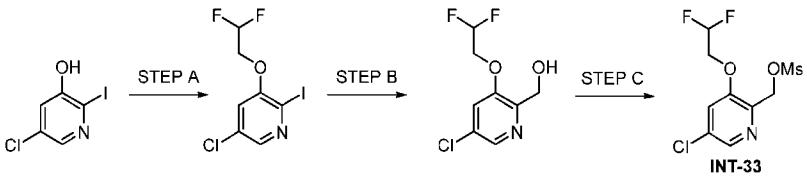
Intermediate	Structure	Name	LC/MS [M+H]
Int-30		2-Chloro-3-ethoxy-5-(trifluoromethyl)pyridine	226
Int-31		2-Chloro-3-(2,2,2-trifluoroethoxy)-5-(trifluoromethyl)pyridine	280

Intermediate 32: 2-Chloro-3-(1,1-difluoropropyl)pyridine

INT-32

At RT under an N_2 atmosphere, to a stirred solution of 1-(2-chloropyridin-3-yl)propan-1-one (500.0 mg, 2.95 mmol) in DCM (6.00 mL) was added DAST (0.779 ml, 5.90 mmol) dropwise. The resulting mixture was stirred at 50 °C for 12 h then quenched with MeOH and stirred at RT for an additional 0.5 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with EtOAc. The combined organic fractions were washed with water then brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (5% EtOAc/hexanes) to give the title compound. LC/MS = 192 [M+H].

Intermediate 33: (5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methyl methanesulfonate



INT-33

STEP A: 5-Chloro-3-(2,2-difluoroethoxy)-2-iodopyridine

To a mixture of 5-chloro-2-iodopyridin-3-ol (2.7 g, 10.6 mmol) and K_2CO_3 (1.9 g, 13.7 mmol) in DMF (8.8 mL) was added 2,2-difluoroethyl trifluoromethanesulfonate (1.7 mL, 11.6 mmol) at RT. After 1 h, the mixture was filtered over celite, and the filtrate was concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 320 [M+1].

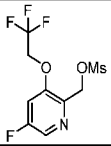
STEP B: (5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methanol

To a mixture of 5-chloro-3-(2,2-difluoroethoxy)-2-iodopyridine (0.88 g, 2.8 mmol) in toluene (15.3 mL) was added *n*-butyllithium solution (2.5 M in hexanes, 1.3 mL, 3.3 mmol) at –78 °C. After 30 min, DMF (0.32 mL, 4.1 mmol) was added at –78 °C. After 1 h, methanol (3.1 mL) followed by sodium borohydride (0.21 g, 5.5 mmol) were sequentially added, and the resulting mixture was then warmed to RT. After 20 min, the mixture was diluted with saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine. The organic layer was then dried over $MgSO_4$ (s), filtered, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 224 [M+1].

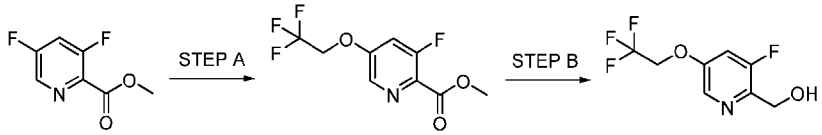
STEP C: (5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methyl methanesulfonate

To a mixture of (5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methanol (0.10 g, 0.45 mmol) and triethylamine (0.14 mL, 0.98 mmol) in DCM (2.2 mL) was added methanesulfonyl chloride (48.8 µL, 0.63 mmol) at –78 °C. After 5 min, the mixture was warmed to RT. After a further 15 min, the mixture was diluted with saturated aqueous NaCl solution, and the aqueous layer was extracted once with DCM. The combined organic layers were dried over $MgSO_4$ (s), filtered, and concentrated in vacuo to afford the title compound. The crude product was used without purification. LC/MS = 302 [M+1].

By using procedures similar to those described in Intermediate 33 with appropriate reagents, the following intermediate was synthesized and characterized by LC/MS.

Intermediate	Structure	Name	LC/MS [M+1]
Int-34		(5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl methanesulfonate	304

Intermediate 35: (3-fluoro-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methanol



STEP A: methyl 3-fluoro-5-(2,2,2-trifluoroethoxy)picolinate

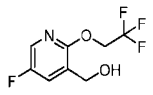
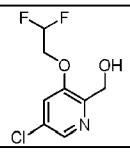
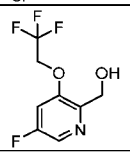
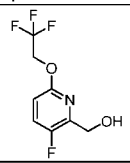
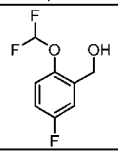
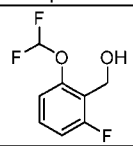
To a mixture of methyl 3,5-difluoropicolinate (1.1 g, 6.4 mmol) and 2,2,2-trifluoroethan-1-ol (0.51 mL, 7.0 mmol) in DMF (6.4 mL) was added Cs_2CO_3 (2.5 g, 7.6 mmol) at RT. After 30 min, the mixture was filtered over celite, and the filtrate was concentrated in vacuo. The crude product

was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 254 [M+H].

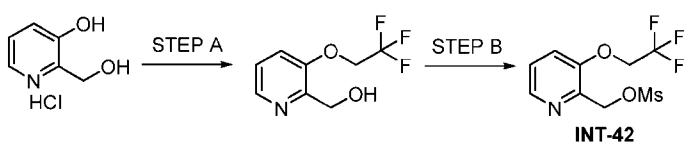
STEP B: (3-fluoro-5-(2,2,2-trifluoroethoxy)pyridin-2-yl)methanol

To a mixture of methyl 3-fluoro-5-(2,2,2-trifluoroethoxy)picolinate (870 mg, 3.4 mmol) in THF (17 mL) was added $LiAlH_4$ solution (2 M in THF, 2.6 mL, 5.2 mmol) at 0 °C. After 30 min, the mixture was diluted with Et_2O, H_2O and aqueous 1 M NaOH solution and then warmed to RT. After 15 min, $MgSO_4$ was added, the mixture was filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 226 [M+H].

By using procedures similar to those described in Intermediate 35 with appropriate reagents, the following intermediates were synthesized. These intermediates were characterized by LC/MS.

Intermediate	Structure	Name	LC/MS [M+H]
Int-36		(5-Fluoro-2-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanol	226
Int-37		(5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methanol	224
Int-38		(5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methanol	226
Int-39		(3-Fluoro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)methanol	226
Int-40		2-(Difluoromethoxy)-5-fluorobenzyl alcohol	193
Int-41		2-(Difluoromethoxy)-6-fluorobenzyl alcohol	193

Intermediate 42: (3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl methanesulfonate



INT-42

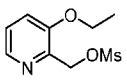
STEP A: (3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methanol

To a mixture of 2-(hydroxymethyl)pyridin-3-ol hydrochloride (500 mg, 3.1 mmol) and K_2CO_3 (1.3 g, 9.3 mmol) in DMF (3.1 mL) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.6 mL, 4.0 mmol) at RT. After 15 h, the mixture was filtered over celite, and the filtrate was concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 208 [M+1].

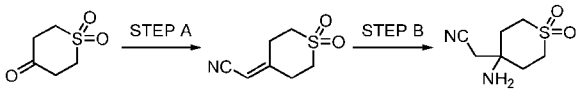
STEP B: (3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl methanesulfonate

To a mixture of (3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methanol (330 mg, 1.6 mmol) and triethylamine (0.29 mL, 2.1 mmol) in DCM (5.3 mL) was added methanesulfonyl chloride (0.15 mL, 1.8 mmol) at 0 °C. After 5 min, the mixture was warmed to RT. After 17 h, the mixture was diluted with saturated aqueous NaCl solution, and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the title compound. The crude product was used without purification. LC/MS = 286 [M+H].

By using procedures similar to those described in Intermediate 42 with appropriate reagents, the following intermediate was synthesized and characterized by LC/MS.

Intermediate	Structure	Name	LC/MS [M+H]
Int-42		(3-ethoxypyridin-2-yl)methyl methanesulfonate	232

Intermediate 43: 2-(4-amino-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)acetonitrile



INT-43

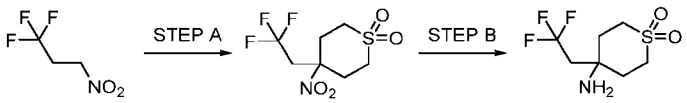
STEP A: 2-(1,1-dioxidotetrahydro-4*H*-thiopyran-4-ylidene)acetonitrile

To a mixture of potassium *tert*-butoxide solution (1 M in THF, 6.1 mL, 6.1 mmol) in THF (15 mL) was added diethyl cyanomethylphosphonate (0.98 mL, 6.1 mmol) at 0 °C. After 15 min, the mixture was warmed to RT. After 30 min, the mixture was cooled to 0 °C, whereupon a solution of tetrahydro-4*H*-thiopyran-4-one 1,1-dioxide (0.90 g, 6.1 mmol) in THF (15 mL) was added. After 1 h, the mixture was warmed to RT. After 16 h, the mixture was poured into water, and the mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, then filtered and concentrated under reduced pressure to afford the title compound. The crude product was used without purification. LC/MS = 172 [M+1].

STEP B: 2-(4-amino-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)acetonitrile

To a mixture of 2-(1,1-dioxidotetrahydro-4*H*-thiopyran-4-ylidene)acetonitrile (0.40 g, 2.3 mmol) in MeOH (1.1 mL) was added aqueous NH_3 solution (29 wt.%, 3.0 mL, 46.7 mmol) at RT. The resulting mixture was heated to 100 °C. After 3 h, the mixture was cooled to RT and concentrated in vacuo to afford the title compound. The crude product was used without purification. LC/MS = 189 [M+1].

Intermediate 44: 4-amino-4-(2,2,2-trifluoroethyl)tetrahydro-2*H*-thiopyran 1,1-dioxide



INT-44

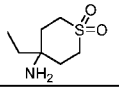
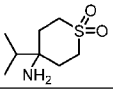
STEP A: 4-nitro-4-(2,2,2-trifluoroethyl)tetrahydro-2*H*-thiopyran 1,1-dioxide

To a mixture of 1,1,1-trifluoro-3-nitropropane (1.0 g, 7.2 mmol) and DBU (0.9 mL, 6.3 mmol) in DCM (40 mL) was added divinyl sulfone (0.6 mL, 6.0 mmol) at RT. After 15 h, the mixture was poured into aqueous 1 M HCl solution, and the mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, then filtered and concentrated under reduced pressure to afford the title compound. The crude product was used without purification. LC/MS = 262 [M+1].

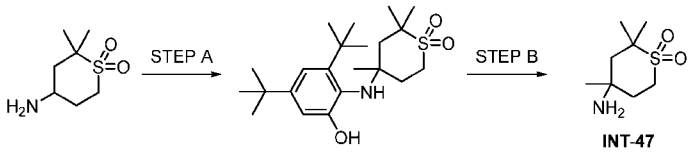
STEP B: 4-amino-4-(2,2,2-trifluoroethyl)tetrahydro-2*H*-thiopyran 1,1-dioxide

To a mixture of 4-nitro-4-(2,2,2-trifluoroethyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (960 mg, 3.7 mmol) in MeOH (18 mL) was added Rh/C (5 wt.%, 378 mg, 0.2 mmol) at RT. A balloon of H_2 was placed over the reaction mixture, the reaction mixture was sparged with H_2 for 5 min, and stirring was then continued under H_2atmosphere. After 72 h, the mixture was filtered over celite, the filter cake was washed with methanol and DCM, and the filtrate was concentrated in vacuo to afford the title compound. The crude product was used without purification. LC/MS = 232 [M+1].

By using procedures similar to those described in Intermediate Int-44 with appropriate reagents, the following intermediates were synthesized. These intermediates were characterized by LC/MS.

Intermediate	Structure	Name	LC/MS [M+H]
Int-45		4-amino-4-ethyltetrahydro-2*H*-thiopyran 1,1-dioxide	178
Int-46		4-amino-4-isopropyltetrahydro-2*H*-thiopyran 1,1-dioxide	192

Intermediate 47: 4-amino-2,2,4-trimethyltetrahydro-2*H*-thiopyran 1,1-dioxide



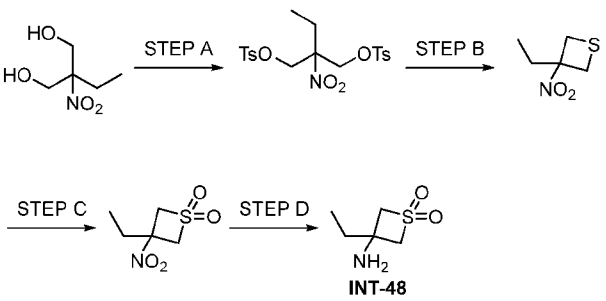
STEP A: 4-((2,4-di-*tert*-butyl-6-hydroxyphenyl)amino)-2,2,4-trimethyltetrahydro-2*H*-thiopyran 1,1-dioxide

To a mixture of 4-amino-2,2-dimethyltetrahydro-2*H*-thiopyran 1,1-dioxide (1.5 g, 8.5 mmol) in DCE (40 mL) was added a solution of 3,5-di-*tert*-butylcyclohexa-3,5-diene-1,2-dione (1.9 g, 8.5 mmol) in DCE (40 mL) at RT. After 5 min, the resulting mixture was warmed to 40 °C. After 15 h, the mixture was cooled to RT and concentrated in vacuo. The residue was dissolved in PhMe (80 mL) and *N*,*N*,*N*',*N*'-tetramethylethane-1,2-diamine (1.3 mL, 8.5 mmol), and the resulting solution was added to MeLi solution (3.1 M in DME, 16.4 mL, 50.8 mmol) in Et_2O (100 mL) at –78 °C. After 1 h, the mixture was warmed to RT. After 3 h, the mixture was poured into saturated aqueous NH_4Cl solution, and the mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, then filtered and concentrated under reduced pressure to afford the title compound. The crude product was used without purification. LC/MS = 396 [M+1]

STEP B: 4-amino-2,2,4-trimethyltetrahydro-2*H*-thiopyran 1,1-dioxide

To a mixture of 4-((2,4-di-*tert*-butyl-6-hydroxyphenyl)amino)-2,2,4-trimethyltetrahydro-2*H*-thiopyran 1,1-dioxide (3.4 g, 8.5 mmol) in water (42 mL) and ACN (42 mL) was added H_5IO_6 (2.1 g, 9.3 mmol) at 0 °C. After 30 min, the organic solvent was removed in vacuo. The aqueous layer was extracted with Et_2O/hexanes (1:1), and the resulting aqueous layer was concentrated in vacuo. The residue was dissolved in aqueous 1 M NaOH solution, and the mixture was extracted with DCM/MeOH. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, then filtered and concentrated under reduced pressure to afford the title compound. The crude product was used without purification. LC/MS = 192 [M+1]

Intermediate 48: 3-amino-3-ethylthietane 1,1-dioxide



STEP A: 2-ethyl-2-nitropropane-1,3-diyl bis(4-methylbenzenesulfonate)

To a mixture of 2-ethyl-2-nitropropane-1,3-diol (10.0 g, 67.0 mmol) in DCM (130 mL) and pyridine (21.7 mL, 268 mmol) was added *p*-toluenesulfonyl chloride (32.0 g, 168 mmol) at 0 °C. After 10 min, the mixture was warmed to RT. After 15 h, the mixture was poured into aqueous 1 M HCl solution and the mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 458 [M+1].

STEP B: 3-ethyl-3-nitrothietane

To a mixture of 2-ethyl-2-nitropropane-1,3-diyl bis(4-methylbenzenesulfonate) (10.5 g, 23.0 mmol) in DMSO (115 mL) was added Na_2S at RT. After 5 min, the resulting mixture was heated to 100 °C. After 16 h, the mixture was cooled to RT, poured into saturated aqueous NaCl solution and the mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 148 [M+1].

STEP C: 3-ethyl-3-nitrothietane 1,1-dioxide

To a mixture of 3-ethyl-3-nitrothietane (150 mg, 1.0 mmol) in DCM (4 mL) was added *m*-chloroperoxybenzoic acid (685 mg, 3.1 mmol) at RT. After 24 h, the mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 180 [M+1].

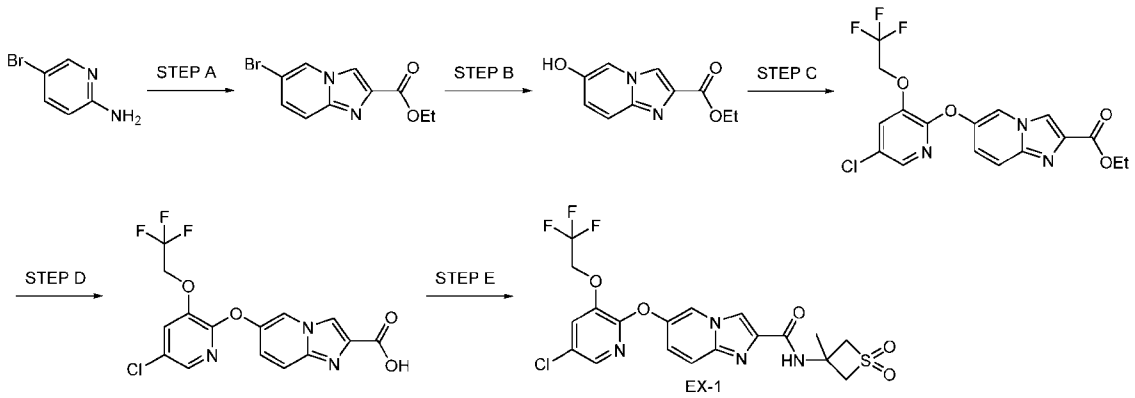
STEP D: 3-amino-3-ethylthietane 1,1-dioxide

To a mixture of 3-ethyl-3-nitrothietane 1,1-dioxide (190 mg, 1.1 mmol) and DIPEA (0.9 mL, 5.3 mmol) in ACN (5.3 mL) was added trichlorosilane (0.4 mL, 3.7 mmol) at RT. After 24 h, the mixture was poured into aqueous 1 M NaOH solution and the mixture was extracted with DCM/MeOH. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, then filtered and concentrated under reduced pressure to afford the title compound. The crude product was used without purification. LC/MS = 150 [M+1].

EXAMPLES

The following experimental procedures detail the preparation of specific examples of the instant disclosure. The examples are for illustrative purposes only and are not intended to limit the scope of the instant disclosure in any way.

EXAMPLE 1: 6-[[5-Chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide



STEP A: Ethyl 6-bromoimidazo[1,2-*a*]pyridine-2-carboxylate

To a mixture of 5-bromopyridin-2-amine (6.00 g, 34.7 mmol) and $NaHCO_3$ (5.83 g, 69.4 mmol) in dioxane (20 mL) was added ethyl-3-bromo-2-oxopropanoate (10.1 g, 52.0 mmol) at RT. The resulting mixture was then heated to 90 °C. After 16 h, the mixture was cooled to RT, filtered over celite, and the filtrate was concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-50% EtOAc/hexanes) to afford the title compound. LC/MS = 268 [M+1].

STEP B: Ethyl 6-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylate

To a mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-2-carboxylate (200 mg, 0.74 mmol), potassium acetate (219 mg, 2.23 mmol), bis(pinacolato)diboron (425 mg, 1.67 mmol) in dioxane (11 mL) was added [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (54.4 mg, 0.07 mmol) at RT. The resulting mixture was then heated to 100 °C. After 2 h, the mixture was cooled to 0 °C, whereupon water (0.2 mL) and HOAc (0.1 mL) were added. After 1 h, aqueous hydrogen peroxide solution (32 wt.%, 0.15 mL, 1.49 mmol) was added, and the resulting mixture was warmed to RT. After 18 h, $MgSO_4$ (s) was added, the mixture was filtered over celite, and the filtrate was concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 207 [M+1].

STEP C: Ethyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylate

To a mixture of ethyl 6-hydroxyimidazo[1,2-a]pyridine-2-carboxylate (500 mg, 2.43 mmol) in DMF (12 mL) was added sodium hydride (60 wt. %, 126 mg, 3.15 mmol) at RT. After 5 min, 5-chloro-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine (724 mg, 3.15 mmol) was added and the resulting mixture was heated to 80 °C. After 48 h, the mixture was cooled to RT, and then was

concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 416 [M+1].

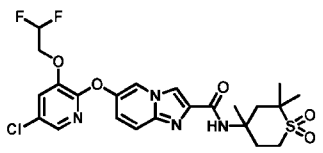
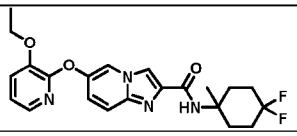
STEP D: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylic acid

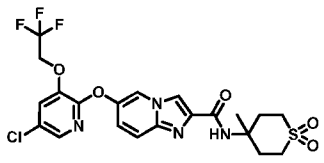
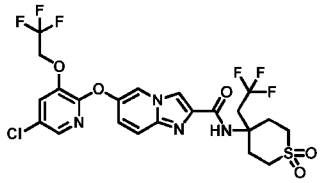
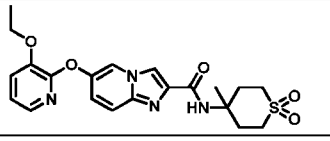
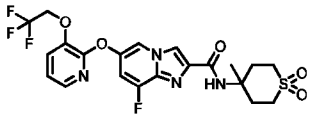
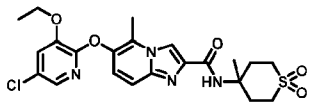
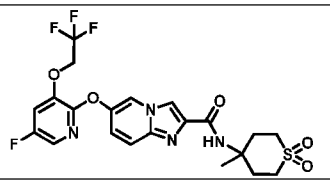
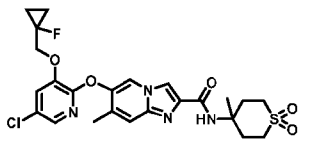
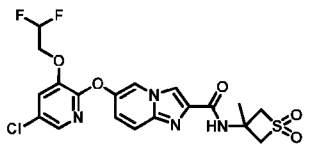
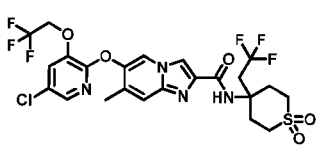
To a mixture of ethyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-a]pyridine-2-carboxylate (1.01 g, 2.43 mmol) in ACN (4 mL) and water (4 mL) was added lithium hydroxide monohydrate (0.31 g, 7.28 mmol) at RT. After 30 min, the mixture was concentrated in vacuo to afford the title compound. The crude product was used without purification. LC/MS = 388 [M+1].

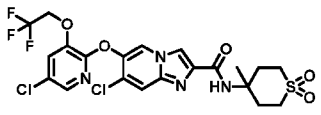
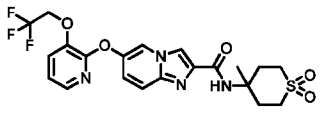
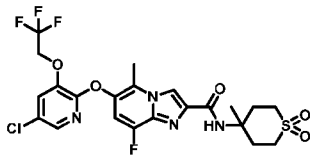
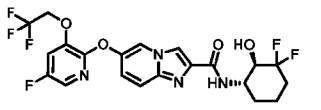
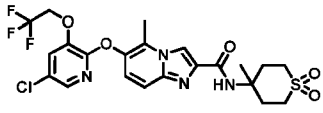
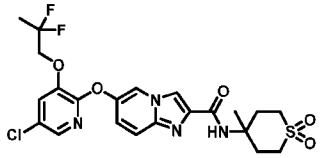
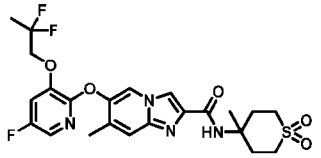
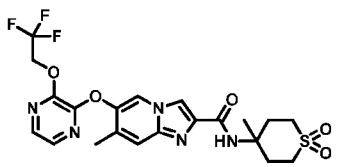
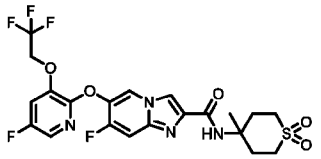
STEP E: 6-[[5-Chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

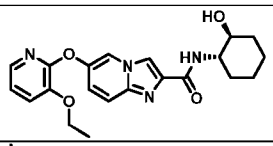
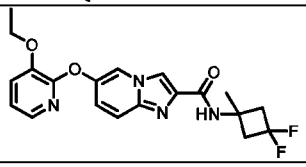
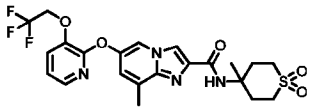
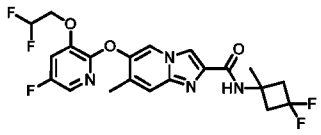
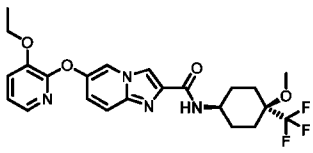
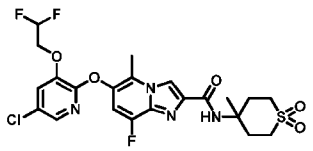
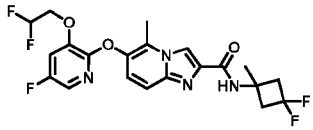
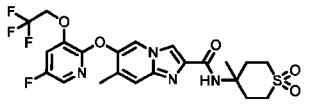
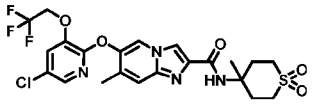
To a mixture of 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-a]pyridine-2-carboxylic acid (70.0 mg, 0.11 mmol), 3-amino-3-methylthietane 1,1-dioxide hydrochloride (22.3 mg, 0.13 mmol), and DIPEA (76.0 µL, 0.43 mmol) in DMF (0.7 mL) was added HATU (49.4 mg, 0.13 mmol) at RT. After 1 h, the reaction mixture was concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 505 [M+1]. ^{1}H NMR (500 MHz, Methanol-d$_4$) δ 8.56 (d, *J* = 1.5 Hz, 1H), 8.33 (s, 1H), 7.79 (d, *J* = 2.1 Hz, 1H), 7.72 (d, *J* = 2.1 Hz, 1H), 7.64 (d, *J* = 9.8 Hz, 1H), 7.33 (dd, *J* = 9.8, 2.2 Hz, 1H), 4.77 (q, *J* = 8.4 Hz, 2H), 4.70 – 4.62 (m, 2H), 4.31 – 4.21 (m, 2H), 1.88 (s, 3H). Human DGAT2 IC$_{50}$ = 5.0 nM.

