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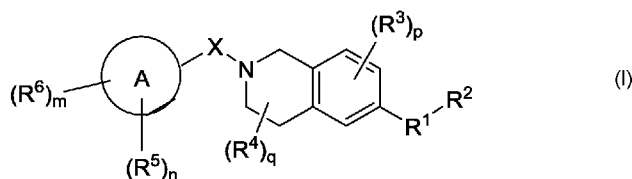
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(54) Title: SUBSTITUTED TETRAHYDROISOQUINOLINE COMPOUNDS USEFUL AS GPR120 AGONISTS



(57) Abstract: Disclosed are compounds represented by formula (I) and pharmaceutically acceptable salts thereof. The compounds are agonists of the G-protein coupled receptor GPR120 and are useful for treating or preventing diabetes, hyperlipidemia, obesity, NASH, inflammation related disorders, and related diseases and conditions.



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SUBSTITUTED TETRAHYDROISOQUINOLINE COMPOUNDS USEFUL AS GPR120 AGONISTS

5 BACKGROUND OF THE INVENTION

The present invention relates to substituted chromane derivatives that are useful in the pharmaceutical field. The compounds act as GPR120 receptor function regulating agents (modulators), which are useful as drugs for treating and/or preventing diabetes, obesity, hyperlipidemia, and inflammation related disorders.

10 GPR120, a G protein-coupled receptor, causes intracellular signaling through binding with unsaturated long chain fatty acids, such as alpha-linoleic acid, to induce various biological reactions. Actions of GPR120 and its ligand(s) have been reported to promote secretion of glucagon-like-peptide-1("GLP-1") functions to reduce blood glucose level in gastrointestinal cell lines (see Nature Medicine, 2005, 11(1), 90-94). GLP-1, which is a peptide hormone, has
15 been found to induce insulin secretion depending on a blood glucose level. GLP-1 is also suggested to be efficacious for delaying the apoptosis of beta cells in type II diabetes mellitus.

GPR120 is expressed in adipocytes. GPR120 has been found to be increasingly expressed by adipose differentiation induction. In addition, actions of GPR120 and its ligand have been reported to suppress lipolysis in adipose-differentiated cells. A high blood lipid level
20 is known to be one of the causes of insulin resistance. Suppression of lipolysis by a GPR120 agonist is thus expected to decrease the levels of free fatty acids in blood to normalize blood lipid levels, resulting in improvement in insulin resistance.

GPR120 is also expressed in the pituitary gland, and a GPR120 ligand is reported to suppress adrenocorticotrophic hormone secretion. Adrenocorticotrophic hormone promotes
25 glucocorticoid secretion downstream thereof to induce action such as promotion of gluconeogenesis in the liver, inhibitory action against glucose uptake in muscle and peripheral tissue, lipolysis in adipose tissue or release of fatty acids or glycerol. Accordingly, GPR120 is considered to exhibit hypoglycemic action or blood lipid lowering action via suppression action against adrenocorticotrophic hormone secretion even in the center.

30 Recently, GPR120 has been shown to play a role in obesity in both mice and humans.

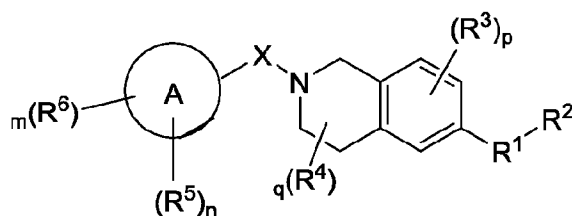
GPR120 knockout mice fed a high fat diet developed obesity, glucose intolerance and fatty liver with decreased adipocyte differentiation and lipogenesis and enhanced hepatic lipogenesis. In the study, insulin resistance in such mice was associated with reduced insulin signaling and enhanced inflammation in adipose tissue. In humans, GPR120 expression in adipose tissue is significantly higher in obese individuals than in lean controls (See Ichimura, et al., Nature, 2012, 483, 350-54; and Cintra, et al., Plos One, 2012, 7(1), 1-15).

