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(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).

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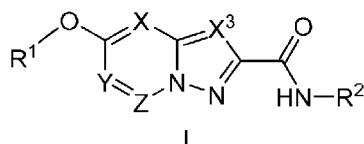
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(54) Title: PREPARATION OF PYRAZOLOPYRIDINE AND TRIAZOLOPYRIDINE DERIVATIVES AS NOVEL DIACYLGLYCERIDE O-ACYLTRANSFERASE 2 INHIBITORS



(57) Abstract: Provided are compounds of Formula I, Formula Ib or Formula Ic and the pharmaceutically acceptable salts, esters, and prodrugs thereof, which are DGAT2 inhibitors. Also provided are methods of making compounds of Formula I, Formula Ib or Formula Ic, pharmaceutical compositions comprising compounds of Formula I, Formula Ib or Formula Ic, and methods of using these compounds to treat 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, comprising administering a compound of Formula I to a patient in need thereof.



PREPARATION OF PYRAZOLOPYRIDINE AND TRIAZOLOPYRIDINE DERIVATIVES AS NOVEL DIACYLGLYCERIDE O-ACYLTRANSFERASE 2 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This international application claims the benefit of priority to U.S. Provisional Application No. 63/421,381, filed November 1, 2022, the entirety of which is incorporated herein by reference.

FIELD OF THE INVENTION

10 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
15 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 OF THE INVENTION

20 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.

25 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
30 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).

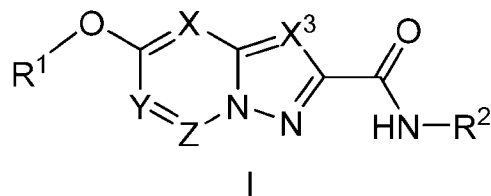
Despite this perinatal lethal phenotype, the metabolic role of DGAT2 has been mostly comprehended from effort exploiting anti-sense oligonucleotides (ASO) in rodents. In this setting, DGAT2 knockdown in *ob/ob* mice with a DGAT2 gene-specific ASO resulted in a dose dependent decrease in very low density 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 OF THE INVENTION

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

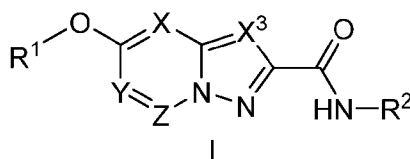


as well as pharmaceutically acceptable salts, esters, and prodrugs thereof, which are DGAT2 inhibitors. Also provided are methods of making compounds of Formula I, pharmaceutical compositions comprising compounds of Formula I, and methods of using these compounds to

5 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.

10 DETAILED DESCRIPTION OF THE INVENTION

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



or a pharmaceutically acceptable salt thereof wherein:

15 X^3 is selected from C(R³) and N;

X, Y, and Z are independently selected from N and C(R⁴)

R¹ is

- (1) a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R⁵, or
- 20 (2) -(C₁₋₆)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 R⁵;

R² is

- 25 (1) a 4- to 7-membered heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S,
- (2) -(C₁₋₆)alkyl-heterocyclyl, wherein the heterocyclyl is a 3- to 6-membered ring containing 1 or 2 heteroatoms independently selected from N, O and S,

- (3) $-(C_{1-6})alkyl$,
- (4) $-(C_{3-6})cycloalkyl$,
- (5) $-(C_{1-6})hydroxyalkyl$,
- (6) $-SO_2(C_{1-6})alkyl$, or
- 5 (7) $-(C_{1-6})alkyl-NH-SO_2-(C_{1-6})alkyl$,

wherein each alkyl, cycloalkyl and heterocycle is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from R^6 ;

R^3 is

- (1) hydrogen,
- 10 (2) halogen,
- (3) $-NH_2$
- (4) $(C_{1-6})alkyl$,
- (5) $(C_{1-6})haloalkyl$,
- (6) $(C_{1-4})alkylhydroxy$, or
- 15 (7) $-(C_{3-6})cycloalkyl$;

each R^4 is independently

- (1) hydrogen,
- (2) halogen, or
- (3) $(C_{1-3})alkyl$;

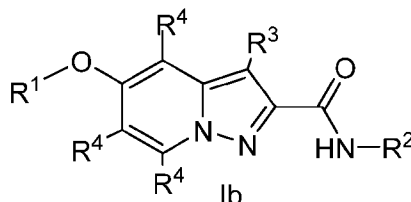
20 when present, each R^5 is independently

- (1) $-OC_{1-6}alkyl$,
- (2) $-O(C_{1-6})haloalkyl$,
- (3) halogen,
- (4) cyano,
- 25 (5) $O-(C_{3-6})cycloalkyl$, optionally substituted with halogen,
- (6) $(C_{1-3})hydroxyalkyl$,
- (7) $(C_{1-6})haloalkyl$ -,
- (8) $(C_{1-3})hydroxyhaloalkyl$, or
- (9) $(C_{1-6})alkyl-(C_{3-7})cycloalkyl-OH$;

30 when present, each R^6 is independently

- (1) oxo,
- (2) $(C_{1-6})alkyl$, or
- (3) $(C_{1-6})haloalkyl$ -.

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



or a pharmaceutically acceptable salt thereof wherein:

5 R^1 is

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

R^2 is

- (1) a 4- to 7-membered heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S,
- (2) $-(C_{1-6})$ alkyl-heterocyclyl, wherein the heterocyclyl is a 3- to 6-membered ring containing 1 or 2 heteroatoms independently selected from N, O and S,
- (3) $-(C_{1-6})$ alkyl,
- (4) $-(C_{3-6})$ cycloalkyl,
- (5) $-(C_{1-6})$ hydroxyalkyl,
- (6) $-SO_2(C_{1-6})$ alkyl, or
- (7) $-(C_{1-6})$ alkyl-NH- SO_2 -($C_{1-6})$ alkyl,

wherein each alkyl, cycloalkyl and heterocycle is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from R^6 ;

when present, R^3 is

- (1) hydrogen,
- (2) halogen,
- (3) $-NH_2$,
- (4) (C_{1-6}) alkyl,
- (5) (C_{1-6}) haloalkyl,
- (6) hydroxy($C_{1-4})$ alkyl, or
- (7) $-(C_{3-6})$ cycloalkyl;

each R⁴ is independently

- (1) hydrogen,
- (2) halogen, or
- (3) (C₁₋₃)alkyl;

5 when present, each R⁵ is independently

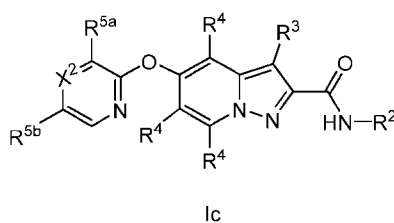
- (1) -OC₁₋₆alkyl,
- (2) -O(C₁₋₆)haloalkyl,
- (3) halogen,
- (4) cyano,
- 10 (5) O-(C₃₋₆)cycloalkyl, optionally substituted with halogen,
- (6) (C₁₋₃)hydroxyalkyl,
- (7) (C₁₋₆)haloalkyl-,
- (8) (C₁₋₃)hydroxyhaloalkyl, or
- (9) (C₁₋₆)hydroxyalkyl-(C₃₋₇)cycloalkyl;

15 when present, each R⁶ is independently

- (1) oxo,
- (2) (C₁₋₆)alkyl, or
- (3) (C₁₋₆)haloalkyl-.

In **Embodiment 3** of this disclosure are compounds of Formula I, or a pharmaceutically

20 acceptable salt thereof, is the compound of Formula Ic;



or a pharmaceutically acceptable salt thereof wherein:

25 X² is CH or N;

R² is

- (1) a 4- to 7-membered heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S,
- (2) -(C₁₋₆)alkyl-heterocyclyl, wherein the heterocyclyl is a 3- to 6-membered ring
- 30 containing 1 or 2 heteroatoms independently selected from N, O and S,

- (3) $-(C_{1-6})alkyl$,
- (4) $-(C_{3-6})cycloalkyl$,
- (5) $-(C_{1-6})hydroxyalkyl$,
- (6) $-SO_2(C_{1-6})alkyl$, or
- 5 (7) $-(C_{1-6})alkyl-NH-SO_2-(C_{1-6})alkyl$,

wherein each alkyl, cycloalkyl and heterocycle is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from R^6 ;

when present, R^3 is

- (1) hydrogen,
- 10 (2) halogen,
- (3) $-NH_2$,
- (4) $(C_{1-6})alkyl$,
- (5) $(C_{1-6})haloalkyl$,
- (6) $hydroxy(C_{1-4})alkyl$, or
- 15 (7) $-(C_{3-6})cycloalkyl$;

each R^4 is independently

- (1) hydrogen,
- (2) halogen, or
- (3) $(C_{1-3})alkyl$;
- 20 when present, each R^{5a} is independently

- (1) $-OC_{1-6}alkyl$,
- (2) $-O(C_{1-6})haloalkyl$, or
- (3) $O-(C_{3-6})cycloalkyl$;

when present, each R^{5b} is independently

- 25 (1) halogen,
- (2) cyano,
- (3) $-OC_{1-6}alkyl$,
- (4) $(C_{1-3})hydroxyalkyl$,
- (5) $(C_{1-3})hydroxyhaloalkyl$, or
- 30 (6) $(C_{1-6})hydroxyalkyl-(C_{3-7})cycloalkyl$;

when present, each R^6 is independently

- (1) oxo,
- (2) $(C_{1-6})alkyl$, or
- (3) $(C_{1-6})haloalkyl$.

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 R¹ is

(1) a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, OC₁₋₆alkyl, O(C₁₋₆)haloalkyl, O-(C₃₋₆)cycloalkyl, cyano, (C₁₋₆)hydroxyalkyl-(C₃₋₆)cycloalkyl, and (C₁₋₃)hydroxyhaloalkyl, or

(2) -(C₁₋₆)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 one, two, or three substituents independently selected from halogen, OC₁₋₆alkyl, and O(C₁₋₆)haloalkyl.

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 R¹ is

(1) a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, OC₁₋₆alkyl, O(C₁₋₆)haloalkyl, O-(C₃₋₆)cycloalkyl, cyano, (C₁₋₆)hydroxyalkyl-(C₃₋₆)cycloalkyl, (C₁₋₃)hydroxyalkyl and (C₁₋₃)hydroxyhaloalkyl, or

(2) -(C₁₋₆)alkyl-heteroaryl, wherein the heteroaryl is a 6-membered heteroaryl containing 1, nitrogen heteroatom, wherein the heteroaryl is unsubstituted or substituted with one or two substituents independently selected from halogen, OC₁₋₆alkyl, and O(C₁₋₆)haloalkyl.

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 R¹ is a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, OC₁₋₆alkyl, O(C₁₋₆)haloalkyl, O-(C₃₋₆)cycloalkyl, cyano, (C₁₋₆)hydroxyalkyl-(C₃₋₆)cycloalkyl, (C₁₋₃)hydroxyalkyl and (C₁₋₃)hydroxyhaloalkyl.

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 R¹ is a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, OCH₂CF₃, OCH₂CF₂H, O-cyclopropyl, CN, CH(cyclopropyl)OH, CH(CH₃)OH, and CH(CF₃)OH.

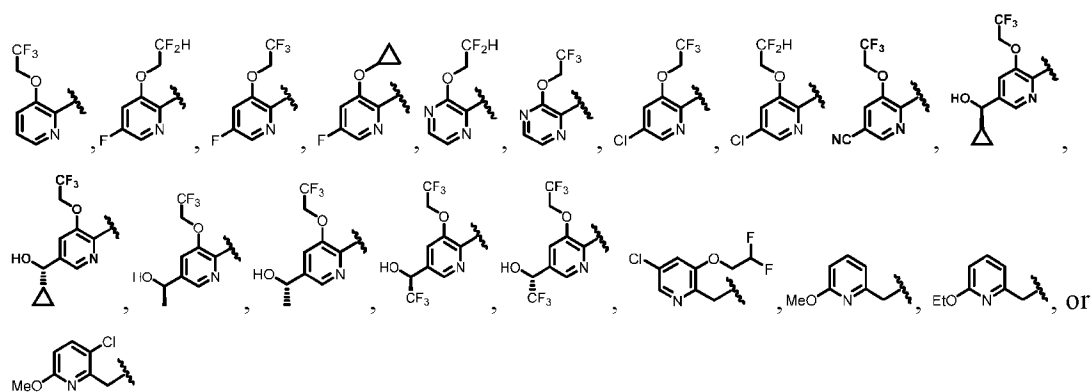
In **Embodiment 8** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-7 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R¹ is a 6-membered heteroaryl containing 1 nitrogen atoms, wherein the heteroaryl is unsubstituted or

substituted with one, two, or three substituents independently selected from F, Cl, OCH₂CF₃, OCH₂CF₂H, O-cyclopropyl, CN, CH(cyclopropyl)OH, CH(CH₃)OH, and CH(CF₃)OH.

In **Embodiment 9** 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 R¹ is
 5 -(C₁₋₃)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 one, two, or three substituents independently selected from Cl, OCH₃, OCH₂CH₃ and OCH₂CHF₂.

In **Embodiment 10** of this disclosure are compounds of Formula I or Formula Ib, or
 10 Embodiments 1-5, 9 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R¹ is -(C₁₋₃)alkyl-heteroaryl, wherein the heteroaryl is a 6-membered heteroaryl containing 1 nitrogen atom, wherein the heteroaryl is unsubstituted or substituted with one or two substituents independently selected from Cl, OCH₃ and OCH₂CHF₂.

In **Embodiment 11** of this disclosure are compounds of Formula I or Formula Ib, or
 15 Embodiments 1-5 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R¹ is



20 In **Embodiment 12** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-11 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is

- (1) a 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
 25 substituents independently selected from oxo, C₁₋₃alkyl, or C₁₋₃haloalkyl,
- (2) -(C₃₋₆)cycloalkyl,
- (3) -(C₁₋₆)hydroxyalkyl, or
- (4) -(C₁₋₆)alkyl-NH-SO₂-(C₁₋₆)alkyl.

In **Embodiment 13** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-12 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is

- (1) a 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 oxo, CH₃, CHF₂, or CH₂CF₃,
- (2) -(C₃₋₆)cycloalkyl,
- (3) -(C₁₋₆)hydroxyalkyl,
- (4) -(C₁₋₆)alkyl-NH-SO₂-(C₁₋₆)alkyl.

In **Embodiment 14** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-12 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is a 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 oxo, C₁₋₃alkyl, or C₁₋₃haloalkyl.

In **Embodiment 15** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-14 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is a 4- to 7-membered heterocyclyl containing 1 or 2 heteroatoms independently selected from N, O and S, optionally substituted with one, two, three, four or five substituents independently selected from oxo, CH₃, CHF₂, or CH₂CF₃.

In **Embodiment 16** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-15 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is a 4-membered heterocyclyl containing 1 sulfur heteroatom, optionally substituted with one, two or three substituents independently selected from oxo or CH₃.

In **Embodiment 17** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-15 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is a 5-membered heterocyclyl containing 1 sulfur heteroatom, optionally substituted with one, two or three substituents independently selected from oxo or CH₃.

In **Embodiment 18** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-15 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R² is a 6-membered heterocyclyl containing 1 sulfur heteroatom, optionally substituted with one, two or three substituents independently selected from oxo, CH₃, CHF₂, or CH₂CF₃.

In **Embodiment 19** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-13 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a 5-membered cycloalkyl.

In **Embodiment 20** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-13 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is $C(CH_3)_2CH_2C(CH_3)_2OH$.

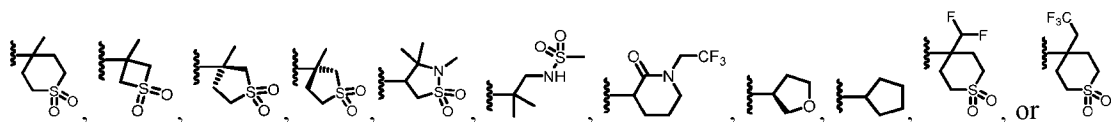
In **Embodiment 21** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-14 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a 6 membered heterocycle containing 1 nitrogen atom optionally substituted with one or two substituents independently selected from oxo, $-(C_{1-3})$ alkyl and $-(C_{1-3})$ haloalkyl.

In **Embodiment 22** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-14 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is a 5 membered heterocycle containing 1 nitrogen atom optionally substituted with one or two substituents independently selected from oxo, $-(C_{1-3})$ alkyl and $-(C_{1-3})$ haloalkyl.

In **Embodiment 23** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-13 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is $-(C_{1-6})$ alkyl-NH-SO₂-(C₁₋₆)alkyl.

In **Embodiment 24** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-13 or 23, or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is $CH(CH_3)_2CH_2NHSO_2CH_3$.

In **Embodiment 25** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-13 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is



In **Embodiment 26** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-25 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is hydrogen, halogen, (C_{1-6}) alkyl, $-(C_{1-6})$ haloalkyl, $-(C_{1-6})$ hydroxyalkyl, $-(C_{3-6})$ cycloalkyl, or $-NH_2$.

In **Embodiment 27** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-26 or a class thereof, or a pharmaceutically acceptable salt of any of the

foregoing, wherein R³ is hydrogen, halogen, CH₃, CH₂CH₃, CH(CH₃)₂, CH(F₂), CH₂OH, CF₃, CH(OH)CH₃, CH₂C(OH)(CH₃)₂, cyclopropyl, or -NH₂.

In **Embodiment 28** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-27 or a class thereof, or a pharmaceutically acceptable salt of any of the

5 foregoing, wherein R³ is hydrogen, F, Cl, CH₃, CH₂CH₃, CH(CH₃)₂, CH(F₂), CH₂OH, CF₃, CH(OH)CH₃, CH₂C(OH)(CH₃)₂, cyclopropyl, or -NH₂.

In **Embodiment 29** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-28 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R⁴ is hydrogen, halogen or (C₁₋₆)alkyl.

10 In **Embodiment 30** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-29 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R⁴ is H, Cl, F, or CH₃.

In **Embodiment 31** 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

15 foregoing, wherein R⁵ is -OC₁₋₆alkyl, -O(C₁₋₆)haloalkyl, halogen, cyano, O-(C₃₋₆)cycloalkyl, (C₁₋₆)haloalkyl-, (C₁₋₃)hydroxyhaloalkyl, (C₁₋₃)hydroxyalkyl or -(C₃₋₇)cycloalkylhydroxy.

In **Embodiment 32** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-3, 31 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R⁵ is -OC₁₋₆alkyl, -O(C₁₋₆)haloalkyl, halogen, cyano, O-(C₃₋₆)cycloalkyl, (C₁₋₃)hydroxyhaloalkyl, (C₁₋₃)hydroxyalkyl or -(C₃₋₇)cycloalkylhydroxy.

20 In **Embodiment 33** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-3, 31-32 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R⁵ is halogen, OCH₃, OCH₂CH₃, -OCH₂CF₃, OCH₂CHF₂, O-cyclopropyl, CN, CH(cyclopropyl)OH, CH(CH₃)OH, or CH(CF₃)OH.

25 In **Embodiment 34** of this disclosure are compounds of Formula I or Formula Ib, or Embodiments 1-3, 31-33 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R⁵ is F, Cl, OCH₃, OCH₂CH₃, -OCH₂CF₃, OCH₂CHF₂, O-cyclopropyl, CN, CH(cyclopropyl)OH, CH(CH₃)OH, or CH(CF₃)OH.

In **Embodiment 35** of this disclosure are compounds of Formula I or Formula Ib, or

30 Embodiments 1-3, 31-34 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R⁵ is OCH₂CF₃ or OCH₂CHF₂.

In **Embodiment 36** of this disclosure are compounds of Formula Ic, or Embodiments 3, 12-30 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^{5a} is OCH₂CHF₂, OCH₂CF₃, O-cyclopropyl.

In **Embodiment 37** of this disclosure are compounds of Formula Ic, or Embodiments 3, 12-30, or 36, or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^{5b} is halogen, CH(cyclopropyl)OH, CN, CH(CH₃)OH, CH(CF₃)OH.

In **Embodiment 38** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-11, 26-37 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R⁶ is oxo, (C₁₋₆)alkyl, or (C₁₋₆)haloalkyl.

In **Embodiment 39** of this disclosure are compounds of Formula I, Formula Ib or Formula Ic, or Embodiments 1-11, 26-38 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R⁶ is oxo, CH₃, CHF₂, or CH₂CF₃.

In **Embodiment 40** of this disclosure are compounds of Formula I, or Embodiments 1, 4-39 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X³ is C(R³).

In **Embodiment 41** of this disclosure are compounds of Formula I, or Embodiments 1, 4-39 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X³ is N.

In **Embodiment 42** of this disclosure are compounds of Formula I, or Embodiments 1, 4-39 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is C(R⁴), Y is C(R⁴), and Z is C(R⁴).

In **Embodiment 43** of this disclosure are compounds of Formula I, or Embodiments 1, 4-39 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is N, Y is C(R⁴), and Z is C(R⁴).

In **Embodiment 44** of this disclosure are compounds of Formula I, or Embodiments 1, 4-39 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is C(R⁴), Y is N, and Z is C(R⁴).

In **Embodiment 45** of this disclosure are compounds of Formula I, or Embodiments 1, 4-39 or a class thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is C(R⁴), Y is C(R⁴), and Z is N.

In **Embodiment 46** of the invention, the compound of Formula I, Formula Ib or Formula Ic, or a pharmaceutically acceptable salt thereof, is:

N-(4-Methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,

5-((3-(2,2,2-Trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(2,3,3-trimethyl-1,1-dioxidoisothiazolidin-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,

N-(2-Methyl-1-(methylsulfonamido)propan-2-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,

- N*-(2-Oxo-1-(2,2,2-trifluoroethyl)piperidin-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- N*-(3-Methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 5 (*S*)-*N*-(Tetrahydrofuran-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- N*-Cyclopentyl-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- (*R*)-5-((3-(2,2-Difluoroethoxy)pyrazin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 10 5-((3-(2,2-Difluoroethoxy)pyrazin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 5-((3-Cyclopropoxy-5-fluoropyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 15 5-((3-(2,2-Difluoroethoxy)-5-fluoropyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 5-((3-Cyclopropoxy-5-fluoropyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- N*-(4-Methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyrazin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 20 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 25 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- (*R*)-5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 30 3-Methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 3-Methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,

- 3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Fluoro-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5 (R)-3-Fluoro-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Chloro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Chloro-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
10 (R)-3-Chloro-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
(S)-3-Chloro-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
15 3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
(R)-3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Chloro-5-((3-(2,2,2-difluoroethoxy)pyrazin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
20 5-((3-(2,2-Difluoroethoxy)pyrazin-2-yl)oxy)-3-fluoro-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5-((3-(2,2-Difluoroethoxy)pyrazin-2-yl)oxy)-3-fluoro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
25 3,4-Dichloro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Chloro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Chloro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyrazin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
30 3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-fluoro-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,

- 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-fluoro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Chloro-5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5 3-Chloro-5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Chloro-5-((5-cyano-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5-((5-Cyano-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-
10 thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
(*R*)-5-((5-(Cyclopropyl(hydroxy)methyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
(*S*)-5-((5-(Cyclopropyl(hydroxy)methyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
15 (*R*)-5-((5-(1-Hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
(*S*)-5-((5-(1-Hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
(*R*)-*N*-(3-Methyl-1,1-dioxidothietan-3-yl)-5-((5-(2,2,2-trifluoro-1-hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
20 (*S*)-*N*-(3-Methyl-1,1-dioxidothietan-3-yl)-5-((5-(2,2,2-trifluoro-1-hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Ethyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
25 3-Ethyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Isopropyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-(Difluoromethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
30 3-(Hydroxymethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
N-(4-Methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,

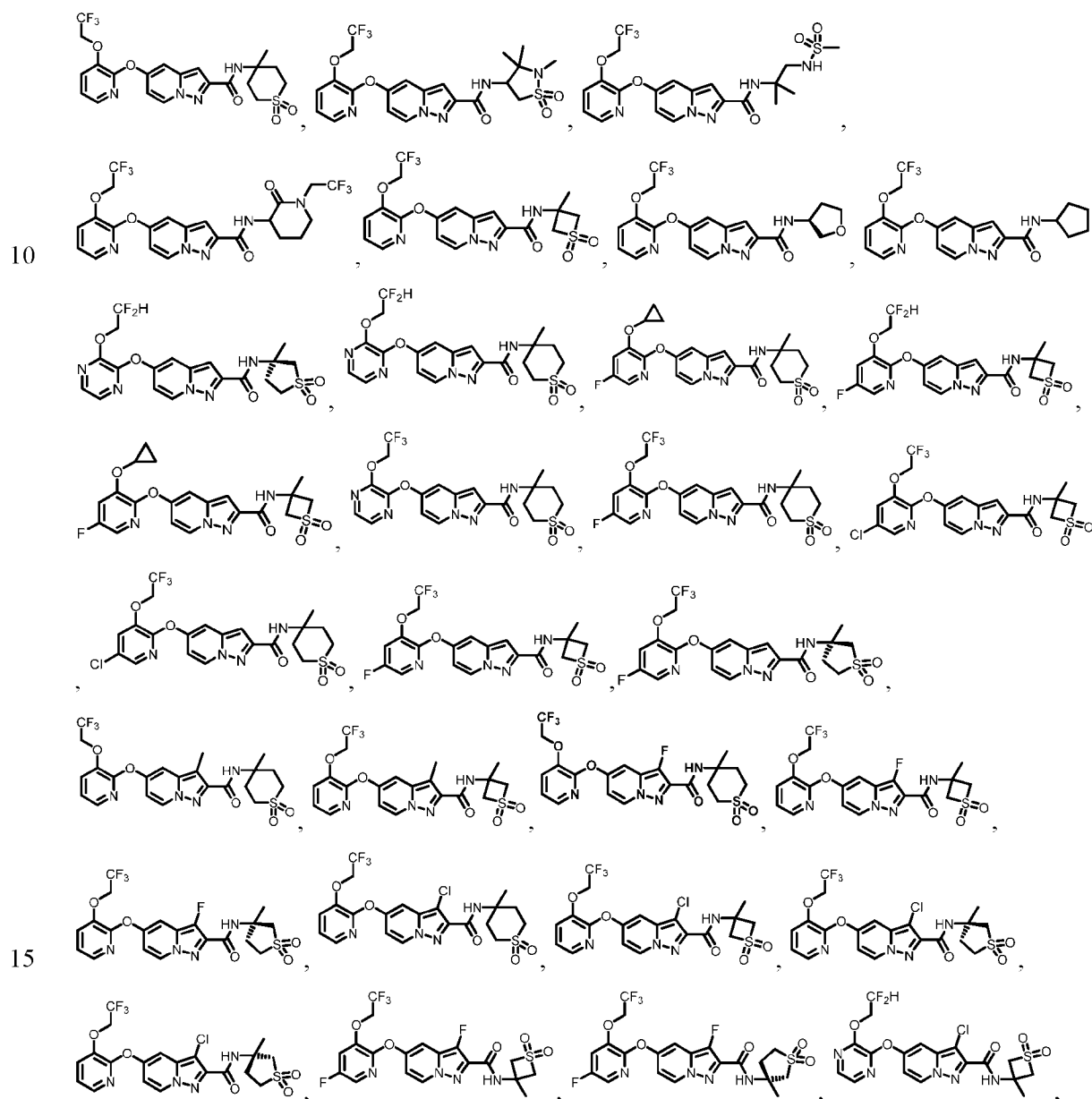
- (*R*)-3-(1-Hydroxyethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- (*S*)-3-(1-Hydroxyethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 5 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(2-hydroxy-2-methylpropyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 3-Cyclopropyl-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 3-Amino-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 10 4-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 6-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 15 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-4-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-6-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 20 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-fluoro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide,
- 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide,
- 25 7-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxamide,
- 7-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-(difluoromethyl)-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxamide,
- 7-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(1,1-dioxido-4-(2,2,2-trifluoroethyl)tetrahydro-2*H*-thiopyran-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxamide,
- 30 7-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxamide,
- 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide,