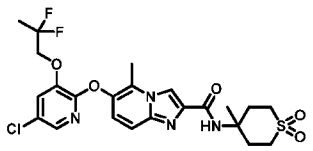
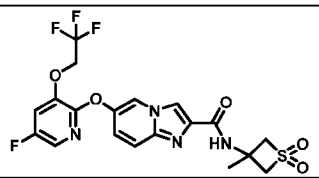
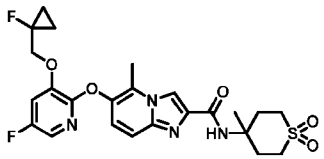
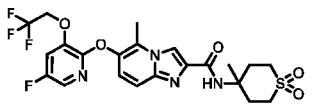
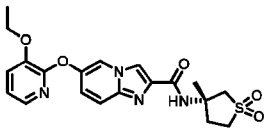
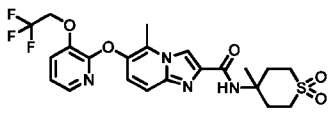
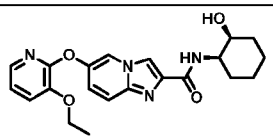
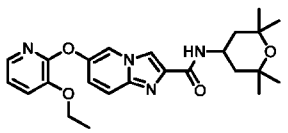
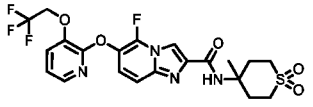
By using procedures similar to those described in **Example 1** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

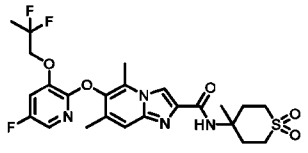
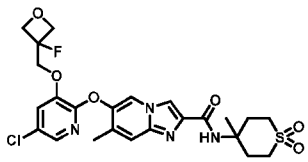
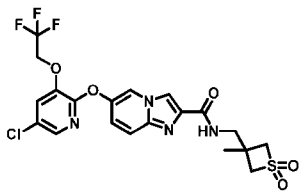
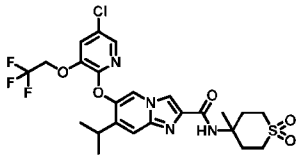
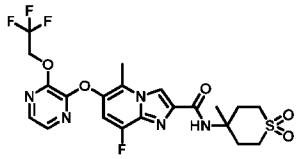
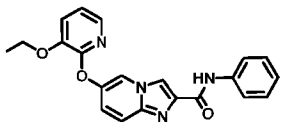
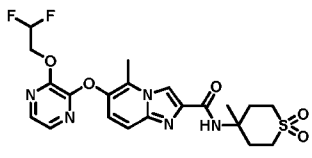
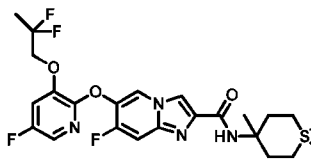
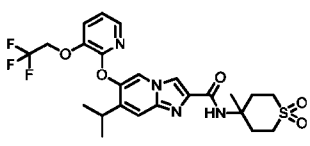
Example	Structure	Name	LC/MS [M+H]	Human DGAT2 IC$_{50}$ (nM)
2		6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(2,2,4-trimethyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (slower eluting with OD-H column, 25% MeOH/CO$_2$)	543	0.6
3		*N*-(4,4-difluoro-1-methyl-cyclohexyl)-6-[(3-ethoxy-2-	431	5.8

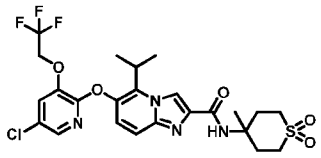
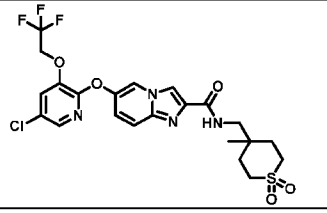
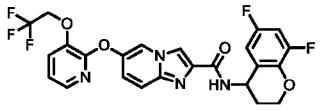
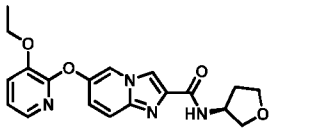
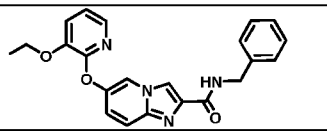
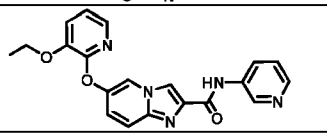
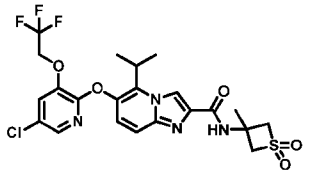
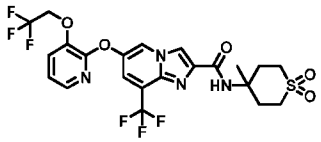
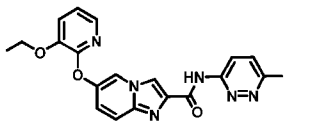
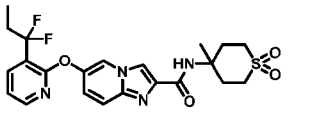
		pyridyl)oxy]imidazo[1,2-*a*]pyridine-2-carboxamide		
4		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	533	1.8
5		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[1,1-dioxo-4-(2,2,2-trifluoroethyl)thian-4-yl]imidazo[1,2-*a*]pyridine-2-carboxamide	601	36
6		6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	445	2.5
7		8-fluoro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	517	4.7
8		6-[(5-chloro-3-ethoxy-2-pyridyl)oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	493	1.4
9		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	517	0.4
10		6-[[5-chloro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	537	13
11		6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	487	23
12		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[1,1-dioxo-4-(2,2,2-trifluoroethyl)thian-4-yl]-7-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	615	5.6

13		7-chloro-6-[5-chloro-3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	567	4.3
14		*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	499	5.3
15		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-8-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	565	11
16		*N*-[(1*S*,2*R*)-3,3-difluoro-2-hydroxy-cyclohexyl]-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	505	4.5
17		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	547	1.4
18		6-[[5-chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	529	2.0
19		6-[[3-(2,2-difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	527	7.7
20		7-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyrazin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide	514	17.3
21		7-fluoro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	535	1.8

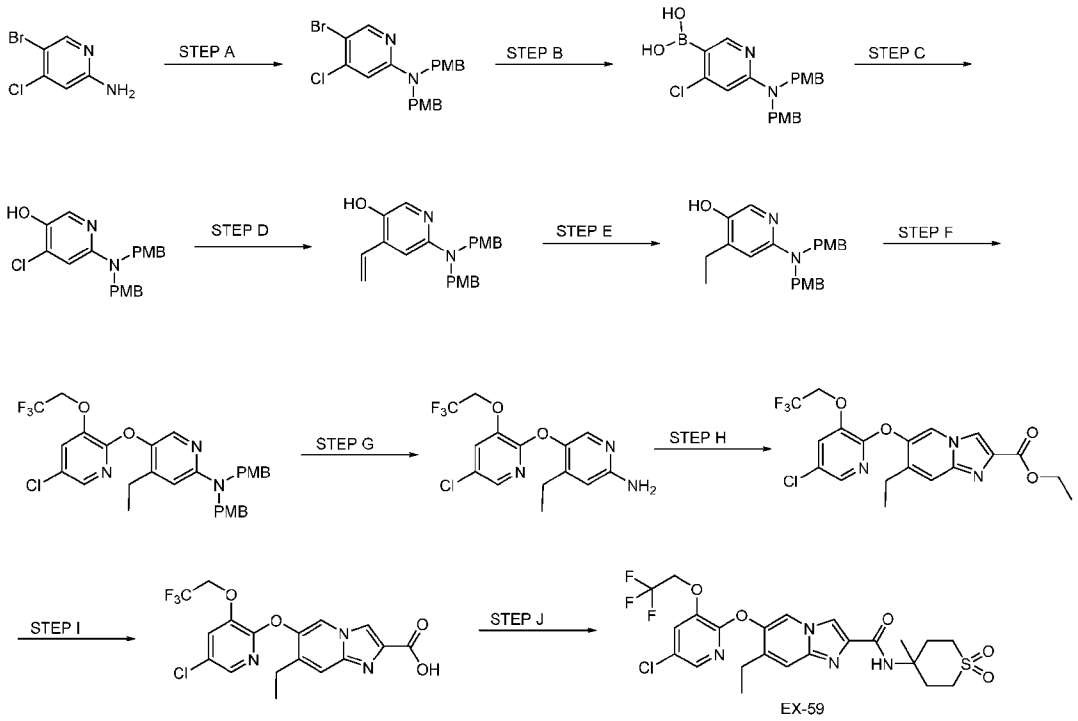
22		6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(1*S*,2*S*)-2-hydroxycyclohexyl]imidazo[1,2-*a*]pyridine-2-carboxamide	397	3.5
23		*N*-(3,3-difluoro-1-methyl-cyclobutyl)-6-[(3-ethoxy-2-pyridyl)oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	403	31
24		8-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	513	117
25		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3,3-difluoro-1-methyl-cyclobutyl)-7-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	471	3.8
26		6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[4-methoxy-4-(trifluoromethyl)cyclohexyl]imidazo[1,2-*a*]pyridine-2-carboxamide	479	10
27		6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-8-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	547	0.8
28		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3,3-difluoro-1-methyl-cyclobutyl)-5-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	471	59
29		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	531	13
30		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	547	6.2

31		6-[[5-chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	543	9.1
32		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	489	31
33		6-[[5-fluoro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	521	5.3
34		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	531	2.8
35		6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(3*S*)-3-methyl-1,1-dioxo-thiolan-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide	431	52
36		5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	513	30
37		6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(1*R*,2*S*)-2-hydroxycyclohexyl]imidazo[1,2-*a*]pyridine-2-carboxamide	397	124
38		6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(2,2,6,6-tetramethyltetrahydropyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	439	56
39		5-fluoro-N-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-a]pyridine-2-carboxamide	517	74

40		6-[[3-(2,2-difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-5,7-dimethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	541	52
41		6-[[5-chloro-3-[(3-fluorooxetan-3-yl)methoxy]-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	553	74
42		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[(3-methyl-1,1-dioxo-thietan-3-yl)methyl]imidazo[1,2-*a*]pyridine-2-carboxamide	519	50
43		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	575	122
44		8-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide	532	68
45		6-[(3-ethoxy-2-pyridyl)oxy]-*N*-phenyl-imidazo[1,2-*a*]pyridine-2-carboxamide;2,2,2-trifluoroacetate	375	168
46		6-[3-(2,2-difluoroethoxy)pyrazin-2-yl]oxy-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	496	42
47		6-((3-(2,2-difluoropropoxy)-5-fluoropyridin-2-yl)oxy)-7-fluoro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	531	8.7
48		7-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	541	59

49		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	575	12
50		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[(4-methyl-1,1-dioxo-thian-4-yl)methyl]imidazo[1,2-*a*]pyridine-2-carboxamide	547	174
51		*N*-(6,8-difluorochroman-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	521	123
52		6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(3*S*)-tetrahydrofuran-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide	369	814
53		*N*-benzyl-6-[(3-ethoxy-2-pyridyl)oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	389	346
54		6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(3-pyridyl)imidazo[1,2-*a*]pyridine-2-carboxamide	376	850
55		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-isopropyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	547	89
56		*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-8-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxamide	567	>9990
57		6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(6-methylpyridazin-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	391	1112
58		6-[[3-(1,1-difluoropropyl)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	479	262

EXAMPLE 59: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-ethyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide



STEP A: 5-Bromo-4-chloro-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine

To a mixture of of 5-bromo-4-chloropyridin-2-amine (3 g, 14.5 mmol) in DMF (40 ml) was added NaH (60 wt.%, 1.74 g, 43.4 mmol) at 0 °C. After 30 min, 1-(chloromethyl)-4-methoxybenzene (6.79 g, 43.4 mmol) was added, and the resulting mixture was warmed to RT. After 18 h, saturated aqueous NH_4Cl solution was added, and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine. The organic layer was then dried over Na_2SO_4 (s), filtered, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 447 [M+1].

STEP B: (6-(bis(4-methoxybenzyl)amino)-4-chloropyridin-3-yl)boronic acid

To a mixture of 5-bromo-4-chloro-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine (3.8 g, 8.49 mmol) in dioxane (50 ml) was added bis(pinacolato)diboron (3.23 g, 12.73 mmol), potassium acetate (2.50 g, 25.5 mmol) and $PdCl_2$(dppf) (0.62 g, 0.85 mmol). The resulting mixture was then heated to 80 °C. After 3 h, the mixture was cooled to RT, filtered over celite, and the filtrate was concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 413 [M+1].

STEP C: 6-(bis(4-methoxybenzyl)amino)-4-chloropyridin-3-ol

To a mixture of (6-(bis(4-methoxybenzyl)amino)-4-chloropyridin-3-yl)boronic acid (2 g, 4.85 mmol) in THF (10 mL) and water (10 mL) was added sodium perborate tetrahydrate (2.24 g, 14.54 mmol) at RT. After 2 h, the mixture was filtered over celite, and the filtrate was concentrated under reduced pressure to afford the title compound. The crude product was used without purification. LC/MS = 385 [M+1].

STEP D: 6-(bis(4-methoxybenzyl)amino)-4-vinylpyridin-3-ol

To a mixture of 6-(bis(4-methoxybenzyl)amino)-4-chloropyridin-3-ol (1.2 g, 3.12 mmol) in dioxane (4 ml) and water (4 ml) was added Na_2CO_3 (0.99 g, 9.35 mmol), potassium vinyltrifluoroborate (2.09 g, 15.59 mmol) and $PdCl_2$(dppf) (0.23 g, 0.31 mmol) at RT. The resulting mixture was then heated to 100 °C. After 12 h, the mixture was cooled to RT, poured into water, and the mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 (s), filtered, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 377 [M+1].

STEP E: 6-(bis(4-methoxybenzyl)amino)-4-ethylpyridin-3-ol

To a mixture of 6-(bis(4-methoxybenzyl)amino)-4-vinylpyridin-3-ol (510 mg, 1.36 mmol) in MeOH (5 ml) was added Pd/C (10 wt.%, 144 mg, 0.135 mmol). The reaction flask was evacuated and backfilled with H_2, and stirring was then continued under H_2 atmosphere. After 2 h, the mixture was filtered over celite, and the filtrate was concentrated under reduced pressure to afford the title compound. The crude product was used without purification. LC/MS = 379 [M+1].

STEP F: 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-4-ethyl-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine

To a mixture of 6-(bis(4-methoxybenzyl)amino)-4-ethylpyridin-3-ol (410 mg, 1.08 mmol) in DMF (3 mL) was added Cs_2CO_3 (529 mg, 1.63 mmol) and 5-chloro-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine (298 mg, 1.30 mmol) at RT. After 2 h, the mixture was poured into water, and the mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 (s), filtered, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 589 [M+1].

STEP G: 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-4-ethylpyridin-2-amine

To a mixture of 5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-4-ethyl-*N*,*N*-bis(4-methoxybenzyl)pyridin-2-amine (560 mg, 0.95 mmol) in DCM (4 mL) was added TFA (2 mL) at RT. After 5 h, the mixture was concentrated under reduced pressure. The residue was dissolved

in EtOAc and then washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 348 [M+1].

STEP H: Ethyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-ethylimidazo[1,2-a]pyridine-2-carboxylate

To a mixture of 5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-4-ethylpyridin-2-amine (100 mg, 0.288 mmol) in dioxane (3 mL) was added ethyl 3-bromo-2-oxopropanoate (112 mg, 0.575 mmol) at RT. The resulting mixture was then heated to 100 °C. After 12 h, the mixture was cooled to RT and then concentrated in vacuo. The crude product was purified by RP HPLC (ACN/water with 0.1% FA modifier) to afford the title compound as the TFA salt. LC/MS = 444 [M+1].

STEP I: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-ethylimidazo[1,2-a]pyridine-2-carboxylic acid

To a mixture of ethyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-ethylimidazo[1,2-a]pyridine-2-carboxylate (45 mg, 0.101 mmol) in THF (2 mL) and water (2 mL) was added lithium hydroxide hydrate (8.51 mg, 0.203 mmol) at RT. After 2 h, the mixture was concentrated under reduced pressure and then was dissolved in water. Aqueous 1 M HCl was added to adjust the pH = 4, whereupon the mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, then filtered and concentrated under reduced pressure to afford the title compound. The crude product was used without purification. LC/MS = 416 [M+1].

STEP J: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-ethyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

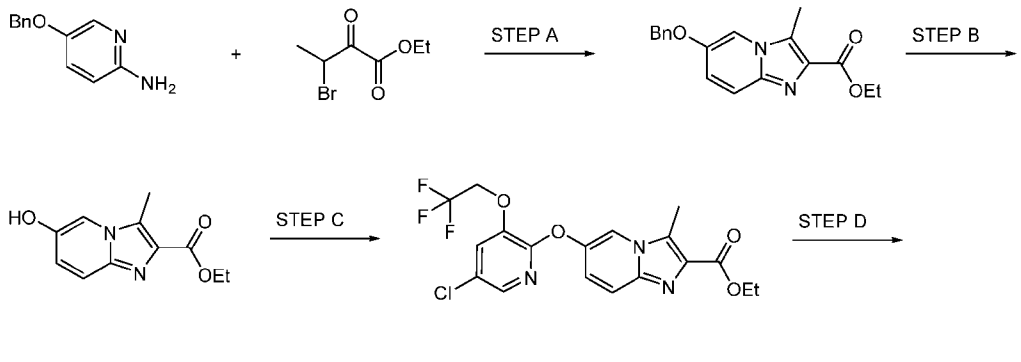
To a mixture of 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-ethylimidazo[1,2-a]pyridine-2-carboxylic acid (35 mg, 0.084 mmol), 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (20.61 mg, 0.126 mmol) and DIPEA (0.044 ml, 0.253 mmol) in DMF (2 mL) was added HATU (48.0 mg, 0.126 mmol) at RT. After 1 h, the reaction mixture was filtered and the filtrate was purified by RP HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound as the TFA salt. LC/MS = 561 [M+1]. ^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.88 (s, 1H), 8.47 - 8.68 (m, 1H), 7.79 - 7.86 (m, 2H), 7.71 - 7.77 (m, 1H), 4.78 - 4.84 (m, 2H), 3.25 - 3.32 (m, 2H), 3.00 - 3.12 (m, 2H), 2.84 - 2.97 (m, 2H), 2.78 (q, J = 7.48 Hz, 2H), 2.20 - 2.37 (m, 2H), 1.54 - 1.70 (m, 3H), 1.33 (t, J = 7.48 Hz, 3H). Human DGAT2 IC_{50} = 9.0 nM.

EXAMPLE 60: 6-[(3-hydroxy-2-pyridyl)oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

EX-60

To a mixture of 6-((3-(benzyloxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (7.0 mg, 0.01 mmol) in DCM (0.5 mL) was added BCl_3 solution (1 M in DCM, 30.0 µL, 0.03 mmol) at 0 °C. The resulting mixture was then warmed to RT. After 3 h, DCM/MeOH (9:1) was added, and the resulting mixture was concentrated. The crude product was purified by mass triggered RP HPLC (ACN/water with 0.1% FA modifier) to afford the title compound. LC/MS = 417 [M+1]. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.57 (s, 1H), 8.51 (d, *J* = 1.9 Hz, 1H), 8.31 (s, 1H), 7.64 (d, *J* = 9.8 Hz, 1H), 7.59 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.05 (dd, *J* = 7.8, 4.9 Hz, 1H), 3.40 – 3.34 (m, 2H), 3.08 – 3.00 (m, 2H), 2.96 – 2.86 (m, 2H), 2.30 – 2.18 (m, 2H), 1.58 (s, 3H). Human DGAT2 IC_{50} = >9990 nM.

EXAMPLE 61: 6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide



EX-61

STEP A: Ethyl 6-(benzyloxy)-3-methylimidazo[1,2-*a*]pyridine-2-carboxylate

At RT, to a stirred solution of 5-(benzyloxy)pyridin-2-amine (4.90 g, 24.5 mmol) in 1,4-dioxane (100.0 mL) was added methyl 3-bromo-2-oxobutanoate (7.16 g, 36.7 mmol). The resulting mixture was heated to 80 °C for 13 h. The mixture was diluted with saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with DCM. The combined organic layers were

dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (100% EtOAc/hexanes) to afford the title compound. LC/MS = 311 [M+H].

STEP B: Ethyl 6-hydroxy-3-methylimidazo[1,2-*a*]pyridine-2-carboxylate

At RT, to a stirred solution of ethyl 6-(benzyloxy)-3-methylimidazo[1,2-*a*]pyridine-2-carboxylate (3.60 g, 11.6 mmol) in DCM (100.0 mL) was added TEA (4.85 mL, 34.8 mmol), triethylsilane (5.56 mL, 34.8 mmol) and palladium(II) chloride (0.411 g, 2.32 mmol). The resulting mixture was stirred at RT for 12 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by mass triggered RP HPLC (C18, 100% ACN, 0.1% FA modifier) to afford the title compound. LC/MS = 221 [M+H].

STEP C: Ethyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*a*]pyridine-2-carboxylate

At RT, to a stirred solution of ethyl 6-hydroxy-3-methylimidazo[1,2-*a*]pyridine-2-carboxylate (70.0 mg, 0.318 mmol) in DMF (0.795 mL) was added sodium hydride (16.5 mg, 0.413 mmol, 60 wt%). The resulting mixture was stirred at RT for 5 min, then 5-chloro-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine (88.0 mg, 0.381 mmol) was added. The resulting reaction mixture was heated to 100 °C for 18 h, then cooled to RT and directly purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 430 [M+H].

STEP D: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*a*]pyridine-2-carboxylic acid

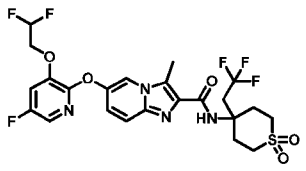
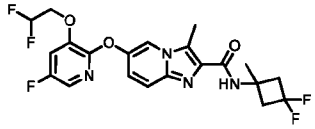
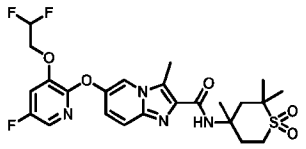
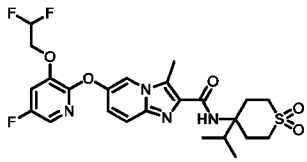
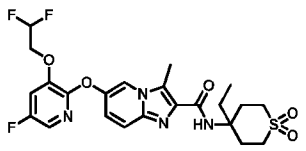
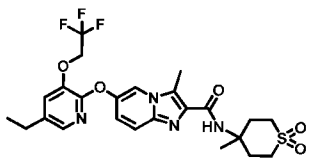
At RT, lithium hydroxide monohydrate (40.1 mg, 0.956 mmol) was added to a mixture of ethyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*a*]pyridine-2-carboxylate (137 mg, 0.319 mmol) in MeOH (0.50 mL), water (1.4 mL), and THF (1.4 mL). The resulting mixture was stirred at RT for 1.5 h, then lyophilized to afford the title compound. LC/MS = 402 [M+H].

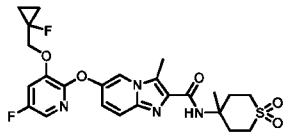
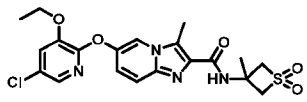
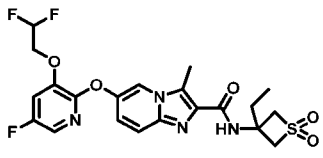
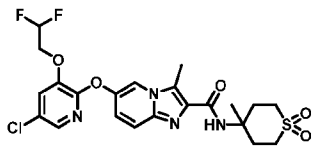
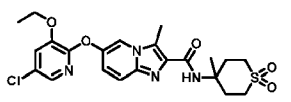
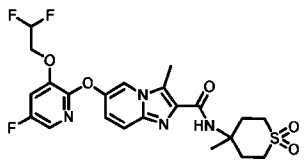
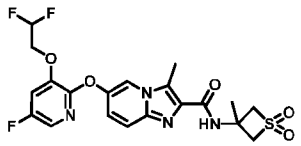
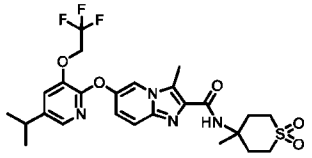
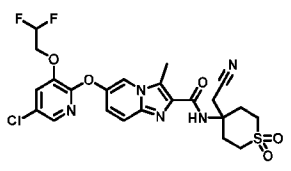
STEP E: 6-[[5-Chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

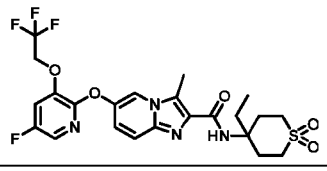
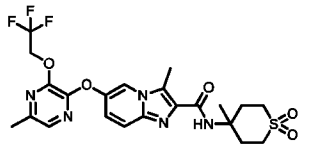
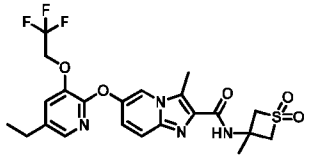
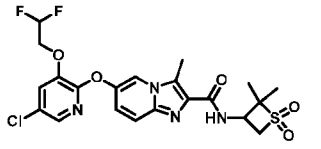
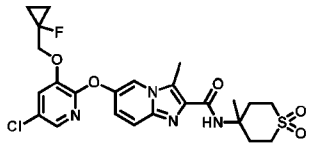
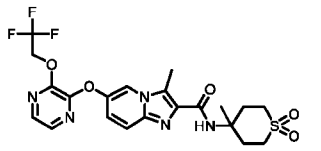
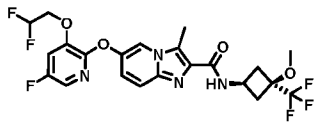
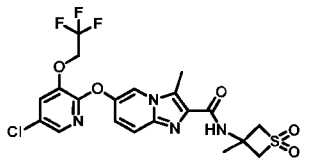
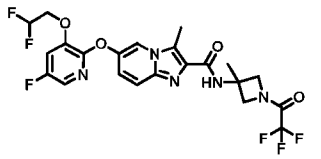
At RT, to a stirred mixture of 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*a*]pyridine-2-carboxylic acid (50.0 mg, 0.100 mmol) and HATU (41.6 mg, 0.110 mmol) in DMF (1.00 mL) and DCM (1.00 mL) was added DIPEA (60.9 µL, 0.348 mmol) then 4-methyltetrahydro-*2H*-thiopyran-4-aminium 1,1-dioxide chloride (21.9 mg, 0.110 mmol). The resulting mixture was stirred at RT for 1 h then diluted with EtOAc, filtered through celite,

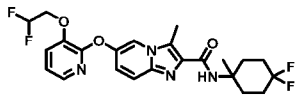
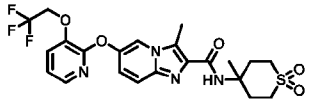
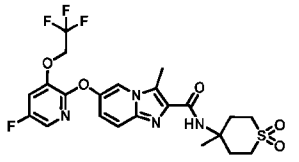
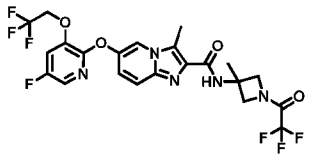
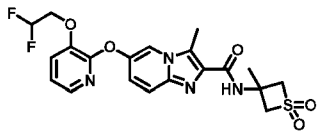
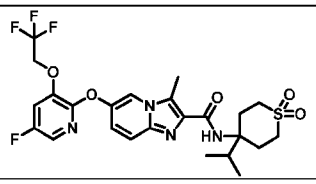
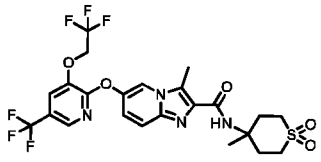
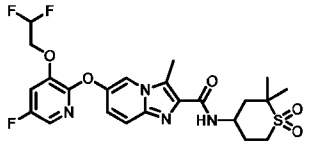
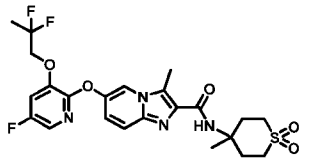
washing with EtOAc. The filtrate was concentrated, and the crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.35 (d, J = 1.8 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 9.8 Hz, 1H), 7.34 (dd, J = 9.8, 2.0 Hz, 1H), 4.78 (q, J = 8.4 Hz, 2H), 3.39 (m, J = 12.5 Hz, 2H), 3.03 (d, J = 14.0 Hz, 2H), 2.90 (d, J = 15.1 Hz, 2H), 2.78 (s, 3H), 2.24 (t, J = 12.5 Hz, 2H), 1.58 (s, 3H). LC/MS = 547 [M+H]. Human DGAT2 IC_{50} = 3.0 nM.