GPR120 has also been shown to play a role in inflammation. Wild-type mice treated with omega-3 fatty acids inhibited macrophage-induced tissue inflammation and enhanced systemic insulin sensitivity. However, this effect was not observed in GPR120 knockout mice (See Oh, et al., Cell, 2010, 142, 687; and Talukar, et al., Trends in Pharmacological Sciences, 2011, 32(9), 543-550).

In light of the above description, a compound having GPR120 agonist activity is considered to be useful as an agent for treating and/or preventing diabetes mellitus, obesity, hyperlipidemia, fatty liver (including non-alcoholic steatohepatitis or NASH), and inflammation related disorders.

SUMMARY OF THE INVENTION

The present invention relates to compounds represented by formula I:



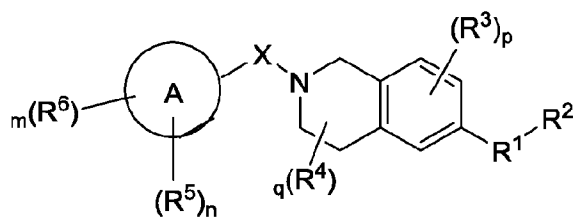
I

as well as pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising a compound of formula I.

The present invention further relates to methods of treating diabetes, obesity, hyperlipidemia, NASH, inflammation related disorders, and related diseases and conditions, comprising administering a compound of formula I to a patient in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds represented by formula I:



I

5 or a pharmaceutically acceptable salt thereof, wherein:

X is

- (1) bond,
- (2) (C₁₋₂)alkyl, or
- (3) halo(C₁₋₂)alkyl;

10 ring A is

- (1) aryl,
- (2) 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from N, O and S, or
- (3) 9- or 10-membered fused heteroaryl containing 1, 2, or 3 heteroatoms

15 independently selected from N, O, and S;

R¹ is

- (1) bond,
- (2) (C₁₋₆)alkyl,
- (3) -O-(C₁₋₆)alkyl-, or
- (4) (C₃₋₆)cycloalkyl;

20

R² is

- (1) hydrogen,
- (2) hydroxy,
- (3) COOH,
- (4) tetrazole,
- (5) hydroxyisoxazole,
- (6) triazole,

25

- 5
- (7) C(O)NH₂,
 - (8) C(O)NHC₁₋₆alkyl,
 - (9) C(O)NHC₃₋₆cycloalkyl,
 - (10) C(O)NHC₂₋₅cycloheteroalkyl,
 - (11) C(O)NH-aryl,
 - (12) C(O)NH-heteroaryl,
 - (13) SO₂C₁₋₆alkyl,
 - (14) SO₂C₃₋₆cycloalkyl,
 - (15) SO₂C₂₋₅cycloheteroalkyl,
 - 10 (16) SO₂-aryl, or
 - (17) SO₂-heteroaryl;

R³ is

- 15
- (1) hydrogen,
 - (2) halogen,
 - (3) cyano, or
 - (4) (C₁₋₃)alkyl;

R⁴ is

- 20
- (1) hydrogen,
 - (2) (C₁₋₃)alkyl,
 - (3) halo(C₁₋₃)alkyl, or
 - (4) halogen;

R⁵ is

- 25
- (1) cyano,
 - (2) (C₁₋₃)alkyl,
 - (3) halo(C₁₋₃)alkyl,
 - (4) (C₁₋₃)alkoxy,
 - (5) halo(C₁₋₃)alkoxy, or
 - (6) halogen;