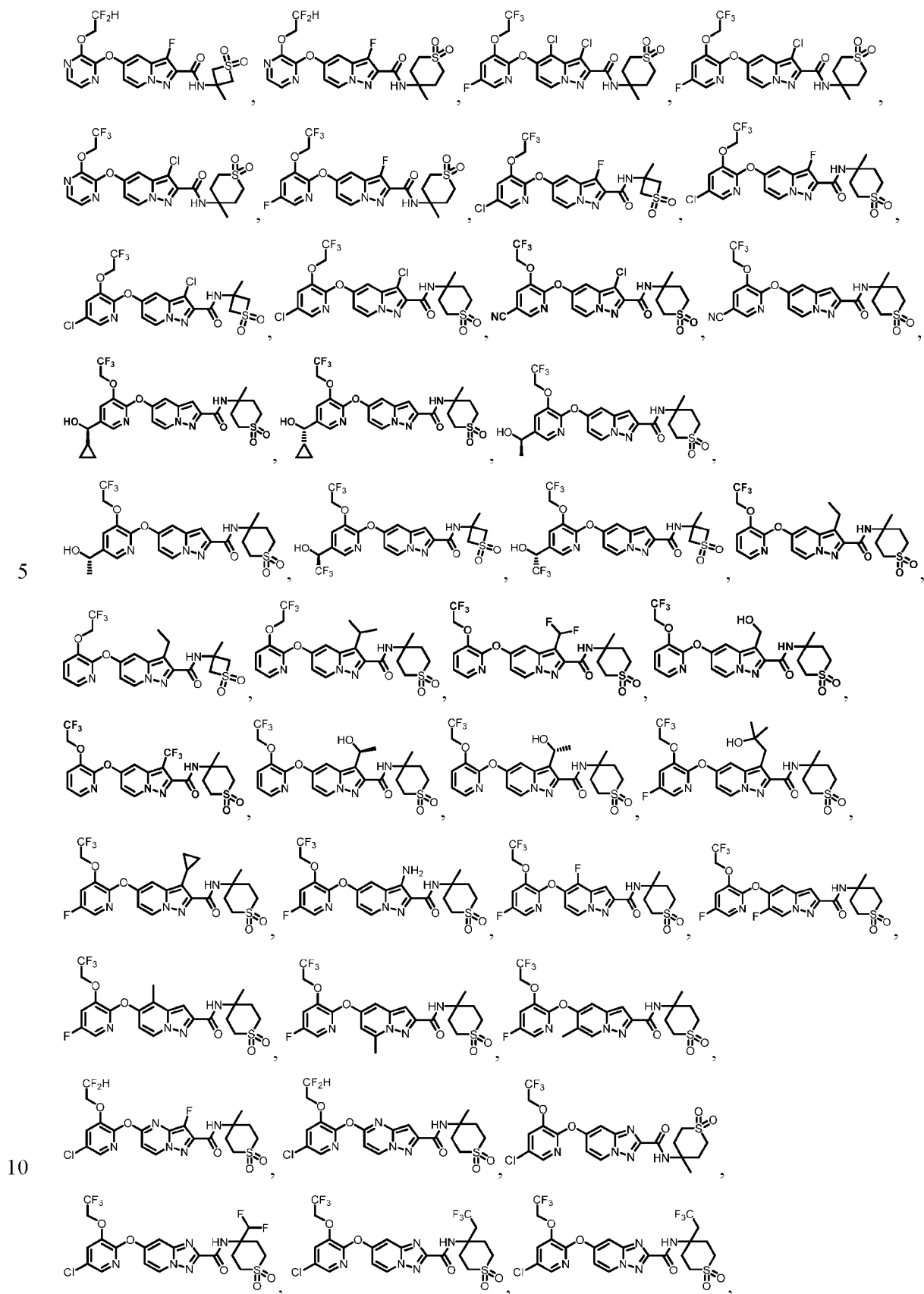
5-((6-Methoxypyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide,

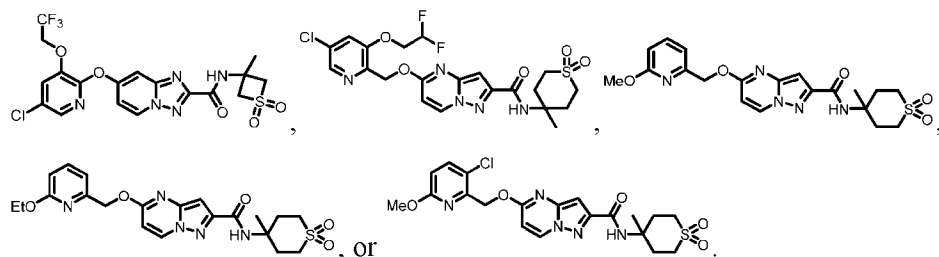
5-((6-Ethoxypyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide, or

5 5-((3-Chloro-6-methoxypyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-
thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide.

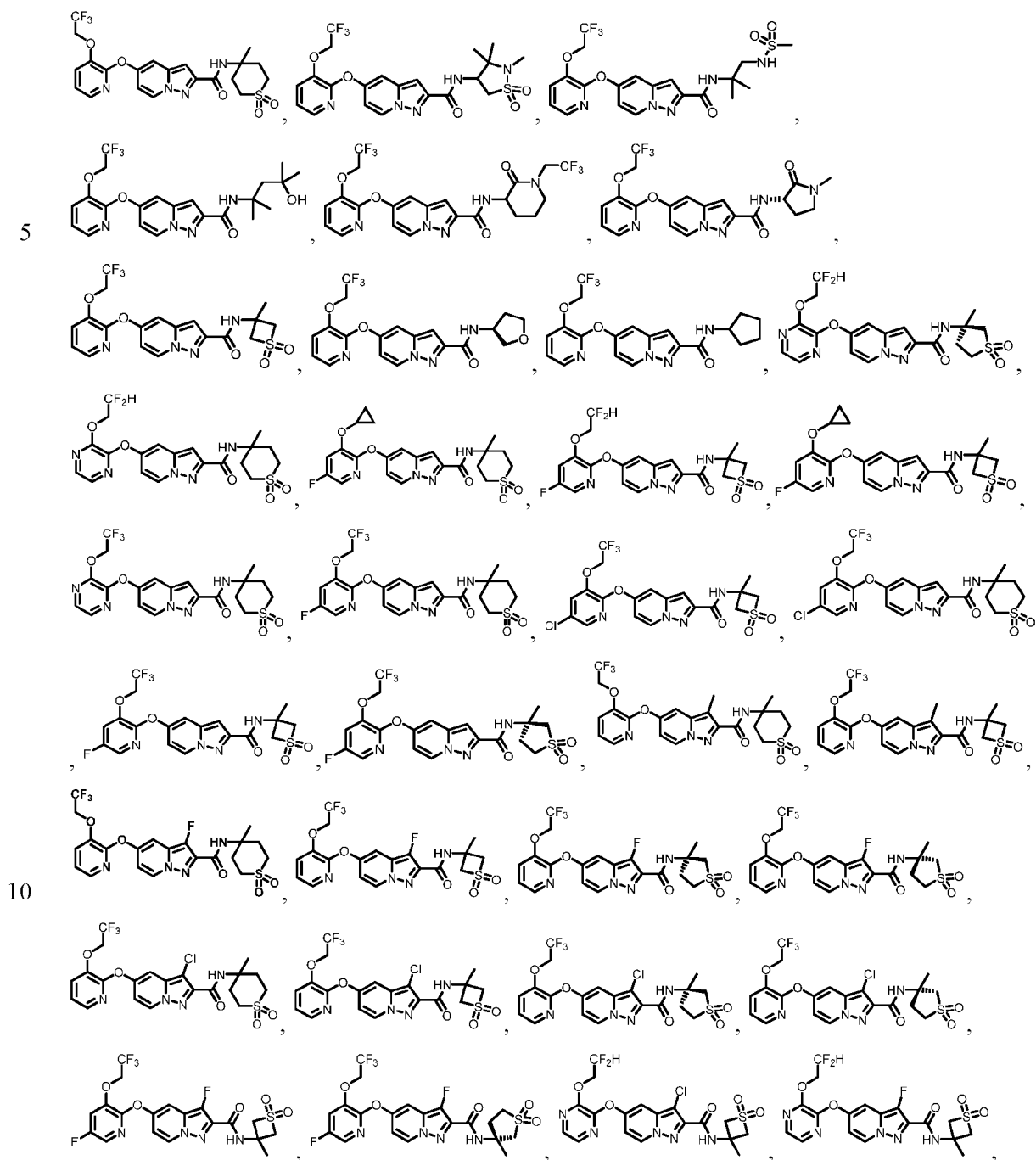
Embodiment 47, the compound of Formula I, Formula Ib, or Formula Ic or a pharmaceutically acceptable salt thereof, is:

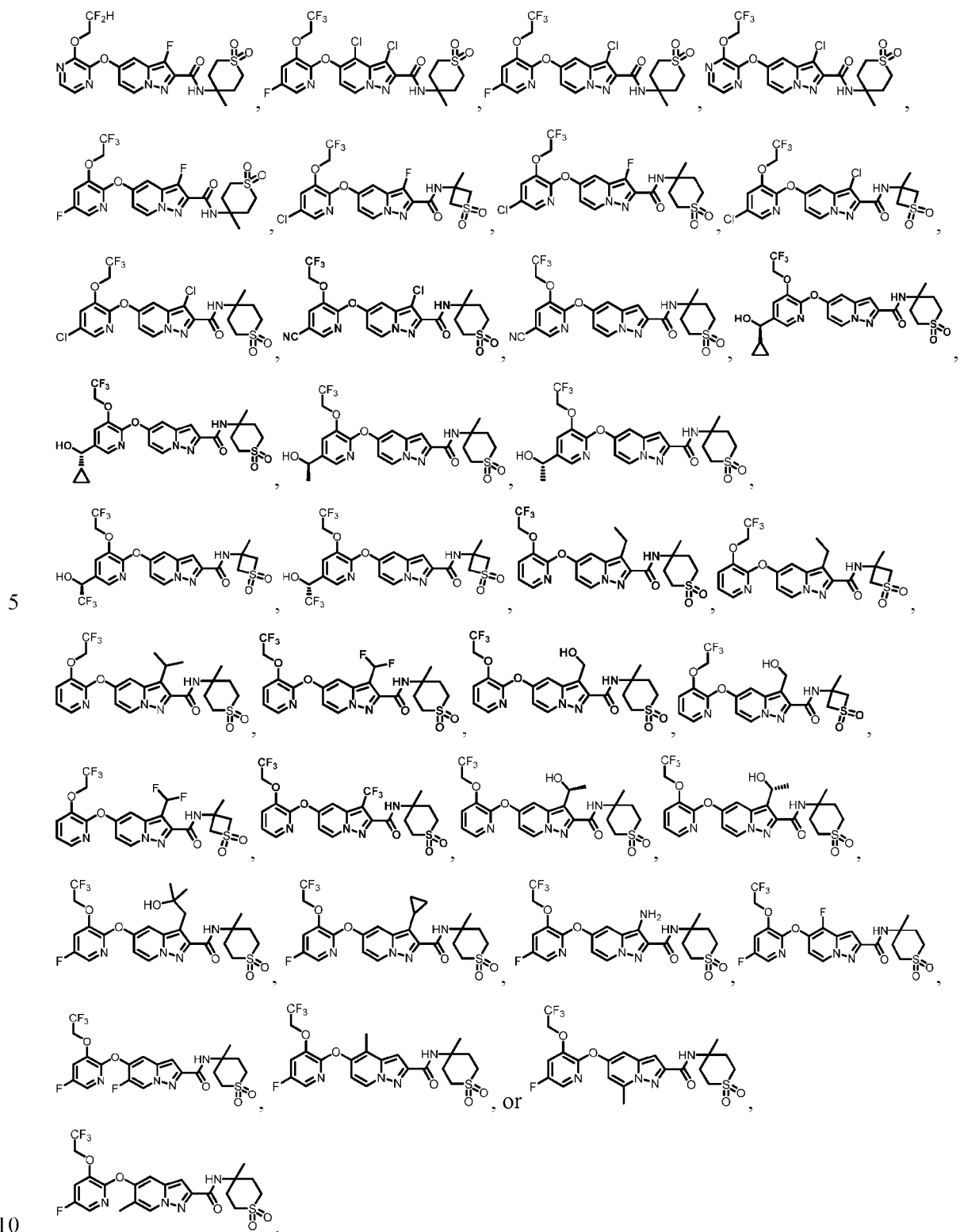




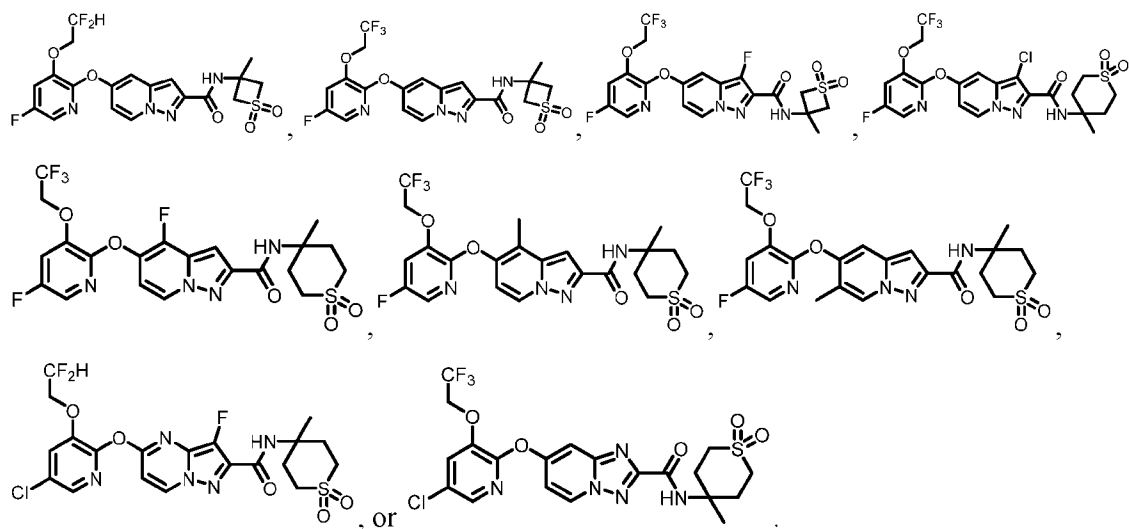


Embodiment 48, the compound of Formula Ib, or a pharmaceutically acceptable salt thereof, is:

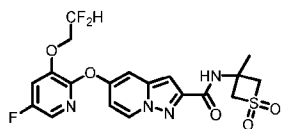




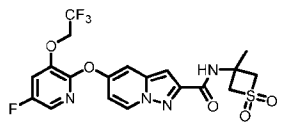
Embodiment 49 is a compound, or a pharmaceutically acceptable salt thereof, which is



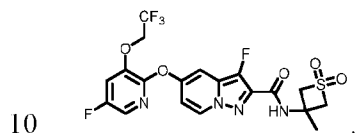
5 **Embodiment 50** is a compound, or a pharmaceutically acceptable salt thereof, which is



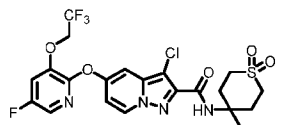
Embodiment 51 is a compound, or a pharmaceutically acceptable salt thereof, which is



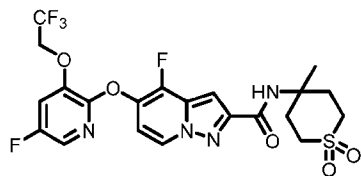
Embodiment 52 is a compound, or a pharmaceutically acceptable salt thereof, which is



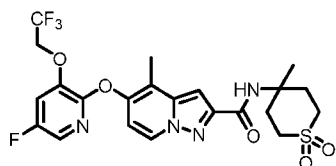
Embodiment 53 is a compound, or a pharmaceutically acceptable salt thereof, which is



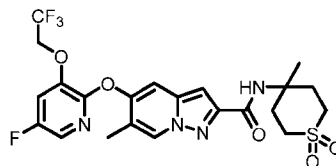
Embodiment 54 is a compound, or a pharmaceutically acceptable salt thereof, which is



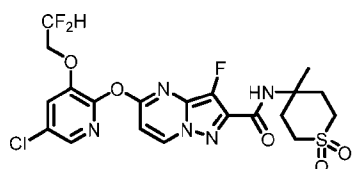
Embodiment 55 is a compound, or a pharmaceutically acceptable salt thereof, which is



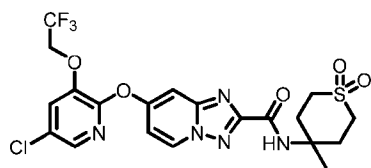
Embodiment 56 is a compound, or a pharmaceutically acceptable salt thereof, which is



5 **Embodiment 57** is a compound, or a pharmaceutically acceptable salt thereof, which is



Embodiment 58 is a compound, or a pharmaceutically acceptable salt thereof, which is



10 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, Formula Ib or Formula Ic, or a pharmaceutically acceptable salt thereof.

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

20 The disclosure also provides a pharmaceutical composition comprising an effective amount of at least one compound of Formula I, Formula Ib or Formula Ic, 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, Formula Ib or Formula Ic, 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,
5 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,
10 hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases such as chronic kidney diseases or heart failure, comprising a compound of Formula I, Formula Ib or Formula Ic, or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a composition for treating hepatic steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, type-2 diabetes mellitus, obesity,
15 hyperlipidemia, hypercholesterolemia, atherosclerosis, cognitive decline, dementia, cardiorenal diseases such as chronic kidney diseases or heart failure, comprising a compound of Formula I, Formula Ib or Formula Ic, 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,
20 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, Formula Ib or Formula Ic, 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
25 said patient a therapeutically effective amount of at least one compound of Formula I, Formula Ib or Formula Ic, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
30

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

5 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, Formula Ib or Formula Ic, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10 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, Formula Ib or Formula Ic, or a pharmaceutically acceptable salt thereof.

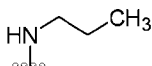
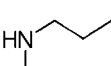
In another embodiment, the present disclosure includes a method of treating NASH and/or fibrosis, comprising administering to a patient in need thereof a composition comprising a compound of Formula I, Formula Ib or Formula Ic, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable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

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

20 In another embodiment, the present disclosure includes the use of a compound of Formula I, Formula Ib or Formula Ic, 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, 25 hexyl, octyl, nonyl, and the like. For example, the term "C₁₋₆alkyl" includes all of "C₁₋₄alkyl" defined as follows, plus the linear or branched chain alkyl groups, including all possible isomers, having 5 or 6 carbon atoms. "C₁₋₆alkyl" 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 C₁₋₆alkyl including each of the hexyl and pentyl isomers as well as *n*-, *iso*-, *sec*- and *tert*- 30 butyl (butyl, *i*-butyl, *s*-butyl, *t*-butyl, collectively "C₄alkyl"; Bu = butyl), *n*- and *i*-propyl (propyl, *i*-propyl, collectively "C₃alkyl"; 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 CH₃ or a symbol that is an

extended bond as the terminal group, e.g., " ξ —", ethyl may be represented by "Et" or CH_2CH_3 , propyl may be represented by "Pr" or $\text{CH}_2\text{CH}_2\text{CH}_3$, butyl may be represented by "Bu" or

$\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, etc. For example, the structures  and  have

equivalent meanings. If no number is specified, 1-6 carbon atoms are intended for linear or
5 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 wherein phenyl is fused to a C_{5-7} cycloalkyl or C_{5-7} cycloalkenyl 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.
10

"**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_{1-6} cycloalkyl" refers to a cycloalkyl group having 1 to 6 ring carbon atoms. The term " C_{3-6} cycloalkyl" refers to a cycloalkyl group having 3 to 6 ring carbon atoms. Thus, for example, " C_{3-6} 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
20 the alkyl group. The following are illustrations of -C_{3-6} cycloalkyl substituents on an alkyl group
25



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 ,

CF₃, CH₂CF₃, CH₂CHF₂, CF₂CF₃, CF₂CHF₂, CH₂Cl, CH₂CF₂CH₃ and CCl₃. The term “C₁₋₆haloalkyl” or “haloC₁₋₆alkyl” refers to a haloalkyl group having from 1 to 6 carbons.

“**Haloalkoxy**,” “haloalkyl-O” and derivatives such as “halo(C₁₋₆)alkoxy” or “O(C₁₋₆)haloalkyl” 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 OCH₂CF₃, OCH₂CHF₂, OCF₂CF₃, and OCF₂CHF₂.

“**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: piperidine, piperazine, morpholine, pyrrolidine, tetrahydrofuran, azetidine, oxirane, or aziridine, 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, indolaziny, 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(C₁₋₃)alkyl**” means an alkyl group having one or more hydrogen atoms replaced by hydroxyl (-OH) groups. An example includes CH(OH)CH₃, CHC(OH)(CH₃)₂ or CH₂OH.

“**Hydroxyhaloalkyl**” means an alkyl group having one or more hydrogen atoms replaced by hydroxyl (-OH) groups, and one or more hydrogen atoms replaced by a halogen substituent. An example includes CH(CF₃)OH.

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 invention is independent of the meaning with reference to the number of chemotherapeutic agents.

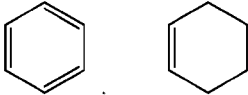
The term “**chemotherapeutic agent**” means a drug (medicament or pharmaceutically active ingredient) for treating cancer (i.e., an antineoplastic agent).

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 C₃ to C₆ monocyclic ring, e.g., C₃₋₆ 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



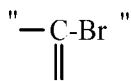
A "**stable**" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration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

The compounds of the present disclosure are limited to stable compounds embraced by Formula I, Formula Ib or Formula Ic and its embodiments. For example, certain moieties as defined in Formula I, Formula Ib or Formula Ic, 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.

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, Formula Ib or Formula Ic, acting as prodrugs and solvates. Any pharmaceutically acceptable pro-drug modification of a compound of the invention which results in conversion in vivo to a compound within the scope of the invention is also within the scope of the invention. Prodrugs, following
5 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, Formula Ib or Formula Ic. 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
10 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
15 the invention 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
20 pharmaceutically acceptable pro-drug modifications include, but are not limited to, -C₁₋₆alkyl esters and -C₁₋₆alkyl substituted with phenyl esters.

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

When any variable (e.g., R¹ etc.) occurs more than one time in any constituent or in Formula I, Formula Ib or Formula Ic or other generic Formula herein, its definition on each
25 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 the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e., R¹ etc., are to be chosen in conformity with well-known principles of chemical structure connectivity and stability. Unless expressly stated to the
30 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, Formula Ib or Formula Ic 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, Formula Ib or Formula Ic 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 of the invention, 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 invention.

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, Formula Ib or Formula Ic.

Compounds of structural Formula I, Formula Ib or Formula Ic 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, Formula Ib or Formula Ic, 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, Formula Ib or Formula Ic may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known absolute configuration. The present invention 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 diastereomeric 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, Formula Ib or Formula Ic 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, Formula Ib or Formula Ic of the present invention.

In the compounds of structural Formula I, Formula Ib or Formula Ic, 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, Formula Ib or Formula Ic, and embodiments thereof. For example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H , 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, Formula Ib or Formula Ic, 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, Formula Ib or Formula Ic, 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, Formula Ib or Formula Ic, 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 the present invention 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 this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts of basic compounds of the present invention 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, glycolylarsanilate, 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 the invention 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, Formula Ib or Formula Ic, form stable alkali metal, alkaline earth metal or optionally substituted ammonium salts.

5 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,
10 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
15 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, Formula Ib or Formula Ic, capable of salt formation, including their stereoisomeric forms is carried out known methods, for example, by mixing a compound of the present invention with an
20 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 present invention and salts thereof may form solvates with a solvent such as water, ethanol, or glycerol. The compounds of the present invention 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.

25 If the compounds of Formula I, Formula Ib or Formula Ic simultaneously contain acidic and basic groups in the molecule the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). Salts can be obtained from the compounds of Formula I, Formula Ib or Formula Ic 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
30 solvent or dispersant, or by anion exchange or cation exchange from other salts.

The present invention includes compounds of structural Formula I, Formula Ib or Formula Ic, 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 the present invention 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, Formula Ib or Formula Ic, including the Examples, are intended to be included within the scope of the present invention. In addition, some of the
5 compounds of the instant invention 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 invention, along with un-solvated and anhydrous forms.

Accordingly, the compounds within the generic structural formulas, embodiments and
10 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,

The invention also relates to medicaments containing at least one compound of the
15 Formula I, Formula Ib or Formula Ic, and/or of a pharmaceutically acceptable salt of the compound of the Formula I, Formula Ib or Formula Ic and/or an optionally stereoisomeric form of the compound of the Formula I, Formula Ib or Formula Ic, or a pharmaceutically acceptable salt of the stereoisomeric form of the compound of Formula I, Formula Ib or Formula Ic, together
20 with a pharmaceutically acceptable vehicle, carrier, additive and/or other active substances and auxiliaries.

The medicaments according to the invention can be administered by oral, inhalative, rectal or transdermal administration or by subcutaneous, intraarticular, intraperitoneal or intravenous injection. Oral administration is preferred.

The invention also relates to a process for the production of a medicament, which
25 comprises bringing at least one compound of the Formula I, Formula Ib or Formula Ic into a suitable administration form using a pharmaceutically acceptable carrier and optionally further suitable active substances, additives or auxiliaries.

The present invention also relates to processes for the preparation of the compounds of
30 Formula I, Formula Ib or Formula Ic which are described in the following and by which the compounds of the invention 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 invention 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, Formula Ib or Formula Ic 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, Formula Ib or Formula Ic and their pharmaceutically acceptable salts 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, Formula Ib or Formula Ic and their

pharmaceutically acceptable salts 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.

- 5 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
10 of need by a medical professional as well as the desire of a patient for such treatment.