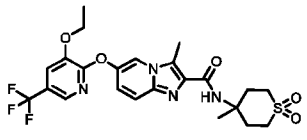
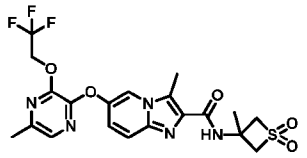
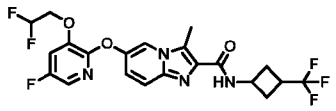
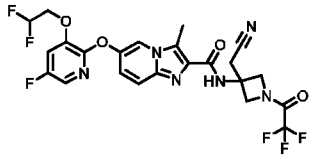
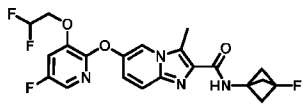
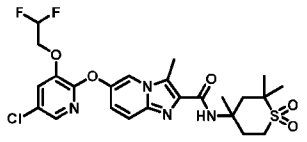
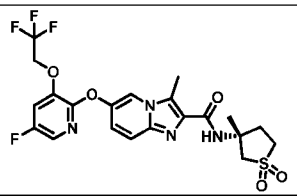
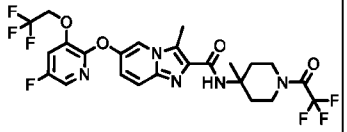
By using procedures similar to those described in **Example 61** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

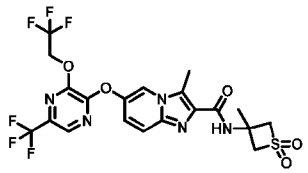
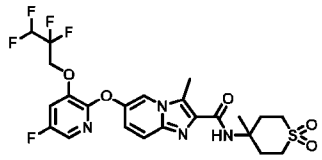
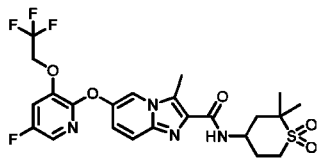
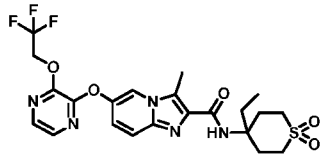
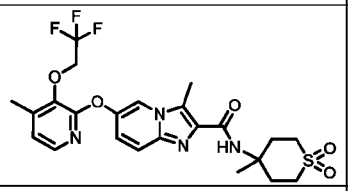
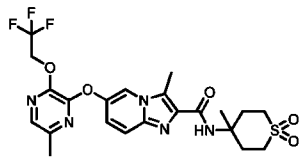
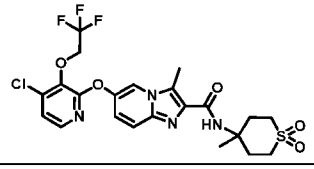
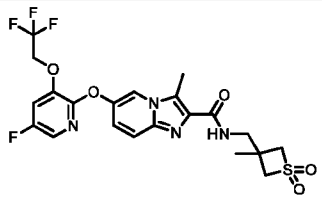
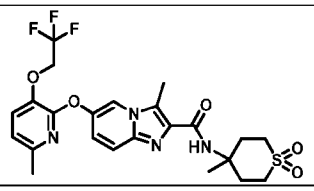
Example	Structure	Name	LC/MS [M+H]	Human DGAT2 IC_{50} (nM)
62		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-[1,1-dioxo-4-(2,2,2-trifluoroethyl)thian-4-yl]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	581	1.5
63		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3,3-difluoro-1-methyl-cyclobutyl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	471	0.6
64		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(2,2,4-trimethyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	541	1.7
65		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-isopropyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	541	434
66		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-ethyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	527	0.8
67		6-[[5-ethyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	541	0.7

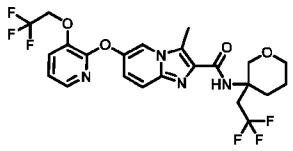
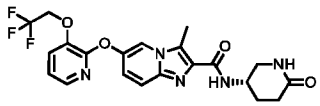
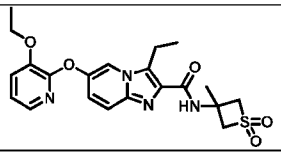
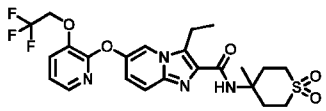
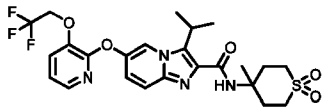
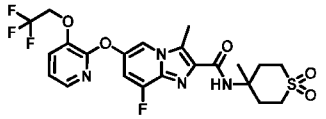
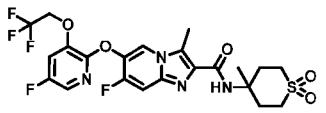
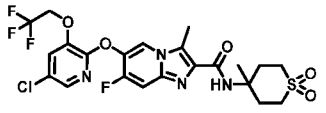
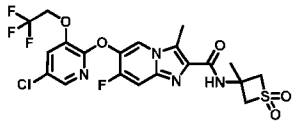
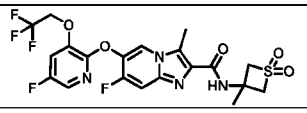
68		6-[[5-fluoro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	521	0.8
69		6-[(5-chloro-3-ethoxy-2-pyridyl)oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	465	2.0
70		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3-ethyl-1,1-dioxo-thietan-3-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	499	74.3
71		6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	529	1.4
72		6-[(5-chloro-3-ethoxy-2-pyridyl)oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	493	0.7
73		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	513	2.6
74		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	485	6.7
75		6-[[5-isopropyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	556	6.6
76		6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-[4-(cyanomethyl)-1,1-dioxo-thian-4-yl]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	555	1.2

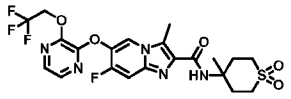
77		N-(4-ethyl-1,1-dioxo-thian-4-yl)-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	546	33
78		3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[5-methyl-3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide	529	3.0
79		6-[[5-ethyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	514	6.8
80		6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(2,2-dimethyl-1,1-dioxo-thietan-3-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	516	3.8
81		6-[[5-chloro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	538	3.5
82		3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide	514	9.1
83		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-[3-methoxy-3-(trifluoromethyl)cyclobutyl]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	519	12
84		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	520	6.2
85		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-[3-methyl-1-(2,2,2-trifluoroacetyl)azetidin-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide	532	1.6

86		6-[[3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(4,4-difluoro-1-methyl-cyclohexyl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	481	6.8
87		3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	514	17
88		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	531	8.3
89		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[3-methyl-1-(2,2,2-trifluoroacetyl)azetidin-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide	550	20
90		6-[[3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	467	5.0
91		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-isopropyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	560	22
92		3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-5-(trifluoromethyl)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	582	17
93		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(2,2-dimethyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	528	2.9
94		6-[[3-(2,2-difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	528	12

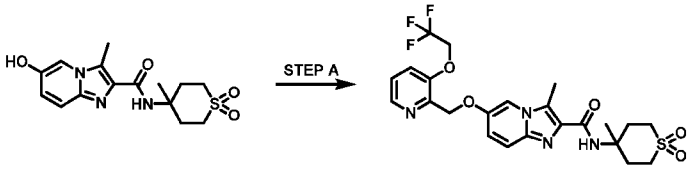
95		6-[[3-ethoxy-5-(trifluoromethyl)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	528	3.0
96		3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)-6-[5-methyl-3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide	500	5.7
97		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-[3-(trifluoromethyl)cyclobutyl]imidazo[1,2-*a*]pyridine-2-carboxamide	489	4.0
98		*N*-[3-(cyanomethyl)-1-(2,2,2-trifluoroacetyl)azetidin-3-yl]-6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	557	0.7
99		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	451	56
100		6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(2,2,4-trimethyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	558	114
101		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[(3*R*)-3-methyl-1,1-dioxo-thiolan-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide	517	88
102		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[4-methyl-1-(2,2,2-trifluoroacetyl)-4-piperidyl]imidazo[1,2-*a*]pyridine-2-carboxamide	578	128

103		3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)-6-[3-(2,2,2-trifluoroethoxy)-5-(trifluoromethyl)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide	534	71
104		6-[[5-fluoro-3-(2,2,3,3-tetrafluoropropoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	564	342
105		N-(2,2-dimethyl-1,1-dioxo-thian-4-yl)-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide	546	193
106		N-(4-ethyl-1,1-dioxo-thian-4-yl)-3-methyl-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide	529	638
107		3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[4-methyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	528	634
108		3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[6-methyl-3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide	529	131
109		6-[[4-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	548	224
110		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[(3-methyl-1,1-dioxo-thietan-3-yl)methyl]imidazo[1,2-*a*]pyridine-2-carboxamide	517	957
111		3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[6-methyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	528	298

112		3-methyl-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[3-(2,2,2-trifluoroethyl)tetrahydropyran-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide	533	3380
113		3-methyl-*N*-[(3*S*)-6-oxo-3-piperidyl]-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	464	>9990
114		6-[(3-ethoxy-2-pyridyl)oxy]-3-ethyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	446	64
115		3-ethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	527	44
116		3-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	542	413
117		8-fluoro-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide	531	1.2
118		7-fluoro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	549	1.4
119		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-fluoro-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	566	1.0
120		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-fluoro-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	538	4.3
121		7-fluoro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-	521	41

		dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide		
122		7-fluoro-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide	532	7.7

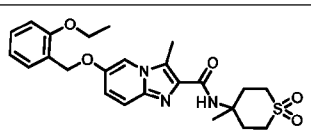
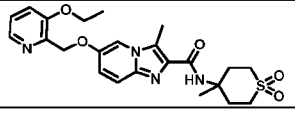
EXAMPLE 123: 3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]methoxy]imidazo[1,2-*a*/pyridine-2-carboxamide

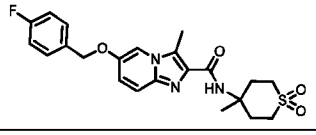
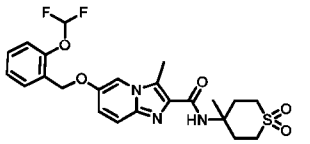


EX-123

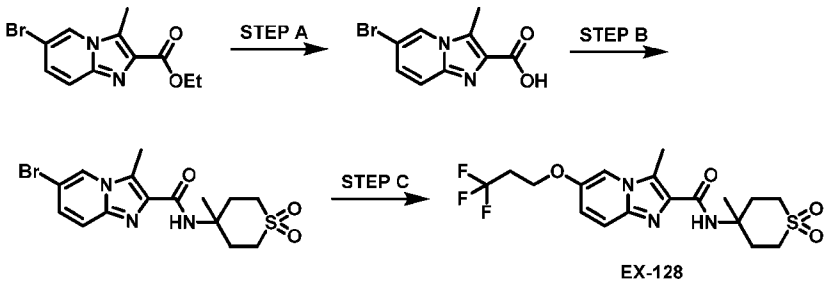
At RT, to a stirred solution of 6-hydroxy-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (30.0 mg, 0.0890 mmol) and K_2CO_3 (24.6 mg, 0.178 mmol) in DMF (445 µL) was added 2-(chloromethyl)-3-(2,2,2-trifluoroethoxy)pyridine (30.1 mg, 0.133 mmol). The resulting mixture was heated to 50 °C for 2 h. The reaction was cooled to RT, and the mixture was directly purified by mass triggered RP HPLC (C18, 20 to 60% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.31 (d, J = 4.7 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.26 (dd, J = 9.8, 2.2 Hz, 1H), 5.33 (s, 2H), 4.76 (q, J = 8.4 Hz, 2H), 3.40 – 3.34 (m, 2H), 3.02 (d, J = 13.4 Hz, 2H), 2.88 (d, J = 14.3 Hz, 2H), 2.78 (s, 3H), 2.22 (t, J = 13.6 Hz, 2H), 1.57 (s, 3H). LC/MS = 527 [M+H]. Human DGAT2 IC_{50} = 93 nM.

By using procedures similar to those described in **Example 123** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

Example	Structure	Name	LC/MS [M+H]	Human DGAT2 IC_{50} (nM)
124		6-[(2-ethoxyphenyl)methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	473	5.7
125		6-[(3-ethoxy-2-pyridyl)methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-	474	4.9

		thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide		
126		6-[(4-fluorophenyl)methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	447	465
127		6-[[2-(difluoromethoxy)phenyl]methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	495	6.5

EXAMPLE 128: 3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-(3,3,3-trifluoropropoxy)imidazo[1,2-*a*]pyridine-2-carboxamide



EX-128

STEP A: 6-Bromo-3-methylimidazo[1,2-*a*]pyridine-2-carboxylic acid

At RT, lithium hydroxide monohydrate (101 mg, 2.40 mmol) was added to a mixture of ethyl 6-bromo-3-methylimidazo[1,2-*a*]pyridine-2-carboxylate (340.0 mg, 1.20 mmol) in MeOH (3.00 mL), water (1.00 mL), and THF (2.00 mL). The resulting mixture was stirred at RT for 5 h, then lyophilized to afford the title compound. LC/MS = 255 / 257 [M+H].

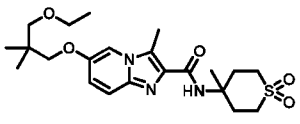
STEP B: 6-Bromo-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT, to a stirred mixture of 6-bromo-3-methylimidazo[1,2-*a*]pyridine-2-carboxylic acid (650.0 mg, 2.55 mmol) and HATU (1.45 g, 3.82 mmol) in DMF (10.0 mL) was added DIPEA (1.33 mL, 7.64 mmol) then 4-methyltetrahydro-*2H*-thiopyran-4-aminium 1,1-dioxide chloride (611 mg, 3.06 mmol). The resulting mixture was stirred at RT for 1 h then diluted with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (60% EtOAc/hexanes) to afford the title compound. LC/MS = 400 / 402 [M+H].

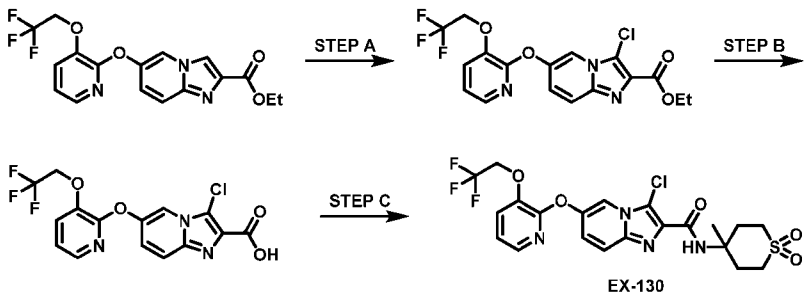
STEP C: 3-Methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-(3,3,3-trifluoropropoxy)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT under an N_2 atmosphere, to a stirred solution of 6-bromo-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (80.0 mg, 0.200 mmol), sodium *tert*-butoxide (23.1 mg, 0.240 mmol), *N,N'*-bis(2-phenylethythl)ethanediamide (11.9 mg, 0.040 mmol), copper(I) iodide (7.61 mg, 0.040 mmol) in 1,4-dioxane (2.00 mL) was added 3,3,3-trifluoro-1-propanol (114 mg, 0.999 mmol). The resulting mixture was heated to 80 °C for 18 h. The reaction mixture was cooled to RT, diluted with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was directly purified by mass triggered RP HPLC (C18, 30 to 50% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.83 (d, J = 1.96 Hz, 1H), 7.50 (d, J = 9.78 Hz, 1H), 7.21 (dd, J = 2.35, 9.78 Hz, 1H), 4.32 (t, J = 5.87 Hz, 2H), 3.32 – 3.39 (m, 2H), 2.98 – 3.01 (m, 2H), 2.84 – 2.88 (m, 2H), 2.72 – 2.82 (m, 5H), 2.17 – 2.24 (m, 2H), 1.55 (s, 3H). LC/MS = 434 [M+H]. Human DGAT2 IC_{50} >9990 nM.

By using procedures similar to those described in **Example 128** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

Example	Structure	Name	LC/MS [M+H]	Human DGAT2 IC_{50} (nM)
129		6-(3-ethoxy-2,2-dimethyl-propoxy)-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	453	161

EXAMPLE 130: 3-chloro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide



EX-130

STEP A: Ethyl 3-chloro-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylate

At RT, to a stirred mixture of ethyl 6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylate (100.0 mg, 0.262 mmol) in DMF (2.00 mL) was added NCS (70.0 mg, 0.525 mmol). The resulting mixture was stirred at RT for 15 h, then diluted with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by preparatory thin layer column chromatography on silica (50% EtOAc/PE) to afford the title compound. LC/MS = 416 [M+H].

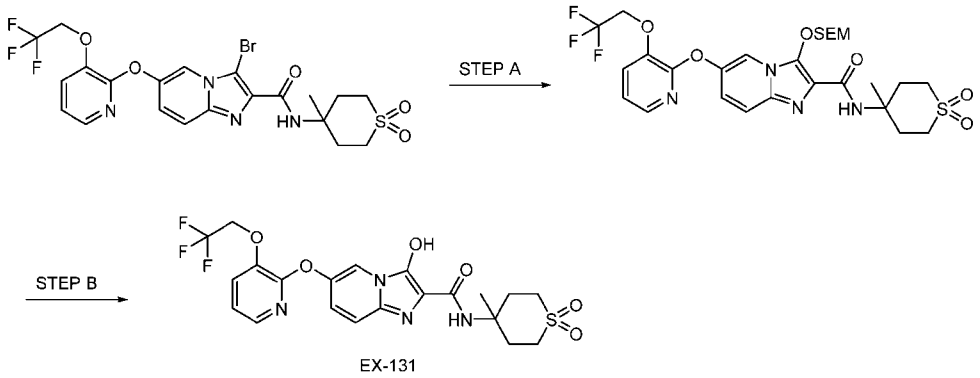
STEP B: 3-Chloro-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylic acid

At RT, lithium hydroxide monohydrate (20.2 mg, 0.481 mmol) was added to a mixture of ethyl 3-chloro-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylate (100.0 mg, 0.241 mmol) in MeOH (1.50 mL), THF (1.00 mL), and water (0.500 mL), diluted with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound. LC/MS = 388 [M+H].

STEP C: 3-Chloro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide;2,2,2-trifluoroacetate

At RT, to a stirred mixture of 3-chloro-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylic acid (70.0 mg, 0.181 mmol) in DMF (2.00 mL) was added DIPEA (95.0 µL, 0.542 mmol) and HATU (103 mg, 0.271 mmol) then 4-methyltetrahydro-*2H*-thiopyran-4-aminium 1,1-dioxide chloride (45.0 mg, 0.225 mmol). The resulting mixture was stirred at RT for 0.5 h, then directly purified by mass triggered Reverse Phase HPLC (C18, 40 to 60% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.44 (d, J = 1.53 Hz, 1H), 7.79 (dd, J = 1.37, 4.88 Hz, 1H), 7.70 (d, J = 9.77 Hz, 1H), 7.61 (dd, J = 1.22, 7.93 Hz, 1H), 7.43 (dd, J = 2.14, 9.77 Hz, 1H), 7.17 (dd, J = 4.88, 8.09 Hz, 1H), 4.73 (q, J = 8.49 Hz, 2H), 3.33 – 3.36 (m, 2H), 3.01 – 3.03 (m, 2H), 2.87 – 2.90 (m, 2H), 2.19 – 2.26 (m, 2H), 1.57 (s, 3H). LC/MS = 533 [M+H]. Human DGAT2 IC_{50} = 3.3 nM.

EXAMPLE 131: 3-hydroxy-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide



EX-131

STEP A: *N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-((2-(trimethylsilyl)ethoxy)methoxy)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT, to a stirred mixture of 2-(trimethylsilyl)ethan-1-ol (10.2 mg, 0.0870 mmol), 3-bromo-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide (50.0 mg, 0.0870 mmol), and sodium 2-methylpropan-2-olate (16.7 mg, 0.173 mmol) was added copper(I) iodide (1.65 mg, 8.66 µmol) in 1,4-dioxane (4.00 mL). The resulting mixture was stirred at 50 °C for 16 h, then concentrated in vacuo. The crude material was purified by preparatory thin layer column chromatography on silica (17% EtOAc/PE) to afford the title compound. LC/MS = 615 [M+H].

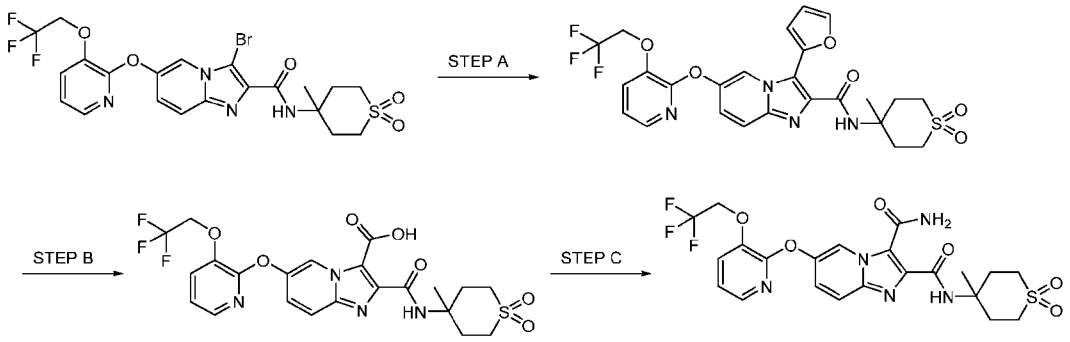
STEP B: 3-Hydroxy-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide;2,2,2-trifluoroacetate

At RT, to a stirred mixture of *N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(2-(trimethylsilyl)ethoxy)imidazo[1,2-*a*]pyridine-2-carboxamide (40.0 mg, 0.0650 mmol) in THF (2.00 mL) was added TBAF (1M in THF, 0.390 mL, 0.390 mmol) dropwise. The resulting mixture was stirred at RT for 1 h, then diluted with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was directly purified by mass triggered RP HPLC (C18, 20 to 60% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.45 (br s, 1H), 8.65 (s, 1H), 8.32 (s, 1H), 7.82 (d, *J* = 5.08 Hz, 1H), 7.55 (br d, *J* = 9.54 Hz, 1H), 7.47 (dd, *J* = 1.83, 9.66 Hz, 1H), 7.37 (d, *J* = 7.34 Hz, 1H), 7.07 (dd, *J* = 4.89, 7.82 Hz, 1H), 4.50 (q, *J* = 7.99 Hz, 2H), 3.23 – 3.37 (m, 2H), 2.99 (br d, *J* = 9.78 Hz, 4H), 2.15 – 2.34 (m, 2H), 1.64 (s, 3H). LC/MS = 515 [M+H]. Human DGAT2 IC_{50} = 34 nM.

EXAMPLE 132and 133:

(Example 132): 2-((4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)carbamoyl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-3-carboxylic acid

(Example 133): *N*2-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2,3-dicarboxamide



STEP A: 3-(Furan-2-yl)-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT, to a stirred solution of 3-bromo-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide (50.0 mg, 0.0870 mmol), K_2CO_3 (48.0 mg, 0.347 mmol), and furan-2-ylboronic acid (12.0 mg, 0.107 mmol) in 1,4-dioxane (1.00 mL) and water (0.100 mL) was added $PdCl_2$(dppf)(6.00 mg, 8.20 µmol). The resulting mixture was stirred at 150 °C under microwave for 20 mins. The reaction was diluted with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by preparatory thin layer column chromatography on silica (100% EtOAc) to afford the title compound. LC/MS = 565 [M+H].

STEP B (Example 132): 2-((4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)carbamoyl)-6-((3-(2,2,2- trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-3-carboxylic acid

At RT, to a stirred solution of 3-(furan-2-yl)-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide (35.0 mg, 0.0620 mmol) in acetone (3.00 mL) and water (1.80 mL) was added $KMnO_4$ (69.0 mg, 0.434 mmol). The resulting mixture was stirred at 60 °C for 5 h. The mixture was filtered through a pad of celite, washed with MeOH, and the filtrate was concentrated in vacuo to afford the title compound. LC/MS = 543 [M+H]. Human DGAT2 IC_{50} > 9990 nM,

STEP C (Example 133): *N*2-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy) pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2,3-dicarboxamide

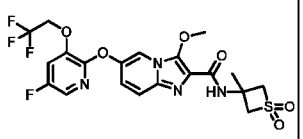
At RT, to a stirred solution of 2-((4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)carbamoyl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-3-carboxylic acid (30.0 mg, 0.0550 mmol) in DMF (1.00 mL) were added NH_4Cl (9.00 mg, 0.166 mmol), 2-(3*H*- [1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (42.0 mg, 0.111 mmol), and *N*-ethyl-*N*-isopropylpropan-2-amine (36.0 mg, 0.277 mmol). The resulting mixture was stirred at RT for 1 h, then directly purified by mass triggered RP HPLC (C18, 30 to 60% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-*d*$_4$) δ 9.79 (br s, 1H), 7.71 – 7.83 (m, 2H), 7.59 (br d, J = 7.83 Hz, 1H), 7.52 (br d, J = 8.80 Hz, 1H), 7.14 (dd, J = 4.89, 8.07 Hz, 1H), 4.70 (q, J = 8.31 Hz, 2H), 3.33 (br s, 2H), 3.02 (m, 2H), 2.91 (m, 2H), 2.18 – 2.28 (m, 2H), 1.57 (s, 3H). LC/MS = 542 [M+H]. Human DGAT2 IC_{50} = 28 nM.

EXAMPLE 134: 3-methoxy-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide

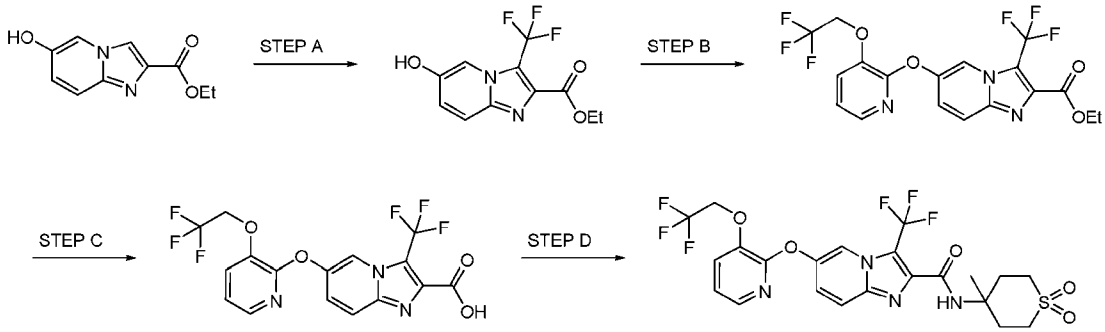
EX-134

At RT under an N_2 atmosphere, to a stirred solution of 3-bromo-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide (20.0 mg, 0.0350 mmol), sodium 2-methylpropan-2-olate (6.66 mg, 0.0690 mmol), copper(I) iodide (0.660 mg, 3.46 μmol), and *N*$_1$,*N*$_2$-diphenethyloxalamide (1.03 mg, 3.46 μmol) in 1,4-dioxane (1.00 mL) was added MeOH (69.4 μg, 1.73 mmol). The resulting mixture was stirred at 60 °C for 16 h. The reaction was concentrated in vacuo, and the crude material was purified by mass triggered RP HPLC (C18, 10 mM aqueous NH_4HCO_3 in ACN) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-*d*$_4$) δ 8.20 (d, *J* = 1.47 Hz, 1H), 7.75 (dd, *J* = 1.22, 4.89 Hz, 1H), 7.57 (dd, *J* = 1.22, 7.83 Hz, 1H), 7.49 (d, *J* = 9.78 Hz, 1H), 7.23 (dd, *J* = 2.08, 9.90 Hz, 1H), 7.13 (dd, *J* = 4.89, 7.83 Hz, 1H), 4.69 (q, *J* = 8.31 Hz, 2H), 4.58 (br s, 1H), 4.17 (s, 3H), 3.31 – 3.38 (m, 1H), 2.99 (m, 2H), 2.86 (m, 2H), 2.14 – 2.24 (m, 2H), 1.54 (s, 3H). LC/MS = 529 [M+H]. Human DGAT2 IC_{50} = 6.2 nM.