R⁶ is

- 30
- (1) (C₁₋₃)alkoxy,
 - (2) halo(C₁₋₃)alkoxy,

- (3) halo(C₁₋₃)alkyl,
 (4) (C₃₋₆)cycloalkyl,
 (5) (C₃₋₆)cycloalkyl-O-,
 (6) (C₃₋₆)cycloalkyl-S-,
 5 (7) (C₃₋₆)cycloalkyl-(C₁₋₂)alkyl-,
 (8) (C₃₋₆)cycloalkyl-halo(C₁₋₂)alkyl-,
 (9) phenyl,
 (10) 5- to 6-membered heteroaryl-O- wherein the heteroaryl contains 1, 2, or 3
 heteroatoms independently selected from N, O and S, or
 10 (11) 5- to 6-membered heteroaryl- wherein the heteroaryl contains 1, 2, or 3
 heteroatoms independently selected from N, O and S,
 wherein alkyl, cycloalkyl, phenyl and heteroaryl are unsubstituted or substituted with 1-3
 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and
 halogen;
 15 n is 0, 1, 2 or 3;
 m is 0 or 1;
 p is 0, 1, 2 or 3; and
 q is 0, 1, or 2.
- In one embodiment of the present invention, X is a bond, (C₁₋₂)alkyl, or halo(C₁₋₂)alkyl.
 20 In another embodiment of the present invention, X is a bond, or (C₁₋₂)alkyl.
 In another embodiment of the present invention, X is a bond, or CH₂.
 In another embodiment of the present invention, X is a bond.
 In another embodiment of the present invention, X is CH₂.
 In another embodiment of the present invention, ring A is aryl, 5- or 6-membered
 25 heteroaryl containing 1, 2, or 3 heteroatoms independently selected from N, O and S, or 9-
 or 10-membered fused heteroaryl containing 1, 2, or 3 heteroatoms independently selected from
 N, O, and S. In a class of this embodiment, ring A is phenyl, pyridine, pyrimidine, pyrazole,
 pyrazine, isothiazole, or benzisoxazole.
- In another embodiment, ring A is 5- or 6-membered heteroaryl containing 1, 2, or 3
 30 heteroatoms independently selected from N, O and S, or 9- or 10-membered fused heteroaryl
 containing 1, 2, or 3 heteroatoms independently selected from N, O, and S. In a class of this

embodiment, ring A is pyridine, pyrimidine, pyrazole, pyrazine, isothiazole, or benzisoxazole.

In another embodiment, ring A is 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from N, O and S. In a class of this embodiment, ring A is pyridine, pyrimidine, pyrazole, pyrazine, or isothiazole.

- 5 In another embodiment, ring A is 9- or 10-membered fused heteroaryl containing 1, 2, or 3 heteroatoms independently selected from N, O, and S. In a class of this embodiment, ring A is benzisoxazole.

In another embodiment, ring A is aryl. In a class of this embodiment, ring A is phenyl.

- 10 In another embodiment of the present invention, R^1 is a bond, (C_{1-6}) alkyl-, $-O-(C_{1-6})$ alkyl-, or (C_{3-6}) cycloalkyl. In a class of this embodiment, R^1 is a bond, CH_2CH_2 , $CH_2CH_2CH_2$, $CH(CH_3)CH_2$, $CH_2CH(CH_3)$, $CH_2CH_2CH_2CH_2$, $CH(CH_3)CH_2CH_2CH_2$, OCH_2CH_2 , $OCH_2CH_2CH_2$, $OCH_2CH_2CH_2CH_2$, or cycloalkyl.

- In another embodiment of the present invention, R^1 is a bond, $-O-(C_{1-6})$ alkyl-, or (C_{3-6}) cycloalkyl. In a class of this embodiment, R^1 is a bond, OCH_2CH_2 , $OCH_2CH_2CH_2$,
15 $OCH_2CH_2CH_2CH_2$, or cycloalkyl.