Furthermore, a subject of the present invention are pharmaceutical preparations (or pharmaceutical compositions) which comprise as active component a therapeutically effective dose of at least one compound of Formula I, Formula Ib or Formula Ic and/or a pharmaceutically acceptable salt thereof and a customary pharmaceutically acceptable carrier, i.e., one or more
15 pharmaceutically acceptable carrier substances and/or additives.

Thus, a subject of the invention 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
20 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 according to the invention 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
25 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
30 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

5 lyophilize the compounds of Formula I, Formula Ib or Formula Ic and their pharmaceutically acceptable salts 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

10 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,

15 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

20 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, Formula Ib or Formula Ic and/or of a

25 pharmaceutically acceptable salt 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

30 acute or chronic or prophylactic, or on whether other active compounds are administered in addition to compounds of Formula I, Formula Ib or Formula Ic.

Combination Agents

The compounds of the present invention 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 the invention 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) 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) 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) 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) and any of the agents described above are administered a few minutes apart, or a few hours apart, or a few days apart.

As one aspect of the present invention contemplates the treatment of the disease/conditions with a combination of pharmaceutically active compounds that may be administered separately, the invention further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of Formula (I), 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, Formula Ib or Formula Ic. 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, Formula Ib or Formula Ic 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, Formula Ib or Formula Ic 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).

5 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
10 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
15 molecule renin inhibitors including diol sulfonamides and, N-morpholino derivatives, N-heterocyclic alcohols and pyroimidazolones; also, pepstatin derivatives and fluoro- and chloro-derivatives of statone-containing peptides, enalkrein, remikiren, A 65317, terlakiren, ES 1005, ES 8891, SQ 34017, SPP600, SPP630 and SPP635), endothelin receptor antagonists, phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil and vardenafil), vasodilators, calcium
20 channel blockers (e.g., amlodipine, nifedipine, verapamil, 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
25 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®),
30 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), NexletolTM (bempedoic acid, ACL inhibitor), and Vascepa® (Icosapent ethyl);

5 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) PPAR γ agonists, such as the glitazones (e.g., pioglitazone, AMG

10 131, mitoglitazone, lobeglitazone, rosiglitazone, and balaglitazone), and other PPAR ligands, including (1) PPAR α/γ dual agonists (e.g. ZYH2, ZYH1, GFT505, chiglitazar, muraglitazar, aleglitazar, sodelglitazar, and naveglitazar); (2) PPAR α agonists such as fenofibric acid derivatives (e.g., gemfibrozil, clofibrate, ciprofibrate, fenofibrate, bezafibrate), (3) selective PPAR γ modulators (SPPAR γ M's), (e.g., such as those disclosed in WO 02/060388, WO

15 02/08188, WO 2004/019869, WO 2004/020409, WO 2004/020408, and WO 2004/066963); (4) PPAR γ 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 GlumetzaTM, FortametTM, and GlucophageXRTM; and (iv) protein tyrosine phosphatase-1B (PTP-1B) inhibitors (e.g., ISIS-113715 and TTP814);

20 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

25 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

30 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 11 β -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, remogliflozin, 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 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., tiplukast), Bifunctional urate inhibitor (e.g., ACQT1127), adiponectin receptor agonist (e.g., ALY688), TNF receptor antagonist (e.g., atosimab), 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 $\alpha\beta$ 1, $\alpha\beta$ 3 and $\alpha\beta$ 6 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 $\alpha\beta$ 6 inhibitor (e.g., MORF beta6), NLRP inflammasome antagonists, siRNA (e.g., OLX 701), dual TFG β /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.,

5 TL012), 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., tirzepatide); dual GLP-1/GRA (e.g., cotadutide, ALT-801, DD 01, G49, PB-718); dual GLP-1

10 (e.g., CT 868); GLP-1/GRA/GIP triple agonist (e.g., HM15211); GRP120 stimulant/inflammasome modulator/PPARγ 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));

15 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),

20 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

25 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-

30 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 PPAR α/γ agonist (e.g., elafibranor), PPAR pan agonist (e.g., lanifibranor), PPAR α agonists (e.g., Parmodia), PPAR γ 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) includes the compounds of other generic structural Formulas, such as Formulas and embodiments that fall within the scope of Formula (I).

Dosages of the Compounds of Formula (I)

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 of the invention 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
5 treated and the response of the patient to the treatment.

The dosage regimen utilizing a compound of the instant invention 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
10 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,
15 *e.g.*, for prevention of an oncological condition.

While individual needs vary, determination of optimal ranges of effective amounts of the compound of the invention 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 the present invention can be about 0.05 mg/kg/day to about
20 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,
25 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
30 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, Formula Ib or Formula Ic and their pharmaceutically acceptable salts 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, Formula Ib or Formula Ic 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 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 of the invention 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, Formula Ib or Formula Ic, 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 the invention 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 invention. 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 invention.

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.

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

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.

The invention further relates to a method of treating hepatic cellular carcinoma in a human patient comprising administration of a compound of the invention (i.e., a compound of

Formula I, Formula Ib or Formula Ic) and a PD-1 antagonist to the patient. The compound of the invention 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 the instant invention, 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[®]); Alemtuzumab (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[®]);

5 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 (Erbix[®]); chlorambucil (Leukeran[®]); cisplatin (Platinol[®]); cladribine (Leustatin[®], 2-CdA[®]); clofarabine (Clolar[®]); cyclophosphamide

10 (Cytosan[®], Neosar[®]); cyclophosphamide (Cytosan Injection[®]); cyclophosphamide (Cytosan 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

15 (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

20 (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

25 (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

30 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 Present Invention

The following examples are provided so that the invention 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 this invention 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, Formula Ib or Formula Ic 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/MeCN = acetonitrile
- aq. = aqueous
- °C = degrees Celcius
- 5 B₂Pin₂ = bis(pinacolato)diboron
- Boc = *tert*-butoxycarbonyl
- CatAXium A Pd G2 = Chloro[(di(1-adamantyl)-*N*-butylphosphine)-2-(2-aminobiphenyl)]palladium(II)
- Cs₂CO₃ = cesium carbonate
- 10 CuI = copper iodide
- DCE = 1,2-dichloroethane
- DMF = dimethylformamide
- DCM = dichloromethane
- DIPEA = *N,N*-diisopropylethylamine
- 15 DMSO = dimethyl sulfoxide
- dppf = 1,1'-bis(diphenylphosphino)ferrocene
- Et = ethyl
- EtOAc = ethyl acetate
- FA = formic acid
- 20 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
- 25 HPLC = high pressure liquid chromatography
- Hex = hexanes
- IPA = isopropyl alcohol
- LCMS or LC/MS = liquid chromatography mass spectrometry
- K₂CO₃ = potassium carbonate
- 30 K₃PO₄ = potassium phosphate
- KOAc = potassium acetate
- Me = methyl
- MeOH = methanol
- Mn(TMHD)₃ = tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III)

- MnO₂ = Manganese(IV) oxide
MsCl = methanesulfonyl chloride
NaCl = sodium chloride
Na₂CO₃ = sodium carbonate
5 Na₂SO₄ = sodium sulfate
NBS = *N*-bromosuccinimide
NFSI = *N*-Fluorobenzenesulfonimide
NIS = *N*-Iodosuccinimide
NMO = *N*-methylmorpholine *N*-oxide
10 NMR = nuclear magnetic resonance
rt or RT = room temperature
SFC = supercritical fluid chromatography
THF = tetrahydrofuran
TFA = trifluoroacetic acid
15 TLC = thin layer chromatography
PE or pet. ether = petroleum ether
PhSiH₃ = phenylsilane
Pd₂(dba)₃ = tris(dibenzylideneacetone)dipalladium (0)
Pd(dppf)Cl₂ = bis(diphenylphosphino)ferrocene]dichloropalladium(II)
20 Pd(PPh₃)₂Cl₂ = Dichlorobis(triphenylphosphine)palladium(II)
RuPhos Pd G3 = (2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate
XPhos Pd G2 = Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)
25 Zn(OAc)₂ = zinc acetate
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
30 Soln. = solution

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

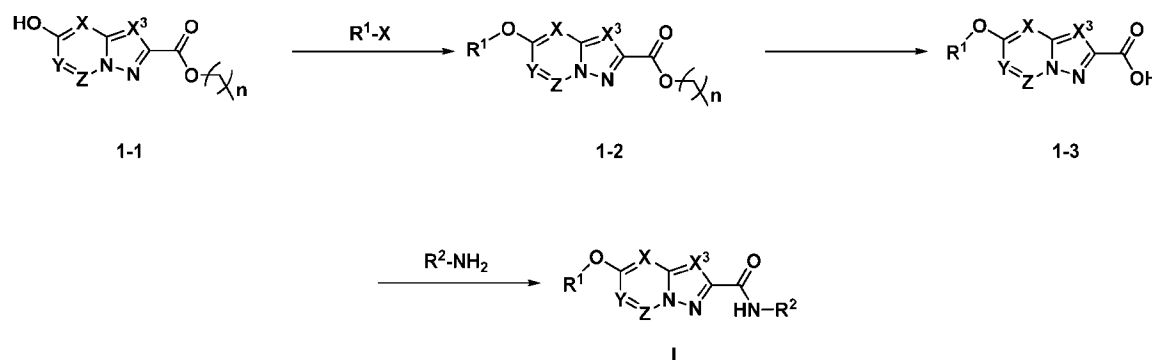
Solvent system: A: Water 0.1% FA, B: ACN 0.1% FA

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 invention.

General Scheme 1

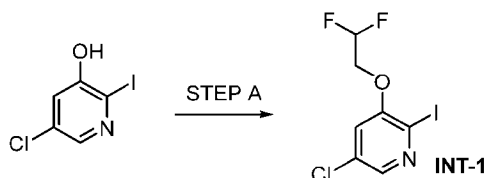


Compounds of the Formula I, Formula Ib or Ic were prepared from 1-1 with $\text{R}^1\text{-X}$ via $\text{S}_{\text{N}}2$, $\text{S}_{\text{N}}\text{Ar}$ or copper-mediated C-O coupling. Saponification of 1-2 provided the corresponding carboxylic acid (1-3) and subsequent amide coupling with the appropriate amines ($\text{R}^2\text{-NH}_2$) provided compounds of formula (I) as described by the general scheme. The order of steps for some examples may be varied to facilitate the syntheses.

INTERMEDIATES

Intermediate 1

5-Chloro-3-(2,2-difluoroethoxy)-2-iodopyridine



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

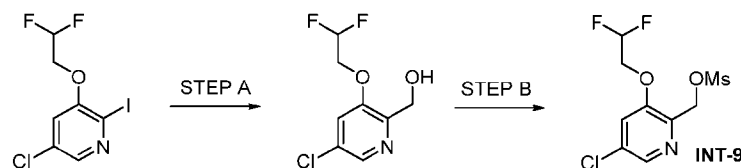
To a mixture of 5-chloro-2-iodopyridin-3-ol (2.7 g, 10.6 mmol) and K_2CO_3 (1.9 g, 13.7 mmol) in DMF (8.8 mL) was added 2,2-difluoroethyl trifluoromethanesulfonate (1.7 mL, 11.6 mmol) at 23 °C. After 1 h, the mixture was filtered over Celite and the filtrate was concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc in hexanes) to afford the title compound. LC/MS = 320 $[\text{M}+1]$.

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

Intermediate	Structure	Name	LCMS [M+1]
2		5-Chloro-2-iodo-3-(2,2,2-trifluoroethoxy)pyridine	338
3		5-Fluoro-2-iodo-3-(2,2,2-trifluoroethoxy)pyridine	322
4		2-Iodo-3-(2,2,2-trifluoroethoxy)pyridine	303
5		2-Bromo-3-(2,2,2-trifluoroethoxy)pyridine	256
6		2,5-Difluoro-3-(2,2,2-trifluoroethoxy)pyridine	214
7		5-Chloro-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine	229
8		2-Fluoro-3-(2,2,2-trifluoroethoxy)pyridine	196

Intermediate 9

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



STEP A: (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 .

10 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 23 °C. After 20 min, the mixture was diluted with saturated aqueous NH₄Cl 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 MgSO₄ (s), filtered, and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography (0-100% EtOAc in hexanes) to afford the title compound. LC/MS = 224 [M+1].

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

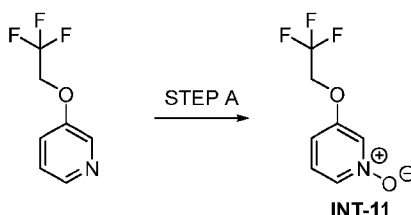
To a mixture of (5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methanol (0.10 g, 0.45 mmol) and triethylamine (0.14 mL, 0.98 mmol) in DCM (2.2 mL) was added MsCl (48.8 μL, 0.63 mmol) at – 78 °C. After 5 min, the mixture was warmed to 23 °C. After further 15 min, the mixture was diluted with saturated aqueous NaCl solution, and the aqueous layer was extracted once with DCM. The combined organic layers were dried over MgSO₄ (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 INT- 9 with appropriate reagents, the following intermediate was synthesized. This intermediate was characterized by LC/MS.

Intermediate	Structure	Name	LCMS [M+1]
10		(5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl methanesulfonate	304

Intermediate 11

3-(2,2,2-Trifluoroethoxy)pyridine 1-oxide



STEP A: 3-(2,2,2-Trifluoroethoxy)pyridine 1-oxide

To a mixture of 3-(2,2,2-trifluoroethoxy)pyridine (1.86 g, 10.5 mmol) in DCM (21.0 mL) was added 3-chloroperbenzoic acid (2.18 g, 12.6 mmol) at 23 °C. After 24 h, the mixture was diluted with saturated aqueous NaHCO₃ solution and DCM, and the organic layer was washed with water and brine. The organic layer was then dried over MgSO₄ (s), filtered, and concentrated in

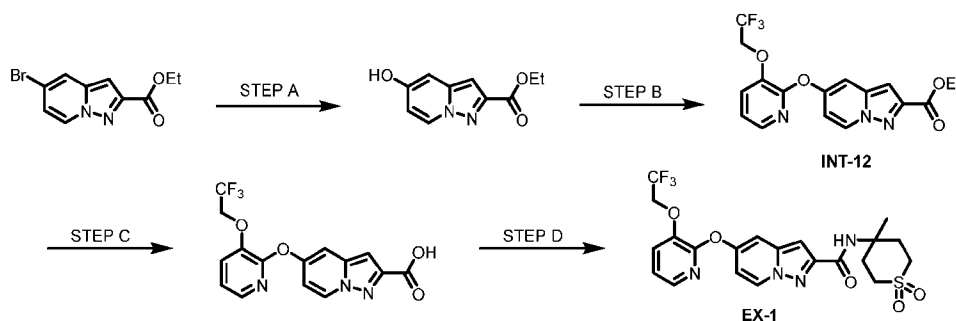
vacuo. The crude product was purified by flash silica gel column chromatography (0-10% methanol in DCM) to afford the title compound. LC/MS = 194 [M+1].

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

EXAMPLE 1: *N*-(4-Methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide



STEP A: Ethyl 5-hydroxypyrazolo[1,5-*a*]pyridine-2-carboxylate

To a stirred mixture of ethyl 5-bromopyrazolo[1,5-*a*]pyridine-2-carboxylate (2.00 g, 7.43 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.25 g, 16.72 mmol), Pd(dppf)Cl₂ (272 mg, 372 μmol), and potassium acetate (2.19 g, 22.30 mmol), was added dioxane (74.3 ml), and the reaction mixture was heated to 100 °C for 2 hrs. The reaction mixture was cooled down to RT and charged with water (535 μl, 29.7 mmol) and acetic acid (850 μl, 14.86 mmol), and the reaction mixture was stirred for 1 hour. Hydrogen peroxide (1.52 mL, 14.86 mmol) was added *via* syringe, and the reaction mixture stirred for an additional 16 hours. The reaction mixture was heated to 35 °C for a further 2 hrs followed by quenching with sodium thiosulfate (sat. aq. soln.). The crude mixture was dried over MgSO₄, filtered, and concentrated. The crude residue was subjected to silica gel flash column chromatography using a 0-7% methanol in DCM gradient to afford the title compound. LC/MS = 207 [M+1].

STEP B: Ethyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate

To a stirred solution of ethyl 5-hydroxypyrazolo[1,5-*a*]pyridine-2-carboxylate (600 mg, 2.91 mmol) and 3-(2,2,2-trifluoroethoxy)pyridine 1-oxide (590 mg, 3.06 mmol) in THF (14.5 mL) was added DIPEA (1.53 mL, 8.73 mmol) and bromotri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (PyBROP) (1.76 g, 3.78 mmol) sequentially. After 16 hours the solvent

was removed in vacuo, and the crude material was subjected to silica gel flash column chromatography using a 0-100% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 382 [M+1].

STEP C: Lithium 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate

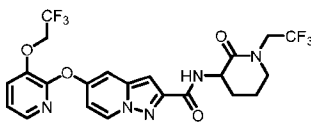
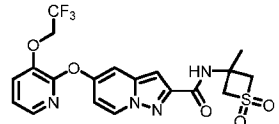
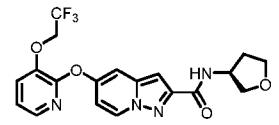
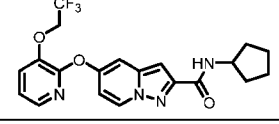
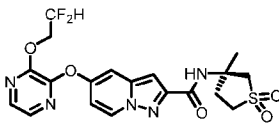
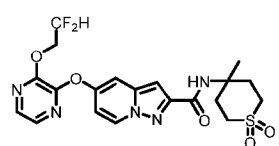
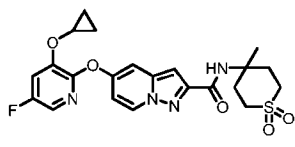
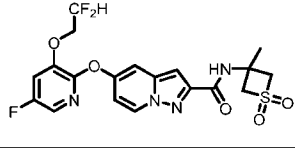
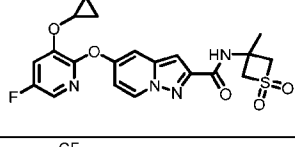
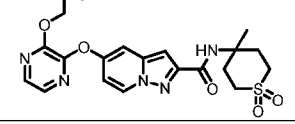
To a stirred solution of ethyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (594 mg, 1.56 mmol) in acetonitrile (8.74 mL) and water (4.37 mL) was added lithium hydroxide (37.3 mg, 1.56 mmol) at 20 °C. After 30 minutes the reaction mixture was concentrated in vacuo, and the crude material was used in subsequent reactions without further purification. LC/MS = 354 [M-5].

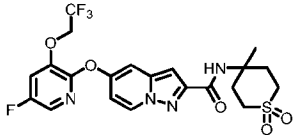
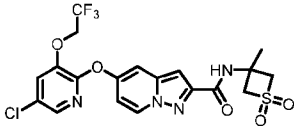
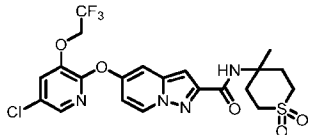
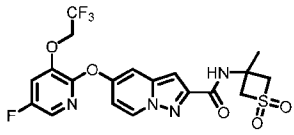
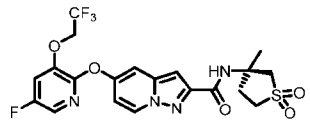
STEP D: *N*-(4-Methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred solution of lithium 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (400 mg, 1.11 mmol), DIPEA (584 µl, 3.34 mmol) and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (234 mg, 1.17 mmol) in DMF (11.1 mL) was added HATU (445 mg, 1.17 mmol). After 18 hours the solvent was removed in vacuo, and the crude mixture was subjected to silica gel flash column chromatography using a 0-100% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 499 [M+1]. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.72 (d, *J* = 7.6 Hz, 1H), 7.99 (s, 1H), 7.88 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 2.5 Hz, 1H), 7.27 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.96 – 6.86 (m, 2H), 4.93 (q, *J* = 8.8 Hz, 2H), 3.09 (d, *J* = 11.6 Hz, 4H), 2.83 (d, *J* = 14.4 Hz, 2H), 2.03 (t, *J* = 10.6 Hz, 2H), 1.45 (s, 3H). Human DGAT2 IC₅₀ = 9.7 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.

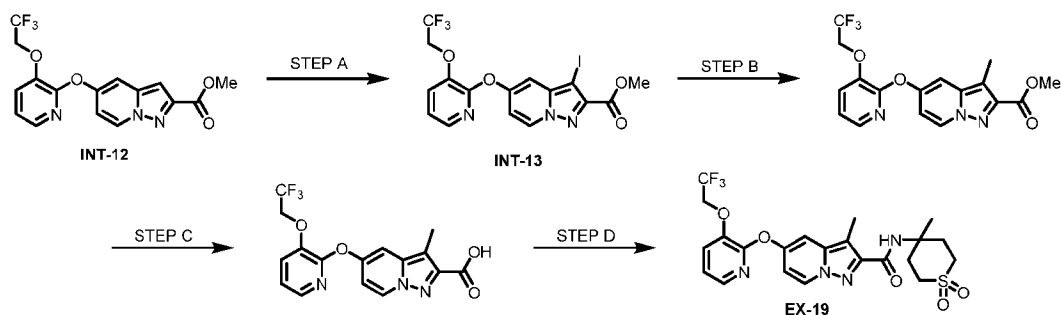
Example	Structure	Name	LCMS [M+1]	Human DGAT2 IC ₅₀ (nM)
2		5-((3-(2,2,2-Trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(2,3,3-trimethyl-1,1-dioxidoisothiazolidin-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide (rac)	514	787
3		<i>N</i> -(2-Methyl-1-(methylsulfonamido)propan-2-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-	502	694

		yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide		
4		<i>N</i> -(2-Oxo-1-(2,2,2-trifluoroethyl)piperidin-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	532	309
5		<i>N</i> -(3-Methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	471	149
6		(<i>S</i>)- <i>N</i> -(Tetrahydrofuran-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	423	>9990
7		<i>N</i> -Cyclopentyl-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	421	1074
8		(<i>R</i>)-5-((3-(2,2-Difluoroethoxy)pyrazin-2-yl)oxy)- <i>N</i> -(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	468	211
9		5-((3-(2,2-Difluoroethoxy)pyrazin-2-yl)oxy)- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	482	2.3
10		5-((3-Cyclopropoxy-5-fluoropyridin-2-yl)oxy)- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	475	85
11		5-((3-(2,2-Difluoroethoxy)-5-fluoropyridin-2-yl)oxy)- <i>N</i> -(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	471	2.5
12		5-((3-Cyclopropoxy-5-fluoropyridin-2-yl)oxy)- <i>N</i> -(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	447	1802
13		<i>N</i> -(4-Methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyrazin-2-	500	17

		yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide		
14		5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	517	1.9
15		5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	505	2.5
16		5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	533	1.1
17		5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	489	72
18		(<i>R</i>)-5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	503	33

EXAMPLE 19

EXAMPLE 21: 3-Methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide



STEP A: Ethyl 5-hydroxypyrazolo[1,5-*a*]pyridine-2-carboxylate

To a stirred solution of methyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (400 mg, 1.09 mmol) in DCE (3.63 mL) was added NIS (294 mg, 1.31

mmol), and the reaction mixture was allowed to stir at 50 °C for 1 hr. The reaction mixture was subjected to silica gel flash column chromatography using a 0-70% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 494 [M+1].

STEP B: Ethyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate

At 20 °C, a screw cap vial containing a magnetic stir bar, methyl 3-iodo-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (187 mg, 379 μmol), trifluoro(methyl)-14-borane potassium salt (55.5 mg, 455 μmol), RuPhos Pd G3 (29.5 mg, 38 μmol), and Cs₂CO₃ (445 mg, 1.37 mmol) was charged with toluene (3.45 mL) and water (345 μl) under nitrogen. The reaction mixture was heated to 80 °C for 16 hrs. The reaction mixture was again charged with trifluoro(methyl)-14-borane, potassium salt (55.5 mg, 455 μmol), Cs₂CO₃ (445 mg, 1.37 mmol), and CatAXium A Pd G2 (25.4 mg, 38 μmol). The reaction mixture was heated to 80 °C for 16 hrs. The reaction mixture was cooled down to RT, diluted with EtOAc, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude residue was subjected to silica gel flash column chromatography using a 0-60% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 382 [M+1].

STEP C: Lithium 3-methyl-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate

To a stirred solution of methyl 3-methyl-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (109 mg, 286 μmol) in THF (1.63 mL), methanol (817 μl), and water (408 μl) was added lithium hydroxide (6.85 mg, 286 μmol) at 20 °C. After 2 hrs, the reaction mixture was concentrated in vacuo to afford the crude title compound. LC/MS = 368 [M-5].

STEP D: 3-Methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred solution of lithium 3-methyl-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (30 mg, 80 μmol), DIPEA (35.1 μl, 0.20 mmol) and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (16.05 mg, 80 μmol) in DMF (804 μl) was added HATU (32.1 mg, 84 μmol). After 18 hrs, the reaction mixture was filtered, and the filtrate was purified by reverse phase HPLC (40-95% MeCN/water with 0.1% FA modifier) to afford the title compound. LC/MS = 513 [M+1]. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.65 (d, *J* = 7.6 Hz, 1H), 7.91 (s, 1H), 7.87 – 7.81 (m, 1H), 7.75 – 7.68 (m, 1H), 7.46 (d, *J* = 2.5 Hz, 1H), 7.24 (dd, *J* = 8.0, 4.9 Hz, 1H), 6.86 (dd, *J* = 7.5, 2.5 Hz, 1H), 4.93 (q, *J* = 8.8 Hz,

2H), 3.15 – 3.04 (m, 4H), 2.82 (d, J = 14.0 Hz, 2H), 2.38 (s, 3H), 2.07 – 1.98 (m, 2H), 1.46 (s, 3H). Human DGAT2 IC₅₀ = 7.2 nM.

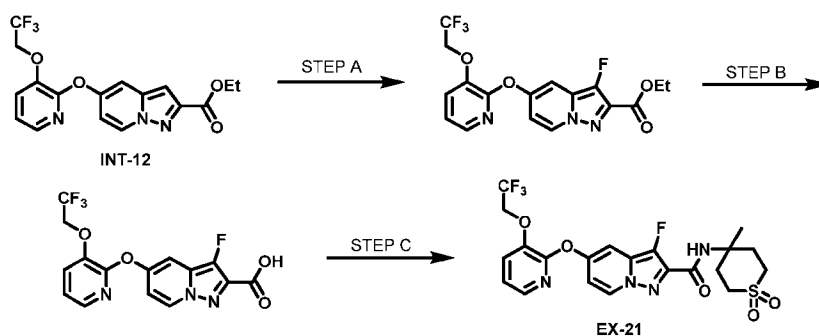
By using procedures similar to those described in **Example 19** with appropriate reagents, the following compound was synthesized. This compound was characterized by LC/MS.