By using procedures similar to those described in **Example 134** with appropriate reagents, the following compound was synthesized and was characterized by LC/MS.

Example	Structure	Name	LC/MS [M+H]	Human DGAT2 IC_{50} (nM)
135		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methoxy-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridin-1-ium-2-carboxamide;2,2,2-trifluoroacetate	520	62

EXAMPLE 136: *N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxamide



EX-136

STEP A: Ethyl 6-hydroxy-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxylate

At RT, to a stirred solution of ethyl 6-hydroxyimidazo[1,2-*a*]pyridine-2-carboxylate (41.2 mg, 0.200 mmol), pyridine-*N*-oxide (57.1 mg, 0.600 mmol), and tris(2,2'-bipyridyl)ruthenium(II) chloride hexahydrate (1.50 mg, 2.000 μmol) in ACN (412 μL) was added TFAA (83.0 μL, 0.600 mmol). The resulting mixture was irradiated with blue LEDs (800 rpm light at 50%) for 16 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography on silica (0-90% EtOAc/hexanes) to afford the title compound. LC/MS = 275 [M+H].

STEP B: Ethyl 6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxylate

At RT, to a stirred solution of 3-(2,2,2-trifluoroethoxy)pyridine 1-oxide (16.3 mg, 0.0840 mmol) and ethyl 6-hydroxy-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxylate (22.0 mg, 0.0800 mmol) in THF (1.00 mL) were added DIPEA (42.0 μL, 0.241 mmol) and PyBrop (48.6 mg, 0.104 mmol). The resulting solution was stirred at RT for 18 h. The mixture was diluted with DCM, washed with 1M aqueous NaOH, water, and then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column

chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 450 [M+H].

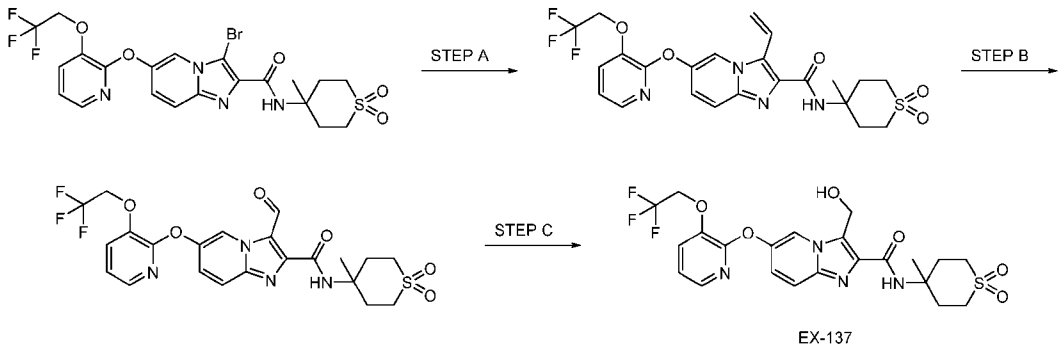
STEP C: 6-((3-(2,2,2-Trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxylic acid

At RT, lithium hydroxide monohydrate (2.06 mg, 0.0490 mmol) was added to a mixture of ethyl 6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxylate (22.0 mg, 0.0490 mmol) in THF (57.6 µL), MeOH (28.8 µL) and water (11.5 µL). The resulting mixture was stirred at RT for 1.5 h, then lyophilized to afford the title compound. LC/MS = 422 [M+H].

STEP D: *N*-(4-Methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT, to a stirred mixture of 6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxylic acid (20.6 mg, 0.0490 mmol) and HATU (37.3 mg, 0.0980 mmol) in DMF (1.00 mL) was added DIPEA (26.0 µL, 0.147 mmol) then 4-methyltetrahydro-*2H*-thiopyran-4-aminium 1,1-dioxide chloride (10.8 mg, 0.0540 mmol). The resulting mixture was stirred at RT for 2 h then directly purified by mass triggered RP HPLC (C18, 50 to 98% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.58 (s, 1H), 7.94 – 7.74 (m, 2H), 7.70 – 7.47 (m, 2H), 7.19 (dd, J = 8.0, 4.9 Hz, 1H), 4.75 (q, J = 8.4 Hz, 2H), 3.41 – 3.33 (m, 2H), 3.03 (d, J = 13.5 Hz, 2H), 2.86 (d, J = 14.4 Hz, 2H), 2.23 (t, J = 13.6 Hz, 2H). LC/MS = 567 [M+H]. Human DGAT2 IC_{50} = 146 nM.

EXAMPLE 137: 3-(hydroxymethyl)-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide



EX-137

STEP A: *N*-(4-Methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-vinylimidazo[1,2-*a*]pyridine-2-carboxamide

At RT under an N_2 atmosphere, to a stirred solution of 3-bromo-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-

a]pyridine-2-carboxamide (40.0 mg, 0.0690 mmol) and potassium trifluoro(vinyl)borate (27.8 mg, 0.208 mmol) in 1,4-dioxane (1.00 mL) and water (0.100 mL) was added $PdCl_2$(dppf)(5.07 mg, 6.93 μmol). The resulting solution was stirred at 100 °C 4 h. The reaction was diluted with water and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by preparatory thin layer column chromatography on silica (100% EtOAc) to afford the title compound. LC/MS = 525 [M+H].

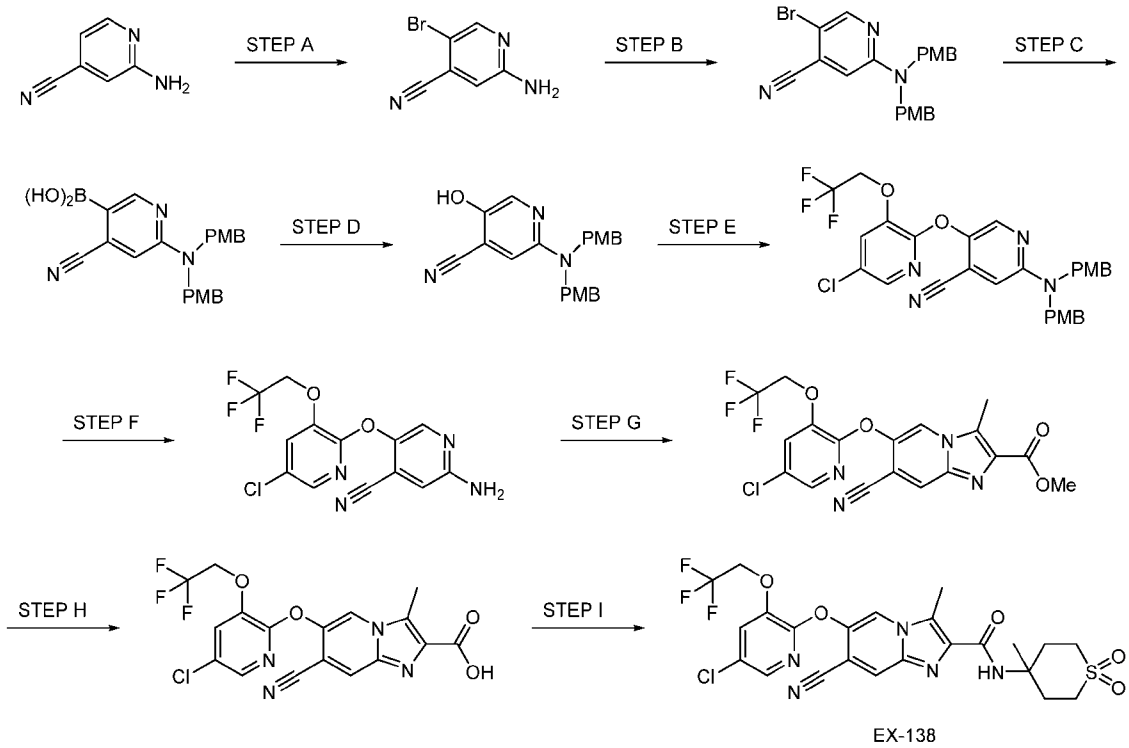
STEP B: 3-Formyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT, to a stirred solution of *N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-vinylimidazo[1,2-*a*]pyridine-2-carboxamide (30.0 mg, 0.0570 mmol) in THF (3.00 mL) and water (0.600 mL) was added 4-methylmorpholine *N*-oxide (6.70 mg, 0.0570 mmol), sodium periodate (24.5 mg, 0.114 mmol), and osmium(VIII) oxide (1.45 mg, 5.72 μmol). The resulting mixture was stirred at 30 °C for 2 h. The reaction was diluted with water and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound. LC/MS = 527 [M+H].

STEP C: 3-(hydroxymethyl)-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide

At RT, to a stirred solution of 3-formyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide (30.0 mg, 0.0570 mmol) in THF (0.800 mL) and MeOH (0.800 mL) was added $NaBH_4$ (2.10 mg, 0.0570 mmol). The resulting mixture was stirred at RT for 1 h. The reaction was diluted with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by mass triggered RP HPLC (C18, ACN in water, 0.1% FA modifier) to afford the title compound.^{1}H NMR (400 MHz, Methanol-d_4) δ 8.74 (s, 1H), 7.70 – 7.84 (m, 3H), 7.61 (dd, *J* = 1.22, 8.07 Hz, 1H), 7.17 (dd, *J* = 5.01, 7.95 Hz, 1H), 5.23 (s, 2H), 4.67 – 4.83 (m, 2H), 2.95 – 3.11 (m, 2H), 2.77 – 2.88 (m, 2H), 2.22 (m 2H), 1.56 (s, 3H). LC/MS = 529 [M+H]. Human DGAT2 IC_{50} = 11 nM.

EXAMPLE 138: 6-[5-chloro-3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-7-cyano-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide



EX-138

STEP A: 2-Amino-5-bromoisonicotinonitrile

At RT, to a stirred solution of 2-aminoisonicotinonitrile (2.00 g, 16.8 mmol) in THF (60.0 mL) was added NBS (3.29 g, 18.5 mmol). The resulting solution was stirred at RT for 2 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 solution, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 198 and 200 [M+H].

STEP B: 2-(Bis(4-methoxybenzyl)amino)-5-bromoisonicotinonitrile

At 0 °C under an N_2 atmosphere, to a stirred solution of 2-amino-5-bromoisonicotinonitrile (3.00 g, 15.2 mmol) in DMF (50.0 mL) was added sodium hydride (1.40 g, 35.0 mmol, 60 wt%). The resulting solution was stirred at 0 °C for 0.5 h, then 1-(chloromethyl)-4-methoxybenzene (5.22 g, 33.3 mmol) was added. The mixture was stirred at 0 °C for an additional 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 438 and 440 [M+H].

STEP C: (6-(Bis(4-methoxybenzyl)amino)-4-cyanopyridin-3-yl)boronate

At RT under an N_2 atmosphere, to a stirred solution of 2-(bis(4-methoxybenzyl)amino)-5-bromoisonicotinonitrile (3.00 g, 6.84 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.48 g, 13.7 mmol), and potassium acetate (2.02 g, 20.5 mmol) in 1,4-dioxane (60.0 mL) was added $PdCl_2$(dppf) (0.501 g, 0.684 mmol). The resulting mixture was stirred at 95 °C for 12 h. The reaction mixture was filtered through a pad of celite, washing with EtOAc, and the filtrate was concentrated in vacuo to afford the title compound. LC/MS = 404 and 486 [M+H].

STEP D: 2-(Bis(4-methoxybenzyl)amino)-5-hydroxyisonicotinonitrile

At RT under an N_2 atmosphere, to a stirred solution of 2-(bis(4-methoxybenzyl)amino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isonicotinonitrile (6-(bis(4-methoxybenzyl)amino)-4-cyanopyridin-3-yl)boronate (4.00 g, 4.50 mmol) in THF (80.0 mL) was added 4-methylmorpholine *N*-oxide (3.00 g, 25.6 mmol). The resulting solution was stirred at 80 °C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 376 [M+H].

STEP E: 2-(Bis(4-methoxybenzyl)amino)-5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)isonicotinonitrile

At RT, to a stirred solution of 2-(bis(4-methoxybenzyl)amino)-5-hydroxyisonicotinonitrile (700.0 mg, 1.87 mmol) in DMF (7.00 mL) was added Cs_2CO_3 (911 mg, 2.80 mmol). The resulting mixture was stirred at 20 °C for 10 min whereupon 5-chloro-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine (556 mg, 2.42 mmol) was added. The mixture was stirred at 60 °C for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 585 [M+H].

STEP F: 2-Amino-5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)isonicotinamide

At RT, to a stirred solution of 2-(bis(4-methoxybenzyl)amino)-5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)isonicotinonitrile (230.0 mg, 0.393 mmol) in DCM (3.00 mL) was added TFA (1.00 mL). The resulting mixture was stirred at RT for 18 h. The solution was concentrated in vacuo to afford the title compound. LC/MS = 345 [M+H].

STEP G: Methyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-cyano-3-methylimidazo[1,2-a]pyridine-2-carboxylate

At RT under an N_2 atmosphere, to a stirred solution of 2-amino-5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)isonicotinonitrile (120 mg, 0.349 mmol) in 1,4-dioxane (4.00 mL) was added methyl 3-bromo-2-oxobutanoate (200 mg, 1.026 mmol). The resulting mixture was stirred at 90 °C for 13 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by preparatory thin layer column chromatography on silica (33% EtOAc/PE) to afford the title compound. LC/MS = 441 [M+H].

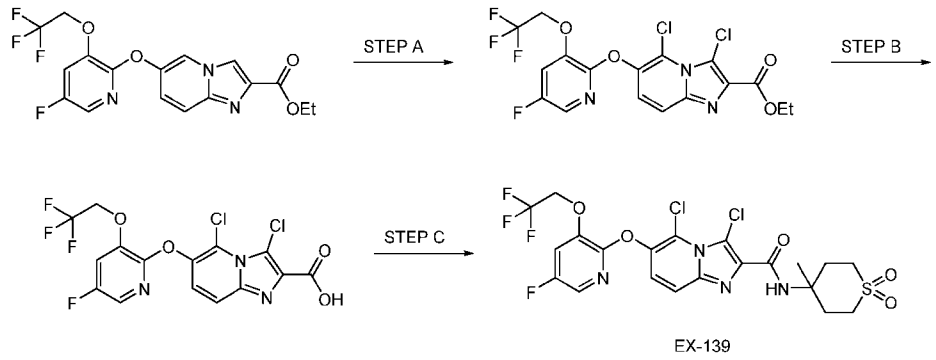
STEP H: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-cyano-3-methylimidazo[1,2-*a*]pyridine-2-carboxylic acid

At RT, to a stirred solution of methyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-cyano-3-methylimidazo[1,2-*a*]pyridine-2-carboxylate (10.0 mg, 0.0230 mmol) in MeOH (1.50 mL) and water (0.150 mL) was added lithium hydroxide monohydrate (4.00 mg, 0.0950 mmol). The resulting mixture was stirred at RT for 3 h, then the mixture was concentrated in vacuo to afford the title compound. LC/MS = 427 [M+H].

STEP I: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridine-2-yl)oxy)-7-cyano-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT, to a stirred mixture of 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-cyano-3-methylimidazo[1,2-*a*]pyridine-2-carboxylic acid (9.00 mg, 0.0210 mmol) and HATU (34.6 mg, 0.0910 mmol) in DMF (1.00 mL) was added DIPEA (24.0 µL, 0.136 mmol) then 4-methyltetrahydro-*2H*-thiopyran-4-aminium 1,1-dioxide chloride (21.9 mg, 0.110 mmol). The resulting mixture was stirred at RT for 1 h then diluted with EtOAc, filtered through celite, washing with EtOAc. The filtrate was concentrated in vacuo, and the crude material was purified by mass triggered RP HPLC (C18, ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.48 (s, 1H), 8.15 (s, 1H), 7.66 – 7.68 (m, 1H), 7.66 (s, 1H), 4.65 – 4.72 (m, 2H), 3.24 (br d, J = 3.10 Hz, 1H), 3.17 (br s, 1H), 2.92 (br d, J = 16.93 Hz, 2H), 2.75 – 2.84 (m, 2H), 2.64 – 2.71 (m, 3H), 2.04 – 2.19 (m, 2H), 1.43 – 1.48 (m, 3H). LC/MS = 572 [M+H]. Human DGAT2 IC_{50} = 25 nM.

EXAMPLE 139: 3,5-dichloro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide



STEP A: Ethyl 3,5-dichloro-6-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylate

At RT, to a stirred solution of ethyl 6-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylate (968 mg, 2.42 mmol) in DMF (15.0 mL) was added NCS (647 mg, 4.85 mmol). The resulting solution was stirred at RT for 72 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 468 [M+H].

STEP B: 3,5-Dichloro-6-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylic acid

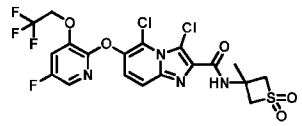
At RT, to a stirred solution of ethyl 3,5-dichloro-6-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylate (0.264 g, 0.563 mmol) in THF (0.663 mL), MeOH (0.331 ml), and water (0.133 mL) was added lithium hydroxide monohydrate (0.0240 g, 0.563 mmol). The resulting mixture was stirred at RT for 3 h then the mixture was concentrated in vacuo to afford the title compound. LC/MS = 441 [M+H].

STEP C: 3,5-Dichloro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

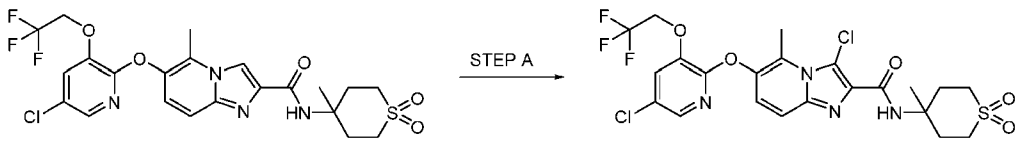
At RT, to a stirred solution of 3,5-dichloro-6-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxylic acid (20.0 mg, 0.0450 mmol), 4-amino-4-methyltetrahydro-*2H*-thiopyran 1,1-dioxide dihydrochloride (9.98 mg, 0.0300 mmol), and DIPEA (0.0140 mL, 0.0770 mmol) in DMF (0.800 mL) was added HATU (16.0 mg, 0.0420 mmol). The resulting solution was stirred at RT for 1.5 h, then the mixture was directly purified by mass triggered RP HPLC (C18, 20 to 60% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.74 (s, 2H), 7.52 (d, J = 9.7 Hz, 1H), 7.28 (d, J = 9.7 Hz, 1H), 4.80 (q, J = 8.3 Hz, 2H), 3.44 – 3.33 (m, 2H), 3.04 (d, J = 14.3 Hz, 2H), 2.93

(s, 5H), 2.23 (t, J = 14.1 Hz, 2H), 1.58 (s, 3H). LC/MS = 586 [M+H]. Human DGAT2 IC_{50} = 0.7 nM.

By using procedures similar to those described in **Example 139** with appropriate reagents, the following compound was synthesized. This compound was characterized by LC/MS.

Example	Structure	Name	LC/MS [M+H]	Human DGAT2 IC_{50} (nM)
140		3,5-dichloro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	558	2.1

EXAMPLE 141: 3-chloro-6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

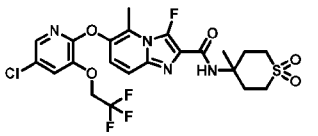
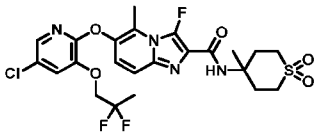


EX-141

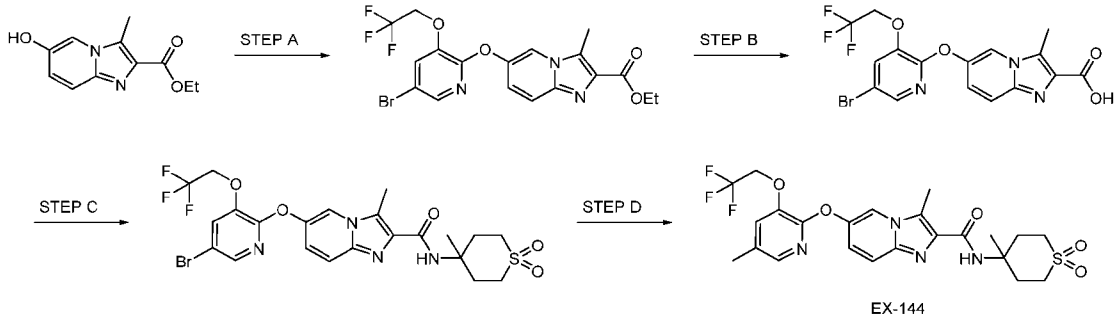
At RT under the exclusion of light, to a stirred solution of 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-5-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (100.0 mg, 0.183 mmol) in THF (914 µL) was added NCS (25.6 mg, 0.192 mmol). The resulting solution was stirred at 80 °C for 18 h, under the exclusion of light, then purified directly by mass triggered RP HPLC (C18, 55 to 98% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7. LC/MS = 582 [M+H]. Human DGAT2 IC_{50} = 2.6 nM.

By using procedures similar to those described in **Example 141** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

Example	Structure	Name	LC/MS [M+H]	Human DGAT2 IC_{50} (nM)

142		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	566	3.5
143		6-[[5-chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-3-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide	562	37

EXAMPLE 144: 3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[5-methyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide



EX-144

STEP A: Ethyl 6-((5-bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*a*]pyridine-2-carboxylate

At RT, to a stirred solution of ethyl 6-hydroxy-3-methylimidazo[1,2-*a*]pyridine-2-carboxylate (200.0 mg, 0.908 mmol) in DMF (2.27 mL) was added sodium hydride (47.2 mg, 1.18 mmol, 60 wt%). The resulting mixture was stirred at RT for 5 min, then 5-bromo-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine (299 mg, 1.09 mmol) was added. The resulting reaction mixture was heated to 80 °C for 18 h, then cooled to RT and diluted with brine. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound. LC/MS = 474 [M+H].

STEP B: 6-((5-Bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*a*]pyridine-2-carboxylic acid

At RT, lithium hydroxide monohydrate (76.0 mg, 1.82 mmol) was added to a mixture of ethyl 6-((5-bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*a*]pyridine-2-carboxylate (431 mg, 0.909 mmol) in MeOH (1.30 mL), water (3.90 mL), and THF (3.90 mL). The resulting mixture was stirred at RT for 1 h then concentrated in vacuo to afford the title compound. LC/MS = 446 [M+H].

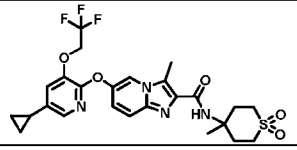
STEP C: 6-[[5-Bromo-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT, to a stirred mixture of 6-((5-bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*a*]pyridine-2-carboxylic acid (406 mg, 0.910 mmol) and HATU (346 mg, 0.910 mmol) in DMF (2.18 mL) and DCM (1.46 mL) was added DIPEA (556 µL, 3.18 mmol) then 4-methyltetrahydro-*2H*-thiopyran-4-aminium 1,1-dioxide chloride (182 mg, 0.910 mmol). The resulting mixture was stirred at RT for 18 h then diluted with water and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the title compound. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes then 0-10% MeOH/DCM) to afford the title compound. LC/MS = 593 [M+H].

STEP D: 3-Methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[5-methyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide

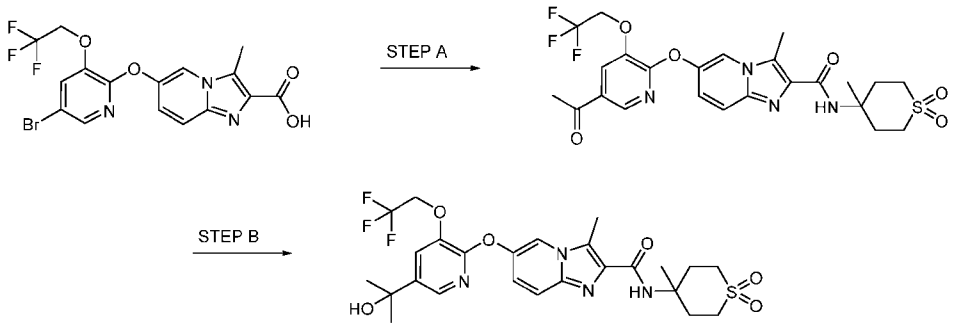
At RT under an N_2 atmosphere, to a stirred solution of 6-((5-bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (40.0 mg, 0.0680 mmol), K_2CO_3 (28.0 mg, 0.203 mmol), and potassium methyltrifluoroborate (20.6 mg, 0.169 mmol) in 1,4-dioxane (564 µL) and water (113 µL) was added $PdCl_2$(dppf) (7.42 mg, 10.2 µmol). The resulting mixture was stirred at 100 °C for 1 h, then cooled to RT and directly purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.29 (d, J = 1.7 Hz, 1H), 7.62 (s, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 7.31 (dd, J = 9.8, 2.1 Hz, 1H), 4.71 (q, J = 8.4 Hz, 2H), 3.38 (t, J = 13.7 Hz, 2H), 3.03 (d, J = 13.5 Hz, 2H), 2.90 (d, J = 14.4 Hz, 2H), 2.77 (s, 3H), 2.34 (s, 3H), 2.23 (t, J = 12.6 Hz, 2H), 1.58 (s, 3H). LC/MS = 527 [M+H]. Human DGAT2 IC_{50} = 8.9 nM.

By using procedures similar to those described in **Example 144** with appropriate reagents, the following compound was synthesized. This compound was characterized by LC/MS.

Example	Structure	Name	LC/MS [M+H]	Human DGAT2 IC_{50} (nM)
145		6-[[5-cyclopropyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-	553	133

		thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide		

EXAMPLE 146: 6-[[5-(1-hydroxy-1-methyl-ethyl)-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide



EX-146

STEP A: 6-((5-acetyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

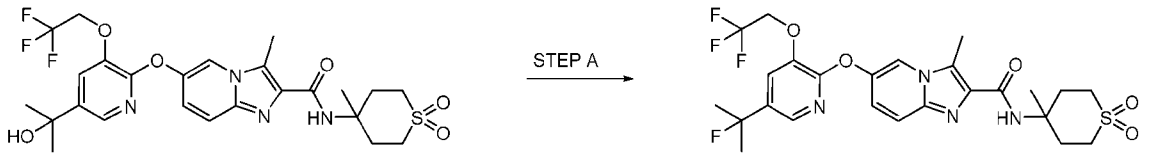
At RT, to a stirred solution of 6-((5-bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (350.0 mg, 0.592 mmol) in toluene (1.97 mL) was added tributyl(1-ethoxyvinyl)tin (300.0 µL, 0.888 mmol) and $(PPh_3)_4Pd$ (68.4 mg, 0.0590 mmol). The resulting mixture was stirred at 100 °C for 7 h, then cooled to 45 °C, and THF (2.00 mL) and 4M aqueous HCl (2.00 mL) were added. The solution was stirred at 45 °C for 1 h, then diluted with saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes then 0-10% MeOH/DCM) to afford the title compound. LC/MS = 555 [M+H].