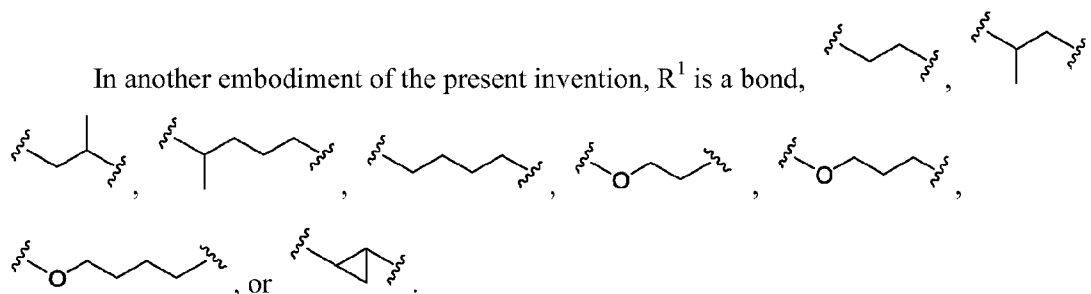
In another embodiment of the present invention, R^1 is a bond.

In another embodiment of the present invention, R^1 is $-O-(C_{1-6})$ alkyl-, or (C_{3-6}) cycloalkyl. In a class of this embodiment, R^1 is OCH_2CH_2 , $OCH_2CH_2CH_2$, $OCH_2CH_2CH_2CH_2$, or cycloalkyl.

- 20 In another embodiment of the present invention, R^1 is $-O-(C_{1-6})$ alkyl-. In a class of this embodiment, R^1 is OCH_2CH_2 , $OCH_2CH_2CH_2$, or $OCH_2CH_2CH_2CH_2$.

In another embodiment of the present invention, R^1 is (C_{3-6}) cycloalkyl. In a class of this embodiment, R^1 is cyclopropyl.

- In another embodiment of the present invention, R^1 is (C_{1-6}) alkyl. In a class of this
25 embodiment, R^1 is CH_2CH_2 , $CH_2CH_2CH_2$, $CH(CH_3)CH_2$, $CH_2CH(CH_3)$, $CH_2CH_2CH_2CH_2$, or $CH(CH_3)CH_2CH_2CH_2$.



In another embodiment of the present invention, R^2 is hydrogen, hydroxy, COOH, tetrazole, hydroxyisoxazole, triazole, $C(O)NH_2$, $C(O)NHC_{1-6}alkyl$, $C(O)NHC_{3-6}cycloalkyl$, $C(O)NHC_{2-5}cycloheteroalkyl$, $C(O)NH-aryl$, $C(O)NH-heteroaryl$, $SO_2C_{1-6}alkyl$, $SO_2C_{3-6}cycloalkyl$, $SO_2C_{2-5}cycloheteroalkyl$, SO_2-aryl , or $SO_2-heteroaryl$.

5 In another embodiment of the present invention, R^2 is hydrogen, hydroxy, COOH, tetrazole, hydroxyisoxazole, or triazole.

In another embodiment of the present invention, R^2 is hydrogen, hydroxy, COOH, or tetrazole.

In another embodiment of the present invention, R^2 is hydrogen, hydroxy, or tetrazole.

10 In another embodiment of the present invention, R^2 is hydrogen.

In another embodiment of the present invention, R^2 is hydroxyl.

In another embodiment of the present invention, R^2 is tetrazole.

In another embodiment of the present invention, R^2 is COOH.

In another embodiment of the present invention, R^3 is hydrogen, halogen, cyano, or
15 $(C_{1-3})alkyl$. In a class of this embodiment, R^3 is hydrogen, F, Cl, cyano, or CH_3 .

In another embodiment of the present invention, R^3 is hydrogen, halogen, or $(C_{1-3})alkyl$.
In a class of this embodiment, R^3 is hydrogen, F, Cl, or CH_3 .

In another embodiment of the present invention, R^3 is hydrogen, or halogen. In a class
of this embodiment, R^3 is hydrogen, F, or Cl. In another class of this embodiment, R^3 is
20 hydrogen, or F.

In another embodiment of the present invention, R^4 is hydrogen, $(C_{1-3})alkyl$,
halo $(C_{1-3})alkyl$, or halogen.