Example	Structure	Name	LCMS [M+1]	Human DGAT2 IC ₅₀ (nM)
20		3-Methyl-N-(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxamide	485	171

5

EXAMPLE 21

EXAMPLE 23: 3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide



10 **STEP A:** Ethyl 5-hydroxypyrazolo[1,5-a]pyridine-2-carboxylate

To a stirred solution of methyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate (175 mg, 476 μmol) in acetonitrile (2.38 mL) was added Selectfluor™ (186 mg, 524 μmol) in a single portion at 0 °C. After 1h the reaction mixture was warmed to 20 °C and stirred for an additional 4 hrs. The reaction mixture was filtered through a plug of SiO₂, concentrated *in vacuo*, and subjected to silica gel flash column chromatography using a 0-80% ethyl acetate in hexanes gradient to afford the desired product as a white solid. LC/MS = 386 [M+1].

15 **STEP B:** Lithium 3-fluoro-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate

20 To a stirred solution of methyl 3-fluoro-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate (74 mg, 192 μmol) in acetonitrile (1.60 ml) and water (320 μl) was added lithium hydroxide (4.60 mg, 192 μmol) at 20 °C. After 30 minutes the

reaction mixture was concentrated *in vacuo* to afford the crude title compound. LC/MS = 378 [M-5].

STEP C: 3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

- 5 To a stirred solution of lithium 3-fluoro-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (19 mg, 50 μ mol), DIPEA (22.00 μ l, 126 μ mol) and 4-amino-4-methyltetrahydro-2H-thiopyran 1,1-dioxide hydrochloride (10.06 mg, 50 μ mol) in DMF (504 μ l) was added HATU (20.11 mg, 53 μ mol) at 20 °C. After 18 hrs, the reaction mixture was filtered, and the filtrate purified by reverse phase HPLC (40-80% MeCN/water with
- 10 0.1% FA modifier) to afford the title compound. LC/MS = 517 [M+1]. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.64 (d, *J* = 7.6 Hz, 1H), 8.09 (s, 1H), 7.88 (dd, *J* = 4.8, 1.3 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.28 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.94 (dd, *J* = 7.6, 2.6 Hz, 1H), 4.93 (q, *J* = 8.8 Hz, 2H), 3.16 – 3.03 (m, 4H), 2.79 (d, *J* = 14.4 Hz, 2H), 2.03 (t, *J* = 11.0 Hz, 2H), 1.46 (s, 3H). Human DGAT2 IC₅₀ = 13 nM.
- 15 By using procedures similar to those described in **Example 21** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

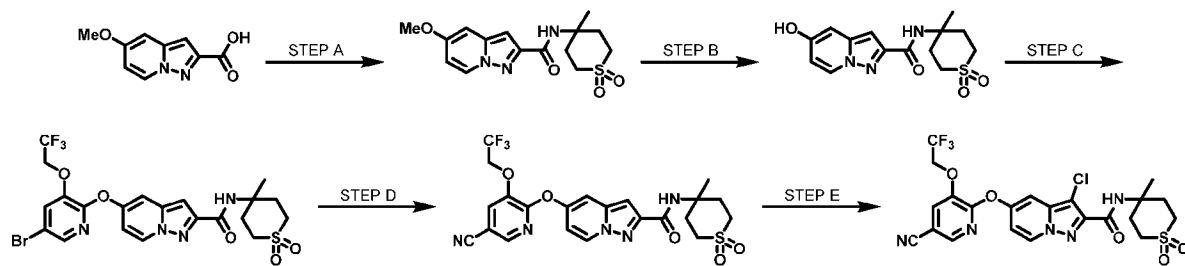
Example	Structure	Name	LCMS [M+1]	Human DGAT2 IC ₅₀ (nM)
22		3-Fluoro-N-(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	489	372
23		(<i>R</i>)-3-Fluoro-N-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	503	817
24		3-Chloro-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	533	9.4
25		3-Chloro-N-(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	505	30

26		(<i>R</i>)-3-Chloro- <i>N</i> -(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	519	388
27		(<i>S</i>)-3-Chloro- <i>N</i> -(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	519	400
28		3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	507	129
29		(<i>R</i>)-3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	521	277
30		3-Chloro-5-((3-(2,2-difluoroethoxy)pyrazin-2-yl)oxy)- <i>N</i> -(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	488	78
31		5-((3-(2,2-difluoroethoxy)pyrazin-2-yl)oxy)-3-fluoro- <i>N</i> -(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	472	194
32		5-((3-(2,2-difluoroethoxy)pyrazin-2-yl)oxy)-3-fluoro- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	500	10
33		3,4-Dichloro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	586	8.8
34		3-Chloro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	551	7.3

		4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide		
35		3-Chloro- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyrazin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	534	18
36		3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	535	7.3
37		5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-fluoro- <i>N</i> -(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	523	7.7
38		5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-fluoro- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	551	0.5
39		3-Chloro-5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	540	2.3
40		3-Chloro-5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	568	1.6

EXAMPLE 41

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



EX-41

STEP A: 5-Methoxy-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred solution of 5-methoxypyrazolo[1,5-*a*]pyridine-2-carboxylic acid (2000 mg, 10.41 mmol), DIPEA (4544 μ l, 26.0 mmol) and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (2078 mg, 10.41 mmol) in DMF (52 mL) was added HATU (4155 mg, 10.93 mmol). After 18 hrs, the solvent was removed in vacuo, and the reaction mixture was subjected to silica gel flash column chromatography using a 0-100% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 338 [M+1].

STEP B: 5-Hydroxy-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred mixture of 5-methoxy-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (2.00 g, 5.93 mmol) and lithium chloride (2.51 g, 59.3 mmol) was added NMP (11.9 mL), and the reaction mixture was heated to 160 °C under a gentle stream of nitrogen. After 16 hours the reaction mixture was poured into HCl (1M aq. soln.) and extracted with DCM. The combined organic fractions were washed with HCl (1M aq. soln.) and NaCl (sat. aq. soln.), dried over MgSO₄, filtered, and concentrated in vacuo. The crude residue was subjected to silica gel flash column chromatography using a 0-7% methanol in DCM gradient to afford the title compound. LC/MS = 324 [M+1].

STEP C: 5-((5-Bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred solution of 5-hydroxy-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (100 mg, 309 μ mol) and CsCO₃ (252 mg, 773 μ mol) in DMF (1.5 mL) was added 5-bromo-2-fluoro-3-(2,2,2-trifluoroethoxy)pyridine (102 mg, 371 μ mol) and the reaction mixture was heated to 60 °C for 16 hrs. The reaction mixture was concentrated in vacuo, and the crude residue was purified via silica gel flash column chromatography using a 0-80% EtOAc in hexanes gradient to afford the title compound. LC/MS = 577 [M+1].

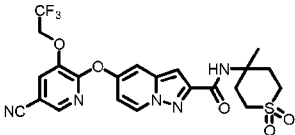
STEP D: 5-((5-Cyano-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred mixture of 5-((5-bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (85 mg, 147 μ mol), dicyanozinc (9.51 mg, 81 μ mol), and Pd(PPh₃)₄ (17.01 mg, 15 μ mol) was added DMF (736 μ l), and the reaction mixture was heated to 80 °C for 16 hrs. The reaction mixture was concentrated in vacuo and the crude residue was purified via silica gel flash column

chromatography using a 0-80% EtOAc in hexanes gradient to afford the title compound. LC/MS = 524 [M+1].

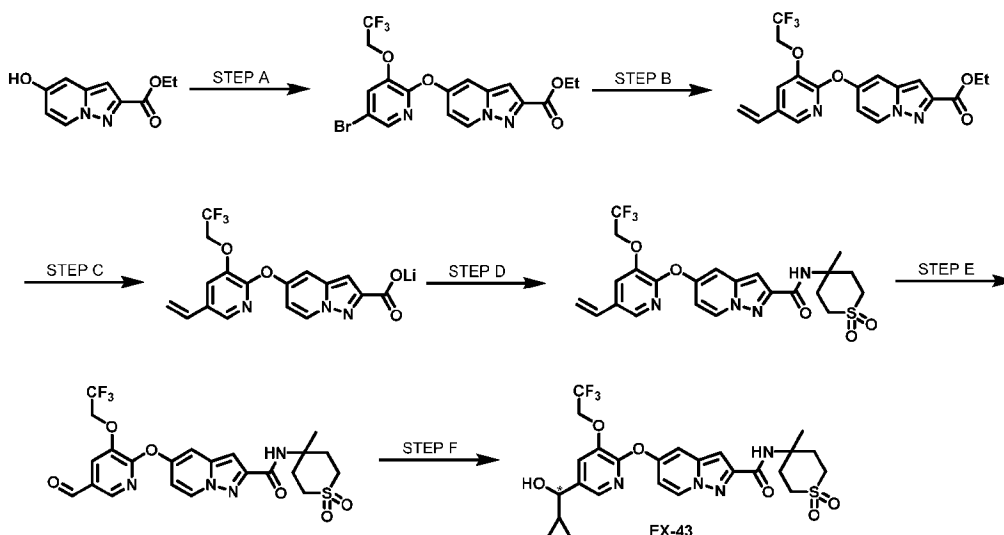
STEP E: 3-Chloro-5-((5-cyano-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

- 5 To a stirred solution of 5-((5-cyano-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (30 mg, 57 μ mol) in DCE (287 μ l) was added 1-chloropyrrolidine-2,5-dione (9.18 mg, 69 μ mol), and the reaction mixture was allowed to stir at 70 °C for 6 hrs. After cooled down to RT, the reaction mixture was concentrated and subjected to silica gel flash column chromatography using a 0-70% ethyl
- 10 acetate in hexanes gradient to afford the title compound. LC/MS = 558 [M+1]. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.85 (d, *J* = 7.5 Hz, 1H), 8.37 (d, *J* = 1.7 Hz, 1H), 8.27 – 8.20 (m, 2H), 7.62 (d, *J* = 2.5 Hz, 1H), 7.11 (dd, *J* = 7.5, 2.5 Hz, 1H), 5.02 (q, *J* = 8.7 Hz, 2H), 3.18 – 3.03 (m, 4H), 2.76 (d, *J* = 14.6 Hz, 2H), 2.03 (t, *J* = 11.4 Hz, 2H), 1.47 (s, 3H). Human DGAT2 IC₅₀ = 5.0 nM.
- 15 By using procedures similar to those described in **Example 41** with appropriate reagents, the following compound was synthesized. This compound was characterized by LC/MS.

Example	Structure	Name	LCMS [M+1]	Human DGAT2 IC ₅₀ (nM)
42		5-((5-Cyano-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	524	20

EXAMPLE 43

5-((5-(Cyclopropyl(hydroxy)methyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide



STEP A: Ethyl 5-((3-(2,2,2-trifluoroethoxy)-5-bromopyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate

To a stirred solution of ethyl 5-hydroxypyrazolo[1,5-a]pyridine-2-carboxylate (300 mg, 1.46 mmol) and Cs₂CO₃ (1.19 g, 3.64 mmol) in DMF (7.3 mL) was added 5-bromo-2-fluoro-3-
 5 (2,2,2-trifluoroethoxy)pyridine (598 mg, 2.18 mmol), and the reaction mixture was heated to 60 °C for 16 hrs. The reaction mixture was concentrated in vacuo, and the crude residue was purified via silica gel flash column chromatography using a 0-80% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 461 [M+1].

STEP B: Ethyl 5-((3-(2,2,2-trifluoroethoxy)-5-vinylpyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate

At 20 °C, a stirred solution of ethyl 5-((5-bromo-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate (278 mg, 604 μmol), EtOH (4.0 mL) and triethylamine (126 μL, 906 μmol) was sparged with nitrogen for 15 minutes. The vial was charged with Pd(dppf)Cl₂ (22.10 mg, 30 μmol), sealed, and heated at 85 °C. After 16 hrs, the
 15 reaction was filtered through a plug of SiO₂ and concentrated in vacuo. The crude residue was subjected to silica gel flash column chromatography using a 0-90% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 408 [M+1].

STEP C: Lithium 5-((3-(2,2,2-trifluoroethoxy)-5-vinylpyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate

To a stirred solution of ethyl 5-((3-(2,2,2-trifluoroethoxy)-5-vinylpyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate (184 mg, 452 μmol) in acetonitrile (6.0 mL) and water (3.0 mL) was added lithium hydroxide (10.82 mg, 452 μmol). After 30 minutes the reaction mixture was concentrated in vacuo to afford the crude title compound. LC/MS = 386 [M-5].

STEP D: Ethyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate

To a stirred solution of lithium 5-((3-(2,2,2-trifluoroethoxy)-5-vinylpyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (87 mg, 226 μ mol), DIPEA (99 μ l, 565 μ mol) and
5 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (45.1 mg, 226 μ mol) in DMF (2.3 mL) was added HATU (90 mg, 237 μ mol). After 18 hrs, solvent was removed *in vacuo* and the crude mixture was subjected to silica gel flash column chromatography using a 0-80% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 525 [M+1].

STEP E: 5-((5-Formyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred solution of *N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)-5-vinylpyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide (118 mg, 225 μ mol), 2,6-dimethylpyridine (52.1 μ l, 450 μ mol) and potassium tetrahydroxydioxidoosmium (2.1 mg, 5.62 μ mol) in 1,4-Dioxane (1.5 mL) and water (3.0 mL) was added sodium periodate (192
15 mg, 900 μ mol) at 0 °C. The reaction mixture was stirred at 20 °C for 3 hrs then diluted with NaCl (sat. aq. soln.) and extracted with ethyl acetate. The combined organic fractions were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude material was subjected to silica gel flash column chromatography using a 0-90% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 527 [M+1].

STEP F: 5-((5-(Cyclopropyl(hydroxy)methyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

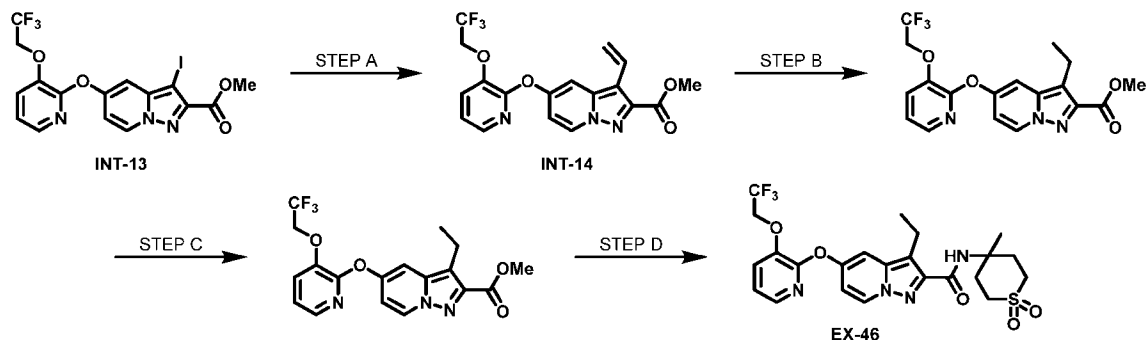
To a stirred solution of 5-((5-formyl-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (20 mg, 38 μ mol) in THF (380 μ l) was added cyclopropylmagnesium bromide (228 μ l, 114 μ mol) at 0 °C. After 6
25 hrs the reaction mixture was quenched with NaHCO₃ (sat. aq. soln.), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude material was purified by reverse phase HPLC (20% MeOH/water with 0.1% FA modifier) to afford the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.71 (d, *J* = 7.6 Hz, 1H), 7.99 (s, 1H), 7.87 (d, *J* = 1.5 Hz, 1H), 7.74 (s, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 6.94 – 6.87 (m, 2H), 5.42 (d, *J* = 4.4 Hz, 1H), 4.93 (q, *J* = 8.8 Hz, 2H), 4.01 (dd, *J* = 7.5, 4.5 Hz, 1H), 3.09 (d, *J* = 11.4 Hz, 4H), 2.83 (d, *J* = 14.4 Hz, 2H), 2.04 (d, *J* = 11.3 Hz, 2H), 1.45 (s, 3H), 1.16 – 1.07 (m, 1H), 0.56 – 0.33 (m, 4H). **EX-43a** (Faster eluting in IB-N column, 20% MeOH/CO₂): LC/MS = 569 [M+1]. Human DGAT2 IC₅₀ = 228 nM. **EX-43b** (Slower eluting in IB-N column, 20% MeOH/CO₂): LC/MS = 569 [M+1]. Human DGAT2 IC₅₀ >9990 nM.

By using procedures similar to those described in **Example 43a and 43b** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

Example	Structure	Name	LCMS [M+1]	Human DGAT2 IC ₅₀ (nM)
44a		5-((5-(1-Hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide (Faster eluting in IB-N column, 20% MeOH/CO ₂)	543	111
44b		5-((5-(1-Hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide (Slower eluting in IB-N column, 20% MeOH/CO ₂)	543	332
45a		<i>N</i> -(3-Methyl-1,1-dioxidothietan-3-yl)-5-((5-(2,2,2-trifluoro-1-hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide (Faster eluting in IB-N column, 20% MeOH/CO ₂)	569	>9990
45b		<i>N</i> -(3-Methyl-1,1-dioxidothietan-3-yl)-5-((5-(2,2,2-trifluoro-1-hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide (Slower eluting in IB-N column, 20% MeOH/CO ₂)	569	1562

EXAMPLE 46

3-Ethyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide



STEP A: Methyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-vinylpyrazolo[1,5-*a*]pyridine-2-carboxylate

At 20 °C, a stirred solution of methyl 3-iodo-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (100 mg, 203 μmol), EtOH (1.35 ml) and triethylamine (42 μl, 304 μmol) was sparged with nitrogen for 15 minutes. The vial was charged with Pd(dppf)Cl₂ (7.42 mg, 10.14 μmol), sealed, and heated at 85 °C. After 16 hrs the reaction mixture was filtered through a plug of SiO₂ and concentrated in vacuo. The crude residue was subjected to silica gel flash column chromatography using a 0-90% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 394 [M+1].

STEP B: Ethyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate

To a stirred solution of methyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-vinylpyrazolo[1,5-*a*]pyridine-2-carboxylate (56 mg, 142 μmol) in ethanol (1.4 mL) under nitrogen was added hydrogen (balloon). The reaction mixture was sparged with hydrogen for 3 minutes and allowed to stir at 20 °C for 1 hr. The reaction mixture was sparged with argon for 5 minutes, diluted with DCM, filtered through celite, and concentrated in vacuo to afford the title compound. LC/MS = 396 [M+1].

STEP C: Lithium 3-ethyl-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate

To a stirred solution of methyl 3-ethyl-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (56 mg, 142 μmol), in acetonitrile (1.9 mL) and water (944 μl) was added lithium hydroxide (3.39 mg, 142 μmol) and the reaction mixture was allowed to stir at 40 °C. After 2 hrs, the reaction mixture was concentrated in vacuo to afford the crude title compound. LC/MS = 388 [M-5].

STEP D: 3-Ethyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred solution of lithium 3-ethyl-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (27 mg, 70 μmol), DIPEA (30.4 μl, 174 μmol) and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (13.92 mg, 70 μmol) in DMF (697 μl) was added HATU (27.8 mg, 73 μmol). After 18 hrs, the reaction mixture was filtered, and the filtrate purified by reverse phase HPLC (30-70% MeCN/water with 0.1% FA modifier) to afford the title compound. LC/MS = 527 [M+1]. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.65 (d, *J* = 7.6 Hz, 1H), 7.93 (s, 1H), 7.84 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 2.5 Hz, 1H), 7.24 (dd, *J* = 8.0, 4.9 Hz, 1H), 6.85 (dd, *J* = 7.6, 2.6 Hz, 1H), 4.93 (q, *J* = 8.8 Hz, 2H), 3.14 – 3.04 (m, 4H), 2.88 (q, *J* = 7.3 Hz, 2H), 2.82 (d, *J* = 14.1 Hz, 2H), 2.03 (dt, *J* = 14.7, 7.2 Hz, 2H), 1.46 (s, 3H), 1.13 (t, *J* = 7.4 Hz, 3H). Human DGAT2 IC₅₀ = 17 nM.

By using procedures similar to those described in **Example 46** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

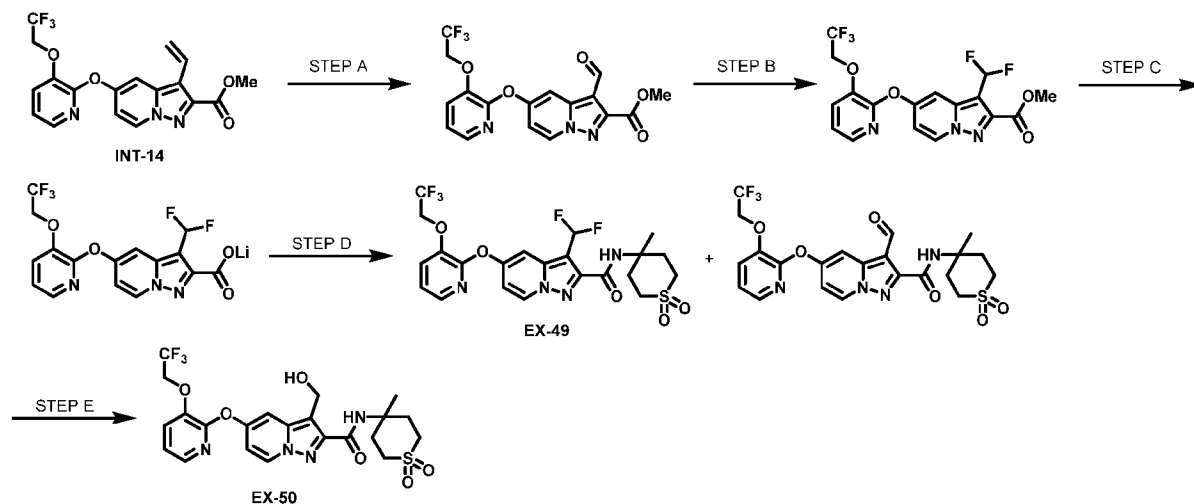
Example	Structure	Name	LCMS [M+1]	Human DGAT2 IC ₅₀ (nM)
47		3-Ethyl- <i>N</i> -(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	499	257
48		3-Isopropyl- <i>N</i> -(4-methyl-1,1-dioxidotetrahydro-2 <i>H</i> -thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5- <i>a</i>]pyridine-2-carboxamide	541	46

15

EXAMPLE 49 and 50

3-(Difluoromethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide (**EX-49**) and 3-(Hydroxymethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide (**EX-50**)

20



STEP A: Methyl 3-formyl-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate

To a stirred solution of methyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-vinylpyrazolo[1,5-a]pyridine-2-carboxylate (237 mg, 603 μ mol), 2,6-dimethylpyridine (140 μ L, 1.21 mmol) and potassium tetrahydroxydioxidoosmium (5.55 mg, 15 μ mol) in 1,4-dioxane (4.0 mL) and water (8.0 mL) was added sodium periodate (516 mg, 2.41 mmol) at 0 $^{\circ}$ C. The reaction mixture was stirred at 20 $^{\circ}$ C. After 3 hrs, the reaction mixture was diluted with NaCl (sat. aq. soln.) and extracted with ethyl acetate. The combined organic fractions were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude material was subjected to silica gel flash column chromatography using a 0-90% ethyl acetate in hexanes gradient to afford the title. LC/MS = 396 [M+1].

STEP B: Methyl 3-(difluoromethyl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate

To a stirred solution of methyl 3-formyl-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate (234 mg, 592 μ mol) in DCM (973 μ L) at -70 $^{\circ}$ C was added 1,1,1-trifluoro-*N,N*-bis(2-methoxyethyl)- λ^4 -sulfanamine (482 μ L, 1.30 mmol). The reaction mixture was allowed to warm to 20 $^{\circ}$ C and stirred for 1 hr. The reaction temperature was increased to 40 $^{\circ}$ C. After 4 hours an additional portion of 1,1,1-trifluoro-*N,N*-bis(2-methoxyethyl)- λ^4 -sulfanamine (482 μ L, 1.30 mmol) was added. After 12 hrs, five additional equivalents of 1,1,1-trifluoro-*N,N*-bis(2-methoxyethyl)- λ^4 -sulfanamine (2.41 mL, 6.51 mmol) were added via syringe. After 16 hours the reaction mixture was poured into ice and allowed to stir for 20 minutes. The biphasic solution was extracted with DCM, dried over Na_2SO_4 and Na_2CO_3 , filtered, and concentrated in vacuo. The crude material was subjected to silica gel flash

column chromatography using a 0-70% ethyl acetate in hexanes gradient to afford the desired product. LC/MS = 418 [M+1].

STEP C: Lithium 3-(difluoromethyl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate

- 5 To a stirred solution of methyl 3-(difluoromethyl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (167 mg, 400 μ mol) in THF (2.3 mL), MeOH (1.1 mL), and water (572 μ l) was added lithium hydroxide (9.58 mg, 400 μ mol) at 20 °C. After 30 minutes. LCMS the reaction mixture was concentrated *in vacuo* to give the title compound. LC/MS = 410 [M-5].

- 10 **STEP D: 3-(Difluoromethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide (EX-52) and 3-Formyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide**

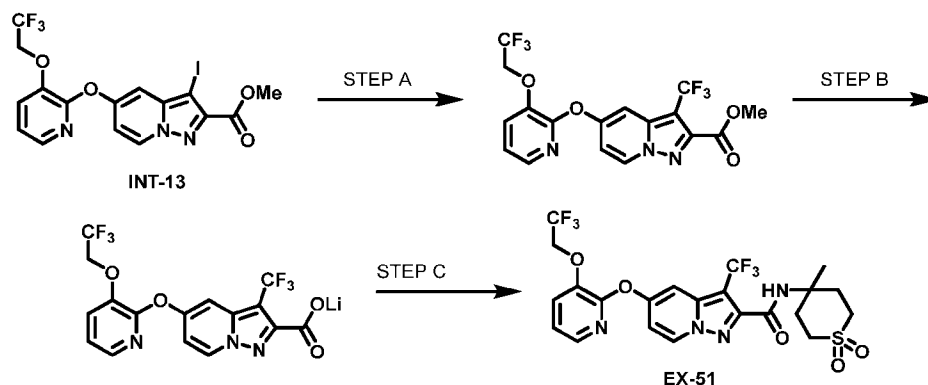
- To a stirred solution of lithium 3-(difluoromethyl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylate (32.8 mg, 80 μ mol), DIPEA (35.0 μ l, 200 μ mol) and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (16.01 mg, 80 μ mol) in DMF (802 μ l) was added HATU (32.0 mg, 84 μ mol). After 18 hrs, the reaction mixture was filtered, and the filtrate purified by reverse phase HPLC (50-98% MeCN/water with 0.1% FA modifier) to afford the title compound (EX-49: LC/MS = 549 [M+1]. Human DGAT2 IC₅₀ = 973 nM and the side aldehyde product (LC/MS = 527 [M+1]).