STEP B: 6-[[5-(1-Hydroxy-1-methyl-ethyl)-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

At 0 °C, to a stirred solution of 6-((5-acetyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (300.0 mg, 0.541 mmol) in THF (5.00 mL) was added methylmagnesium bromide (721 µL, 2.16 mmol). The resulting mixture was stirred at 0 °C for 10 min then quenched with saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by mass triggered RP HPLC (C18, 40 to 80% CAN in water, 0.1% FA modifier) to afford the title compound. ^1H NMR (500 MHz, Methanol-d_4) δ 8.33 (d, J = 1.6 Hz, 1H), 7.89 (d,

J = 2.0 Hz, 1H), 7.70 (d, J = 1.9 Hz, 1H), 7.62 (d, J = 9.9 Hz, 1H), 7.33 (dd, J = 9.8, 2.1 Hz, 1H), 4.75 (q, J = 8.5 Hz, 2H), 3.39 (d, J = 12.5 Hz, 2H), 3.03 (d, J = 13.6 Hz, 2H), 2.90 (d, J = 14.4 Hz, 2H), 2.78 (s, 3H), 2.24 (t, J = 12.3 Hz, 2H), 1.58 (d, J = 5.8 Hz, 9H). LC/MS = 571 [M+H]. Human DGAT2 IC_{50} = 102 nM.

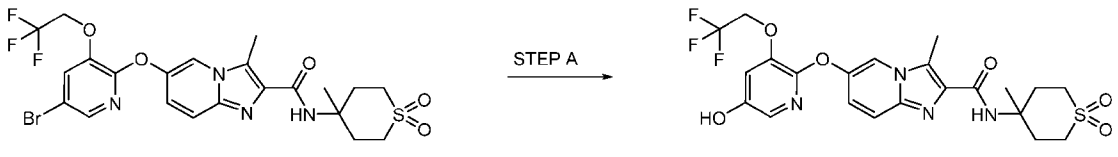
EXAMPLE 147: 6-[[5-(1-fluoro-1-methyl-ethyl)-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide



EX-147

At -78 °C, to a stirred solution of 6-((5-(2-hydroxypropan-2-yl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (45.0 mg, 0.0790 mmol) in DCM (526 µL) was added DAST (31.3 µL, 0.237 mmol). The resulting mixture was stirred at RT for 20 min then cooled to 0 °C and quenched with MeOH and water. The resulting solution was concentrated in vacuo and directly purified by mass triggered RP HPLC (C18, 20 to 60% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.35 (d, J = 1.6 Hz, 1H), 7.83 (d, J = 1.6 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.34 (dd, J = 9.7, 2.1 Hz, 1H), 4.78 (q, J = 8.4 Hz, 2H), 3.43 – 3.35 (m, 2H), 3.03 (d, J = 13.8 Hz, 2H), 2.90 (d, J = 14.4 Hz, 2H), 2.78 (s, 3H), 2.24 (t, J = 12.5 Hz, 2H), 1.72 (d, J = 21.9 Hz, 6H), 1.58 (s, 3H). LC/MS = 573 [M+H]. Human DGAT2 IC_{50} = 41 nM.

EXAMPLE 148: 6-[[5-hydroxy-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

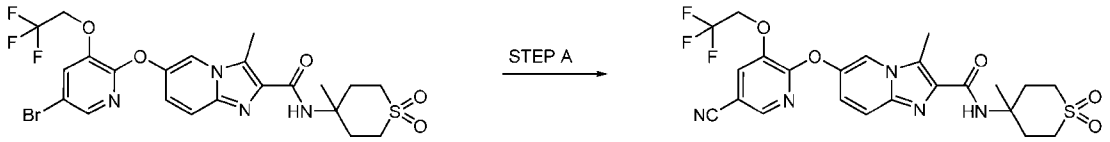


EX-148

At RT, to a stirred solution of 6-((5-bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (70.0 mg, 0.118 mmol), $PdCl_2$(dppf) (13.0 mg, 0.0180 mmol), and KOAc (34.8 mg, 0.355 mmol) in 1,4-dioxane (395 µL) was added bis(pinacolato)diboron (67.6 mg, 0.266 mmol). The resulting mixture was stirred at 100 °C for 1 h, then cooled to RT and quenched with water (0.100 mL) and HOAc (20.3 µL, 0.355 mmol). The mixture was stirred at RT for an additional 1 h, then H_2O

(31.1 µL, 0.355 mmol) was added. After 2 h, the reaction mixture was diluted with brine, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes then 0-10% MeOH/DCM) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.19 (s, 1H), 7.59 (d, J = 9.7 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.29 (dd, J = 9.8, 2.1 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 4.68 (q, J = 8.4 Hz, 2H), 3.42 – 3.35 (m, 2H), 3.02 (d, J = 13.5 Hz, 2H), 2.90 (d, J = 14.2 Hz, 2H), 2.76 (s, 3H), 2.23 (t, J = 13.5 Hz, 2H), 1.58 (s, 3H). LC/MS = 529 [M+H]. Human DGAT2 IC_{50} = 80 nM.

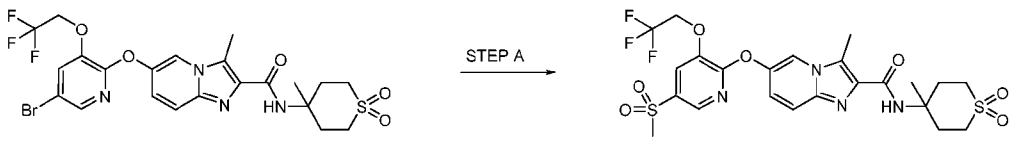
EXAMPLE 149: 6-[[5-cyano-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide



EX-149

At RT, to a stirred solution of 6-((5-bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (60.0 mg, 0.101 mmol), $PdCl_2$(dppf) (7.42 mg, 0.0102 mmol), and zinc (1.33 mg, 0.0200 mmol) in DMF (338 µL) was added zinc cyanide (35.7 mg, 0.304 mmol). The resulting mixture was stirred at 120 °C in the microwave for 1 h, then filtered and directly purified by mass triggered RP HPLC (C18, 20 to 60% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.42 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 1.7 Hz, 1H), 7.95 (d, J = 1.6 Hz, 1H), 7.65 (d, J = 9.8 Hz, 1H), 7.37 (dd, J = 9.8, 2.1 Hz, 1H), 4.86 – 4.77 (m, 3H), 3.38 (t, J = 10.5 Hz, 2H), 3.03 (d, J = 13.5 Hz, 2H), 2.90 (d, J = 14.8 Hz, 2H), 2.78 (s, 3H), 2.24 (t, J = 12.4 Hz, 2H), 1.58 (s, 3H). LC/MS = 538 [M+H]. Human DGAT2 IC_{50} = 33 nM.

EXAMPLE 150: 3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[5-methylsulfonyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide

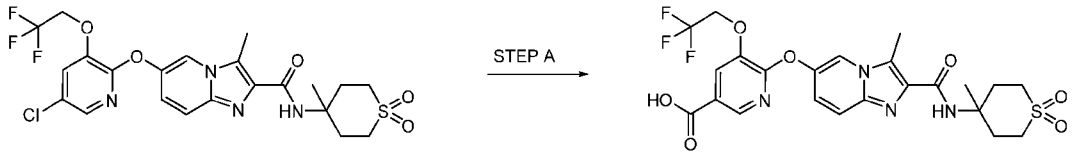


EX-150

At RT, to a stirred solution of 6-((5-bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

(110.0 mg, 0.186 mmol) and copper(I) iodide (106 mg, 0.558 mmol) in DMSO (620 µL) was added sodium methanesulfinate (57.0 mg, 0.558 mmol). The resulting mixture was stirred at 110 °C for 18 h, then saturated aqueous $NaHCO_3$was added, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes then 0-10% MeOH/DCM) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.43 (d, J = 1.6 Hz, 1H), 8.31 (d, J = 1.9 Hz, 1H), 8.03 (d, J = 1.9 Hz, 1H), 7.66 (d, J = 9.8 Hz, 1H), 7.39 (dd, J = 9.8, 2.1 Hz, 1H), 4.88 (s, 2H), 3.39 (d, J = 12.6 Hz, 2H), 3.23 (s, 3H), 3.03 (d, J = 13.7 Hz, 2H), 2.90 (d, J = 14.3 Hz, 2H), 2.79 (s, 3H), 2.24 (t, J = 13.4 Hz, 2H), 1.58 (s, 3H). LC/MS = 591 [M+H]. Human DGAT2 IC_{50} = 58 nM.

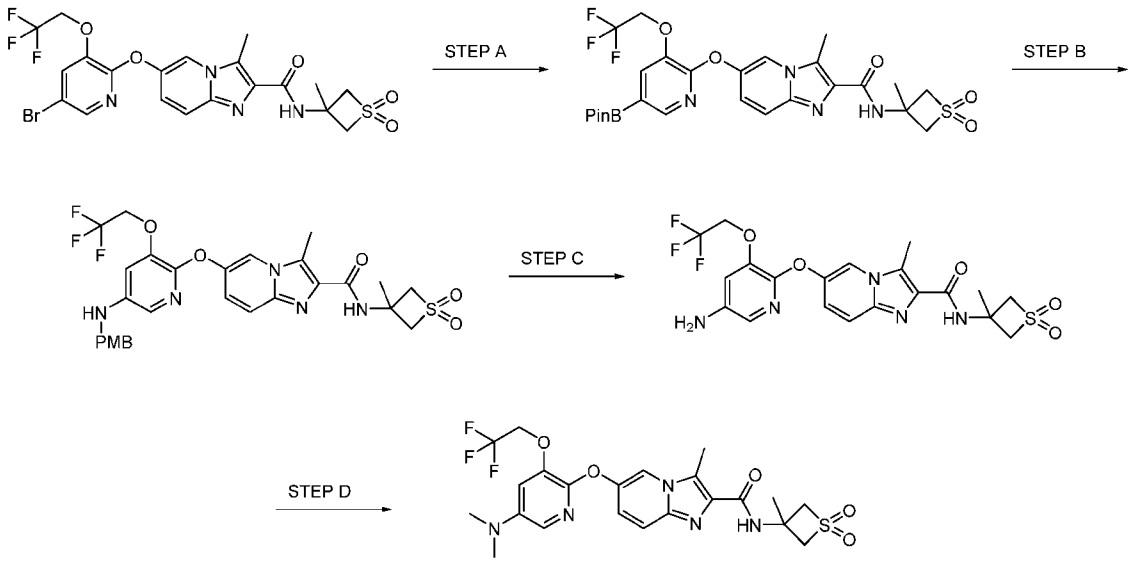
EXAMPLE 151: 6-[3-methyl-2-[(4-methyl-1,1-dioxo-thian-4-yl)carbamoyl]imidazo[1,2-*a*]pyridine-6-yl]oxy-5-(2,2,2-trifluoroethoxy)pyridine-3-carboxylic acid



EX-151

At RT, to a stirred solution of 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (30.0 mg, 0.0550 mmol), K_2CO_3 (15.2 mg, 0.110 mmol), $Pd(OAc)_2$ (1.23 mg, 5.49 µmol), and DCPP (3.35 mg, 5.49 µmol) in DMSO (2.00 mL) and water (0.200 mL) was added CO (15 psi). The resulting mixture was stirred at 110 °C for 12 h, then directly purified by mass triggered RP HPLC (C18, 31 to 51% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (d, *J* = 1.56 Hz, 1H), 8.29 (d, *J* = 1.96 Hz, 1H), 8.01 (d, *J* = 1.56 Hz, 1H), 7.90 (s, 1H), 7.66 (d, *J* = 9.78 Hz, 1H), 7.37 (dd, *J* = 2.15, 9.59 Hz, 1H), 5.05 (q, *J* = 8.87 Hz, 2H), 3.06 (br s, 4H), 2.83 (br d, *J*= 14.09 Hz, 2H), 2.69 (s, 3H), 1.94 – 2.13 (m, 2H), 1.43 (s, 3H). LC/MS = 557 [M+H]. Human DGAT2 IC_{50} = >9990 nM.

EXAMPLE 152: 6-[5-(dimethylamino)-3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridin-1-ium-2-carboxamide



EX-152

STEP A: 3-Methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-6-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT under an N_2 atmosphere, to a stirred solution of 6-((5-bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (500.0 mg, 0.888 mmol), bis(pinacolato)diboron (451 mg, 1.78 mmol), and KOAc (174 mg, 1.78 mmol) in 1,4-dioxane (10.0 mL) was added $PdCl_2$(dppf) (64.9 mg, 0.0890 mmol). The resulting mixture was stirred at 100 °C for 3 h, then cooled to RT, diluted with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. LC/MS = 611 [M+H].

STEP B: 6-((5-((4-Methoxybenzyl)amino)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT, to a stirred solution of 3-methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-6-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide (450.0 mg, 0.737 mmol), (4-methoxyphenyl)methanamine (303 mg, 2.21 mmol) in ACN (5.00 mL) was added copper(II) acetate (26.8 mg, 0.147 mmol), boric acid (91.0 mg, 1.47 mmol), and 4Å molecular sieves. The resulting mixture was stirred at 80 °C under an O_2 atmosphere for 16 h, then concentrated in vacuo. The residue was dissolved in water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4,

filtered, and concentrated in vacuo. The crude material was purified by preparatory thin layer chromatography on silica (33% EtOAc/hexanes) to afford the title compound. LC/MS = 620 [M+H].

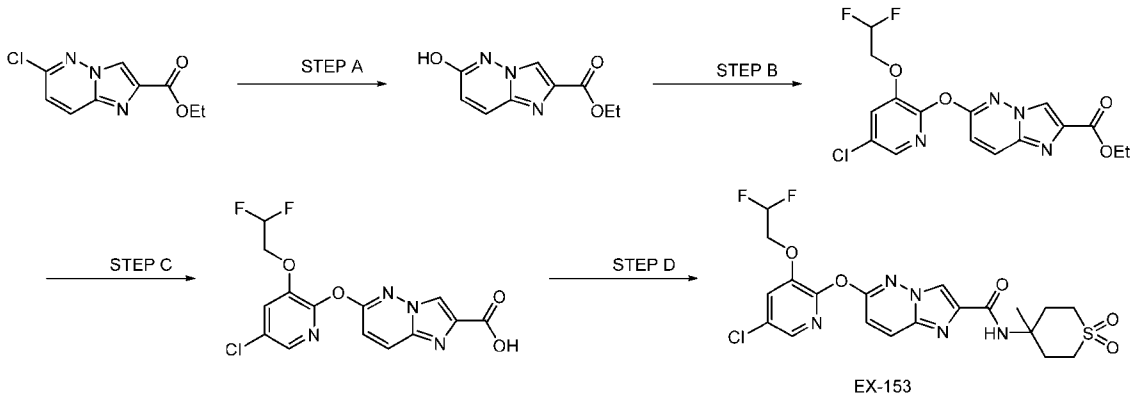
STEP C: 6-((5-Amino-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT, 6-((5-((4-methoxybenzyl)amino)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (10.0 mg, 0.0160 mmol) was dissolved in TFA (0.500 mL). The resulting mixture was stirred at RT for 1 h, then concentrated in vacuo. The crude material was purified by preparatory thin layer chromatography on silica (100% EtOAc) to afford the title compound. LC/MS = 500 [M+H].

STEP D: 6-((5-(Dimethylamino)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

At RT, to a stirred solution of 6-((5-amino-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide (25.0 mg, 0.0500 mmol) in MeOH (0.500 mL) was added formaldehyde (6.62 mg, 0.220 mmol) and sodium triacetoxyborohydride (53.0 mg, 0.250 mmol). The resulting mixture was stirred at RT for 2 h, then diluted with water, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by purified by mass triggered RP HPLC (C18, 31 to 51% ACN in water, 0.1% FA modifier) to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.32 (s, 1H), 7.69 (d, J = 9.78 Hz, 1H), 7.52 (br d, J = 9.78 Hz, 1H), 7.31 (d, J = 2.35 Hz, 1H), 7.07 (d, J = 2.35 Hz, 1H), 4.69 (m, 2H), 4.61 (m, 2H), 4.25 (m, 2H), 2.98 (s, 6H), 2.75 (s, 3H), 1.86 (s, 3H). LC/MS = 528 [M+H]. Human DGAT2 IC_{50} = 63 nM.

EXAMPLE 153: 6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide



EX-153

STEP A: Ethyl 6-hydroxyimidazo[1,2-*b*]pyridazine-2-carboxylate

To a stirred mixture of ethyl 6-chloroimidazo[1,2-*b*]pyridazine-2-carboxylate (5.00 g, 22.16 mmol), *N*-hydroxyacetamide (3.33 g, 44.3 mmol), and K_2CO_3 (9.19 g, 66.5 mmol) was added DMF (111 ml) and the reaction mixture was heated to 80 °C. After 16 hours the reaction mixture was treated with hydrogen chloride (111 ml, 111 mmol) (1M, aq. soln.), and the precipitated solid was collected via filtration, washed with water and ethyl acetate, and dried in vacuo to afford the desired product. LC/MS = 208 [M+1].

STEP B: Ethyl 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*b*]pyridazine-2-carboxylate

To a stirred solution of ethyl 6-hydroxyimidazo[1,2-*b*]pyridazine-2-carboxylate (200 mg, 965 µmol), *N*1,*N*2-bis(4-hydroxy-2,6-dimethylphenyl)oxalamide (127 mg, 386 µmol), CuI (46.0 mg, 241 µmol) and K_3PO_4 (512 mg, 2.41 mmol) in DMSO (4.8 mL) was added 5-chloro-3-(2,2-difluoroethoxy)-2-iodopyridine (648 mg, 2.03 mmol), and the reaction mixture was heated to 80 °C. After 16 hours, the reaction mixture was diluted with ethyl acetate and filtered through a plug of SiO_2. The filtrate was diluted with water and extracted with ethyl acetate. The combined organic fractions were washed with LiCl (1M aq. soln.) and NaCl (sat. aq. soln.), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was subjected to silica gel flash column chromatography using a 0-100% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 399 [M+1].

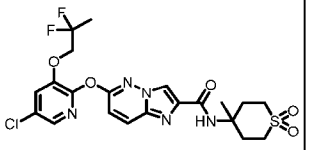
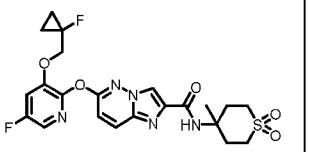
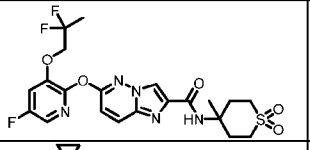
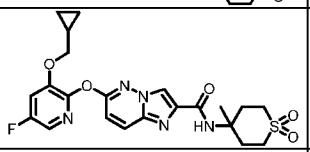
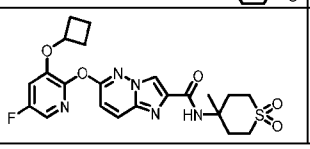
STEP C: Lithium 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*b*]pyridazine-2-carboxylate

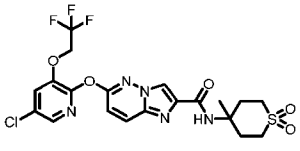
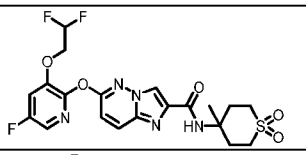
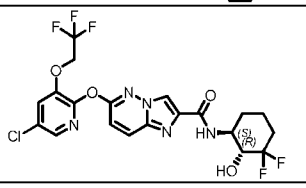
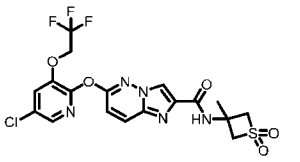
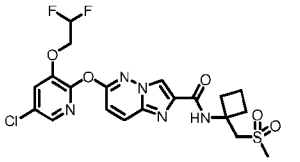
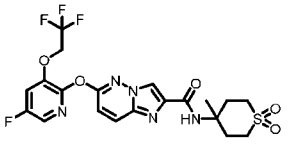
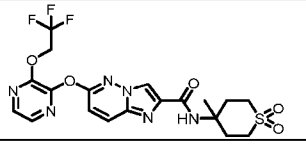
To a stirred solution of ethyl 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*b*]pyridazine-2-carboxylate (111 mg, 278 µmol) in acetonitrile (1.9 mL) and water (930 µL) was added lithium hydroxide (6.67 mg, 278 µmol). After 30 minutes the reaction mixture was concentrated *in vacuo* to afford the title compound. LC/MS = 371 [M-5].

STEP D: 6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide

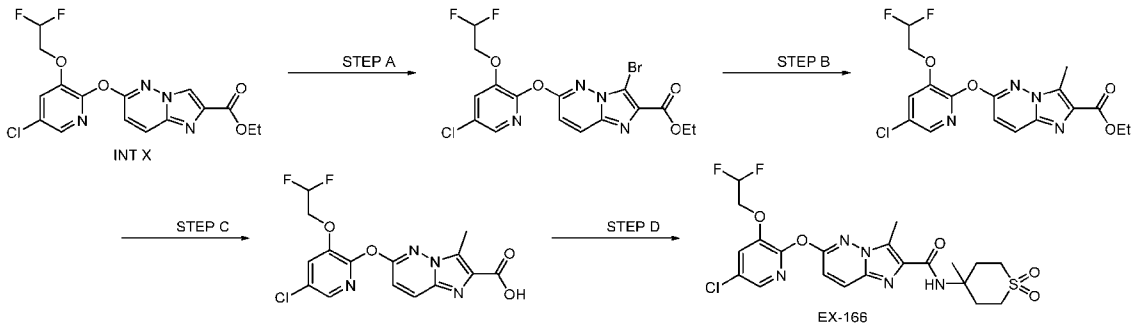
To a stirred solution of lithium 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*b*]pyridazine-2-carboxylate (30 mg, 80 µmol), DIPEA (42 µl, 239 µmol) and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (16.70 mg, 84 µmol) in DMF (797 µl) was added HATU (31.8 mg, 84 µmol). After 18 hours the reaction mixture was filtered, and the filtrate purified by RP HPLC (10-80% ACN/water with 0.1% FA modifier) to afford the title compound. LC/MS analysis indicated high conversion to the desired product. LC/MS = 516 [M+1]. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.28 (d, J = 9.8 Hz, 1H), 8.04 – 7.99 (m, 2H), 7.95 (s, 1H), 7.36 (d, J = 9.8 Hz, 1H), 6.44 – 6.12 (m, 1H), 4.50 (td, J = 14.6, 3.3 Hz, 2H), 3.12 – 3.03 (m, 4H), 2.83 (d, J = 13.9 Hz, 2H), 2.03 (dt, J = 14.5, 7.0 Hz, 2H), 1.44 (s, 3H). Human DGAT2 IC_{50} = 3.2 nM.

By using procedures similar to those described in **Example 153** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

Example	Structure	Name	LC/MS [M+1]	Human DGAT 2 IC_{50} (nM)
154		6-[[5-Chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	530	154
155		6-[[5-Fluoro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	508	186
156		6-[[3-(2,2-Difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	514	988
157		6-[[3-(Cyclopropylmethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	490	18
158		6-[[3-(Cyclobutoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	490	590

159		6-[[5-Chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	534	211
160		6-[[3-(2,2-Difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	500	3.9
161		6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-((1*S*,2*R*)-3,3-difluoro-2-hydroxycyclohexyl)imidazo[1,2-*b*]pyridazine-2-carboxamide	522	37
162		6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-N-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-b]pyridazine-2-carboxamide	506	474
163		6-[[5-Chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-[1-(methylsulfonylmethyl)cyclobutyl]imidazo[1,2-*b*]pyridazine-2-carboxamide	516	207
164		6-[[5-Fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	518	16
165		*N*-(4-Methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*b*]pyridazine-2-carboxamide	501	901

EXAMPLE 166: 6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide



STEP A: Ethyl 3-bromo-6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*b*]pyridazine-2-carboxylate

To a stirred solution of ethyl 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*b*]pyridazine-2-carboxylate (468 mg, 1.17 mmol) in DCE (5868 µl) was added 1-bromopyrrolidine-2,5-dione (230 mg, 1.29 mmol) in a single portion at 20 °C. After 1 hour the reaction mixture was warmed to 40 °C. After 16 hours the crude residue was cooled to RT and subjected to silica gel flash column chromatography using a 0-90% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 478 [M+1].

STEP B: ethyl 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*b*]pyridazine-2-carboxylate

At 20 °C a 5 mL screw cap vial containing a magnetic stir bar, ethyl 3-bromo-6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*b*]pyridazine-2-carboxylate (548 mg, 1.15 mmol), and CatAXium A Pd G2 (77 mg, 115 µmol) was charged with tetrahydrofuran (11.5 mL) and trimethylaluminum (1M (toluene), 1.15 mL, 2.30 mmol). The reaction mixture was heated to 60 °C. After 16 hours the reaction mixture was diluted with EtOAc and quenched with MeOH followed by water. The reaction mixture was filtered through celite and extracted with EtOAc. The combined organic fractions were washed with NaCl (sat. aq. soln.), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to SiO_2 flash column chromatography using a 0-100% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 413 [M+1].

STEP C: 6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*b*]pyridazine-2-carboxylic acid

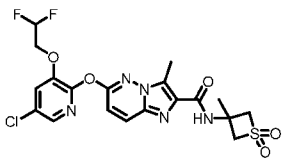
To a stirred solution of ethyl 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*b*]pyridazine-2-carboxylate (181 mg, 0.44 mmol) in tetrahydrofuran (2.5 mL), methanol (1.3 mL) and water (600 µL) was added lithium hydroxide (10.50 mg, 0.44 mmol) at 20 °C. After 16 hours the reaction mixture was acidified with HCl (1M, aq. soln.), diluted with water, and extracted with EtOAc. The combined organic fractions were washed with NaCl (sat. aq. soln.), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound. LC/MS = 385 [M+1].

STEP D: 6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide

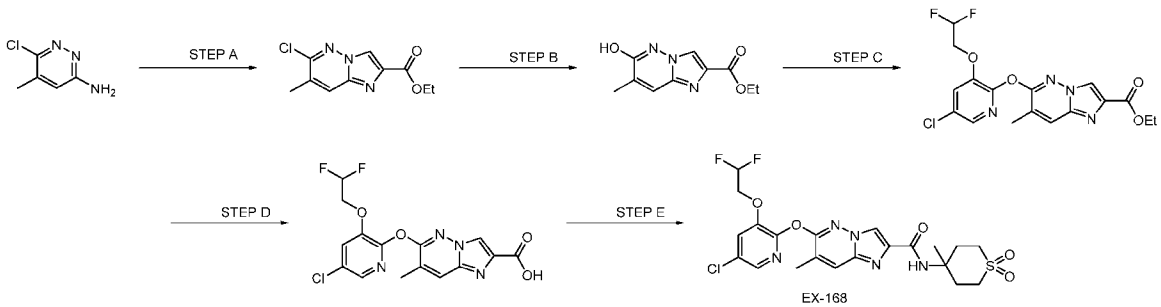
To a stirred solution of 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-methylimidazo[1,2-*b*]pyridazine-2-carboxylic acid (33 mg, 86 µmol), DIPEA (37 µl, 214 µmol) and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (17 mg, 86 µmol) in

DCM (572 µL) was added HATU (33 mg, 86 µmol). After 18 hours the reaction mixture was subjected to SiO_2 flash column chromatography using a 0-10% MeOH in DCM gradient to afford the title compound. LC/MS = 530 [M+1]. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (d, J = 9.7 Hz, 1H), 8.00 (d, J = 2.1 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.91 (s, 1H), 7.31 (d, J = 9.7 Hz, 1H), 6.45 – 6.19 (m, 1H), 4.51 (td, J = 14.7, 3.3 Hz, 2H), 3.07 (d, J = 5.6 Hz, 4H), 2.85 (d, J = 15.0 Hz, 2H), 2.56 (s, 3H), 2.03 (dt, J = 14.1, 7.0 Hz, 2H), 1.45 (s, 3H). Human DGAT2 IC_{50} = 6.8 nM.