In another embodiment of the present invention, R^4 is hydrogen, or $(C_{1-3})alkyl$. In a
class of this embodiment, R^4 is hydrogen, or CH_3 .

25 In another embodiment of the present invention, R^4 is $(C_{1-3})alkyl$. In a class of this
embodiment, R^4 is CH_3 .

In another embodiment of the present invention, R^4 is hydrogen.

In another embodiment of the present invention, R^5 is cyano, $(C_{1-3})alkyl$, halo $(C_{1-3})alkyl$,
 $(C_{1-3})alkoxy$, halo $(C_{1-3})alkoxy$, or halogen.

30 In another embodiment of the present invention, R^5 is cyano, $(C_{1-3})alkyl$, halo $(C_{1-3})alkyl$,
 $(C_{1-3})alkoxy$, or halogen. In a class of this embodiment, R^5 is cyano, CH_3 , CF_3 , CHF_2 , OCH_3 , F,

or Cl.

In another embodiment of the present invention, R⁵ is cyano or halogen. In a class of this embodiment, R⁵ is cyano, F, or Cl.

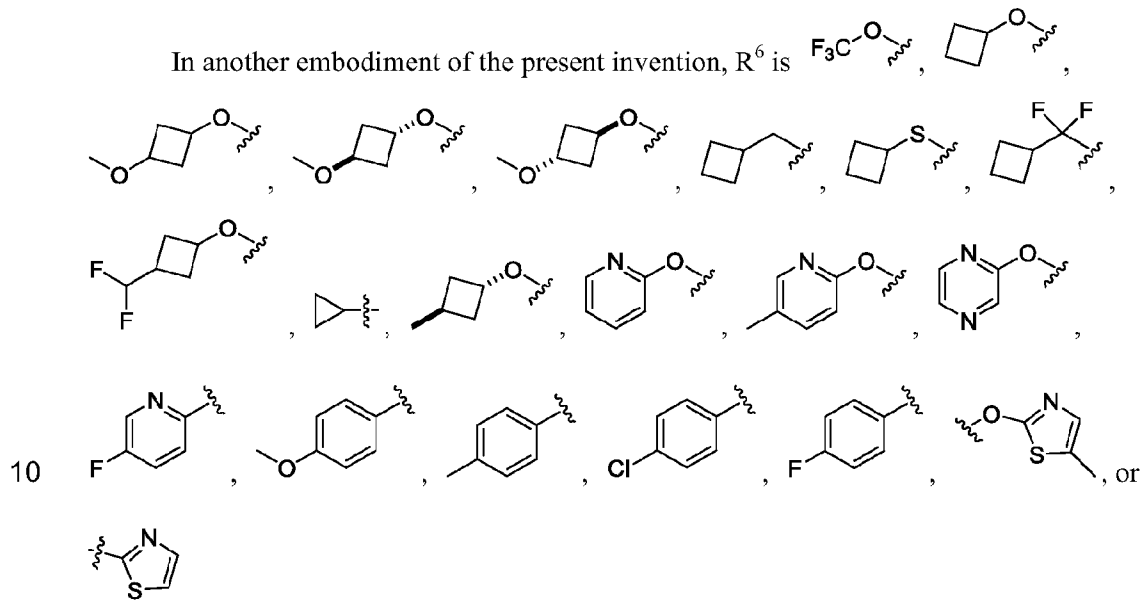
In another embodiment of the present invention, R⁶ is halo(C₁₋₃)alkoxy, halo(C₁₋₃)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl-O-, (C₃₋₆)cycloalkyl-S-, (C₃₋₆)cycloalkyl-(C₁₋₂)alkyl-, phenyl, 5- to 6-membered heteroaryl-O- wherein the heteroaryl contains 1, 2, or 3 heteroatoms independently selected from N, O and S, or 5- to 6-membered heteroaryl- wherein the heteroaryl contains 1, 2, or 3 heteroatoms independently selected from N, O and S, wherein alkyl, cycloalkyl, phenyl and heteroaryl are unsubstituted or substituted with 1-3 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and halogen. In a class of this embodiment of the present invention, R⁶ is OCF₃, CF₃, cyclopropyl, cyclobutyl-O-, cyclobutyl-S-, cyclobutyl-CH₂-, phenyl, thiazolyl-O-, pyridyl-O-, pyrazinyl-O-, or thienyl, wherein cyclopropyl, cyclobutyl, phenyl, thiazolyl, pyridyl, pyrazinyl and thienyl are unsubstituted or substituted with 1-3 substituents selected from OCH₃, CHF₂, CH₃, F, and Cl.