- 20 **STEP E: 3-(Hydroxymethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide**

- To a stirred solution of 3-formyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide (12.6 mg, 24 μ mol) in methanol (239 μ l) was added NaBH₄ (1.9 mg, 50 μ mol). After 1 hr, the reaction mixture was filtered and the filtrate purified by reverse phase HPLC (40-95% MeCN/water with 0.1% FA modifier) to afford the title compound (EX-50). LC/MS = 511 [M-18]. ¹H NMR (500 MHz, Acetonitrile-*d*₃) δ 8.47 (d, *J* = 7.6 Hz, 1H), 7.88 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.55 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.44 (s, 1H), 7.38 (d, *J* = 2.1 Hz, 1H), 7.21 (dd, *J* = 8.0, 4.9 Hz, 1H), 6.86 (dd, *J* = 7.6, 2.6 Hz, 1H), 4.81 (s, 2H), 4.67 (q, *J* = 8.5 Hz, 2H), 4.31 (s, 1H), 3.24 – 3.13 (m, 2H), 2.98 (d, *J* = 14.4 Hz, 2H), 2.85 (d, *J* = 15.0 Hz, 2H), 1.57 (s, 3H). Human DGAT2 IC₅₀ = 10 nM.

EXAMPLE 51

N-(4-Methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)pyrazolo[1,5-*a*]pyridine-2-carboxamide



STEP A: Methyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)pyrazolo[1,5-a]pyridine-2-carboxylate

To a stirred solution of methyl 3-iodo-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate (150 mg, 304 μ mol) and copper(I) iodide (87 mg, 456 μ mol) in *N*-methyl-2-pyrrolidinone (3.0 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (116 μ l, 912 μ mol), and the reaction mixture was heated to 110 °C. After 1 hr, the solvent was removed in vacuo. The crude residue was subjected to silica gel flash column chromatography using a 0-80% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 436 [M+1].

STEP B: Lithium 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)pyrazolo[1,5-a]pyridine-2-carboxylate

To a stirred solution of methyl 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)pyrazolo[1,5-a]pyridine-2-carboxylate (125 mg, 287 μ mol) in acetonitrile (3.8 mL) and water (1.9 mL) was added lithium hydroxide (6.88 mg, 0.287 mmol) at 40 °C. After 30 minutes, the reaction mixture was concentrated *in vacuo* to give the title product. LC/MS = 428 [M-5].

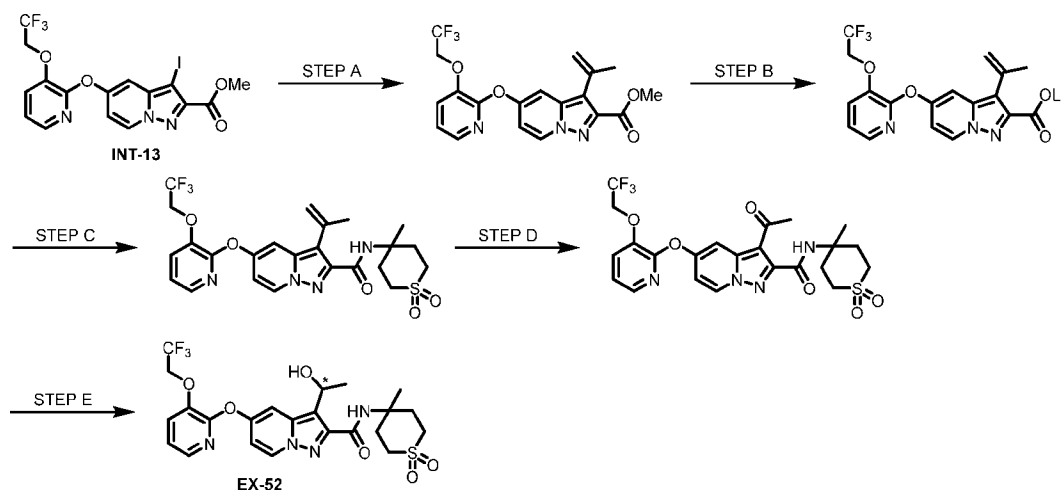
STEP C: N-(4-Methyl-1,1-dioxotetrahydro-2H-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)pyrazolo[1,5-a]pyridine-2-carboxamide

To a stirred solution of lithium 5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)pyrazolo[1,5-a]pyridine-2-carboxylate (31 mg, 73 μ mol), DIPEA (31.7 μ l, 181 μ mol) and 4-amino-4-methyltetrahydro-2H-thiopyran 1,1-dioxide hydrochloride (14.49 mg, 73 μ mol) in DMF (726 μ l) was added HATU (29.0 mg, 76 μ mol) at 20 °C. After 18 hrs, the reaction mixture was filtered, and the filtrate purified by reverse phase HPLC (60-90% MeCN/water with 0.1% FA modifier) to afford the title compound. LC/MS = 567 [M+1]. ¹H NMR (500 MHz, DMSO-d₆) δ 8.96 (d, J = 7.6 Hz, 1H), 8.45 (s, 1H), 7.90 (dd, J = 4.8, 1.3 Hz, 1H), 7.78 (dd, J = 8.1, 1.2 Hz, 1H), 7.39 (s, 1H), 7.32 (dd, J = 8.0, 4.8 Hz, 1H), 7.15 (dd, J = 7.6, 2.5 Hz, 1H), 4.94

(q, J = 8.8 Hz, 2H), 3.09 (s, 4H), 2.71 (d, J = 13.7 Hz, 2H), 2.02 (dt, J = 14.9, 7.7 Hz, 2H), 1.45 (s, 3H). Human DGAT2 IC₅₀ = 828 nM.

EXAMPLE 52

3-(1-Hydroxyethyl)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxamide



STEP A: Methyl 3-(prop-1-en-2-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate

At 20 °C, a stirred solution of methyl 3-iodo-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate (221 mg, 448 μmol), EtOH (3.0 mL) and TEA (94 μL, 672 μmol) was sparged with nitrogen for 15 minutes. The vial was charged with Pd(dppf)Cl₂ (16 mg, 22 μmol) and heated to 85 °C. After 16 hrs, the reaction was filtered through a plug of SiO₂ and concentrated in vacuo. The crude residue was subjected to silica gel flash column chromatography using a 0-80% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 408 [M+1].

STEP B: Lithium 3-(prop-1-en-2-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate

To a stirred solution of methyl 3-(prop-1-en-2-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate (182 mg, 448 μmol) in acetonitrile (6.0 mL) and water (3.0 mL) was added lithium hydroxide (10.73 mg, 448 μmol) at 40 °C. After 2 hrs, the reaction mixture was concentrated in vacuo to afford the title compound. LC/MS = 394 [M-5].

STEP C: N-(4-Methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-3-(prop-1-en-2-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxamide

To a stirred solution of lithium 3-(prop-1-en-2-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate (179 mg, 448 μmol), DIPEA (196 μL, 1.12 mmol)

and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (89 mg, 448 μ mol) in DMF (4.5 mL) was added HATU (179 mg, 470 μ mol) at 20 °C. After 18 hrs, the volatiles were removed *in vacuo*, and the reaction mixture was subjected to silica gel flash column chromatography using a 0-70% ethyl acetate in hexanes gradient to afford the title compound.

5 LC/MS = 539 [M+1].

STEP D: 3-Acetyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred solution of *N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-3-(prop-1-en-2-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide (150 mg, 279 μ mol), 2,6-dimethylpyridine (64.5 μ l, 557 μ mol) and potassium tetrahydroxydioxidoosmium (2.57 mg, 6.96 μ mol) in 1,4-dioxane (1.9 mL) and water (3.7 mL) was added sodium periodate (238 mg, 1.11 mmol) at 0 °C, and the mixture was allowed to warm to 20 °C. After 3 hrs, the reaction mixture was diluted with NaCl (sat. aq. soln.) and extracted with ethyl acetate. The combined organic fractions were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude material was subjected to silica gel flash column chromatography using a 0-90% ethyl acetate in hexanes gradient to afford the title compound. LC/MS = 541 [M+1].

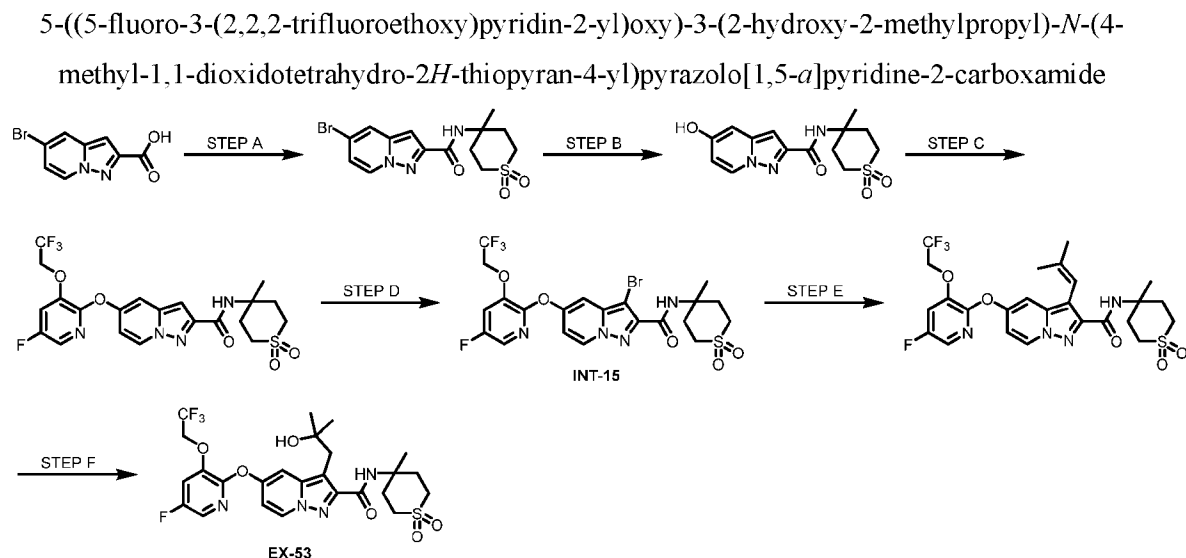
STEP E: 3-(1-Hydroxyethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide (Peak 2)

To a stirred solution of 3-acetyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide (40 mg, 74 μ mol) in methanol (740 μ l) was added NaBH₄ (5.88 mg, 155 μ mol) at 20 °C. After 1 hour the reaction mixture was quenched with NaHCO₃, dried over MgSO₄, filtered, and concentrated. The crude residue was subjected to silica gel flash column chromatography using a 0-100% EtOAc in hexanes gradient to afford the crude racemic compound. SFC chiral resolution provided the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.67 (d, *J* = 7.6 Hz, 1H), 8.21 (s, 1H), 7.86 (d, *J* = 3.5 Hz, 1H), 7.73 (d, *J* = 7.0 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.25 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.89 (dd, *J* = 7.6, 2.6 Hz, 1H), 5.48 – 5.37 (m, 2H), 4.93 (q, *J* = 8.7 Hz, 2H), 3.10 (d, *J* = 3.9 Hz, 4H), 2.79 (s, 2H), 2.04 (dd, *J* = 14.8, 6.9 Hz, 2H), 1.46 (s, 3H), 1.40 (d, *J* = 6.2 Hz, 3H).

30 **EX-52a** (Faster eluting in AD-H column, 25% MeOH/CO₂): LC/MS = 525 [M-18]. Human DGAT2 IC₅₀ = 1588 nM.

EX-52b (Slower eluting in AD-H column, 25% MeOH/CO₂). LC/MS = 525 [M-18]. Human DGAT2 IC₅₀ = 333 nM.

EXAMPLE 53



STEP A: 5-Bromo-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a mixture of 5-bromopyrazolo[1,5-*a*]pyridine-2-carboxylic acid (1.4 g, 5.81 mmol), 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide dihydrochloride (1.65 g, 6.97 mmol), DIEA (5.07 mL, 29.0 mmol) in DMF (25 mL) was added HATU (3.31 g, 8.71 mmol). The reaction was stirred at 25 °C for 0.5 hours and poured into NH₄Cl (300 mL, sat. aq. soln.) and extracted with DCM (100 mL x 3). The combined organic layers were washed with NaCl (100 mL, sat. aq. soln.), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography using a 0-80% ethyl acetate/pet. ether gradient to afford the title compound. LC/MS = 386 [M+1].

STEP B: 5-Hydroxy-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

A mixture of 5-bromo-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (2 g, 5.18 mmol), B₂Pin₂ (3.2 g, 12.60 mmol), KOAc (1.85 g, 18.85 mmol) and Pd(dppf)Cl₂ (0.379 g, 518 μmol) in dioxane (50 mL) was degassed and backfilled with N₂ (three times). The mixture was heated to 90 °C for 13 hrs. After cooled down to RT, the mixture was filtered and concentrated *in vacuo*. Crude (2-((4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)carbamoyl)pyrazolo[1,5-*a*]pyridin-5-yl)boronic acid (1.82 g, 5.18 mmol) and NMO (1.83 g, 15.62 mmol) in THF (45 mL) was degassed and backfilled with N₂ gas (3x). The mixture was heated to 80 °C for 3 hrs under N₂. The mixture was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography using a 0-40% ethyl acetate/pet. ether gradient to afford the title compound. LC/MS = 324 [M+1].

STEP C: 5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a mixture of 5-hydroxy-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (600 mg, 1.86 mmol), 5-fluoro-2-iodo-3-(2,2,2-trifluoroethoxy)pyridine (670 mg, 2.09 mmol), picolinic acid (54 mg, 439 μ mol) and picolinic acid (54 mg, 439 μ mol) in DMSO (7 mL) was added CuI (71 mg, 373 μ mol) in a glove box, and the reaction mixture was stirred at 80 °C. After 15 hrs, the reaction mixture was washed with NH₄Cl (100 mL, sat. aq. soln.) and extracted with EtOAc (60 mL $\times$ 3). The combined organic layers were washed with NaCl (10 mL, sat. aq. soln.), dried over Na₂SO₄ and filtered. The filtrate was concentrated, and the crude residue was subjected to silica gel flash column chromatography using a 0-40 % EtOAc gradient to afford the title compound. LC/MS = 517 [M+1].

STEP D: 3-Bromo-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

NBS (197 mg, 1.11 mmol) was added to a mixture of 5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (440 mg, 852 μ mol) in THF (10 mL) at 25 °C. After 2 hours the reaction mixture was quenched with Na₂SO₃ (sat. aq. soln.) (30 mL), then extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, concentrated, and subjected to silica gel flash column chromatography using a 0~45% EtOAc/Pet.ether gradient to afford the title compound. LC/MS = 597 [M+1].

STEP E: 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-3-(2-methylprop-1-en-1-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

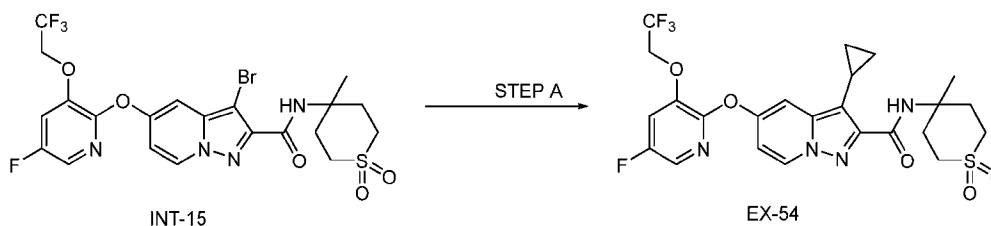
Pd(dppf)Cl₂ (13 mg, 18 μ mol) was added to a mixture of 3-bromo-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (100 mg, 168 μ mol), 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (62 mg, 341 μ mol) and Na₂CO₃ (54 mg, 509 μ mol) in dioxane (4 mL) and H₂O (0.4 mL) under N₂ atmosphere. The reaction mixture was stirred at 100 °C. After 5 hrs, the mixture was poured into sat. NH₄Cl (10 mL), extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (7 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography using a 0-55% ethyl acetate/pet. ether gradient at 30 mL/min) to give the title compound. LC/MS = 571 [M+1].

STEP F: 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(2-hydroxy-2-methylpropyl)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide

A mixture of 5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-3-(2-methylprop-1-en-1-yl)pyrazolo[1,5-a]pyridine-2-carboxamide (40 mg, 70 μ mol), Mn(TMHD)₃ (10 mg, 17 μ mol) and PhSiH₃ (40 mg, 0.37 mmol) in DCM (0.5 mL)/i-PrOH (5 mL) was stirred at 30 °C under O₂ (15 psi). After 14 hr, MeCN (1 mL) was added, and the mixture was filtered and purified by reverse phase HPLC (35-65% MeCN/water with 10mM NH₄HCO₃ modifier) to afford the title compound. LC/MS = 589 [M+1]. ¹H NMR (500 MHz, Methanol-d₄) δ 8.55 (d, J=7.63 Hz, 1H), 7.79 (d, J=2.29 Hz, 1H), 7.64 (dd, J=2.14, 9.00 Hz, 1H), 7.34 (d, J=2.14 Hz, 1H), 6.87 (dd, J=2.21, 7.55 Hz, 1H), 4.74 (q, J=8.34 Hz, 2H), 3.34-3.36 (m, 1H), 3.30 (br s, 1H), 3.11 (s, 2H), 3.03 (br d, J=13.58 Hz, 2H), 2.90 (br d, J=14.50 Hz, 2H), 2.21 (br t, J=13.66 Hz, 2H), 1.57 (s, 3H), 1.22 (s, 6H). Human DGAT2 IC₅₀ = 368 nM.

EXAMPLE 54

3-cyclopropyl-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide

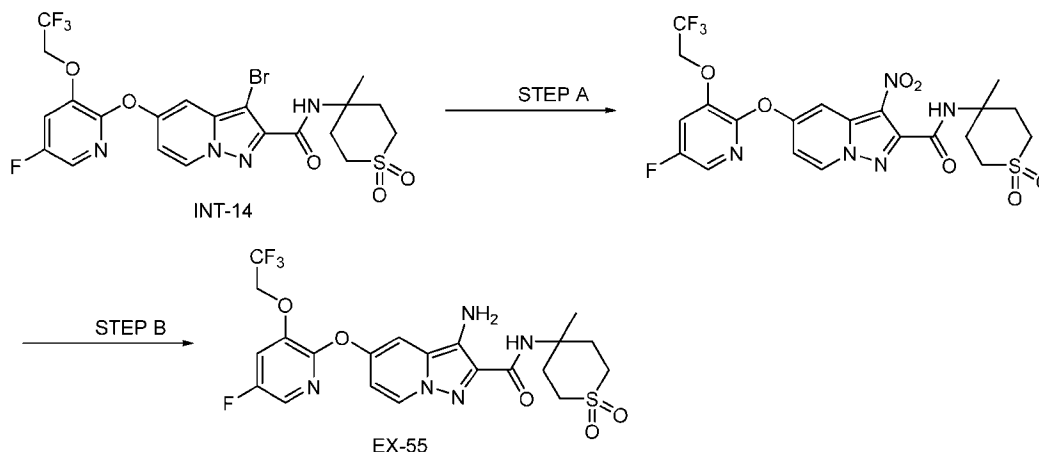


STEP A: 5-Bromo-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide

RuPhos (33 mg, 71 μ mol) was added to a stirred mixture of 3-bromo-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide (200 mg, 336 μ mol), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (300 mg, 1.79 mmol) and Cs₂CO₃ (328 mg, 1.01 mmol) in toluene (4 mL) and H₂O (0.4 mL) under N₂ atmosphere. The reaction mixture was stirred at 100 °C for 10 hrs under N₂. The mixture was concentrated *in vacuo* and purified by reverse phase HPLC (60-80% MeCN/water with 0.1% TFA modifier) to afford the title compound. ¹H NMR (500 MHz, MeCN-d₃) δ 8.42 (d, J=7.63 Hz, 1H), 7.78 (d, J=2.44 Hz, 1H), 7.46 (dd, J=2.44, 9.16 Hz, 1H), 7.28 (d, J=2.44 Hz, 1H), 7.06 (br s, 1H), 6.76 (dd, J=2.52, 7.55 Hz, 1H), 4.68 (q, J=8.29 Hz, 2H), 3.12-3.23 (m, 2H), 2.94-3.03 (m, 2H), 2.78-2.90 (m, 2H), 2.15-2.21 (m, 3H), 1.55 (s, 3H), 0.92-0.98 (m, 2H), 0.72-0.78 (m, 2H). LC/MS = 557 [M+1]. Human DGAT2 IC₅₀ = 48 nM.

EXAMPLE 55

3-Amino-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide



5 **STEP A: 5-Bromo-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide**

Potassium nitroperoxous acid (12 mg, 119 μmol) was added to a mixture of 5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (40 mg, 77 μmol) in H_2SO_4 (0.5 mL) at 0 $^\circ\text{C}$, and the mixture was stirred for 2 h. The mixture was poured to sat. Na_2CO_3 (40 mL) at 0 $^\circ\text{C}$, stirred at 0 $^\circ\text{C}$ for 0.2 h, and extracted with DCM (15 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified by Pre-TLC (SiO_2 , ethyl acetate/pet. ether = 2;1) to afford the title compound. LC/MS = 562 [$\text{M}+1$].

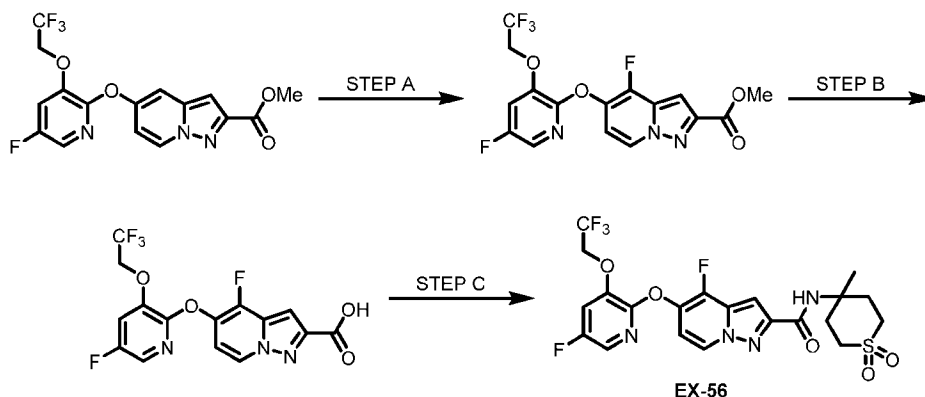
15 **STEP B: 3-Amino-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide**

Pd-C (5 mg, 47 μmol) and ammonium hydroxide solution (0.1 mL, 27 μmol) were added to a solution of 5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-3-nitropyrazolo[1,5-*a*]pyridine-2-carboxamide (15 mg, 27 μmol) in EtOAc (5 mL) under N_2 atmosphere. The mixture was degassed and backfilled with H_2 three times. The resulting mixture was stirred under H_2 (15 psi) at 25 $^\circ\text{C}$. After 1 h, the mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by reverse phase HPLC (60-80% MeCN/water with 0.1% TFA modifier) to give the title compound. LC/MS = 532 [$\text{M}+1$]. ^1H NMR (500 MHz, Methanol- d_4) δ 8.63 (br d, $J=7.17$ Hz, 1H), 7.85 (d, $J=2.59$ Hz, 1H), 7.70 (dd, $J=2.59, 9.00$ Hz, 1H), 7.39 (br s, 1H), 7.00 (br d, $J=7.02$ Hz, 1H), 4.76 (q,

J=8.34 Hz, 2H), 3.25-3.32 (m, 2H), 3.05 (br d, J=14.04 Hz, 2H), 2.95 (br d, J=14.80 Hz, 2H), 2.19-2.30 (m, 2H), 1.59 (s, 3H). Human DGAT2 IC₅₀ = 16 nM.

EXAMPLE 56

4-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide



STEP A: 4-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylic acid

A mixture of NFSI (319 mg, 1.012 mmol), Pd₂(dba)₃ (30.9 mg, 34 μmol), methyl 5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate (130 mg, 337 μmol) and EtOAc (5 mL) was stirred at 80 °C for 12 hrs. The reaction mixture was concentrated *in vacuo* and purified by prep-HPLC (TFA condition) to afford the title compound. LC/MS = 404 [M+1].

STEP B: 4-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylic acid

To a mixture of methyl 4-fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxylate (11 mg, 27 μmol) in water (1 mL)/MeOH (1.0 mL) was added LiOH (3 mg, 125 μmol). The reaction mixture was stirred at 20 °C for 1 h, dissolved in H₂O and treated with HCl (1N aq. soln.) until pH = 4. The mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with NaCl (20 mL, sat. aq. soln.), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the title compound. LC/MS = 390 [M+1].

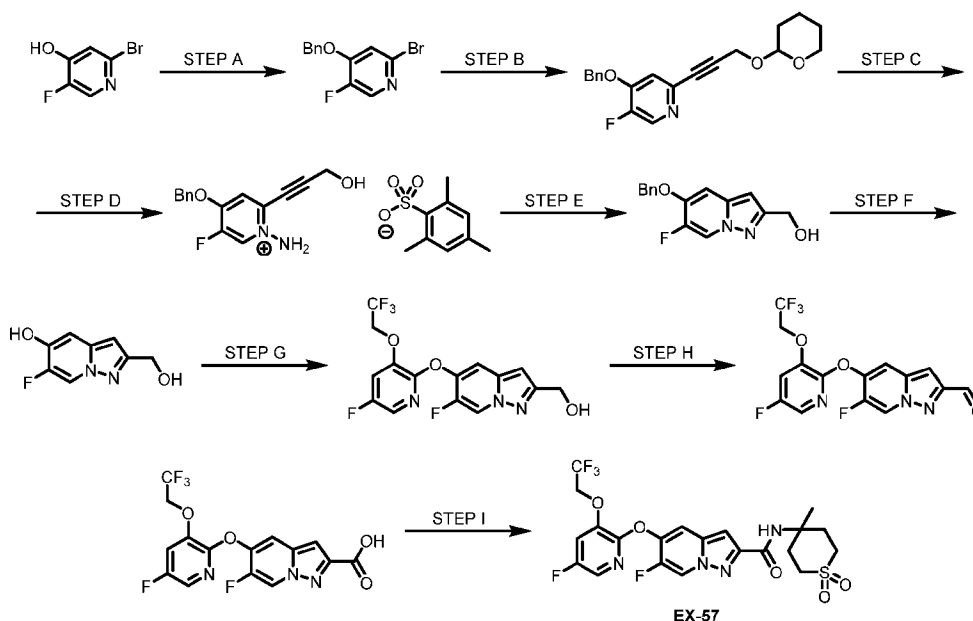
STEP C: 4-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide

A mixture of DIPEA (22 μL, 128 μmol) and 4-amino-4-methyltetrahydro-2H-thiopyran 1,1-dioxide (6 mg, 37 μmol), 4-fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-

yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (10 mg, 26 μ mol), HATU (18 mg, 47 μ mol) in DMF (1 mL) was stirred at 20 °C for 2 h. The residue was purified by reverse phase HPLC (43-63% MeCN/water with 0.1% FA modifier) to afford the title compound. LC/MS = 535 [M+1].
¹H NMR (400 MHz, Methanol-*d*₄) δ 8.50 (br d, *J*=7.58 Hz, 1H), 7.99 (br s, 1H), 7.66 (d, *J*=2.20 Hz, 1H), 7.64-7.67 (m, 1H), 7.59 (dd, *J*=2.32, 8.93 Hz, 1H), 7.57-7.61 (m, 1H), 7.57-7.61 (m, 1H), 7.11 (s, 1H), 6.96 (br t, *J*=7.34 Hz, 1H), 4.74 (br d, *J*=8.31 Hz, 2H), 3.22-3.23 (m, 1H), 3.23 (br d, *J*=14.18 Hz, 1H), 3.01 (br d, *J*=13.69 Hz, 1H), 2.98-3.04 (m, 1H), 2.89 (br d, *J*=14.92 Hz, 2H), 2.17-2.24 (m, 2H), 1.54 (s, 3H). Human DGAT2 IC₅₀ = 20 nM.