By using procedures similar to those described in **Example 166** with appropriate reagents, the following compound was synthesized and characterized by LC/MS.

Example	Structure	Name	LC/MS [M+1]	Human DGAT 2 IC_{50} (nM)
167		6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	502	11

EXAMPLE 168: 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-7-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide



STEP A: Ethyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate

At 20 °C, 6-chloro-5-methylpyridazin-3-amine (5.00 g, 34.8 mmol) was dissolved in dioxane (232 ml) and ethyl 3-bromo-2-oxopropanoate (4.37 ml, 34.8 mmol). The mixture was heated to 100 °C. After 6 hours the solvent was removed in vacuo, and the crude residue was dissolved with ethyl acetate. The organic phase was washed with LiCl (1M aq. soln.), NaCl (sat. aq. soln.), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was subjected to SiO_2 flash column chromatography using a 0-100% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 240 [M+1].

STEP B: Ethyl 6-hydroxy-7-methylimidazo[1,2-*b*]pyridazine-2-carboxylate

To a stirred mixture of ethyl 6-chloro-7-methylimidazo[1,2-*b*]pyridazine-2-carboxylate (4.50 g, 18.78 mmol), *N*-hydroxyacetamide (2.82 g, 37.6 mmol), and K_2CO_3 (7.79 g, 56.3 mmol) was added DMSO (94 ml) and the reaction mixture was heated to 80 °C for 16 hours. LC/MS indicated high conversion to the desired product. The reaction mixture was treated with hydrogen chloride (94 ml, 94 mmol) (1M aq. soln.), and the precipitated solid was collected via filtration, washed with water and ethyl acetate, and dried in vacuo to afford the title compound. LC/MS = 222 [M+1].

STEP C: Ethyl 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-7-methylimidazo[1,2-*b*]pyridazine-2-carboxylate

To a stirred solution of ethyl 6-hydroxy-7-methylimidazo[1,2-*b*]pyridazine-2-carboxylate (400 mg, 1.81 mmol), *N*1,*N*2-bis(4-hydroxy-2,6-dimethylphenyl)oxalamide (238 mg, 723 µmol), CuI (86 mg, 452 µmol) and K_3PO_4 (960 mg, 4.52 mmol) in DMSO (9.04 ml) was added 5-chloro-3-(2,2-difluoroethoxy)-2-iodopyridine (1.21 g, 3.80 mmol), and the reaction mixture was heated to 80 °C. After 16 hours the reaction mixture was diluted with ethyl acetate and filtered through a plug of SiO_2. The filtrate was diluted with water and extracted with ethyl acetate. The combined organic fractions were washed with LiCl (1M aq. soln.) and NaCl (sat. aq. soln.), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was subjected to silica gel flash column chromatography using a 0-100% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 413 [M+1].

STEP D: Lithium 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-7-methylimidazo[1,2-*b*]pyridazine-2-carboxylate

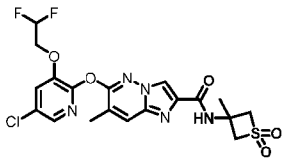
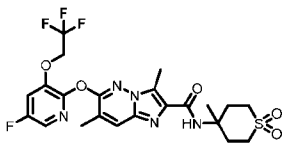
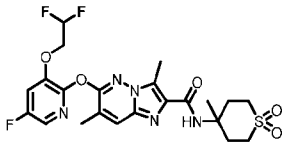
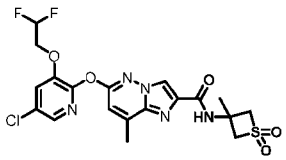
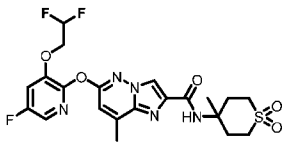
To a stirred solution of ethyl 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-7-methylimidazo[1,2-*b*]pyridazine-2-carboxylate (77 mg, 187 µmol) in acetonitrile (1.2 mL) and water (622 µl) was added lithium hydroxide (4.47 mg, 187 µmol) at 20 °C. After 30 minutes the reaction mixture was concentrated in vacuo to afford the crude title compound. LC/MS = 385 [M-5].

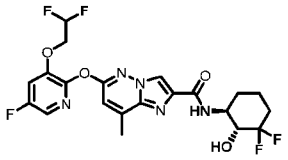
STEP E: 6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-7-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide

To a stirred solution of lithium 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-7-methylimidazo[1,2-*b*]pyridazine-2-carboxylate (36 mg, 92 µmol), DIPEA (48.3 µl, 276 µmol) and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (19.32 mg, 97 µmol) in DMF (922 µl) was added HATU (36.8 mg, 97 µmol). After 18 hours the solvent was removed *in vacuo*, and the crude residue was subjected to silica gel flash column chromatography using a 0-

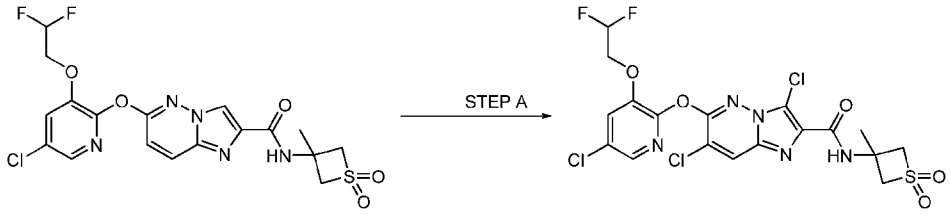
100% ethyl acetate in hexanes gradient to afford the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.12 (s, 1H), 8.02 (q, J = 2.1 Hz, 2H), 7.96 (s, 1H), 7.90 (s, 1H), 6.25 (tt, J = 54.0, 3.2 Hz, 1H), 4.48 (td, J = 14.7, 3.2 Hz, 2H), 3.09 – 3.04 (m, 4H), 2.83 (d, J = 14.2 Hz, 2H), 2.35 (s, 3H), 2.02 (dt, J = 14.6, 6.6 Hz, 2H), 1.43 (s, 3H). LC/MS = 530 [M+1]. Human DGAT2 IC_{50} = 1.0 nM.

By using procedures similar to those described in **Example 168** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

Example	Structure	Name	LC/MS [M+1]	Human DGAT2 IC_{50} (nM)
169		6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-7-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	502	121
170		6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3,7-dimethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	546	15
171		6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3,7-dimethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	528	1.3
172		6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-8-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	502	30
173		6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-8-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	530	11

174		*N*-((1*S*,2*R*)-3,3-difluoro-2-hydroxycyclohexyl)-6-((3-(2,2-difluoroethoxy)-5-fluoropyridin-2-yl)oxy)-8-methylimidazo[1,2-*b*]pyridazine-2-carboxamide	518	14

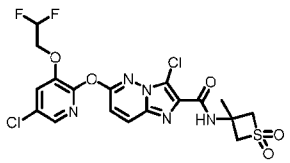
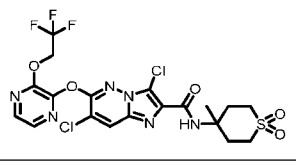
EXAMPLE 175: 3,7-dichloro-6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide

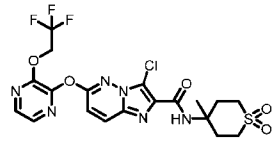
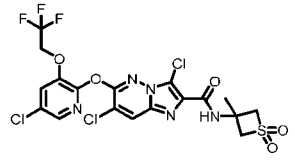


EX-175

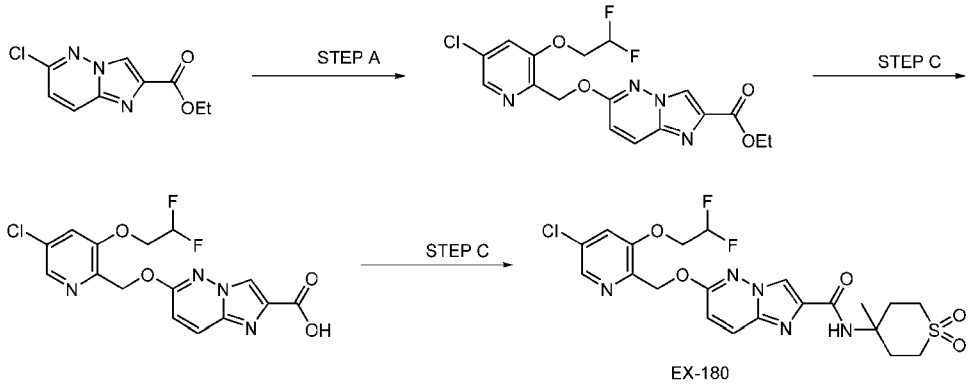
At 20 °C, 6-chloro-5-methylpyridazin-3-amine (5.00 g, 34.8 mmol) was dissolved in dioxane (232 ml) and ethyl 3-bromo-2-oxopropanoate (4.37 ml, 34.8 mmol). The mixture was heated to 100 °C. After 6 hours the solvent was removed in vacuo, and the crude residue was dissolved with ethyl acetate. The organic phase was washed with LiCl (1M aq. soln.), NaCl (sat. aq. soln.), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was subjected to SiO_2 flash column chromatography using a 0-100% ethyl acetate in hexanes gradient to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.55 (s, 1H), 8.03 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H), 6.31 – 6.04 (m, 1H), 4.69 (d, J = 14.7 Hz, 2H), 4.48 (td, J = 14.2, 3.3 Hz, 2H), 4.30 (d, J = 14.8 Hz, 2H), 1.87 (s, 4H). LC/MS = 557 [M+1]. Human DGAT2 IC_{50} = 0.4 nM.

By using procedures similar to those described in **Example 175** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

Example	Structure	Name	LC/MS [M+1]	Human DGAT 2 IC_{50} (nM)
176		3-chloro-6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	523	24
177		3,7-dichloro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*b*]pyridazine-2-carboxamide	570	391

178		3-chloro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*b*]pyridazine-2-carboxamide	535	4002
179		3,7-dichloro-6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	575	101

EXAMPLE 180: 6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide



EX-180

STEP A: Methyl 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)imidazo[1,2-*b*]pyridazine-2-carboxylate

A solution of (5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methanol (174 mg, 780 µmol) in DMF (2.4 mL) was treated sequentially with NaH (34.0 mg, 851 µmol) and methyl 6-chloroimidazo[1,2-*b*]pyridazine-2-carboxylate (150 mg, 709 µmol) at RT. After 15 minutes the mixture was subjected to silica gel flash column chromatography using a 0 to 100% EtOAc/hexanes gradient to afford the title compound. LC/MS = 399 [M+1].

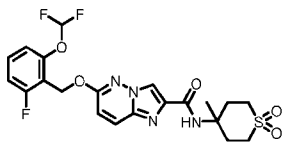
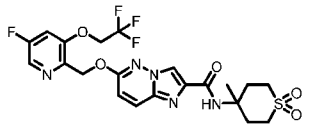
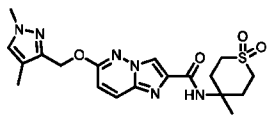
STEP B: 6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)imidazo[1,2-*b*]pyridazine-2-carboxylic acid

A mixture of methyl 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)imidazo[1,2-b]pyridazine-2-carboxylate (236 mg, 0.592 mmol) and LiOH*water (37.3 mg, 888 µmol) in water (1.5 mL) and acetonitrile (1.5 mL) was stirred at 40 °C. After 15 minutes the solvent was removed *in vacuo* to afford the title compound. LC/MS = 385 [M+1].

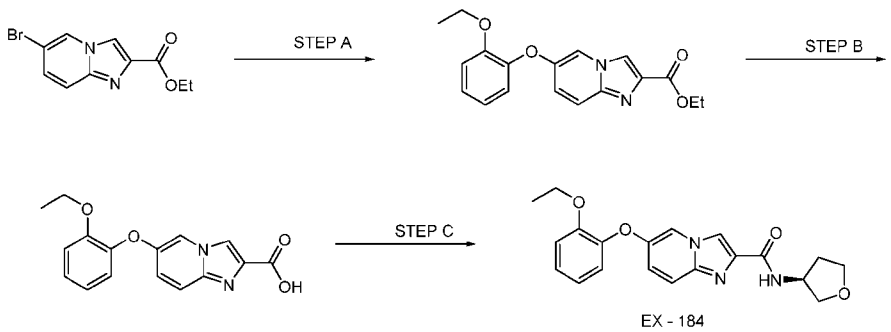
STEP C: 6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide

A mixture of 6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)imidazo[1,2-*b*]pyridazine-2-carboxylic acid (70 mg, 82 μmol) and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (43.6 mg, 218 μmol) in DMF (910 μl) and DIPEA (111 μl, 637 μmol) was treated with HATU (83 mg, 0.218 mmol) at RT. After 30 minutes the mixture was subjected to silica gel flash column chromatography using a 0 to 100% EtOAc/hexanes gradient followed by 0 to 10% methanol in DCM to afford the title compound. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.32 (s, 1H), 8.22 (d, J = 1.6 Hz, 1H), 7.97 (d, J = 9.8 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.03 (d, J = 9.8 Hz, 1H), 6.23 (tt, J = 54.6, 3.5 Hz, 1H), 5.57 (s, 2H), 4.44 (td, J = 13.8, 3.5 Hz, 2H), 3.03 (d, J = 13.8 Hz, 2H), 2.90 (d, J = 14.5 Hz, 2H), 2.23 (t, J = 13.7 Hz, 2H), 1.57 (s, 3H). LC/MS = 530 [M+1]. Human DGAT2 IC_{50} = 53 nM.

By using procedures similar to those described in **Example 180** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

Example	Structure	Name	LC/MS [M+1]	Human DGAT2 IC_{50} (nM)
181		6-[[2-(Difluoromethoxy)-6-fluoro-phenyl]methoxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	499	25
182		6-[[5-Fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]methoxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	532	11
183		6-((1,4-dimethyl-1*H*-pyrazol-3-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide	433	808

EXAMPLE 184: (*S*)-6-(2-ethoxyphenoxy)-*N*-(tetrahydrofuran-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide



EX - 184

STEP A: Ethyl 6-(2-ethoxyphenoxy)imidazo[1,2-a]pyridine-2-carboxylate

A mixture of 2-ethoxylphenol (51.3 mg, 372 µmol), copper (II) acetate (7.08 mg, 37.2 µmol), cesium carbonate (242 mg, 743 µmol), 1,10-phenanthroline (6.70 mg, 37.2 µmol), and ethyl 6-bromoimidazo[1,2-*a*]pyridine-2-carboxylate (100 mg, 372 µmol) in DMSO (1.9 mL) was stirred at 100 °C for 18 h, whereupon the mixture was cooled to RT and concentrated in vacuo. The crude material was purified via flash column chromatography on silica (0-10% MeOH/DCM) to afford the title compound. LC/MS = 327 [M+H].

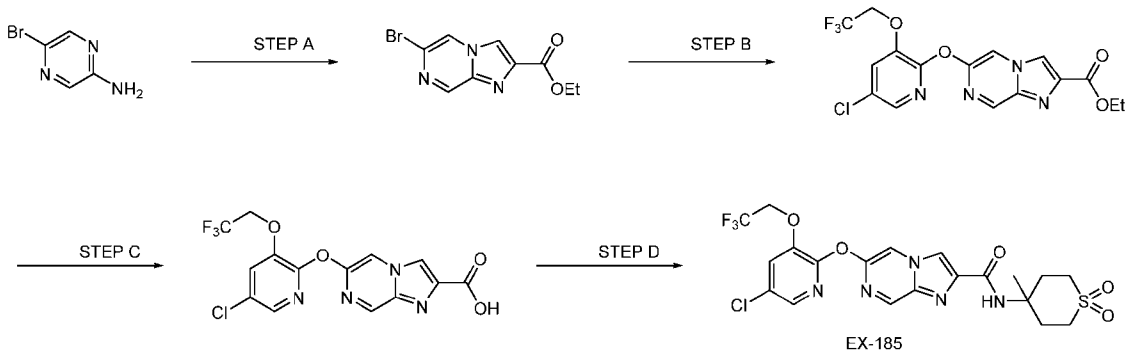
STEP B: 6-(2-ethoxyphenoxy)imidazo[1,2-a]pyridine-2-carboxylic acid

To a mixture of ethyl 6-(2-ethoxyphenoxy)imidazo[1,2-a]pyridine-2-carboxylate (121 mg, 0.372 mmol) in THF (2.2 mL), MeOH (1.1 mL), and water (0.44 mL) was added lithium hydroxide monohydrate (16.0 mg, 0.372 mmol) at RT. After 18 h, the mixture was concentrated in vacuo to afford the title compound. The crude product was used without purification. LC/MS = 299 [M+1].

STEP C: (*S*)-6-(2-ethoxyphenoxy)-*N*-(tetrahydrofuran-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

To a mixture of 6-(2-ethoxyphenoxy)imidazo[1,2-a]pyridine-2-carboxylic acid (111 mg, 0.372 mmol), (S)-tetrahydrofuran-3-aminium chloride (55.2 mg, 0.446 mmol), and DIPEA (195 µL, 1.12 mmol) in DMF (1.5 mL) was added HATU (184 mg, 0.484 mmol) at RT. After 2 h, the reaction mixture was concentrated in vacuo. The crude material was purified by mass triggered RP HPLC (C18, 30 to 60% ACN in water, 0.1% FA modifier) to afford the title compound. LC/MS = 368 [M+1]. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.18 (s, 1H), 8.00 – 7.87 (m, 1H), 7.54 (d, J = 9.8 Hz, 1H), 7.31 – 7.15 (m, 2H), 7.15 – 7.09 (m, 2H), 6.99 (td, J = 7.7, 1.5 Hz, 1H), 4.60 (ddd, J = 9.6, 7.6, 3.8 Hz, 1H), 4.16 – 3.89 (m, 4H), 3.85 (td, J = 8.4, 5.6 Hz, 1H), 3.75 (dd, J = 9.2, 3.6 Hz, 1H), 2.32 (dq, J = 13.0, 7.7 Hz, 1H), 2.07 – 1.94 (m, 1H), 1.21 (t, J = 7.0 Hz, 3H). Human DGAT2 IC_{50} = 6342 nM.

EXAMPLE 185: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyrazine-2-carboxamide



STEP A: Ethyl 6-bromoimidazo[1,2-*a*]pyrazine-2-carboxylate

To a mixture of 5-bromopyrazin-2-amine (2.00 g, 11.5 mmol) in 1,4-dioxane (20 mL) was added ethyl 3-bromo-2-oxopropanoate (3.36 g, 17.2 mmol). The resulting mixture was stirred at 100 °C for 12 h, whereupon the mixture was cooled to RT and filtered. The filtrate was diluted with saturated aqueous $NaHCO_3$ until the pH = 8 and the solution was extracted with EtOAc. The combined organic layers were washed with water then brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified via flash column chromatography on silica (20% EtOAc/hexanes) to afford the title compound. LC/MS = 270 and 272 [M+H].

STEP B: Ethyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyrazine-2-carboxylate

A mixture of ethyl 6-bromoimidazo[1,2-*a*]pyrazine-2-carboxylate (100 mg, 0.370 mmol), 5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-ol (101 mg, 0.444 mmol), K_2CO_3 (102 mg, 0.741 mmol), *N*,*N*-dimethylglycine (7.64 mg, 0.0741 mmol), and copper(I) iodide (7.05 mg, 0.0371 mmol) in DMSO (2.0 mL) was stirred at 100 °C for 12 h under a nitrogen atmosphere. The reaction mixture was directly purified via RP HPLC (C18, ACN in water, 0.1% FA modifier) to afford the title compound. LC/MS = 417 [M+H].

STEP C: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyrazine-2-carboxylic acid

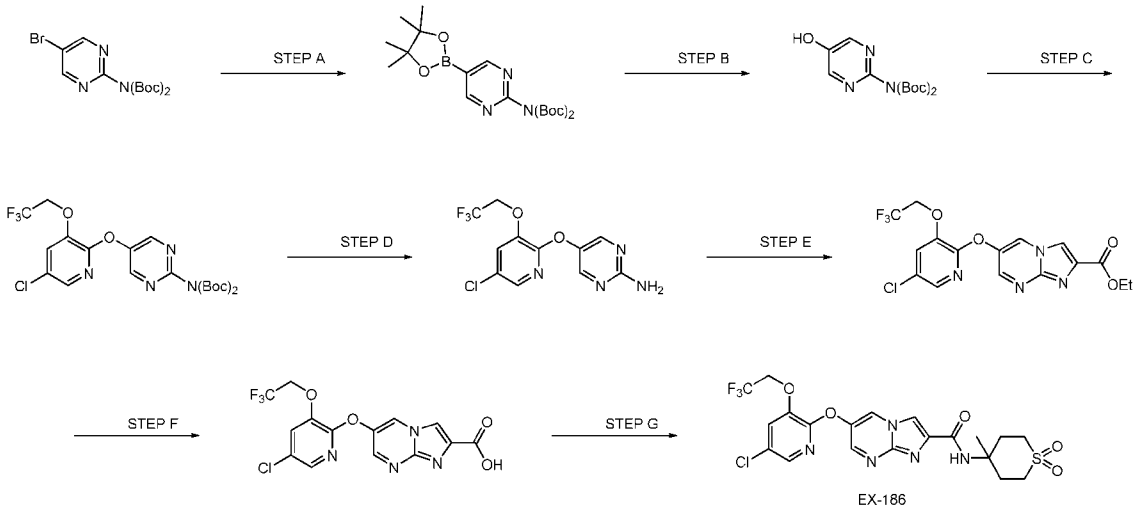
To a mixture of ethyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyrazine-2-carboxylate (15 mg, 0.037 mmol) in MeOH (1.0 mL) and water (1.0 mL) was added lithium hydroxide monohydrate (2.7 mg, 0.11 mmol) at RT. After 1 h, the mixture was dissolved in water, acidified to pH = 4 with 1 M HCl, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to

afford the title compound. The crude product was used without purification. LC/MS = 389 [M+1].

STEP D: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyrazine-2-carboxamide

To a mixture 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyrazine-2-carboxylic acid (13 mg, 0.033 mmol), 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (8.0 mg, 0.049 mml), and DIPEA (29 µL, 0.17 mmol) in DMF (1.0 mL) was added HATU (25 mg, 0.067 mmol) at 30 °C. After 2 h, the reaction mixture was concentrated in vacuo. The crude material was purified by RP HPLC (C18, ACN in water, 0.1% FA modifier) to afford the title compound. LC/MS = 534 [M+1]. ^{1}H NMR (400 MHz, Methanol-d$_4$) δ 8.89 (s, 1H), 8.53 (s, 1H), 8.47 (s, 1H), 8.08 (br s, 1H), 7.79 (br d, J = 1.96 Hz, 1H), 7.73 (br d, J = 1.96 Hz, 1H), 4.71 (q, J = 8.31 Hz, 2H), 3.30 – 3.34 (m, 1H), 3.26 (br s, 1H), 3.01 (br d, J = 14.18 Hz, 2H), 2.89 (br d, J = 14.67 Hz, 2H), 2.17 – 2.25 (m, 2H), 1.54 (s, 3H). Human DGAT2 IC$_{50}$ = 5.3 nM.

EXAMPLE 186: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyrimidine-2-carboxamide



STEP A: *Tert*-butyl (*tert*-butoxycarbonyl)(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)carbamate

To a suspension of *tert*-butyl (5-bromopyrimidin-2-yl)(*tert*-butoxycarbonyl)carbamate (500 mg, 1.34 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (407 mg, 1.60 mmol), potassium acetate (393 mg, 4.01 mmol) in DMF (8.0 mL) was added Pd(OAc)$_2$ (150 mg, 0.668 mmol). The mixture was stirred at 85 °C for 16 h, whereupon the mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over

Na_2SO_4, filtered, and concentrated in vacuo to afford title compound. The crude product was used without purification. LCMS-$B(OH)_2$=184.0 [M+H-156].

STEP B: *Tert*-butyl (*tert*-butoxycarbonyl)(5-hydroxypyrimidin-2-yl)carbamate

To a suspension of *tert*-butyl (*tert*-butoxycarbonyl)(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)carbamate (560 mg, 1.33 mmol) in THF (4.0 mL) and water (4 mL) was added $NaBO_3 \cdot 4H_2O$ (422 mg, 3.99 mmol) at RT. The mixture was stirred at RT for 16 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford title compound. The crude product was used without purification. LC/MS=312 [M+H].

STEP C: *Tert*-butyl (*tert*-butoxycarbonyl)(5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrimidin-2-yl)carbamate

A mixture of *tert*-butyl (*tert*-butoxycarbonyl)(5-hydroxypyrimidin-2-yl)carbamate (180 mg, 0.578 mmol), 5-chloro-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine (159 mg, 0.694 mmol)), Cs_2CO_3 (377 mg, 1.16 mmol) in DMA (8.0 mL) was stirred at 50 °C for 16 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford title compound. The crude product was purified by preparatory TLC (25% EtOAc/PE) to afford title compound. LC/MS= 321 [M+H-200].

STEP D: 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrimidin-2-amine

To a mixture of *tert*-butyl (*tert*-butoxycarbonyl)(5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrimidin-2-yl)carbamate (170 mg, 0.326 mmol) in DCM (5.0 mL) was added TFA (1.0 mL) and stirred at RT for 1 h, whereupon the reaction was concentrated in vacuo. The mixture was diluted with water and EtOAc then saturated aqueous Na_2CO_3 to adjust the pH = 7. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford title compound. The crude product was used without purification. LC/MS=321 [M+H].

STEP E: Ethyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-a]pyrimidine-2-carboxylate

To a mixture of 5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrimidin-2-amine (100 mg, 0.312 mmol) in 1,4-dioxane (10.0 mL) was added ethyl 3-bromo-2-oxopropanoate (73.0 mg, 0.374 mmol). The mixture was stirred at 80 °C for 12 h, whereupon the mixture was concentrated in vacuo. The residue directly was purified via preparatory TLC (20% EtOAc/PE) to afford title compound LC/MS=417 [M+H].

STEP F: 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-a]pyrimidine-2-carboxylic acid

To a mixture of ethyl 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-a]pyrimidine-2-carboxylate (40.0 mg, 0.096 mmol) in THF (3.0 mL) and water (1.0 mL) was added $LiOH.H_2O$ (4.03 mg, 0.096 mmol). The reaction was stirred at RT for 1 h, whereupon the mixture was diluted with water and acidified with 1 M HCl to pH = 4. The mixture was extracted with EtOAc, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound. The crude product was used without purification. LC/MS=389 [M+H].

STEP G: 6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyrimidine-2-carboxamide

To a mixture 6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyrimidine-2-carboxylic acid (38 mg, 0.033 mmol), 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (19 mg, 0.12 mml), and DIPEA (34 µL, 0.20 mmol) in DMF (3.0 mL) was added HATU (56 mg, 0.15 mmol) at RT. After 1 h, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by preparatory TLC (20% EtOAc/PE) to afford the title compound. LC/MS = 534 [M+1]. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.61 (d, J=7.00 Hz, 2H), 8.07 (s, 1H), 7.79 (s, 1H), 7.27-7.46 (m, 2H), 4.52 (q, J=7.93 Hz, 2H), 3.21-3.30 (m, 2H), 2.97 (br d, J=12.97 Hz, 2H), 2.86 (br d, J=14.50 Hz, 2H), 2.26-2.36 (m, 2H), 1.57 (br s, 3H). Human DGAT2 IC_{50} = 33 nM.

ASSAYS

Insect cell expression and membrane preparation

Sf-9 insect cells were maintained in Grace's insect cell culture medium with 10 % heated-inactivated fetal bovine serum, 1 % Pluronic F-68 and 0.14 µg/ml Kanamycine sulfate at 27 °C in a shaker incubator. After infection with untagged baculovirus expressing human DGAT2 (hDGAT2) at multiplicity of infection (MOI) 3 for 48 hours, cells were harvested. Cell pellets were suspended in buffer containing 10 mM Tris-HCl pH 7.5, 1 mM EDTA, 250 mM sucrose and Complete Protease Inhibitor Cocktail (Sigma Aldrich), and sonicated on ice. Cell debris were removed by centrifugation at 2000 x g for 15 minutes. Membrane fractions were isolated by ultracentrifugation (100,000 x g), resuspended in the same buffer, and frozen (- 80 °C) for later use. The protein concentration was determined with the Pierce™ BCA Protein Assay Kit (Thermo Fisher Scientific). Expression of protein levels was analyzed by immunoblotting with

rabbit anti-DGAT2 antibody (Abcam, ab102831) and donkey anti-rabbit IgG H&L Alexa Fluor® 647 (Abcam, ab150075) followed by detection using Typhoon FLA9000 (GE Healthcare).

LC/MS/MS analysis method

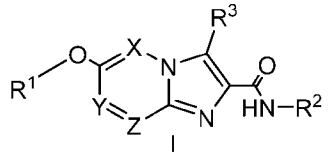
LC/MS/MS analyses were performed using Thermal Fisher's LX4-TSQ Vantage system. This system consists of an Agilent binary high-performance liquid chromatography (HPLC) pump and a TSQ Vantage triple quadrupole MS/MS instrument. For each sample, 2 µL samples from the top organic layer of in-plate liquid-liquid extraction were injected onto a Thermo Betabasic C4 column (2.1 mm x 20 mm, 5 µm particle size). The samples were then eluted using the following conditions; mobile phase: Isopropanol: acetonitrile/10mM ammonium formate = 50/35/15 (v/v/v), flow rate: 0.8 mL/min, temperature: 25 °C. Data was acquired in positive mode using a heated electrospray ionization (HESI) interface. The operational parameters for the TSQ Vantage MS/MS instrument were a spray voltage of 3000 V, capillary temperature of 280°C, vaporizer temperature 400 °C, sheath gas 45 arbitrary unit, Aux gas 10 arbitrary units, S-lens 165 and collision gas 1.0mTorr. Standard reference material (SRM) chromatograms of $^{13}C_{18}$-triolein (Q1: 920.8>Q3:621.3) and internal standard $^{13}C_{21}$-triolein (Q1: 923.8>Q3:617.3) were collected for 33 sec. The peak area was integrated by Xcalibur Quan software. The ratio between the $^{13}C_{18}$triolein generated in the reaction and spiked in internal standard $^{13}C_{21}$-triolein was used to generate percentage inhibition and IC_{50} values. Compound percentage inhibition was calculated by the following formula: Inhibition %=1-[(compound response – low control)/(high control – low control)] x 100%. Potent compounds were titrated and IC_{50} were calculated by 4 parameter sigmoidal curve fitting formula.

DGAT2 enzymatic activity assay

DGAT2 activity was determined by measuring the amount of enzymatic product $^{13}C_{18}$-triolein (^{13}C-1,2,3-Tri(cis-9-octadecenoyl)glycerol) using the membrane prep mentioned above. The assay was carried out in ABgene 384-well assay plates in a final volume of 25 µL at rt. The assay mixture contained the following: assay buffer (100 mM Tris•Cl, pH 7.0, 20 mM $MgCl_2$, 5% ethanol), 25 µM of diolein, 5 µM of ^{13}C oleoyl-CoA and 8 ng/µL of DGAT2 membrane.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof wherein:

X, Y, and Z are independently selected from N and C(R^4);

R^1 is

(1) 6-membered aryl unsubstituted or substituted with 1, 2, or 3 R^5,

(2) 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(3) -(C_{1-6})alkyl-aryl, wherein the aryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(4) -(C_{1-6})alkyl-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from N, O and S, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(5) -(C_{1-3})haloalkyl, or

(6) -(C_{1-6})alkyl-O-(C_{1-6})alkyl optionally substituted with 1, 2, or 3 R^5;

R^2 is

(1) 4- to 7-membered heterocyclyl containing 1, 2 or 3 heteroatoms independently selected from N, O and S,

(2) phenyl,

(3) 5- or 6-membered heteroaryl containing 1, 2 or 3 heteroatoms independently selected from N, O, and S,

(4) -(C_{1-6})alkyl-heterocyclyl, wherein the heterocyclyl is a 4, 5- or 6-membered heterocyclyl containing 1, 2, or 3 heteroatoms independently selected from N, O and S,

(5) -(C_{1-6})alkyl-aryl,

(6) -(C_{3-6})cycloalkyl,

(7) -(C_{3-6})cyclic amine,

(8) -(C_{3-6})cycloalkyl-(C_{1-6})alkyl-SO_2(C_{1-6})alkyl, or

(9) 8-10-membered fused bicyclic heterocyclic ring comprising 1 or 2 heteroatoms independently selected from N, O and S and wherein the bicyclic ring is optionally independently substituted with one, two, or three halogens,

wherein each alkyl, aryl, cycloalkyl, heteroaryl, cyclic amine and heterocyclyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 R^6;

R^3 is

(1) hydrogen,
(2) halogen,
(3) hydroxy,
(4) (C_{1-6})alkyl,
(5) (C_{1-6})haloalkyl,
(6) (C_{1-6})alkylhydroxy,
(7) (C_{1-6})alkoxyl-,
(8) $C(=O)NH_2$,
(9) C(=O)OH, or
(10) O-(C_{1-6})alkyl;

when present, each R^4 is independently

(1) hydrogen,
(2) halogen,
(3) (C_{1-3})alkyl,
(4) C_{1-3}haloalkyl, or
(5) cyano;

when present, each R^5 is independently

(1) hydrogen,
(2) halogen,
(3) hydroxy,
(4) CN,
(5) C(O)OH,
(6) (C_{1-6})alkyl,
(7) (C_{1-6})haloalkyl,
(8) (C_{1-3})alkyl-OH,
(9) -OC_{1-6}alkyl,
(10) O-(C_{1-6})haloalkyl,
(11) $SO_2(C_{1-6})$alkyl,

(12) N(C_{1-6})alkyl,

(13) (C_{3-6})cycloalkyl,

(14) O-(C_{3-7})cycloalkyl,

(15) -OC_{1-6}alkyl-oxetanyl optionally substituted with halogen, or

(16) O-C_{1-6}alkyl-(C_{3-7})cycloalkyl optionally substituted with halogen;

when present, each R^6 is independently

(1) halogen,

(2) oxo,

(3) OH,

(4) C_{1-3}alkyl,

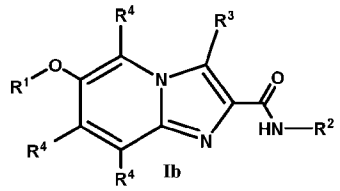
(5) C_{1-3}haloalkyl,

(6) C_{1-3}alkyl-CN,

(7) OC_{1-3}alkyl, or

(8) C(O)C_{1-3}haloalkyl.

2. A compound of claim 1, of Formula Ib,



Ib

wherein:

R^1 is

(1) 6-membered aryl unsubstituted or substituted with 1, 2, or 3 R^5,

(2) 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(3) -(C_{1-6})alkyl-aryl, wherein the aryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(4) -(C_{1-6})alkyl-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1 nitrogen atom, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(5) -(C_{1-3})haloalkyl, or

(6) -(C_{1-6})alkyl-O-(C_{1-6})alkyl optionally substituted with 1, 2, or 3 R^5;

R^2 is

(1) 4- to 7-membered heterocyclyl containing 1, 2 or 3 heteroatoms independently selected from N, O and S,

(2) phenyl,

(3) 5- or 6-membered heteroaryl containing 1, 2 or 3 heteroatoms independently selected from N,

(4) -(C_{1-6})alkyl-heterocyclyl, wherein the heterocyclyl is a 4, 5 or 6-membered heterocyclyl containing 1 or 2 heteroatoms independently selected from S,

(5) -(C_{1-6})alkyl-aryl,

(6) -(C_{3-6})cycloalkyl,

(7) -(C_{3-6})cyclic amine,

(8) -(C_{3-6})cycloalkyl-(C_{1-6})alkyl-SO_2(C_{1-6})alkyl, or

(9) 10-membered fused bicyclic heterocyclic ring comprising 1 heteroatoms independently selected from N, O and S and wherein the bicyclic ring is optionally independently substituted with one, two, or three halogens,

wherein each alkyl, aryl, cycloalkyl, heteroaryl, cyclic amine and heterocyclyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 R^6;

R^3 is

(1) hydrogen,

(2) halogen,

(3) hydroxy,

(4) (C_{1-6})alkyl,

(5) (C_{1-6})haloalkyl,

(6) (C_{1-6})alkylhydroxy,

(7) (C_{1-6})alkoxyl-,

(8) C(=O)NH_2,

(9) C(=O)OH, or

(10) O-(C_{1-6})alkyl;

when present, each R^4 is independently

(1) hydrogen,

(2) halogen,

(3) (C_{1-3})alkyl,

(4) C_{1-3}haloalkyl, or

(5) cyano;

when present, each R^5 is independently

(1) hydrogen,
(2) halogen,
(3) hydroxy,
(4) CN,
(5) C(O)OH,
(6) (C_{1-6})alkyl,
(7) (C_{1-6})haloalkyl,
(8) (C_{1-3})alkyl-OH,
(9) -OC_{1-6}alkyl,
(10) O-(C_{1-6})haloalkyl,
(11) SO_2(C_{1-6})alkyl,
(12) N(C_{1-6})alkyl,
(13) (C_{3-6})cycloalkyl,
(14) O-(C_{3-7})cycloalkyl,
(15) -OC_{1-6}alkyl-oxetanyl optionally substituted with halogen, or
(16) O-C_{1-6}alkyl-(C_{3-7})cycloalkyl optionally substituted with halogen;

when present, each R^6 is independently
(1) halogen,
(2) oxo,
(3) OH,
(4) C_{1-3}alkyl,
(5) C_{1-3}haloalkyl,
(6) C_{1-3}alkyl-CN,
(7) OC_{1-3}alkyl, or
(8) C(O)C_{1-3}haloalkyl.

3. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt thereof, wherein R^1 is
(1) 6-membered aryl unsubstituted or substituted with 1, 2, or 3 R^5,
(2) 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,
(3) -CH_2-aryl, wherein the aryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(4) -CH_2-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^5,

(5) -(C_{1-3})haloalkyl, or

(6) -(C_{1-6})alkyl-O-(C_{1-6})alkyl optionally substituted with 1, 2, or 3 R^5.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^1 is

(1) 6-membered aryl unsubstituted or substituted with -OC_{1-6}alkyl, or O-(C_{1-6})haloalkyl,

(2) 6-membered heteroaryl containing one or two nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, hydroxy, -O(C_{1-6})alkyl, (C_{1-6})alkyl, (C_{1-6})haloalkyl, O-(C_{1-6})haloalkyl, (C_{1-3})alkyl-OH, SO_2(C_{1-6})alkyl, N(C_{1-6})alkyl, (C_{3-6})cycloalkyl, O-(C_{3-7})cycloalkyl, CN, C(O)OH, O-C_{1-6}alkyl-(C_{3-7})cycloalkyl optionally substituted with halogen, and -OC_{1-6}alkyl-oxetanyl optionally substituted with halogen,

(3) -CH_2-aryl, wherein the aryl is substituted with one or two substituents independently selected from halogen, -OC_{1-3}alkyl, or -OC_{1-3}haloalkyl,

(4) -CH_2-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 substituents selected from halogen, C_{1-3}alkyl, C_{1-3}haloalkyl, -OC_{1-3}alkyl, and -OC_{1-3}haloalkyl,

(5) -(C_{1-3})haloalkyl, or

(6) -(C_{1-6})alkyl-O-(C_{1-6})alkyl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^1 is

(1) 6-membered aryl unsubstituted or substituted with OCH_2CH_3, or OCH_2CF_3,

(2) 6-membered heteroaryl containing one or two nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from Cl, F, OH, CN, CH_3, CF_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_2OH$, $C(CH_3)_2F$, CF_3, $C(F)_2CH_2CH_3$, C(O)OH, OCH_2CH_3, OCH_2CF_3,

OCH_2CHF_2, $OCH_2C(F)_2CH_3$, $OCH_2C(F)_2CH(F)_2$, $S(O)_2CH_3$, cyclopropyl, OCH_2-cyclopropyl, OCH_2-fluorocyclopropyl, O-cyclobutyl, OCH_2-oxetanyl-F and $N(CH_3)_2$,

(3) -CH_2-aryl, wherein the aryl is substituted with one or two substituents independently selected from F, OCH_2CH_3, and $OCHF_2$,

(4) -CH_2-heteroaryl, wherein the heteroaryl is a 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 substituents selected from OCH_2CHF_2, F, Cl, OCH_2CF_3, CH_3, CF_3 and OCH_2CH_3,

(5) $CH_2CH_2CF_3$, or

(6) $CH_2(CH_3)_2CH_2OCH_2CH_3$.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^2 is

(1) 4- to 7-membered heterocyclyl containing 1, 2 or 3 heteroatoms independently selected from N, O and S,

(2) phenyl,

(3) 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms,

(4) -CH_2-heterocyclyl, wherein the heterocyclyl is a 4, 5- or 6-membered heterocyclyl containing 1, 2, or 3 sulfur atoms,

(5) -CH_2-aryl, wherein the aryl is a 6 membered aryl,

(6) -(C_{3-6})cycloalkyl,

(7) -(C_{3-6})cyclic amine,

(8) -(C_{3-6})cycloalkyl-CH_3-SO_2CH_3, or

(9) 10-membered fused bicyclic heterocyclic ring comprising 1 oxygen atom wherein the bicyclic ring is optionally independently substituted with one, two, or three halogens,

wherein each alkyl, aryl, cycloalkyl, heteroaryl, cyclic amine and heterocyclyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 R^6.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^2 is

(1) 4- to 7-membered heterocyclyl containing 1, 2 or 3 heteroatoms independently selected from N, O and S, optionally substituted with one, two, or

three substituents independently selected from halogen, oxo, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{1-3}alkyl-CN, and C(O)C_{1-3}haloalkyl,

(2) phenyl,

(3) 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms optionally substituted with C_{1-3}alkyl,

(4) -CH_2-heterocyclyl, wherein the heterocyclyl is a 4 or 6 -membered heterocyclyl containing 1, 2, or 3 sulfur atoms, optionally substituted with one, two, three, four or five substituents independently selected from oxo, and C_{1-3}alkyl,

(5) -CH_2-aryl, wherein the aryl is a 6 membered aryl,

(6) -(C_{3-6})cycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3}alkyl, C_{1-3}haloalkyl, OC_{1-3}alkyl, and OH,

(7) -(C_{3-6})cyclic amine optionally substituted with one, two, or three substituents independently selected from oxo,

(8) -(C_4)cycloalkyl-CH_3-SO_2CH_3, or

(9) chromane optionally substituted with one, two, or three halogen,

wherein each alkyl, aryl, cycloalkyl, heteroaryl, cyclic amine and heterocyclyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 R^6.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^2 is

(1) 4- to 7-membered heterocyclyl containing 1, 2 or 3 heteroatoms independently selected from N, O and S, optionally substituted with one, two, three, four or five substituents independently selected from halogen, oxo, CH_3, CH_2CF_3, $CH(CH_3)_2$, CH_2CH_3, CH_2CN, C(O)CF_3, and $(CH_3)_2$,

(2) phenyl,

(3) 5- or 6-membered heteroaryl containing 1 or 2 nitrogen atoms optionally substituted with CH_3,

(4) -CH_2-heterocyclyl, wherein the heterocyclyl is a 4 or 6-membered heterocyclyl containing 1 sulfur atom optionally substituted with one, two, or three substituents independently selected from oxo and CH_3,

(5) -CH_2-aryl, wherein the aryl is a 6 membered aryl,

(6) -(C_{3-6})cycloalkyl optionally substituted with one, two, or three substituents independently selected from F, CH_3, CF_3, OH, F_2 and OCH_3,

(7) -(C_{3-6})cyclic amine optionally substituted with oxo,

(8) -(C_4)cycloalkyl-CH_3-SO_2CH_3. or

(9) chromane substituted independently with halogens.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 4- to 7-membered heterocyclyl containing 1 heteroatom selected from sulfur, nitrogen and oxygen, and optionally substituted with one, two, three, four or five substituents independently selected from halogen, oxo, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{1-3}alkyl-CN, and $C(O)C_{1-3}$haloalkyl.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 4- to 7-membered heterocyclyl containing 1 heteroatom selected from sulfur, nitrogen and oxygen, and optionally substituted with one, two, three, four or five substituents independently selected from halogen, oxo, CH_3, CH_2CF_3, $CH(CH_3)_2$, CH_2CH_3, CH_2CN, $C(O)CF_3$, and $(CH_3)_2$.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 4- to 7-membered heterocyclyl containing 1 sulfur atom, and optionally substituted with one, two, three, four or five substituents independently selected from oxo, CH_3, CH_2CF_3, $CH(CH_3)_2$, CH_2CH_3, CH_2CN and $(CH_3)_2$.

12. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 4- to 7-membered heterocyclyl containing 1 nitrogen atom, and optionally substituted with one, two or three substituents independently selected from CH_3, CH_2CN, and $C(O)CF_3$.

13. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 4- to 7-membered heterocyclyl containing 1 oxygen atom, and optionally substituted with one, two, three, four or five substituents independently selected from CH_3, $(CH_3)_2$ and CH_2CF_3.

14. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^2 is a -(C_{3-6})cycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3}alkyl, C_{1-3}haloalkyl, OC_{1-3}alkyl, and OH.

15. The compound of any one of claims 1-8 and 14, or a pharmaceutically acceptable salt thereof, wherein R^2 is a -(C_{3-6})cycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, oxo, CH_3, CH_2CF_3, $CH(CH_3)_2$, CH_2CH_3, CH_2CN, $C(O)CF_3$, and $(CH_3)_2$.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, halogen, C_{1-6}alkyl, OH, C(O)OH, $C(O)NH_2$, OC_{1-6}alkyl, C_{1-6}haloalkyl, or C_{1-6}alkyl-OH.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, halogen, C_{1-3}alkyl, OH, C(O)OH, $C(O)NH_2$, OC_{1-3}alkyl, C_{1-3}haloalkyl, or C_{1-3}alkyl-OH.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, Cl, F, CH_3, $CH(CH_3)_2$, CH_2CH_3, OH, C(O)OH, $C(O)NH_2$, OCH_3, CF_3, or CH_2OH.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen or CH_3.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.

21. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^3 is CH_3.

22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein when present, each R^4 is independently selected from hydrogen, halogen, C_{1-3}alkyl, C_{1-3}haloalkyl and CN.

23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein when present, each R^4 is independently selected from hydrogen, CH_3, F, Cl, $CH(CH_3)_2$, CF_3, CH_2CH_3 and CN.

24. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein when present, each R^4 is independently selected from hydrogen, Cl, F and CH_3.

25. The compound of any one of claims 1-3, 6-24, or a pharmaceutically acceptable salt thereof, wherein when present, each $R^5$is hydrogen, halogen, hydroxy, CN, C(O)OH, (C_{1-6})alkyl, (C_{1-6})haloalkyl, (C_{1-3})alkyl-OH, $-OC_{1-6}$alkyl, $O-(C_{1-6})$haloalkyl, $SO_2(C_{1-6})$alkyl, $N(C_{1-6})$alkyl, (C_{3-6})cycloalkyl, $O-(C_{3-7})$cycloalkyl, $-OC_{1-6}$alkyl-oxetanyl optionally substituted with halogen and $O-C_{1-6}$alkyl-(C_{3-7})cycloalkyl optionally substituted with halogen.

26. The compound of any one of claims 1-3, 6-25, or a pharmaceutically acceptable salt thereof, wherein when present, each $R^5$is $R^5$is hydrogen, Cl, F, OH, CN, CH_3, CF_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_2OH$, $C(CH_3)_2F$, CF_3, $C(F)_2CH_2CH_3$, C(O)OH, OCH_2CH_3, $OCHF_2$, OCH_2CF_3, OCH_2CHF_2, $OCH_2C(F)_2CH_3$, $OCH_2C(F)_2CH(F)_2$, $S(O)_2CH_3$, cyclopropyl, OCH_2-cyclopropyl, OCH_2-fluorocyclopropyl, O-cyclobutyl, OCH_2-oxetanyl-F and $N(CH_3)_2$.

27. The compound of any one of claims 1-7, 16-26, or a pharmaceutically acceptable salt thereof, wherein when present, each R^6 is independently selected from halogen, oxo, OH, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{1-3}alkyl-CN, OC_{1-3}alkyl, and $C(O)C_{1-3}$haloalkyl.

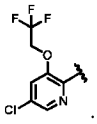
28. The compound of any one of claims 1-7, 16-27, or a pharmaceutically acceptable salt thereof, wherein when present, each R^6 is independently selected from halogen, oxo, CH_3, CF_3, OH, CH_2CF_3, $CH(CH_3)_2$, CH_2CH_3, OCH_3, CH_2CN, $C(O)CF_3$, and $(CH_3)_2$.

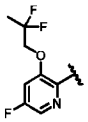
29. The compound of any one of claims 1, 3-28, or a pharmaceutically acceptable salt thereof, wherein X is $C(R^4)$, Y is $C(R^4)$, and Z is $C(R^4)$.

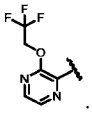
30. The compound of any one of claims 1, 3-28, or a pharmaceutically acceptable salt thereof, wherein X is N, Y is $C(R^4)$, and Z is $C(R^4)$.

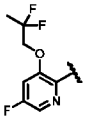
31. The compound of any one of claims 1, 3-28, or a pharmaceutically acceptable salt thereof, wherein X is $C(R^4)$, Y is N, and Z is $C(R^4)$.

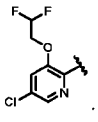
32. The compound of any one of claims 1, 3-28, or a pharmaceutically acceptable salt thereof, wherein X is $C(R^4)$, Y is $C(R^4)$, and Z is N.

33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein R^1 is  .

34. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein R^1 is  .

35. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein R^1 is  .

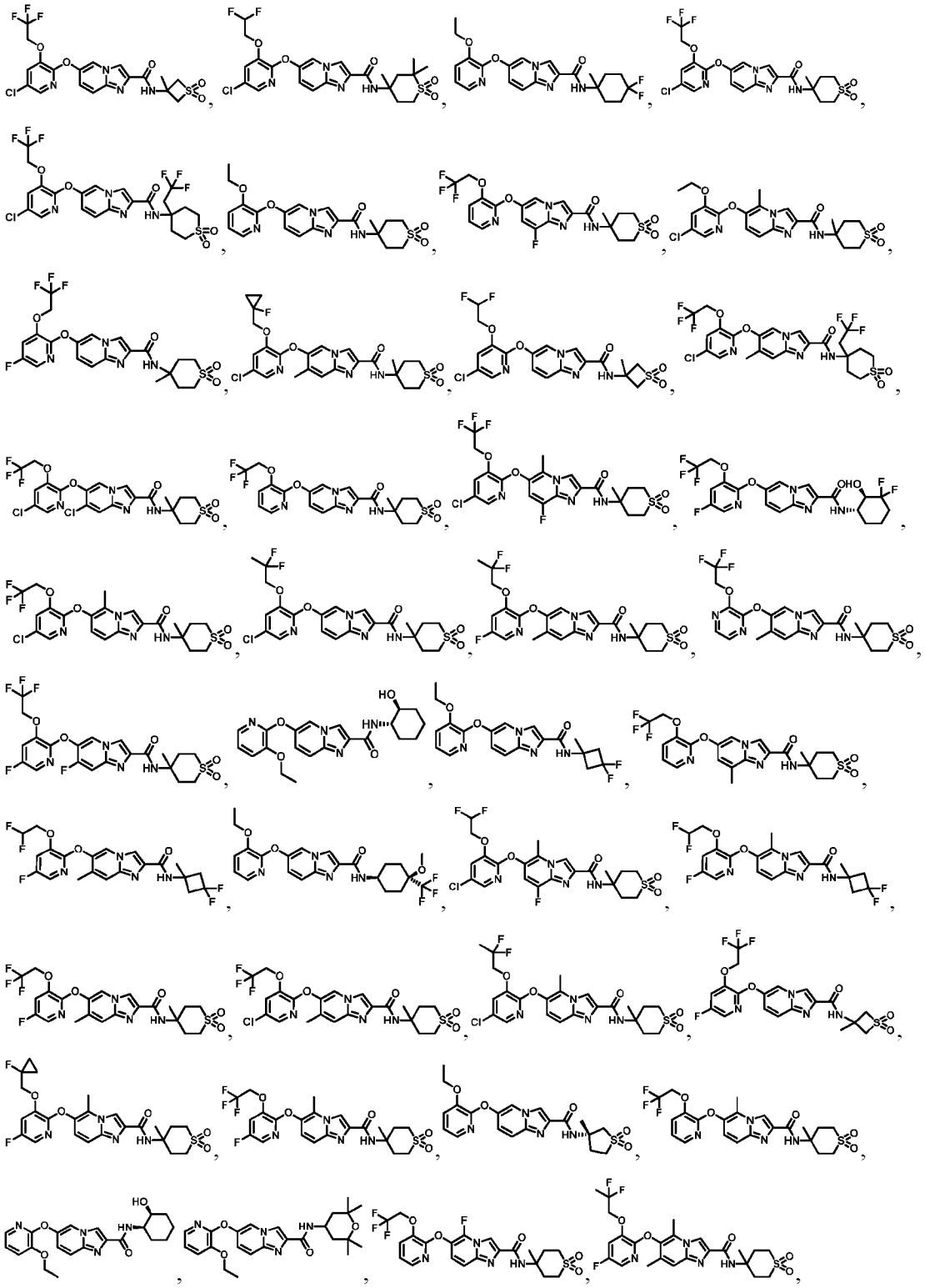
36. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein R^1 is  .