EXAMPLE 57

6-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide



STEP A: 4-(Benzyloxy)-2-bromo-5-fluoropyridine

To a stirred solution of 2-bromo-5-fluoropyridin-4-ol (0.5 g, 2.60 mmol) in DMF (7 mL) was added NaH (60% in oil) (0.156 g, 3.91 mmol) at 0 °C. After 30 minutes (bromomethyl)benzene (0.464 mL, 3.91 mmol) was added, and the mixture was warmed to 25 °C. After 2 hours the reaction mixture was poured into NH₄Cl (70 mL, sat. aq. solution) and extracted with DCM (3x50 mL). The combined organic layers were washed with NaCl (100 mL, sat. aq. soln.), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography using a 0-30% EtOAc in pet. ether gradient to afford the title compound. LC/MS = 282.0 and 284.0 [M+H].

STEP B: 4-(Benzyloxy)-5-fluoro-2-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine

To a stirred solution of 4-(benzyloxy)-2-bromo-5-fluoropyridine (100 mg, 0.35 mmol), tetrahydro-2-(2-propynyloxy)-2H-pyran (100 mg, 0.71 mmol), Pd(PPh₃)₂Cl₂ (50 mg, 71 μmol), and TEA (75 mg, 0.74 mmol) in THF (3 mL) was added CuI (15 mg, 79 μmol) in the glovebox. The reaction mixture was heated to 70 °C. After 10 hrs, the reaction mixture was poured into

5 NH₄Cl (20 mL, sat. aq. soln.) and extracted with DCM (3x15 mL). The combined organic layers were washed with NaCl (10 mL, sat. aq. soln.), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography using a 0-20% EtOAc / pet. ether gradient to afford the title compound. LC/MS=342.1 [M+H].

STEP C: 1-Amino-4-(benzyloxy)-5-fluoro-2-(3-hydroxyprop-1-yn-1-yl)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate

10

To a stirred solution of *O*-(mesitylsulfonyl)hydroxylamine (1.706 g, 7.93 mmol) in DCM (25 mL) was added 4-(benzyloxy)-5-fluoro-2-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine (1.7 g, 4.98 mmol). After 15 hrs, the reaction mixture was concentrated under reduced pressure to afford the crude title compound. LC/MS = 273.1 [M+H].

STEP D: (5-(Benzyloxy)-6-fluoropyrazolo[1,5-*a*]pyridin-2-yl)methanol

15

To a stirred solution of 1-amino-4-(benzyloxy)-5-fluoro-2-(3-hydroxyprop-1-yn-1-yl)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate (2.3 g, 4.87 mmol) in DMF (20 mL) was added K₂CO₃ (4.04 g, 29.2 mmol). After 15 hours the mixture was poured into NH₄Cl (200 mL, sat. aq. soln.) and extracted with DCM (50 mL x 3). The combined organic layers were washed with NaCl (40 mL,

20 sat. aq. soln.), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography using a 0-40% EtOAc in pet. ether gradient to afford the title compound. LC/MS=273.1 [M+H].

STEP E: 6-Fluoro-2-(hydroxymethyl)pyrazolo[1,5-*a*]pyridin-5-ol

To a stirring solution of (5-(benzyloxy)-6-fluoropyrazolo[1,5-*a*]pyridin-2-yl)methanol (180 mg, 0.66 mmol) in MeOH (5 mL) and DCM (5 mL) was added Pd-C (50 mg, 0.47 mmol) under N₂. The mixture was degassed and backfilled with H₂ (three times) and warmed to 45 °C under H₂ (15 psi). After 1 hr, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (40-70% MeCN/water with 0.1% TFA modifier) to afford the title compound. LC/MS = 183.1 [M+H].

STEP F: (6-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridin-2-yl)methanol

30

To a stirred solution of K₃PO₄ (175 mg, 0.82 mmol), picolinic acid (20 mg, 0.16 mmol), 6-fluoro-2-(hydroxymethyl)pyrazolo[1,5-*a*]pyridin-5-ol (50 mg, 0.27 mmol) and 5-fluoro-2-iodo-3-(2,2,2-trifluoroethoxy)pyridine (132 mg, 0.41 mmol) in DMSO (2 mL) was added CuI (11 mg,

58 μmol) and the reaction mixture was heated to 95 °C. After 15 hrs, the mixture was filtered and the filtrate was purified by reverse phase HPLC (40-70% MeCN/water with 0.1% TFA modifier) to afford the title compound. LC/MS = 376.0 [M+H].

**STEP G: 6-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-
a]pyridine-2-carbaldehyde**

To a stirred solution of (6-fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridin-2-yl)methanol (10 mg, 27 μmol) in CHCl_3 (1.5 mL) was added MnO_2 (17 mg, 0.20 mmol) at 25 °C. After 1 hr, the mixture was filtered, and the filtrate was concentrated under reduced pressure to afford the crude title compound. LC/MS = 374.0 [M+H].

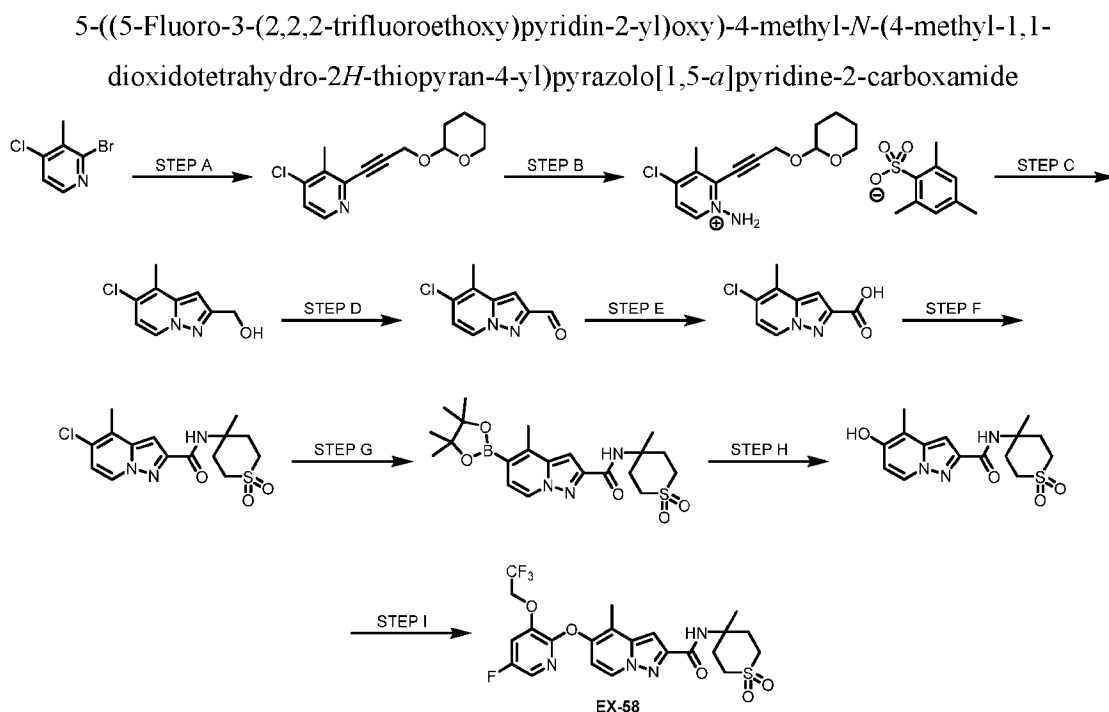
**STEP H: 6-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-
a]pyridine-2-carboxylic acid**

To a stirred solution of 6-fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carbaldehyde (8 mg, 21 μmol) in DMSO (3 mL) was sequentially added KH_2PO_4 (1 mg, 7.35 μmol) in water (1 mL) and NaClO_2 (3 mg, 33 μmol) in water (2 mL) at 25 °C. After 1 hr, the mixture was poured into H_2O (10 mL) and freeze-dried to afford the crude title compound. LC/MS = 390.0 [M+H].

STEP I: 6-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxido-2,3,4,5-tetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred solution of 6-fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid (8 mg, 21 μmol), 4-amino-4-methyltetrahydro-2H-thiopyran 1,1-dioxide dihydrochloride (10 mg, 42 μmol) and DIPEA (18 μl , 103 μmol) in DMF (2.5 mL) was added HATU (15.63 mg, 41 μmol) at 25 °C. After 30 minutes, the reaction mixture was filtered, and the residue was purified by reverse phase HPLC (40-70% MeCN/water with 0.1% TFA modifier) to afford the title compound. LC/MS = 535.1 [M+1]. ^1H NMR (400 MHz, Methanol- d_4) δ 8.87 (d, $J=5.48$ Hz, 1H), 7.72 (d, $J=2.50$ Hz, 1H), 7.64 (dd, $J=2.44$, 9.00 Hz, 1H), 7.60 (d, $J=7.87$ Hz, 1H), 7.04 (s, 1H), 4.78 (q, $J=8.34$ Hz, 2H), 3.22-3.30 (m, 2H), 2.99-3.10 (m, 2H), 2.85-2.97 (m, 2H), 2.18-2.30 (m, 2H), 1.57 (s, 3H). Hu DGAT2 IC_{50} = 1.8 nM.

EXAMPLE 58



STEP A: 4-Chloro-3-methyl-2-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine

To a stirring solution of 2-bromo-4-chloro-3-methylpyridine (2g, 9.69 mmol), 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (2.04 g, 14.53 mmol), and TEA (2.70 mL, 19.37 mmol) in THF (20 mL) was added Pd(PPh₃)₂Cl (0.68 g, 0.97 mmol) and CuI (0.18 g, 0.97 mmol) in a glovebox at 25 °C. Then the reaction was sealed and stirred at 60 °C for 16 hrs. The crude product was extracted with EtOAc (40 mL × 3), washed with H₂O (50 mL). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated to give a residue which was purified by silica gel flash chromatography using 13% EtOAc gradient in hexanes to afford the title compound. LC/MS = 266 [M+1].

STEP B: 1-Amino-4-chloro-3-methyl-2-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate

4-chloro-3-methyl-2-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine (1.5 g, 5.64 mmol) was added to a mixture of *O*-(mesitylsulfonyl)hydroxylamine in DCM (15 mL) (2.048 g, 9.51 mmol) at 0 °C, then the mixture was stirred at 20 °C for 15 hrs. The mixture was diluted with MTBE (80 mL). The precipitated crystals were collected via filtration and dried in vacuo to give the title compound which was used directly in next step. LC/MS = 281 [M++1].

STEP C: (5-Chloro-4-methylpyrazolo[1,5-*a*]pyridin-2-yl)methanol

To a stirred solution of 1-amino-4-chloro-3-methyl-2-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate (2.0 g, 2.08 mmol) in DMF (20 mL) was

added K₂CO₃ (0.58 g, 4.16 mmol). After 15 hrs, the crude product was extracted with EtOAc (50 mL × 3), washed with H₂O (80 mL) and brine (80 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by prep-TLC (SiO₂, pet. ether / EtOAc = 1/1) further purified by reversed-phase column chromatography using 40% MeCN to afford the title compound. LC/MS = 197 [M+1].

STEP D: 5-Chloro-4-methylpyrazolo[1,5-*a*]pyridine-2-carbaldehyde

To a stirred solution of (5-chloro-4-methylpyrazolo[1,5-*a*]pyridin-2-yl)methanol (170 mg, 0.87 mmol) in CHCl₃ (5 mL) was added manganese(IV) oxide (1.13 g, 12.97 mmol), and the mixture was heated to 60 °C. After 15 hrs, the mixture was filtered and concentrated to afford the title compound. LC/MS = 195 [M+1].

STEP E: 5-Chloro-4-methylpyrazolo[1,5-*a*]pyridine-2-carboxylic acid

To a stirred solution of 5-chloro-4-methylpyrazolo[1,5-*a*]pyridine-2-carbaldehyde (170 mg, 0.87 mmol) in DMSO (2 mL) was sequentially added KH₂PO₄ (36 mg, 0.27 mmol) in water (0.5 mL) and NaClO₂ (118 mg, 1.31 mmol) in water (1.5 mL). After 15 hrs, the reaction mixture was diluted with 15 mL water, the pH was adjusted to 10 with NaOH (2M aq. soln.), and the mixture was washed with EtOAc (20 mL × 3). The pH was then adjusted to 4 with HCl (1N aq. soln.), extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the title compound. LC/MS = 211 [M+1].

STEP F: 5-Chloro-4-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred solution of 5-chloro-4-methylpyrazolo[1,5-*a*]pyridine-2-carboxylic acid (170 mg, 0.81 mmol), HATU (460 mg, 1.21 mmol) and DIPEA (0.42 mL, 2.42 mmol) in DMF (3 mL) was added 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (193 mg, 0.97 mmol). After 1 hr, the crude product was extracted with EtOAc (20 mL × 3), washed with H₂O (30 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was subjected to SiO₂ flash column chromatography using EtOAc to afford the title compound. LC/MS = 356 [M+1].

STEP G: 4-Methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a mixture of 5-chloro-4-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (250 mg, 0.70 mmol), B₂Pin₂ (268 mg, 1.05 mmol), potassium acetate (207 mg, 2.11 mmol) in 1,4-dioxane (2 mL) was added XPhos Pd G2 (55.3 mg, 70 μmol) under N₂ atmosphere. The mixture was stirred at 85 °C for 12 hrs. The crude

product was extracted with EtOAc (20 mL × 3), washed with H₂O (30 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was subjected to silica gel flash column chromatography using 50% EtOAc in hexanes to afford the title compound. LC/MS = 448 [M+1].

5 **STEP H: 5-Hydroxy-4-methyl-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide**

To a suspension of 4-methyl-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (160 mg, 0.36 mmol) in THF (2 mL) and water (2 mL) was added NaBO₃·4H₂O (114 mg, 1.07 mmol) at 20 °C.

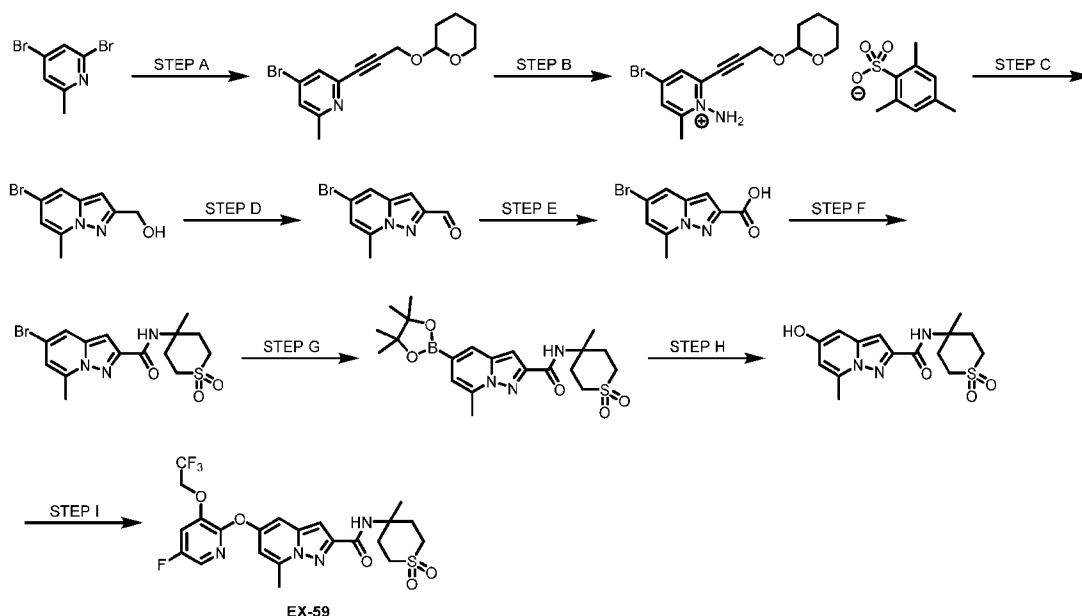
10 After 3 hrs, the crude product was extracted with EtOAc (20 mL × 3), washed with H₂O (30 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated to give a residue which was purified by prep-TLC (SiO₂, pet. ether / EtOAc = 0/1) to afford the title compound. LC/MS = 338 [M+1].

15 **STEP I: 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-4-methyl-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide**

To a stirred solution of 5-hydroxy-4-methyl-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (80 mg, 0.24 mmol), 5-fluoro-2-iodo-3-(2,2,2-trifluoroethoxy)pyridine (114 mg, 0.36 mmol), dimethylglycine (5 mg, 0.048 mmol) and K₃PO₄ (151 mg, 0.711 mmol) in DMSO (2 mL) was added Copper(I) Iodide (5 mg, 0.026 mmol) in a glove box, and the reaction mixture was stirred at 95 °C for 15 hrs. The mixture was filtered to give a residue which was purified by reverse phase HPLC (10-90% MeCN/water with 0.1% TFA modifier) to afford the title compound. LC/MS = 531 [M+1]. ¹H NMR (400 MHz, METHANOL-d₄) δ 8.46 (d, J=7.39 Hz, 1H), 7.66 (d, J=2.50 Hz, 1H), 7.59 (dd, J=2.44, 9.00 Hz, 1H), 7.04 (br s, 1H), 6.80 (d, J=7.39 Hz, 1H), 4.76 (q, J=8.34 Hz, 2H), 3.24-3.30 (m, 2H), 3.00-3.04 (m, 2H), 2.89-2.92 (m, 2H), 2.33 (s, 3H), 2.17-2.26 (m, 2H), 1.56 (s, 3H), 1.55-1.57 (m, 1H). Human DGAT2 IC₅₀ = 6.6 nM.

EXAMPLE 59

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



STEP A: 4-Bromo-2-methyl-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine

To a stirred solution of 2,4-dibromo-6-methylpyridine (3.5 g, 13.95 mmol), 2-
 ((ethynyloxy)methyl)tetrahydro-2H-pyran (2.35 g, 16.74 mmol), Pd(PPh₃)₂Cl₂ (979 mg, 1.40
 5 μmol), and CuI (266 mg, 1.40 mmol) in THF (40 mL) was added TEA (3.89 mL, 27.9 mmol) in
 a glovebox. The reaction mixture heated to 80 °C. After 16 hrs, the crude product was extracted
 with EtOAc (50 mL × 3), washed with H₂O (40 ml). The combined organic layers were washed
 with brine (40 ml), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was
 purified by silica gel flash column chromatography using a 0-20 % EtOAc in pet. ether gradient
 10 to afford the title compound. LC/MS = 325 [M].

STEP B: 1-Amino-4-bromo-2-methyl-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate

4-bromo-2-methyl-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine (200 mg, 645
 μmol) was added to a stirring mixture of *O*-(mesitylsulfonyl)hydroxylamine in DCM (15 mL) (341
 15 mg, 1.57 mmol) at 0°C, then the reaction mixture was warmed to 15 °C. After 15 hrs, the mixture
 was concentrated afford the title compound. LC/MS = 310 [M+1].

STEP C: (5-Bromo-7-methylpyrazolo[1,5-a]pyridin-2-yl)methanol

To a stirring solution of 1-amino-4-bromo-2-methyl-6-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-
 yn-1-yl)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate (832 mg, 1.583 mmol) in DMF (3 mL) was
 20 added K₂CO₃ (656 mg, 4.75 mmol) at 0°C. The mixture was warmed to 15 °C. After 15 hrs,
 water (20 mL) was added, and the mixture was extracted with EtOAc (30 mL). The combined
 organic fractions were washed with brine (20 mL), dried (Na₂SO₄), filtered, and the solvent was

evaporated under reduced pressure. The residue was purified by Prep-TLC (1:1 pet. Ether / EtOAc) to afford the title compound. LC/MS = 241 [M+1].

STEP D: 5-Bromo-7-methylpyrazolo[1,5-*a*]pyridine-2-carbaldehyde

To a stirring solution of (5-bromo-7-methylpyrazolo[1,5-*a*]pyridin-2-yl)methanol (10 mg, 41
5 μmol) in CHCl_3 (2 mL) was added MnO_2 (72.1 mg, 0.83 mmol), and the reaction mixture was heated to 60 °C. After 15 hrs, the mixture was filtered and concentrated to afford the title compound. LC/MS = 239 [M+1].

STEP E: 5-Bromo-7-methylpyrazolo[1,5-*a*]pyridine-2-carboxylic acid

To a stirred solution of 5-bromo-7-methylpyrazolo[1,5-*a*]pyridine-2-carbaldehyde (9 mg, 38
10 μmol) in DMSO (0.4 mL) was added KH_2PO_4 (2 mg, 15 μmol) in water (0.1 mL) followed by NaClO_2 (5 mg, 55 μmol) in water (0.3 mL) at 15 °C. After 15 hrs, the reaction mixture was diluted with water, and the pH adjusted to 10 with NaOH (2N aq. soln.). The mixture was washed with EtOAc (2 mL $\times$ 3), the pH was adjusted to 4 with HCl (1N aq. soln.), and the resultant solution was extracted with EtOAc (2 mL $\times$ 3). The combined organic layers were
15 washed with brine (3 mL), dried over Na_2SO_4 , filtered and concentrated to afford the title compound. LC/MS = 255 [M+1].

STEP F: 5-Bromo-7-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred solution of 5-bromo-7-methylpyrazolo[1,5-*a*]pyridine-2-carboxylic acid (1.1 g, 4.31
20 mmol), HATU (2.46 g, 6.47 mmol) and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (1.1 g, 6.74 mmol) in DMF (20 mL) was added DIPEA (2.26 mL, 12.94 mmol) at 20 °C. After 30 minutes, water (100 mL) was added, and the mixture was extracted with EtOAc (150 mL). The combined organic fractions were washed with brine (120 mL), dried (Na_2SO_4), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash column
25 chromatography using 100% EtOAc to afford the title compound. LC/MS = 401 [M+1].

STEP G: 7-Methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

A 8 mL of tube was charged with 5-bromo-7-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-
thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (1.45 g, 3.62 mmol), B_2Pin_2 (1.84 g, 7.24
30 mmol), KOAc (1.067 g, 10.87 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (265 mg, 362 μmol) in dioxane (40 mL) was bubbled with a stream of N_2 for 2 min. The tube was sealed and heated to 100 °C. After 3 hrs, the mixture was cooled down to RT, water (10 mL) was added, and the mixture was extracted with EtOAc (15 mL). The combined organic fractions were washed with brine (15 mL), dried (Na_2SO_4), filtered, and the solvent was evaporated under reduced pressure. The residue was

purified by silica gel flash column chromatography using a 0~30% EtOAc in pet. ether gradient to afford the title compound.

STEP H: 5-Hydroxy-7-methyl-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide

- 5 To a suspension of 7-methyl-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine-2-carboxamide (1.54 g, 3.44 mmol) in THF (10 mL) and water (10 mL) was added NaBO₃·4H₂O (1.10 g, 10.33 mmol) at 15 °C. The mixture was stirred at 15 °C for 2 hrs. The crude product was extracted with EtOAc (20 mL × 3), and washed with H₂O (30 mL). The combined organic layers were washed with brine (30 mL),
10 dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography using 100% EtOAc to afford the title compound.

STEP I: 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-methyl-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide

- To a stirred solution of 5-hydroxy-7-methyl-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide (50 mg, 0.15 mmol), 5-fluoro-2-iodo-3-(2,2,2-trifluoroethoxy)pyridine (95 mg, 296 μmol), K₂CO₃ (61.4 mg, 445 μmol), and *N,N*-dimethylglycine (3 mg, 29 μmol) in DMSO (2 mL) was added CuI (3 mg, 16 μmol) in a glovebox, and the mixture was heated to 90 °C. After 12hrs, the mixture was purified by reverse phase HPLC (42-62% MeCN/water with 0.1% FA modifier) to afford the title compound.

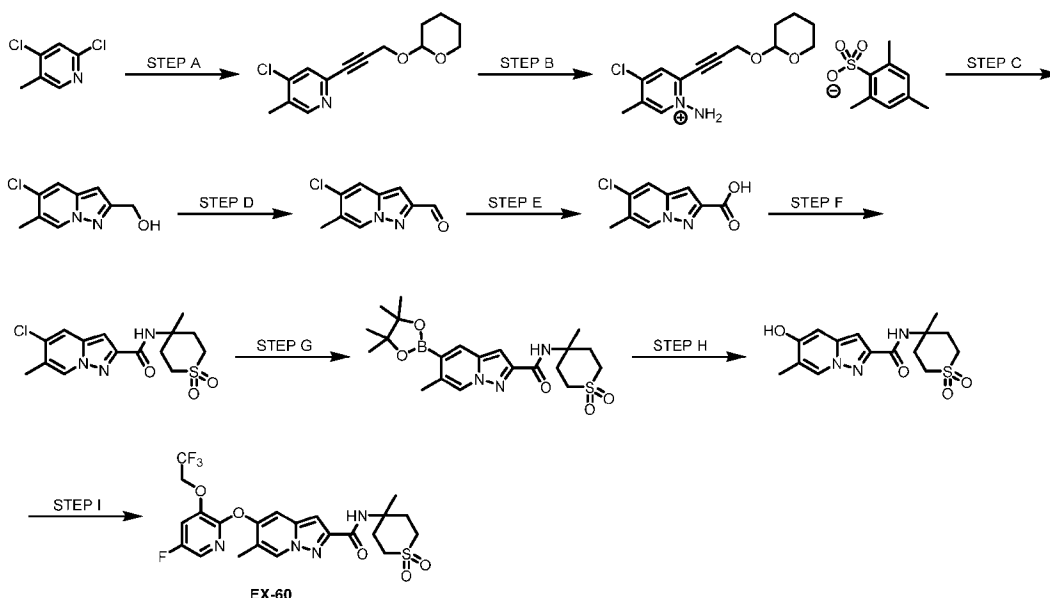
- 20 LC/MS = 531 [M+1].