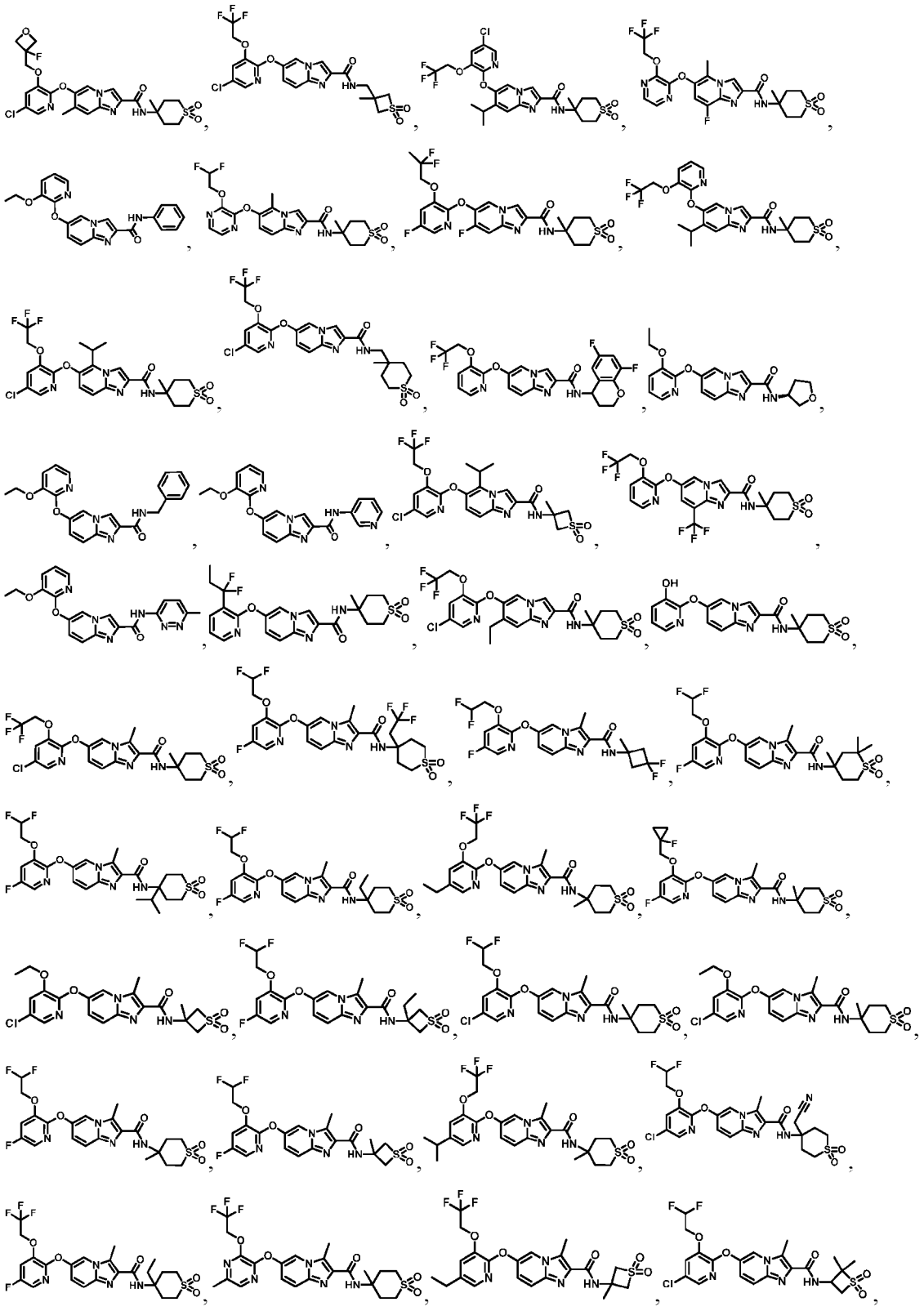
37. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein R^1 is  .

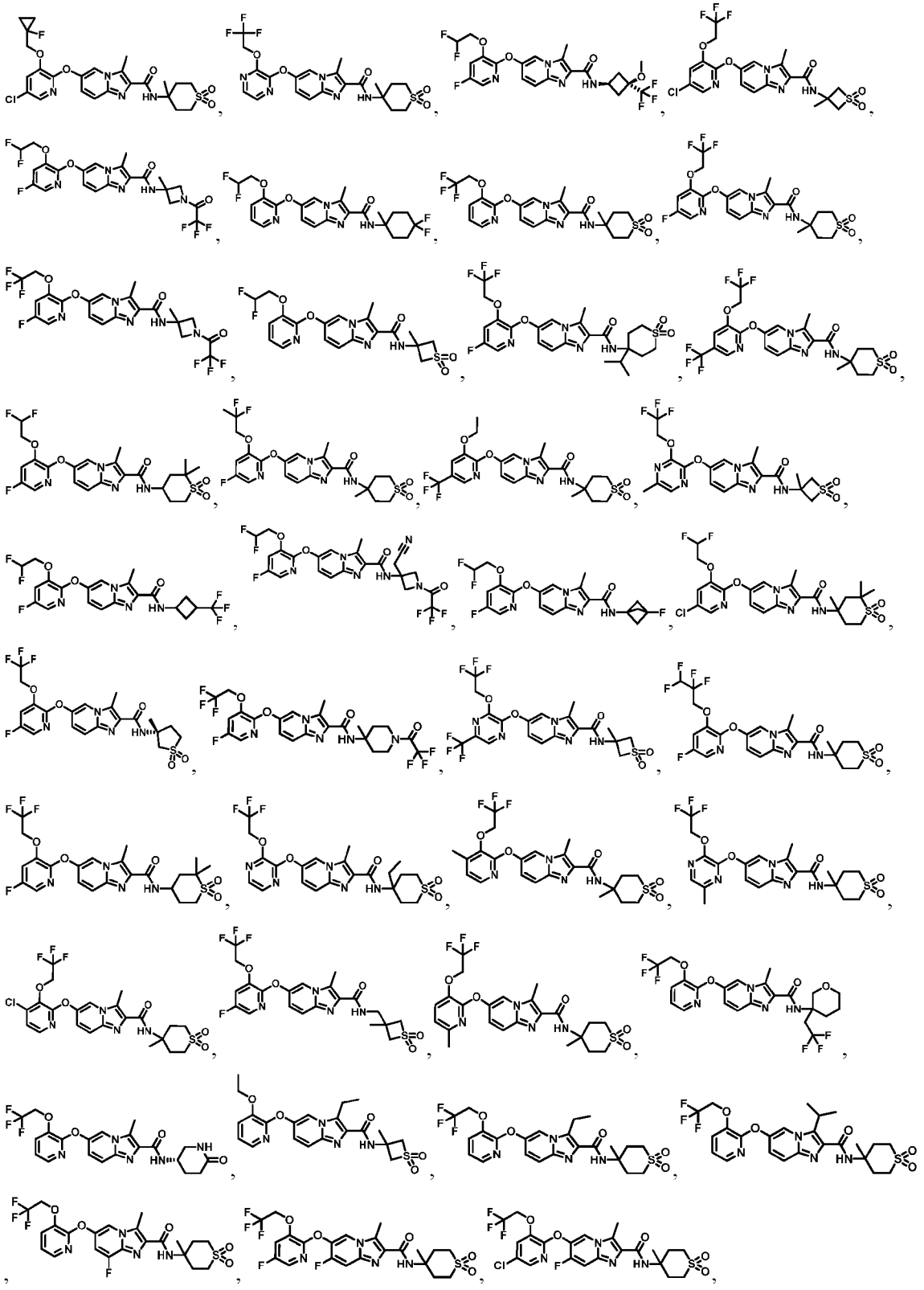
38. The compound of any one of claims 1-11, 16-32, or a pharmaceutically acceptable salt thereof, wherein R^2 is  .

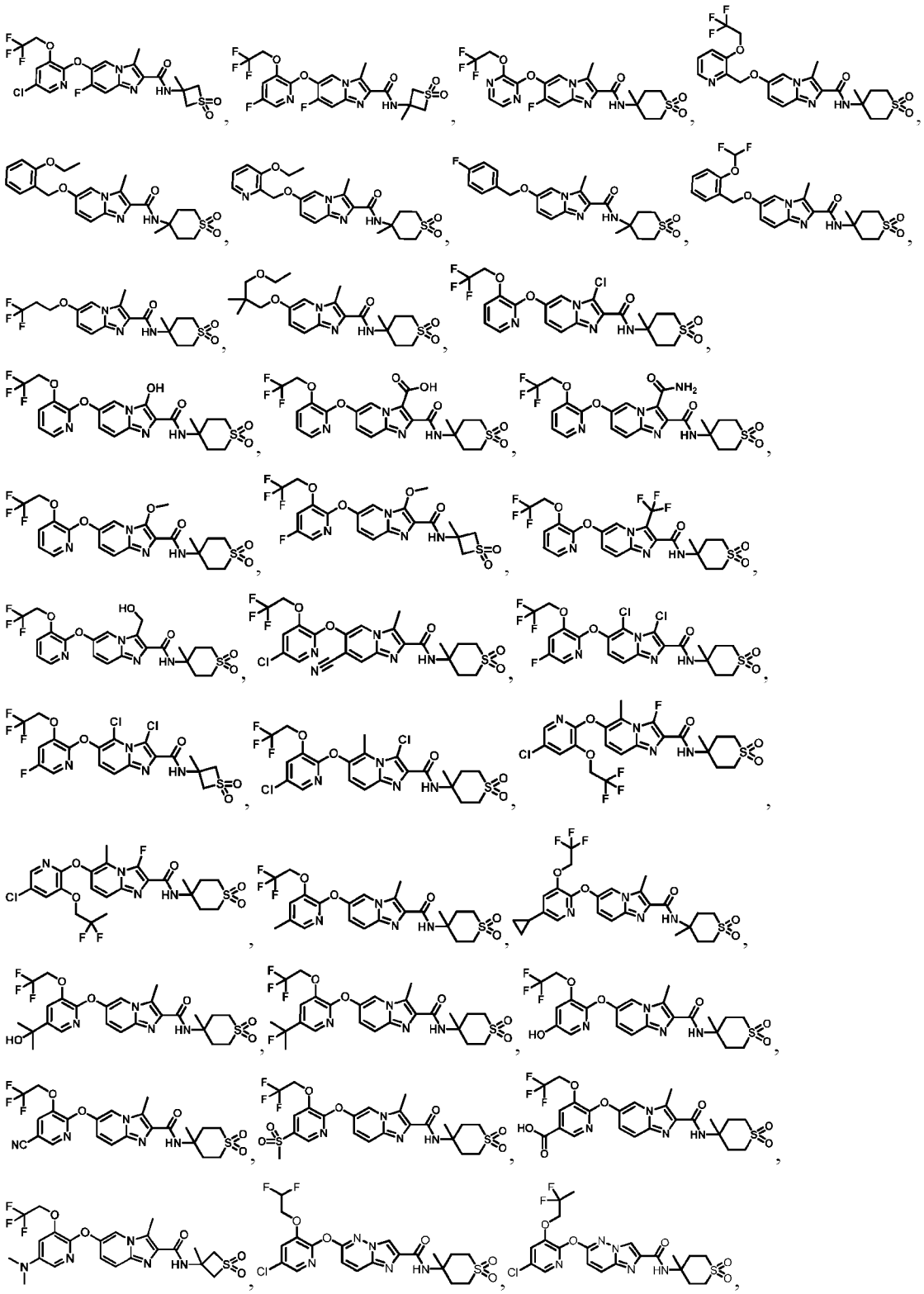
39. The compound of any one of claims 1-11, 16-32, or a pharmaceutically acceptable salt thereof, wherein R^2 is  .

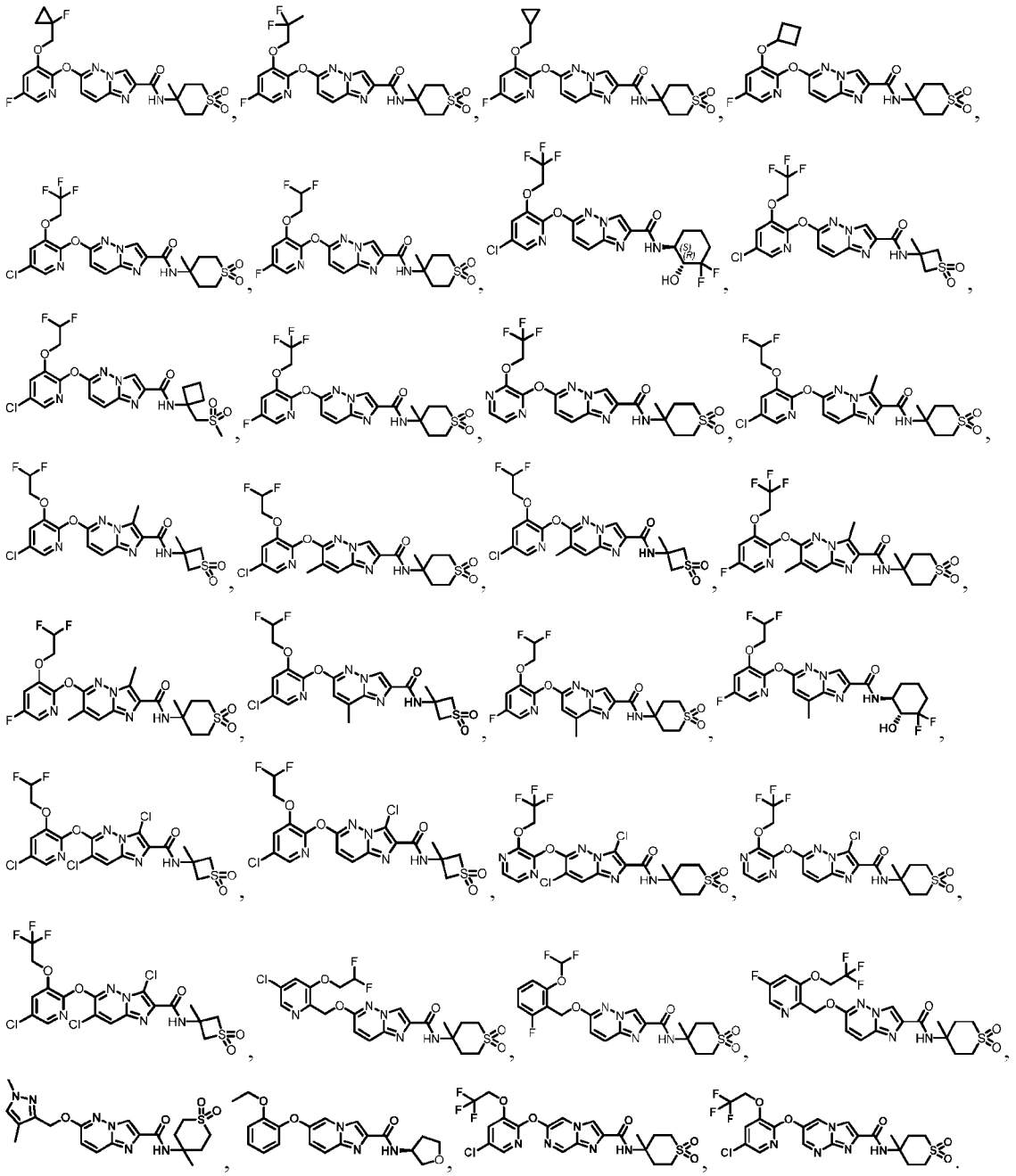
40. The compound of claim 1, or a pharmaceutically acceptable salt thereof, which is:











41. The compound of claim 1, or a pharmaceutically acceptable salt thereof, which is:

6-[[5-Chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(2,2,4-trimethyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(4,4-difluoro-1-methyl-cyclohexyl)-6-[(3-ethoxy-2-pyridyl)oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[1,1-dioxo-4-(2,2,2-trifluoroethyl)thian-4-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

8-fluoro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(5-chloro-3-ethoxy-2-pyridyl)oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[1,1-dioxo-4-(2,2,2-trifluoroethyl)thian-4-yl]-7-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

7-chloro-6-[5-chloro-3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-8-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

N-[(1*S*,2*R*)-3,3-difluoro-2-hydroxy-cyclohexyl]-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

7-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-6-((3-(2,2,2-trifluoroethoxy)pyrazin-2-yl)oxy)imidazo[1,2-*a*]pyridine-2-carboxamide,
7-fluoro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(1*S*,2*S*)-2-hydroxycyclohexyl]imidazo[1,2-*a*]pyridine-2-carboxamide,
N-(3,3-difluoro-1-methyl-cyclobutyl)-6-[(3-ethoxy-2-pyridyl)oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
8-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3,3-difluoro-1-methyl-cyclobutyl)-7-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[4-methoxy-4-(trifluoromethyl)cyclohexyl]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-8-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3,3-difluoro-1-methyl-cyclobutyl)-5-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(3*S*)-3-methyl-1,1-dioxo-thiolan-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,
5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(1*R*,2*S*)-2-hydroxycyclohexyl]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(2,2,6,6-tetramethyltetrahydropyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

5-fluoro-N-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-a]pyridine-2-carboxamide,

6-[[3-(2,2-difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-5,7-dimethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-[(3-fluorooxetan-3-yl)methoxy]-2-pyridyl]oxy]-7-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[(3-methyl-1,1-dioxo-thietan-3-yl)methyl]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

8-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-phenyl-imidazo[1,2-*a*]pyridine-2-carboxamide;2,2,2-trifluoroacetate,

6-[3-(2,2-difluoroethoxy)pyrazin-2-yl]oxy-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-((3-(2,2-difluoropropoxy)-5-fluoropyridin-2-yl)oxy)-7-fluoro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

7-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[(4-methyl-1,1-dioxo-thian-4-yl)methyl]imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(6,8-difluorochroman-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-[(3*S*)-tetrahydrofuran-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,

N-benzyl-6-[(3-ethoxy-2-pyridyl)oxy]imidazo[1,2-*a*]pyridine-2-carboxamide

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(3-pyridyl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-isopropyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-8-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-*N*-(6-methylpyridazin-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide

6-[[3-(1,1-difluoropropyl)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-ethyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-hydroxy-2-pyridyl)oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-[1,1-dioxo-4-(2,2,2-trifluoroethyl)thian-4-yl]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3,3-difluoro-1-methyl-cyclobutyl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(2,2,4-trimethyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-isopropyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-ethyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-ethyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(5-chloro-3-ethoxy-2-pyridyl)oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3-ethyl-1,1-dioxo-thietan-3-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(5-chloro-3-ethoxy-2-pyridyl)oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-isopropyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-[4-(cyanomethyl)-1,1-dioxo-thian-4-yl]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(4-ethyl-1,1-dioxo-thian-4-yl)-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[5-methyl-3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-ethyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(2,2-dimethyl-1,1-dioxo-thietan-3-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-[3-methoxy-3-(trifluoromethyl)cyclobutyl]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-[3-methyl-1-(2,2,2-trifluoroacetyl)azetidin-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(4,4-difluoro-1-methyl-cyclohexyl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[3-methyl-1-(2,2,2-trifluoroacetyl)azetidin-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-isopropyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,
3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-5-(trifluoromethyl)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(2,2-dimethyl-1,1-dioxo-thian-4-yl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-ethoxy-5-(trifluoromethyl)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)-6-[5-methyl-3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-*N*-[3-(trifluoromethyl)cyclobutyl]imidazo[1,2-*a*]pyridine-2-carboxamide,
N-[3-(cyanomethyl)-1-(2,2,2-trifluoroacetyl)azetidin-3-yl]-6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(2,2,4-trimethyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[(3*R*)-3-methyl-1,1-dioxo-thiolan-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[4-methyl-1-(2,2,2-trifluoroacetyl)-4-piperidyl]imidazo[1,2-*a*]pyridine-2-carboxamide,
3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)-6-[3-(2,2,2-trifluoroethoxy)-5-(trifluoromethyl)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,3,3-tetrafluoropropoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
N-(2,2-dimethyl-1,1-dioxo-thian-4-yl)-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-imidazo[1,2-*a*]pyridine-2-carboxamide,

N-(4-ethyl-1,1-dioxo-thian-4-yl)-3-methyl-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[4-methyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[6-methyl-3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[4-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-[(3-methyl-1,1-dioxo-thietan-3-yl)methyl]imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[6-methyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-[3-(2,2,2-trifluoroethyl)tetrahydropyran-3-yl]imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-[(3*S*)-6-oxo-3-piperidyl]-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[(3-ethoxy-2-pyridyl)oxy]-3-ethyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

3-ethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

3-isopropyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

8-fluoro-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,

7-fluoro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-fluoro-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-7-fluoro-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

7-fluoro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

7-fluoro-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,

3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]methoxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[(2-ethoxyphenyl)methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[(3-ethoxy-2-pyridyl)methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[(4-fluorophenyl)methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[2-(difluoromethoxy)phenyl]methoxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-(3,3,3-trifluoropropoxy)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-(3-ethoxy-2,2-dimethyl-propoxy)-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3-chloro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
3-hydroxy-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
2-((4-methyl-1,1-dioxidotetrahydro-*2H*-thiopyran-4-yl)carbamoyl)-6-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)imidazo[1,2-*a*]pyridine-3-carboxylic acid
*N*2-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2,3-dicarboxamide,
3-methoxy-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methoxy-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridin-1-ium-2-carboxamide;2,2,2-trifluoroacetate,
N-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-(trifluoromethyl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3-(hydroxymethyl)-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[5-chloro-3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-7-cyano-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3,5-dichloro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,

3,5-dichloro-6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3-chloro-6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-3-fluoro-5-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[5-methyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-cyclopropyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-(1-hydroxy-1-methyl-ethyl)-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-(1-fluoro-1-methyl-ethyl)-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-hydroxy-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[[5-cyano-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*a*]pyridine-2-carboxamide,
3-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[[5-methylsulfonyl-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]imidazo[1,2-*a*]pyridine-2-carboxamide,
6-[3-methyl-2-[(4-methyl-1,1-dioxo-thian-4-yl)carbamoyl]imidazo[1,2-*a*]pyridine-6-yl]oxy-5-(2,2,2-trifluoroethoxy)pyridine-3-carboxylic acid,
6-[5-(dimethylamino)-3-(2,2,2-trifluoroethoxy)pyridine-2-yl]oxy-3-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*a*]pyridin-1-ium-2-carboxamide,
6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,
6-[[5-Chloro-3-(2,2-difluoropropoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,
6-[[5-Fluoro-3-[(1-fluorocyclopropyl)methoxy]-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,
6-[[3-(2,2-Difluoropropoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[3-(Cyclopropylmethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[3-(Cyclobutoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-Chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[3-(2,2-Difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-((1*S*,2*R*)-3,3-difluoro-2-hydroxycyclohexyl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-N-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-b]pyridazine-2-carboxamide,

6-[[5-Chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-[1-(methylsulfonylmethyl)cyclobutyl]imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-Fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

N-(4-Methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-7-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-7-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-3,7-dimethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

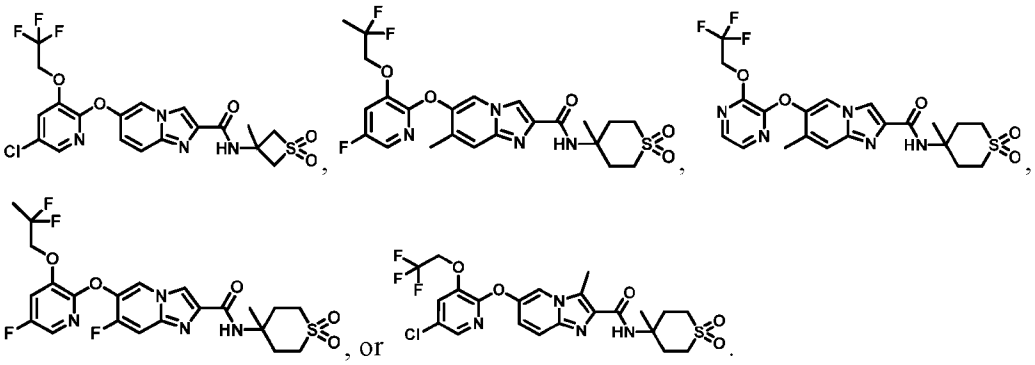
6-[[3-(2,2-difluoroethoxy)-5-fluoro-2-pyridyl]oxy]-3,7-dimethyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-8-methyl-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

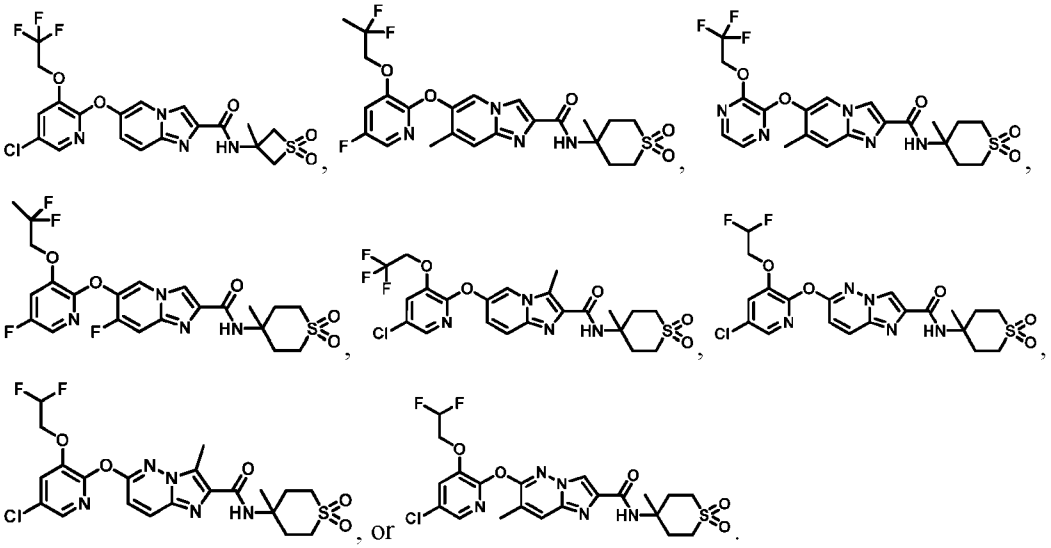
6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-8-methyl-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,

N-((1*S*,2*R*)-3,3-difluoro-2-hydroxycyclohexyl)-6-((3-(2,2-difluoroethoxy)-5-fluoropyridin-2-yl)oxy)-8-methylimidazo[1,2-*b*]pyridazine-2-carboxamide,
3,7-dichloro-6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,
3-chloro-6-[[5-chloro-3-(2,2-difluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,
3,7-dichloro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*b*]pyridazine-2-carboxamide,
3-chloro-*N*-(4-methyl-1,1-dioxo-thian-4-yl)-6-[3-(2,2,2-trifluoroethoxy)pyrazin-2-yl]oxy-imidazo[1,2-*b*]pyridazine-2-carboxamide,
3,7-dichloro-6-[[5-chloro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]oxy]-*N*-(3-methyl-1,1-dioxo-thietan-3-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,
6-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,
6-[[2-(Difluoromethoxy)-6-fluoro-phenyl]methoxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,
6-[[5-Fluoro-3-(2,2,2-trifluoroethoxy)-2-pyridyl]methoxy]-*N*-(4-methyl-1,1-dioxo-thian-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,
6-((1,4-dimethyl-1*H*-pyrazol-3-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*b*]pyridazine-2-carboxamide,
(*S*)-6-(2-ethoxyphenoxy)-*N*-(tetrahydrofuran-3-yl)imidazo[1,2-*a*]pyridine-2-carboxamide
6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyrazine-2-carboxamide, or
6-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)imidazo[1,2-*a*]pyrimidine-2-carboxamide.

42. The compound of claim 41, or a pharmaceutically acceptable salt thereof, which is selected from one of the following:



43. The compound of claim 41, or a pharmaceutically acceptable salt thereof, which is



44. A composition for treating a condition selected from hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases and heart failure comprising a compound of any of claims 1 to 41, or a pharmaceutically acceptable salt thereof, and a pharmaceutically carrier.

45. A composition comprising a pharmaceutically acceptable carrier and a compound according to any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof.

46. A method for treating a condition selected from hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases and heart

failure comprising administering to a patient in need thereof of a therapeutically effective amount of a compound of any of claims 1 to 41, or a pharmaceutically acceptable salt thereof.

47. Use of a compound of any of claims 1 to 41, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a condition selected from hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity, hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases and heart failure.