¹H NMR (400 MHz, Methanol-d₄) δ 7.81 (d, *J*=2.50 Hz, 1H), 7.64 (dd, *J*=2.50, 9.06 Hz, 1H), 7.21 (d, *J*=2.38 Hz, 1H), 6.97 (s, 1H), 6.81 (d, *J*=1.55 Hz, 1H), 4.73 (q, *J*=8.34 Hz, 2H), 3.23-3.32 (m, 2H), 3.05 (br d, *J*=13.83 Hz, 2H), 2.94 (br d, *J*=14.66 Hz, 2H), 2.80 (s, 3H), 2.18-2.32 (m, 2H), 1.59 (s, 3H). Human IC₅₀ = 6.0 nM.

- 25

EXAMPLE 60

5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-6-methyl-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide



STEP A: 4-Chloro-5-methyl-2-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine

To a stirred solution of 2,4-dichloro-5-methylpyridine (2.00 g, 12.34 mmol), 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (2.25 g, 16.05 mmol), TEA (3.44 mL, 24.69 mmol) in THF (25 mL) was added Pd(PPh₃)₂Cl₂ (866 mg, 1.23 mmol) and CuI (235 mg, 1.23 mmol) under a N₂ atmosphere, and the reaction mixture was warmed to 60 °C. After 16 hrs, the crude product was extracted with EtOAc (40 mL × 3), washed with H₂O (50 mL) and NaCl (40 mL sat. aq. soln.), dried over Na₂SO₄, filtered, and concentrated. The crude residue was subjected to silica gel flash column chromatography using 10% EtOAc in hexanes to afford the title compound. LC/MS = 266 [M+1].

STEP B: 1-Amino-4-chloro-5-methyl-2-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate

To a stirred solution of O-(mesitylsulfonyl)hydroxylamine in DCM (15 mL) (1.706 g, 0.00 mmol) at 0°C was added 4-chloro-5-methyl-2-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridine (480 mg, 1.806 mmol), and the reaction mixture was warmed to 15 °C. After 15 hrs, the mixture was concentrated to afford the crude title compound. LC/MS = 281 [M].

STEP C: (5-Chloro-6-methylpyrazolo[1,5-a]pyridin-2-yl)methanol

To a stirred solution of 1-amino-4-chloro-5-methyl-2-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate (3.81 g, 7.92 mmol) in DMF (10 mL) was added K₂CO₃ (2.19 g, 15.84 mmol) at 20 °C. After 15 hours the crude product was extracted with EtOAc (40 mL × 3), washed with H₂O (80 mL) and NaCl (50 mL sat. aq. soln.), dried over Na₂SO₄, filtered and concentrated to give a residue which was purified by reverse phase HPLC

(10-90% MeCN/water with 0.1% TFA modifier) to afford the title compound. LC/MS = 197 [M+1].

STEP D: 5-Chloro-6-methylpyrazolo[1,5-*a*]pyridine-2-carbaldehyde

To a stirred solution of (5-chloro-6-methylpyrazolo[1,5-*a*]pyridin-2-yl)methanol (45 mg, 229 μ mol) in CHCl_3 (3 mL) was added MnO_2 (398 mg, 4.58 mmol), and the mixture was stirred at 60 °C. After 15 hrs, the mixture was filtered, and the filtrate was concentrated to afford the title compound. LC/MS = 195 [M+1].

STEP E: 5-Chloro-6-methylpyrazolo[1,5-*a*]pyridine-2-carboxylic acid

5-Chloro-6-methylpyrazolo[1,5-*a*]pyridine-2-carbaldehyde (35 mg, 180 μ mol) was dissolved in DMSO (2 mL). KH_2PO_4 (8 mg, 59 μ mol) in water (0.5 mL) was added, followed by sodium chlorite (25 mg, 276 μ mol) in water (1.5 mL), and the resulting mixture was stirred at 15 °C. After 2 hours the reaction was diluted with water (15 mL), the pH was adjusted to 10 with NaOH (2M aq. soln.), and the mixture was washed with EtOAc (20 mL $\times$ 3). The pH of the aqueous layer was adjusted to 4 with HCl (1N aq. soln.) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with NaCl (30 mL sat. aq. soln.), dried over Na_2SO_4 , filtered, and concentrated to afford the title compound. LC/MS = 211 [M+1].

STEP F: 5-Chloro-6-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a stirred solution of 5-chloro-6-methylpyrazolo[1,5-*a*]pyridine-2-carboxylic acid (30 mg, 142 μ mol), HATU (81 mg, 214 μ mol) and DIPEA (75 μ L, 427 μ mol) in DMF (1 mL) was added 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (34.1 mg, 171 μ mol). The mixture was stirred at 15 °C. After 1 hour the crude product was extracted with EtOAc (20 mL $\times$ 3), washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4 , and filtered. The filtrate was concentrated to give a residue which was purified by prep-TLC (SiO_2 , pet. ether / EtOAc = 1/1) to afford the title compound. LC/MS = 356 [M+1].

STEP G: 6-Methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

To a mixture of 5-chloro-6-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (30 mg, 84 μ mol), B_2Pin_2 (32 mg, 126 μ mol), potassium acetate (25 mg, 255 μ mol) in 1,4-dioxane (2 mL) was added XPhos Pd G2 (7 mg, 8.90 μ mol) under N_2 atmosphere. The mixture was stirred at 85 °C for 12 h. The crude product was extracted with EtOAc (20 mL $\times$ 3), washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4 , and filtered. The filtrate was concentrated to give a residue which was purified by prep-TLC (SiO_2 , pet. ether / EtOAc = 1/2) to afford the title compound. LC/MS = 448 [M+1].

STEP H: 5-Hydroxy-6-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide

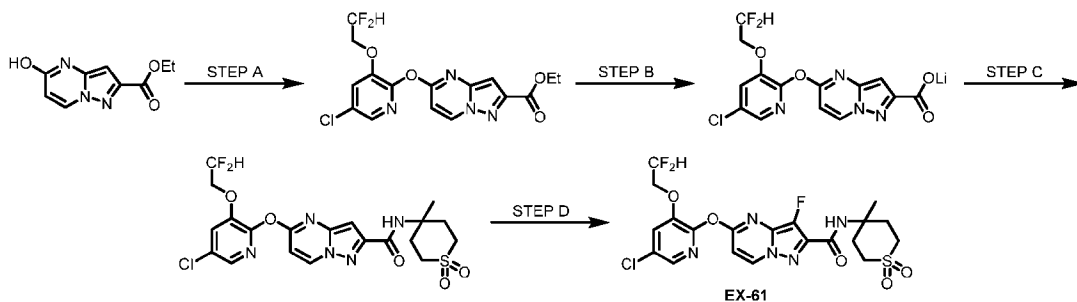
To a suspension of 6-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (25 mg, 56 μ mol) in THF (1 mL) and water (1 mL) was added $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ (18 mg, 169 μ mol). The mixture was stirred at 15 °C. After 1 hour the crude product was extracted with EtOAc (20 mL $\times$ 3), washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4 , and filtered. The filtrate was concentrated to give a residue which was purified by prep-TLC (SiO_2 , pet. ether/EtOAc = 0/1) to afford the title compound. LC/MS = 338 [M+1].

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

To a stirred solution of 5-hydroxy-6-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (15 mg, 44 μ mol), 5-fluoro-2-iodo-3-(2,2,2-trifluoroethoxy)pyridine (22 mg, 69 μ mol), dimethylglycine (1 mg, 9.70 μ mol) and K_3PO_4 (28 mg, 132 μ mol) in DMSO (1 mL) was added CuI (2 mg, 10.50 μ mol) in a glove box, and the reaction mixture was heated to 100 °C. After 15 hrs, the mixture was cooled down to RT and filtered to give a residue which was purified by reverse phase HPLC (10-90% MeCN/water with 0.1% FA modifier) to afford the title compound. LC/MS = 531 [M+1]. ^1H NMR (500 MHz, Methanol- d_4) δ 8.50 (s, 1H), 7.78-7.80 (m, 1H), 7.64 (dd, J =2.44, 9.16 Hz, 1H), 7.20 (s, 1H), 6.85 (s, 1H), 4.73 (q, J =8.24 Hz, 2H), 3.23-3.30 (m, 2H), 3.00-3.03 (m, 2H), 2.87-2.90 (m, 2H), 2.25 (s, 3H), 2.17-2.24 (m, 2H), 1.55 (s, 3H). Human DGAT2 IC_{50} = 3.5 nM.

EXAMPLE 61

5-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-fluoro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide



STEP A: 5-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyrimidine-2-carboxylic acid

To a stirred solution of ethyl 5-hydroxypyrazolo[1,5-*a*]pyrimidine-2-carboxylate (240 mg, 1.16 mmol), *N*1,*N*2-bis(4-hydroxy-2,6-dimethylphenyl)oxalamide (152 mg, 463 μ mol), CuI (55 mg, 290 μ mol) and K₃PO₄ (615 mg, 2.90 mmol) in DMSO (5.8 mL) was added 5-chloro-3-(2,2-difluoroethoxy)-2-iodopyridine (777 mg, 2.43 mmol), and the reaction mixture was heated to 90 °C. After 16 hours the reaction mixture was diluted with 50 mL EtOAc and filtered through celite. The solution was then washed with LiCl (1N aq. soln.) twice and NaCl (sat. aq. soln.), dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude material 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].

10 **STEP B: 5-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyrimidine-2-carboxylic acid**

To a stirring solution of ethyl 5-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyrimidine-2-carboxylate (182 mg, 0.456 mmol) in acetonitrile (3043 μ L) and water (1521 μ L) was added lithium hydroxide (13.66 mg, 0.571 mmol) at 20 °C. After 30 minutes the solvent was removed *in vacuo* to afford the title compound. LC/MS = 371 [M+1].

STEP C: 5-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide

To a stirred solution of lithium 5-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyrimidine-2-carboxylate (169 mg, 449 μ mol), DIPEA (235 μ L, 1.35 mmol) and 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide hydrochloride (94 mg, 471 μ mol) in DMF (4.5 μ L) was added HATU (179 mg, 471 μ mol). After 18 hours the reaction mixture was filtered, and the solvent was removed *in vacuo*. The crude residue was subjected to SiO₂ flash column chromatography using a 0-100% ethyl acetate in hexane to afford the title compound. LC/MS = 516 [M+1].

25 **STEP D: 5-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-fluoro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide**

To a stirred solution of 5-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide (86 mg, 167 μ mol) in acetonitrile (833 μ L) was added Selectfluor™ (70.9 mg, 200 μ mol) in a single portion at 0 °C. After 1h the reaction mixture was allowed to warm to RT and stirred for an additional 24 hrs. The reaction mixture was filtered through a plug of silica gel, concentrated *in vacuo*, and subjected to silica gel flash column chromatography using a 0-60% ethyl acetate in hexanes gradient followed by reverse phase HPLC (35-70% MeCN/water with 0.1% FA modifier) to afford the title compound. LC/MS = 534 [M+1]. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.11 (d, J =

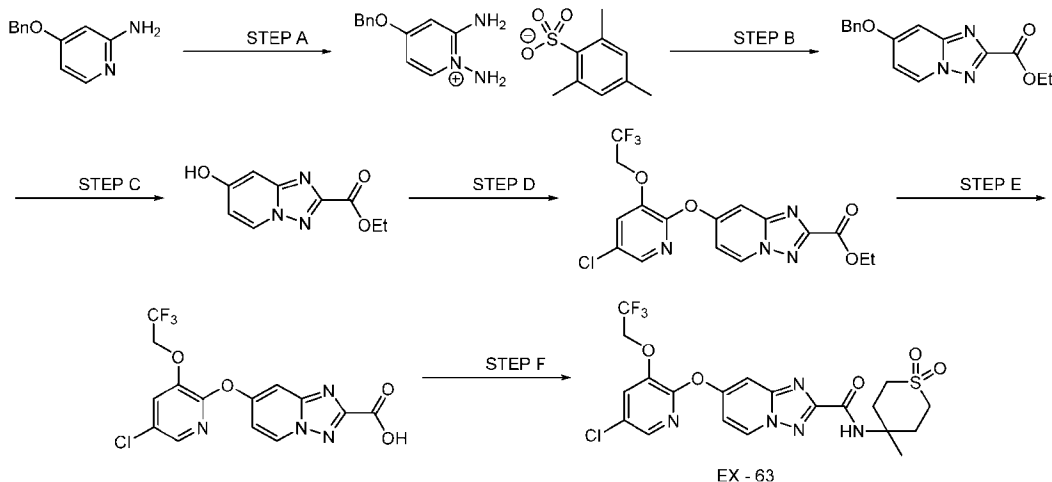
7.7 Hz, 1H), 8.17 (s, 1H), 8.11 (d, J = 2.1 Hz, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 6.22 (t, J = 53.9 Hz, 1H), 4.47 (td, J = 14.7, 3.2 Hz, 2H), 3.08 (s, 4H), 2.76 (d, J = 13.9 Hz, 2H), 2.03 (d, J = 9.6 Hz, 2H), 1.44 (s, 3H). Human DGAT2 IC₅₀ = 133 nM.

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

Example	Structure	Name	LCMS [M+1]	Human DGAT2 IC ₅₀ (nM)
62		5-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide	516	86

Example 63

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



STEP A: 1,2-Diamino-4-(benzyloxy)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate

4-(benzyloxy)pyridin-2-amine (0.64 g, 3.17 mmol) was added to a mixture of O-(mesitylsulfonyl)hydroxylamine in DCM (10 mL) (0.68 g, 3.17 mmol) at 20 °C. After 15 hrs, the reaction mixture was concentrated under reduced pressure to give the crude title compound.

LC/MS = 216 [M+1]

STEP B: Ethyl 7-(benzyloxy)-[1,2,4]triazolo[1,5-a]pyridine-2-carboxylate

To a stirred solution of 1,2-diamino-4-(benzyloxy)pyridin-1-ium 2,4,6-trimethylbenzenesulfonate (1.32 g, 3.17 mmol) in pyridine (20 mL) was added ethyl oxalyl chloride (866 mg, 6.34 mmol), and the reaction mixture was heated to 100 °C. After two hours the mixture was poured into Na₂CO₃ (sat. aq. soln.) (70 mL) and extracted 3 times with DCM (70 mL). The combined organic layers were washed with brine (60 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography using a 0-80% ethyl acetate in pet. ether gradient to afford the title compound. LC/MS = 298 [M+1]

STEP C: Ethyl 7-hydroxy-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxylate

To a stirred solution of 7-(benzyloxy)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxylate (500 mg, 1.68 mmol), TEA (938 µL, 6.73 mmol) and PdCl₂ (149 mg, 841 µmol) in THF (9 mL) was added triethylsilane (1.34 mL, 8.41 mmol) dropwise at 25 °C. After 2 hours the reaction mixture was filtered, concentrated under reduced pressure, and the residue was purified by silica gel flash column chromatography using a 0-90% ethyl acetate in pet. ether gradient to afford the title compound. LC/MS = 208 [M+1]

STEP D: Ethyl 7-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxylate

To a stirred solution of ethyl 7-hydroxy-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxylate (250 mg, 1.21 mmol), 2-bromo-5-chloro-3-(2,2,2-trifluoroethoxy)pyridine (456 mg, 1.57 mmol), 1,10-phenanthroline (43.5 mg, 241 µmol) and K₂CO₃ (500 mg, 3.62 mmol) in DMSO (4 mL) was added CuI (46.0 mg, 241 µmol) in the glove box, and the reaction mixture was heated to 100 °C. After 12 hrs, the mixture was cooled down to RT and filtered, and the filtrate was purified by reverse phase HPLC (43-73% ACN / 10 mM NH₄HCO₃) to afford the title compound. LC/MS = 417 [M+1]

STEP E: 7-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxylic acid

To a stirred solution of ethyl 7-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxylate (100 mg, 240 µmol) in MeOH (8 mL) and H₂O (0.4 mL) was added LiOH (30 mg, 714 µmol). After 13 hrs, the reaction mixture was concentrated under reduced pressure to give the crude title compound. LC/MS = 389 [M+1]

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

To a stirred solution of 7-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxylic acid (30 mg, 77 µmol), 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide dihydrochloride (22 mg, 93 µmol), and HATU (44.0 mg, 116 µM) in

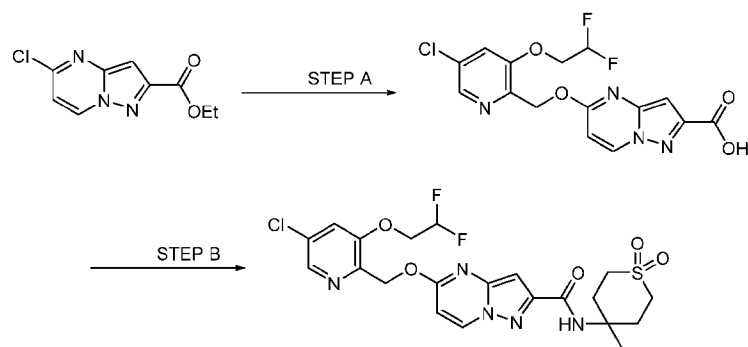
DMF (1 mL) was added DIPEA (67 μ L, 386 μ mol), and the mixture was stirred at 25 °C. After 30 minutes, MeCN (1 mL) was added. The mixture was filtered, and the filtrate was purified by reverse-phase HPLC (60-80% MeCN/water with 0.1% FA modifier) to afford the title compound. LCMS = 534 [M+1]. ¹H NMR (400 MHz, Methanol-d₄) δ 8.84 (d, *J*=7.58 Hz, 1H), 7.91 (d, *J*=2.20 Hz, 1H), 7.81 (d, *J*=1.96 Hz, 1H), 7.49 (d, *J*=2.20 Hz, 1H), 7.19 (dd, *J*=2.45, 7.58 Hz, 1H), 4.74 (q, *J*=8.31 Hz, 2H), 3.25 (br d, *J*=2.45 Hz, 2H), 3.02 (br d, *J*=13.94 Hz, 2H), 2.89 (br d, *J*=14.43 Hz, 2H), 2.15-2.28 (m, 2H), 1.56 (s, 3H). Human DGAT2 IC₅₀ = 349 nM.

By using procedures similar to those described in **Example 63** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

Example	Structure	Name	LCMS [M+1]	Human DGAT2 IC ₅₀ (nM)
64		7-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-N-(4-(difluoromethyl)-1,1-dioxido-2H-thiopyran-4-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-carboxamide	570	165
65		7-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-N-(1,1-dioxido-4-(2,2,2-trifluoroethyl)tetrahydro-2H-thiopyran-4-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-carboxamide	602	160
66		7-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-N-(3-methyl-1,1-dioxidothietan-3-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-carboxamide	506	67

EXAMPLE 67

5-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide



EX - 67

STEP A: 5-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid

To a stirred solution of sodium hydride (10.64 mg, 0.27 mmol) in THF (1.3 mL) was added (5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methanol (49.6 mg, 0.22 mmol) at 0 °C. After 10 minutes, ethyl 5-chloropyrazolo[1,5-a]pyrimidine-2-carboxylate (50 mg, 0.22 mmol) was added and the mixture was allowed to warm to 20 °C. After 2 hrs, LiOH (7.96 mg, 0.33 mmol), MeOH (633 µL), and water (317 µL) were added. After 3 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 Na₂SO₄, filtered, and concentrated *in vacuo* to afford the title compound. LC/MS = 385 [M+1].

STEP B: 5-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)-N-(4-methyl-1,1-dioxido-2,3,4,5-tetrahydrothiopyran-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide

To a stirred solution of 5-((5-chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (33 mg, 86 µmol), DIPEA (37 µl, 214 µmol) and 4-amino-4-methyl-1,1-dioxido-2,3,4,5-tetrahydrothiopyran 1,1-dioxide hydrochloride (17 mg, 86 µmol) in DMF (572 µL) was added HATU (33 mg, 86 µmol). After 18 hours the solvent was removed in *vacuo*, and the crude material was subjected to silica gel flash column chromatography using a 0-100% EtOAc in hexanes gradient to afford the title compound. LC/MS = 530 [M+1]. ¹H NMR (500 MHz, Methanol-d₄) δ 8.19 (s, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.72 (s, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.20 (tt, *J* = 54.7, 3.7 Hz, 1H), 5.64 (s, 2H), 4.44 (td, *J* = 13.8, 3.6 Hz, 2H), 4.09 (s, 3H), 3.42 – 3.35 (m, 2H), 3.06 – 2.95 (m, 2H), 2.93 – 2.84 (m, 2H), 2.29 – 2.17 (m, 2H), 1.57 (s, 3H). Human DGAT2 IC₅₀ = 3.3 nM.

By using procedures similar to those described in **Example 67** with appropriate reagents, the following compounds were synthesized. These compounds were characterized by LC/MS.

Example	Structure	Name	LCMS [M+1]	Human DGAT2 IC ₅₀ (nM)
68		5-((6-Methoxypyridin-2-yl)methoxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide	446	>9990
69		5-((6-Ethoxypyridin-2-yl)methoxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide	460	264
70		5-((3-Chloro-6-methoxypyridin-2-yl)methoxy)-N-(4-methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyrimidine-2-carboxamide	480	82

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

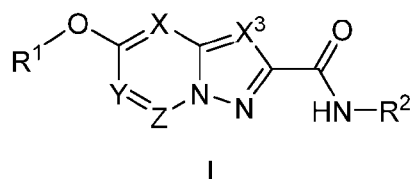
top organic layer of in-plate liquid-liquid extraction were injected onto a Thermo Betabasic C4 column (2.1 mm x 20 mm, 5 µm particle size). The samples were then eluted using the following conditions; mobile phase: Isopropanol: acetonitrile/10mM ammonium formate = 50/35/15 (v/v/v), flow rate: 0.8 mL/min, 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 ¹³C₁₈-triolein (Q1: 920.8>Q3:621.3) and internal standard ¹³C₂₁-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 ¹³C₁₈triolein generated in the reaction and spiked in internal standard ¹³C₂₁-triolein was used to generate percentage inhibition and IC₅₀ 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 IC₅₀ were calculated by 4 parameter sigmoidal curve fitting formula.

DGAT2 enzymatic activity assay

DGAT2 activity was determined by measuring the amount of enzymatic product ¹³C₁₈-triolein (¹³C-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 MgCl₂, 5% ethanol), 25 µM of diolein, 5 µM of ¹³C oleoyl-CoA and 8 ng/µL of DGAT2 membrane.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



- 5 or a pharmaceutically acceptable salts thereof wherein:

X^3 is selected from $C(R^3)$ and N;

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

R^1 is

- (1) a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl
 10 is unsubstituted or substituted with 1, 2, or 3 R^5 , or
 (2) $-(C_{1-6})$ 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 ;

15 R^2 is

- (1) a 4- to 7-membered heterocycle containing 1, 2 or 3 heteroatoms independently
 selected from N, O and S,
 (2) $-(C_{1-6})$ alkyl-heterocyclyl, wherein the heterocyclyl is a 3- to 6-membered ring
 containing 1 or 2 heteroatoms independently selected from N, O and S,
 20 (3) $-(C_{1-6})$ alkyl,
 (4) $-(C_{3-6})$ cycloalkyl,
 (5) $-(C_{1-6})$ hydroxyalkyl,
 (6) $-SO_2(C_{1-6})$ alkyl, or
 (7) $-(C_{1-6})$ alkyl-NH- $SO_2-(C_{1-6})$ alkyl,

25 wherein each alkyl, cycloalkyl and heterocycle is unsubstituted or substituted with 1, 2, 3, 4, or 5
 substituents selected from R^5 ;

when present, R^3 is

- (1) hydrogen,
 (2) halogen,
 30 (3) $-NH_2$
 (4) (C_{1-6}) alkyl,

- (5) (C₁₋₆)haloalkyl,
- (6) (C₁₋₄)alkylhydroxy, or
- (7) -(C₃₋₆)cycloalkyl;

when present, each R⁴ is independently

- 5 (1) hydrogen,
- (2) halogen, or
- (3) (C₁₋₃)alkyl;

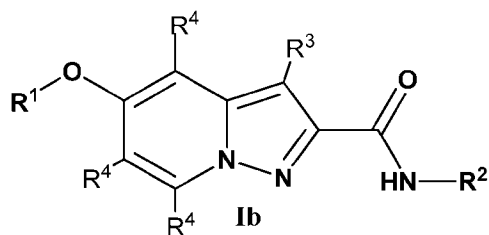
when present, each R⁵ is independently

- (1) -OC₁₋₆alkyl,
- 10 (2) -O(C₁₋₆)haloalkyl,
- (3) halogen,
- (4) cyano,
- (5) O-(C₃₋₆)cycloalkyl, optionally substituted with halogen,
- (6) (C₁₋₃)hydroxyalkyl,
- 15 (7) (C₁₋₆)haloalkyl-,
- (8) (C₁₋₃)hydroxyhaloalkyl, or
- (9) (C₁₋₆)alkyl-(C₃₋₇)cycloalkyl-OH;

when present, each R⁶ is independently

- (1) oxo,
- 20 (2) (C₁₋₆)alkyl, or
- (3) (C₁₋₆)haloalkyl-.

2. A compound of claim 1, of Formula Ib,



25 wherein:

or a pharmaceutically acceptable salts thereof wherein:

R¹ is

- (1) a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1, 2, or 3 R⁵, or

- (2) $-(C_{1-6})\text{alkyl-heteroaryl}$, 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 ;

R^2 is

- 5 (1) a 4- to 7-membered heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S,
- (2) $-(C_{1-6})\text{alkyl-heterocyclyl}$, wherein the heterocyclyl is a 3- to 6-membered ring containing 1 or 2 heteroatoms independently selected from N, O and S,
- (3) $-(C_{1-6})\text{alkyl}$,
- 10 (4) $-(C_{3-6})\text{cycloalkyl}$,
- (5) $-(C_{1-6})\text{hydroxyalkyl}$,
- (6) $-\text{SO}_2(C_{1-6})\text{alkyl}$, or
- (7) $-(C_{1-6})\text{alkyl-NH-SO}_2-(C_{1-6})\text{alkyl}$,

wherein each alkyl, cycloalkyl and heterocycle is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from R^6 ;

when present, R^3 is

- (1) hydrogen,
- (2) halogen,
- (3) $-\text{NH}_2$
- 20 (4) $(C_{1-6})\text{alkyl}$,
- (5) $(C_{1-6})\text{haloalkyl}$,
- (6) hydroxy $(C_{1-4})\text{alkyl}$, or
- (7) $-(C_{3-6})\text{cycloalkyl}$;

each R^4 is independently selected from

- 25 (1) hydrogen,
- (2) halogen, or
- (3) $(C_{1-3})\text{alkyl}$;

when present, each R^5 is independently selected from

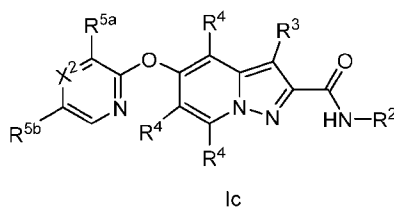
- (1) $-\text{OC}_{1-6}\text{alkyl}$,
- 30 (2) $-\text{O}(C_{1-6})\text{haloalkyl}$,
- (3) halogen,
- (4) cyano,
- (5) $\text{O}-(C_{3-6})\text{cycloalkyl}$, optionally substituted with halogen,
- (6) $(C_{1-3})\text{hydroxyalkyl}$,

- (7) (C₁₋₆)haloalkyl-,
- (8) (C₁₋₃)hydroxyhaloalkyl, or
- (9) (C₁₋₆)hydroxyalkyl-(C₃₋₇)cycloalkyl;

when present, each R⁶ is independently

- (1) oxo,
- (2) (C₁₋₆)alkyl, or
- (3) (C₁₋₆)haloalkyl-.

3. A compound of claim 1, of Formula Ic,



or a pharmaceutically acceptable salt thereof wherein:

X² is CH or N;

R² is

- (1) a 4- to 7-membered heterocycle containing 1, 2 or 3 heteroatoms independently selected from N, O and S,
- (2) -(C₁₋₆)alkyl-heterocyclyl, wherein the heterocyclyl is a 3- to 6-membered ring containing 1 or 2 heteroatoms independently selected from N, O and S,
- (3) -(C₁₋₆)alkyl,
- (4) -(C₃₋₆)cycloalkyl,
- (5) -(C₁₋₆)hydroxyalkyl,
- (6) -SO₂(C₁₋₆)alkyl, or
- (7) -(C₁₋₆)alkyl-NH-SO₂-(C₁₋₆)alkyl,

wherein each alkyl, cycloalkyl and heterocycle is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from R⁶;

- when present, R³ is

- (1) hydrogen,
- (2) halogen,
- (3) -NH₂
- (4) (C₁₋₆)alkyl,
- (5) (C₁₋₆)haloalkyl,

(6) hydroxy(C₁₋₄)alkyl, or

(7) -(C₃₋₆)cycloalkyl;

each R⁴ is independently

(1) hydrogen,

5 (2) halogen, or

(3) (C₁₋₃)alkyl;

when present, each R^{5a} is independently

(1) -OC₁₋₆alkyl,

(2) -O(C₁₋₆)haloalkyl, or

10 (3) O-(C₃₋₆)cycloalkyl;

when present, each R^{5b} is independently

(1) halogen,

(2) cyano,

(3) -OC₁₋₆alkyl,

15 (4) (C₁₋₃)hydroxyalkyl,

(5) (C₁₋₃)hydroxyhaloalkyl, or

(6) (C₁₋₆)hydroxyalkyl-(C₃₋₇)cycloalkyl;

when present, each R⁶ is independently

(1) oxo,

20 (2) (C₁₋₆)alkyl, or

(3) (C₁₋₆)haloalkyl.

4. The compound of any of the claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R¹ is

25 (1) a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, OC₁₋₆alkyl, O(C₁₋₆)haloalkyl, O-(C₃₋₆)cycloalkyl, cyano, (C₁₋₆)hydroxyalkyl-(C₃₋₆)cycloalkyl, and (C₁₋₃)hydroxyhaloalkyl, or

30 (2) -(C₁₋₆)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 one, two, or three substituents independently selected from halogen, OC₁₋₆alkyl, and O(C₁₋₆)haloalkyl.

5. The compound of any one of claims 1-2, 4, or a pharmaceutically acceptable salt thereof, wherein R¹ is

- 5 (1) a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, OC₁₋₆alkyl, O(C₁₋₆)haloalkyl, O-(C₃₋₆)cycloalkyl, cyano, (C₁₋₆)hydroxyalkyl-(C₃₋₆)cycloalkyl, (C₁₋₃)hydroxyalkyl and (C₁₋₃)hydroxyhaloalkyl, or
- 10 (2) -(C₁₋₆)alkyl-heteroaryl, wherein the heteroaryl is a 6-membered heteroaryl containing 1, nitrogen heteroatom, wherein the heteroaryl is unsubstituted or substituted with one or two substituents independently selected from halogen, OC₁₋₆alkyl, and O(C₁₋₆)haloalkyl.

6. The compound of any one of claims 1-2, 4-5, or a pharmaceutically acceptable salt thereof, wherein R¹ is a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, OC₁₋₆alkyl, O(C₁₋₆)haloalkyl, O-(C₃₋₆)cycloalkyl, cyano, (C₁₋₆)hydroxyalkyl-(C₃₋₆)cycloalkyl, (C₁₋₃)hydroxyalkyl and (C₁₋₃)hydroxyhaloalkyl.

20 7. The compound of any one of claims 1-2, 4-6, or a pharmaceutically acceptable salt thereof, wherein R¹ is a 6-membered heteroaryl containing 1 or 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, OCH₂CF₃, OCH₂CF₂H, O-cyclopropyl, CN, CH(cyclopropyl)OH, CH(CH₃)OH, and CH(CF₃)OH.

25 8. The compound of any one of claims 1-2, 4-5, or a pharmaceutically acceptable salt thereof, wherein R¹ is a -(C₁₋₃)alkyl-heteroaryl, wherein the heteroaryl is a 6-membered heteroaryl containing 1 nitrogen atom, wherein the heteroaryl is unsubstituted or substituted with one, two, or three substituents independently selected from Cl, OCH₃, OCH₂CH₃ and

30 OCH₂CHF₂.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R² is

(1) a 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 oxo, C₁₋₃alkyl, or C₁₋₃haloalkyl,

- 5 (2) -(C₃₋₆)cycloalkyl,
(3) -(C₁₋₆)hydroxyalkyl, or
(4) -(C₁₋₆)alkyl-NH-SO₂-(C₁₋₆)alkyl.

10 10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R² is a 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 oxo, C₁₋₃alkyl, or C₁₋₃haloalkyl.

15 11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R² is a 4- to 7-membered heterocyclyl containing 1 or 2 heteroatoms independently selected from N, O and S, optionally substituted with one, two, three, four or five substituents independently selected from oxo, CH₃, CHF₂, or CH₂CF₃.

20 12. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R² is C(CH₃)₂CH₂C(CH₃)₂OH.

25 13. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R² is a 6 membered heterocycle containing 1 nitrogen atom optionally substituted with one or two substituents independently selected from oxo, -(C₁₋₃)alkyl and -(C₁₋₃)haloalkyl.

30 14. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R² is a 5 membered heterocycle containing 1 nitrogen atom optionally substituted with one or two substituents independently selected from oxo, -(C₁₋₃)alkyl and -(C₁₋₃)haloalkyl.

15. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R² is -(C₁₋₆)alkyl-NH-SO₂-(C₁₋₆)alkyl.

16. The compound of any one of claims 1-9 or 15, or a pharmaceutically acceptable salt thereof, wherein R² is CH(CH₃)₂CH₂NHSO₂CH₃.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen, halogen, (C₁₋₆)alkyl, -(C₁₋₆)haloalkyl, -(C₁₋₆)hydroxyalkyl, -(C₃₋₆)cycloalkyl, or -NH₂,

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen, halogen, CH₃, CH₂CH₃, CH(CH₃)₂, CH(F₂), CH₂OH, CF₃, CH(OH)CH₃, CH₂C(OH)(CH₃)₂, cyclopropyl, or -NH₂.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein R⁴ is hydrogen, halogen or (C₁₋₆)alkyl.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R⁴ is H, Cl, F, or CH₃.

21. The compound of any one of claims 1-2, 9-20, or a pharmaceutically acceptable salt thereof, wherein R⁵ is -OC₁₋₆alkyl, -O(C₁₋₆)haloalkyl, halogen, cyano, O-(C₃₋₆)cycloalkyl, (C₁₋₆)haloalkyl-, (C₁₋₃)hydroxyhaloalkyl, (C₁₋₃)hydroxyalkyl or -(C₃₋₇)cycloalkylhydroxy.

22. The compound of any one of claims 1-2, 9-21, or a pharmaceutically acceptable salt thereof, wherein R⁵ is halogen, OCH₃, OCH₂CH₃, OCH₂CF₃, OCH₂CHF₂, O-cyclopropyl, CN, CH(cyclopropyl)OH, CH(CH₃)OH, or CH(CF₃)OH.

23. The compound of any one of claims 3, 9-20, or a pharmaceutically acceptable salt thereof, wherein R^{5a} is OCH₂CHF₂, OCH₂CF₃, O-cyclopropyl.

24. The compound of any one of claims 3, 9-20 or 23, or a pharmaceutically acceptable salt thereof, wherein R^{5b} is halogen, CH(cyclopropyl)OH, CN, CH(CH₃)OH, CH(CF₃)OH.

25. The compound of any one of claims 1-2 or 9-22, or a pharmaceutically acceptable salt thereof, wherein R⁶ is oxo, (C₁₋₆)alkyl, or (C₁₋₆)haloalkyl-.

26. The compound of any one of claims 1-2, 9-22 or 25, or a pharmaceutically acceptable salt thereof, wherein R⁶ is oxo, CH₃, CHF₂, or CH₂CF₃.

27. The compound of any one of claims 1, 4-22, or 25-26, or a pharmaceutically acceptable salt thereof, wherein X is C(R⁴), Y is C(R⁴), and Z is C(R⁴).

28. The compound of any one of claims 1, 4-22, or 25-26, or a pharmaceutically acceptable salt thereof, wherein X is N, Y is C(R⁴), and Z is C(R⁴).

29. The compound of any one of claims 1, 4-22, or 25-26, or a pharmaceutically acceptable salt thereof, wherein X is C(R⁴), Y is N, and Z is C(R⁴).

30. The compound of any one of claims 1, 4-22, or 25-26, or a pharmaceutically acceptable salt thereof, wherein X is C(R⁴), Y is C(R⁴), and Z is N.

31. The compound of any one of claims 1, 4-22, or 25-26, or a pharmaceutically acceptable salt thereof, wherein X³ is N.

32. The compound of any one of claims 1, 4-22, or 25-26, or a pharmaceutically acceptable salt thereof, wherein X³ is C(R³).

33. The compound of claim 1, or a pharmaceutically acceptable salt thereof, which is:
N-(4-Methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5-((3-(2,2,2-Trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(2,3,3-trimethyl-1,1-dioxidoisothiazolidin-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
N-(2-Methyl-1-(methylsulfonamido)propan-2-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
N-(4-Hydroxy-2,4-dimethylpentan-2-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
N-(2-Oxo-1-(2,2,2-trifluoroethyl)piperidin-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,

- N*-(3-Methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 (S)-*N*-(Tetrahydrofuran-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 5 *N*-Cyclopentyl-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 (R)-5-((3-(2,2-Difluoroethoxy)pyrazin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 5-((3-(2,2-Difluoroethoxy)pyrazin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 10 5-((3-Cyclopropoxy-5-fluoropyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 5-((3-(2,2-Difluoroethoxy)-5-fluoropyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 15 5-((3-Cyclopropoxy-5-fluoropyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
N-(4-Methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyrazin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 20 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 25 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 (R)-5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 3-Methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 30 3-Methyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
 3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,

- 3-Fluoro-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
(*R*)-3-Fluoro-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5 3-Chloro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Chloro-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
(*R*)-3-Chloro-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
10 (*S*)-3-Chloro-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
15 (*R*)-3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidotetrahydrothiophen-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Chloro-5-((3-(2,2-difluoroethoxy)pyrazin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5-((3-(2,2-Difluoroethoxy)pyrazin-2-yl)oxy)-3-fluoro-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
20 5-((3-(2,2-Difluoroethoxy)pyrazin-2-yl)oxy)-3-fluoro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3,4-Dichloro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
25 3-Chloro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Chloro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyrazin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
30 5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-fluoro-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-fluoro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,

- 3-Chloro-5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 3-Chloro-5-((5-chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 5 3-Chloro-5-((5-cyano-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 5-((5-Cyano-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- (*R*)-5-((5-(Cyclopropyl(hydroxy)methyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 10 (*S*)-5-((5-(Cyclopropyl(hydroxy)methyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- (*R*)-5-((5-(1-Hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 15 (*S*)-5-((5-(1-Hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- (*R*)-*N*-(3-Methyl-1,1-dioxidothietan-3-yl)-5-((5-(2,2,2-trifluoro-1-hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- (*S*)-*N*-(3-Methyl-1,1-dioxidothietan-3-yl)-5-((5-(2,2,2-trifluoro-1-hydroxyethyl)-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 20 3-Ethyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 3-Ethyl-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 25 3-Isopropyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 3-(Difluoromethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 3-(Hydroxymethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- 30 *N*-(4-Methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(trifluoromethyl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
- (*R*)-3-(1-Hydroxyethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,

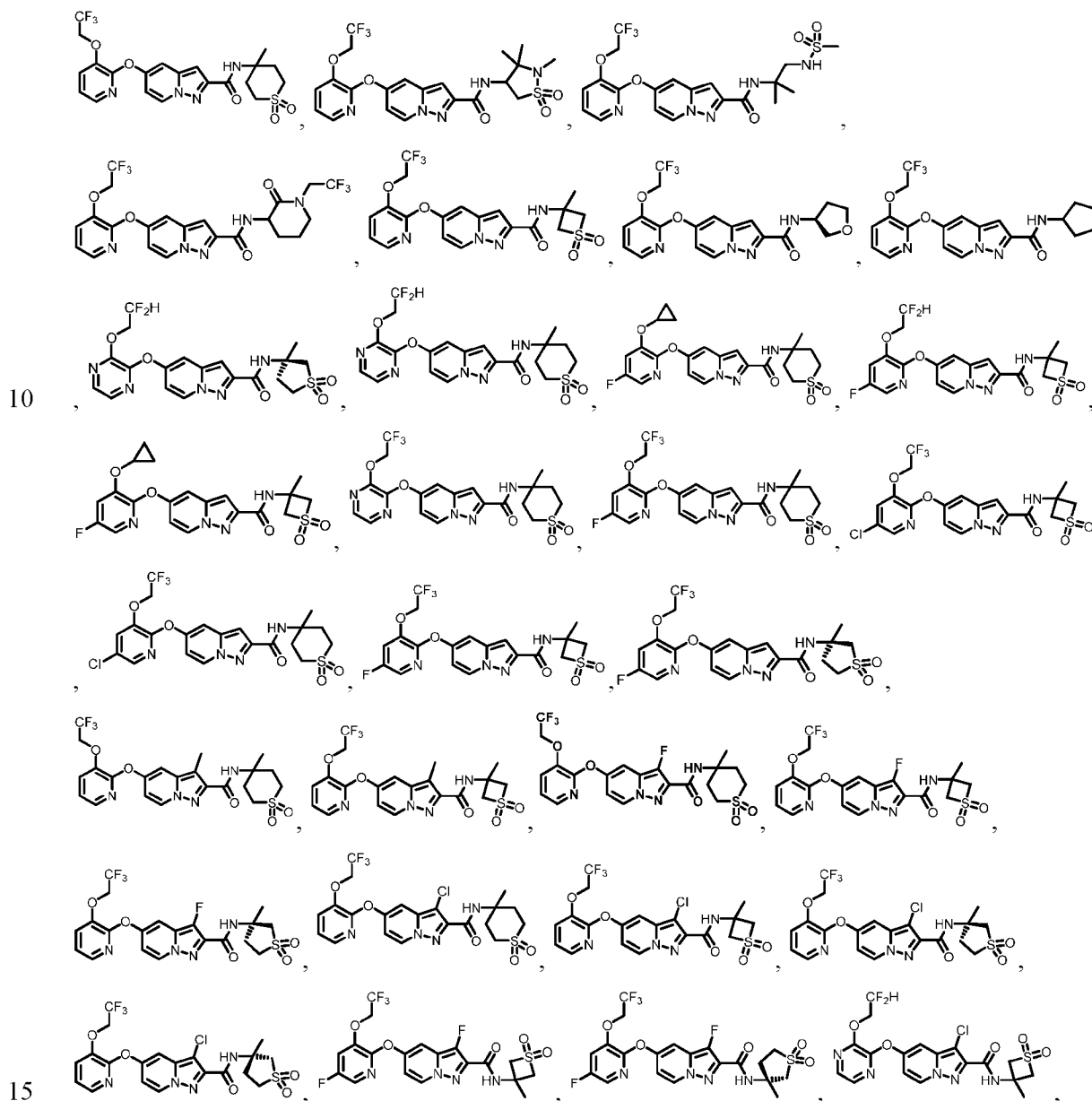
- (*S*)-3-(1-Hydroxyethyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-3-(2-hydroxy-2-methylpropyl)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5 3-Cyclopropyl-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
3-Amino-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
4-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
10 6-Fluoro-5-((5-fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-4-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
15 5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-7-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5-((5-Fluoro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-6-methyl-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyridine-2-carboxamide,
5-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-3-fluoro-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide,
20 5-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide,
7-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxamide,
25 7-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(4-(difluoromethyl)-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxamide,
7-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(1,1-dioxido-4-(2,2,2-trifluoroethyl)tetrahydro-2*H*-thiopyran-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxamide,
7-((5-Chloro-3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)-*N*-(3-methyl-1,1-dioxidothietan-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridine-2-carboxamide,
30 [1,2,4]triazolo[1,5-*a*]pyridine-2-carboxamide,
5-((5-Chloro-3-(2,2-difluoroethoxy)pyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide,
5-((6-Methoxypyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide,

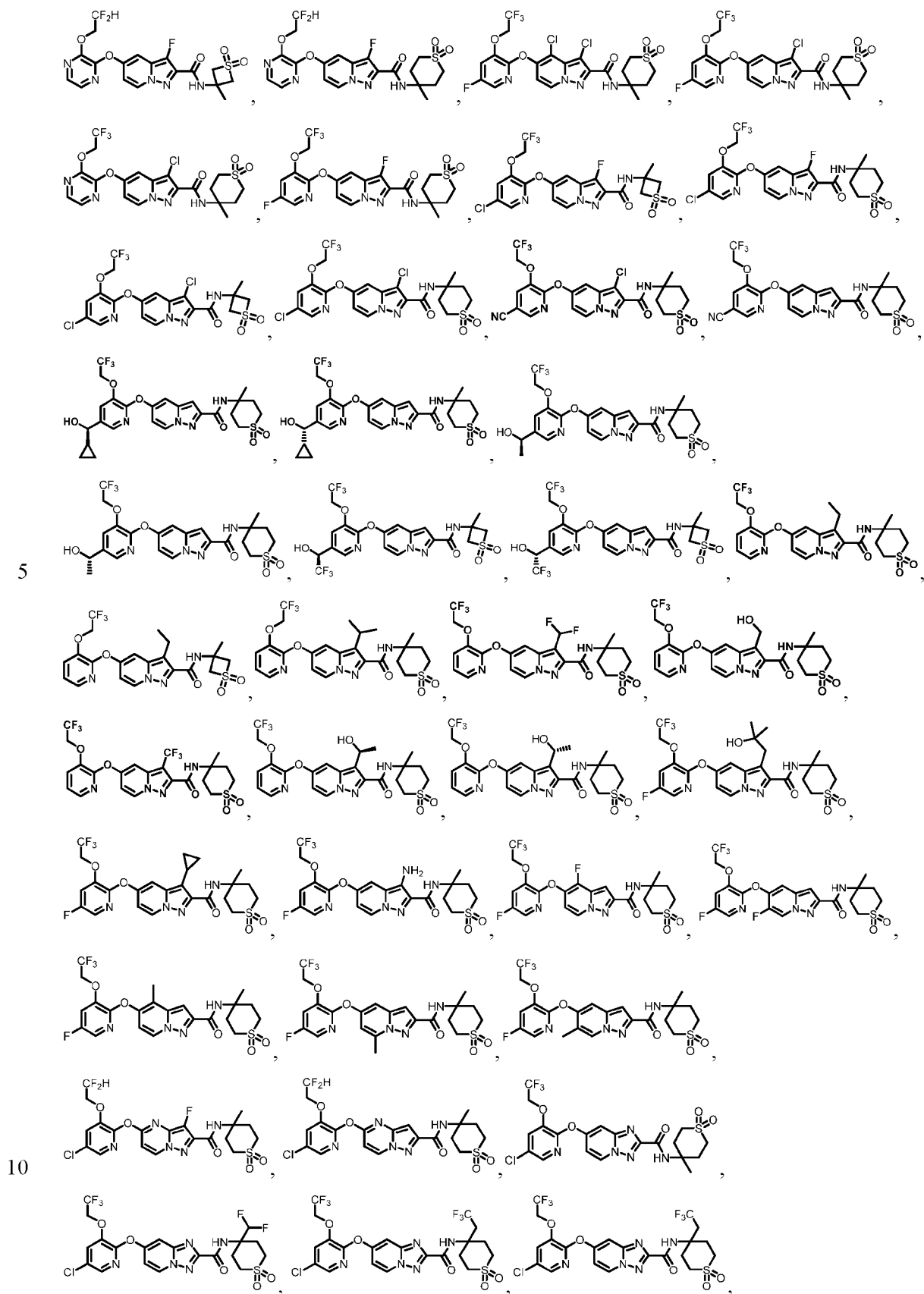
5-((6-Ethoxypyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide, or

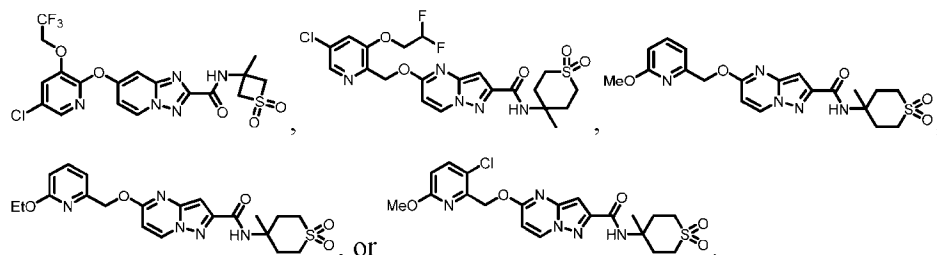
5-((3-Chloro-6-methoxypyridin-2-yl)methoxy)-*N*-(4-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxamide.

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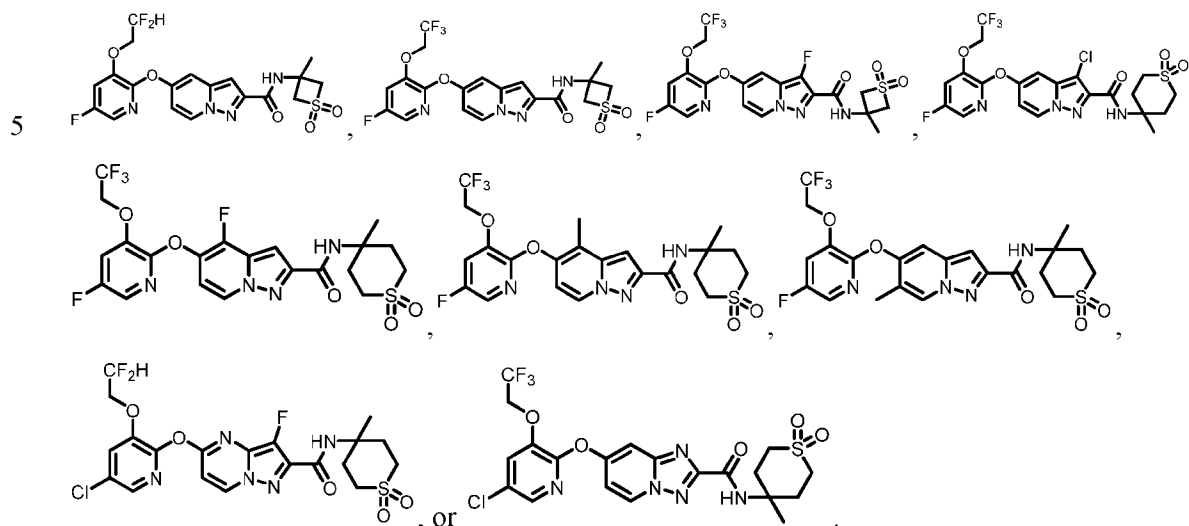
34. The compound of claim 1, or a pharmaceutically acceptable salt thereof, which is:







35. The compound of claim 34, or a pharmaceutically acceptable salt thereof, which is



36. 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 one of claims 1 to 35, or a pharmaceutically acceptable salt thereof, and a pharmaceutically carrier.

37. A composition comprising a pharmaceutically acceptable carrier and a compound according to any one of claims 1 to 35, or a pharmaceutically acceptable salt thereof.

38. 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 35, or a pharmaceutically acceptable salt thereof.

39. Use of a compound of any of claims 1 to 35, 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
- 5 diseases and heart failure.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/077842

A. CLASSIFICATION OF SUBJECT MATTERIPC: **C07D 471/04** (2023.01); **A61K 31/407** (2023.01); **A61P 1/16** (2023.01); **A61P 3/04** (2023.01)CPC: **C07D 471/04**; **A61K 31/407**; **A61P 1/16**; **A61P 3/04**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PUBCHEM, SID 438868337, Modify Date: 19 December 2020 [retrieved on 10 January 2024]. Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/substance/438868337 > entire document	1-4, 33, 34
A	WO 2020/125759 A1 (HUIHAN MEDICAL TECHNOLOGIES LTD. CO.) 25 June 2020 (25.06.2020) entire document	1-4, 33, 34
A	WO 2021/236401 A1 (MERCK SHARP & DOHME CORP.) 25 November 2021 (25.11.2021) entire document	1-4, 33, 34



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“D” document cited by the applicant in the international application

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

20 January 2024 (20.01.2024)

Date of mailing of the international search report

05 March 2024 (05.03.2024)

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. **571-273-8300**

Authorized officer

MATOS
TAINA

Telephone No. **571-272-4300**

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: **5-32, 36-39**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-4 and 33-35 are drawn to compounds of Formula I, or a pharmaceutically acceptable salt thereof.

The first invention of Group I+ is restricted to a compound of Formula I, or a pharmaceutically acceptable salt thereof, specifically wherein the compound is N-(4-Methyl-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-5-((3-(2,2,2-trifluoroethoxy)pyridin-2-yl)oxy)pyrazolo[1,5-a]pyridine-2-carboxamide. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed compound species presented in the claims (see claim 33). It is believed that claims 1-4, 33, and 34 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of Formula I, or a pharmaceutically acceptable salt thereof, specifically wherein the compound is 5-((3-(2,2,2-Trifluoroethoxy)pyridin-2-yl)oxy)-N-(2,3,3-trimethyl-1,1-dioxidoisothiazolidin-4-yl)pyrazolo[1,5-a]pyridine-2-carboxamide. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables, X3, X, Y, Z, R1, R2, and accordingly these groups lack unity a priori.

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structure of Formula I, or a pharmaceutically acceptable salt thereof, these shared technical features do not represent a contribution over the prior art as disclosed by Substance Record for SID 438868337 to PubChem (hereinafter, "PubChem").

PubChem teaches a compound having the core structure of Formula (I) (Pg. 2, compound as shown).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-4, 33, 34**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.