In another embodiment of the present invention, R⁶ is (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl-O-, (C₃₋₆)cycloalkyl-S-, (C₃₋₆)cycloalkyl-(C₁₋₂)alkyl-, phenyl, 5- to 6-membered heteroaryl-O- wherein the heteroaryl contains 1, 2, or 3 heteroatoms independently selected from N, O and S, or 5- to 6-membered heteroaryl- wherein the heteroaryl contains 1, 2, or 3 heteroatoms independently selected from N, O and S, wherein cycloalkyl, phenyl and heteroaryl are unsubstituted or substituted with 1-3 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and halogen. In a class of this embodiment of the present invention, R⁶ is cyclopropyl, cyclobutyl-O-, cyclobutyl-S-, cyclobutyl-CH₂-, phenyl, thiazolyl-O-, pyridyl-O-, pyrazinyl-O-, or thienyl, wherein cyclopropyl, cyclobutyl, phenyl, thiazolyl, pyridyl, pyrazinyl and thienyl are unsubstituted or substituted with 1-3 substituents selected from OCH₃, CHF₂, CH₃, F, and Cl.

In another embodiment of the present invention, R⁶ is halo(C₁₋₃)alkoxy, or halo(C₁₋₃)alkyl, wherein alkyl is unsubstituted or substituted with 1-3 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and halo. In a class of this embodiment, R⁶ is halo(C₁₋₃)alkoxy, or halo(C₁₋₃)alkyl. In another class of this embodiment, R⁶ is OCF₃, or CF₃.

In another embodiment of the present invention, R⁶ is (C₃₋₆)cycloalkyl-O-, wherein

cycloalkyl is unsubstituted or substituted with 1-3 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and halogen. In a class of this embodiment, R⁶ is cyclobutyl-O-, wherein cycloalkyl is unsubstituted or substituted with 1-3 substituents selected from OCH₃, CHF₂, CH₃, F, and Cl. In another class of this embodiment, R⁶ is cyclobutyl-O-, wherein cycloalkyl is unsubstituted or substituted with 1-3 substituents selected from OCH₃.



In another embodiment of the present invention, n is 0, 1, 2 or 3. In a class of this embodiment, n is 1, 2 or 3. In another class of this embodiment, n is 0, 1, or 2. In another class of this embodiment, n is 1, 2 or 3. In another class of this embodiment, n is 0, 1 or 2. In another class of this embodiment, n is 1 or 3. In another class of this embodiment, n is 0. In another class of this embodiment, n is 1. In another class of this embodiment, n is 2. In another class of this embodiment, n is 3.

In another embodiment of the present invention, m is 0 or 1. In a class of this embodiment, m is 0. In another class of this embodiment, m is 1.

20 In another embodiment of the present invention, p is 0, 1, 2 or 3. In a class of this embodiment, p is 1, 2 or 3. In another class of this embodiment, p is 0, 1, or 2. In another class of this embodiment, p is 0 or 2. In another class of this embodiment, p is 1 or 2. In another class of this embodiment, p is 0 or 1. In another class of this embodiment, p is 0. In another class of this embodiment, p is 1. In another class of this embodiment, p is 2. In another class of this

embodiment, p is 3.

In another embodiment of the present invention, q is 0, 1, or 2. In a class of this embodiment, q is 0 or 1. In another class of this embodiment, q is 1 or 2. In another class of this embodiment, q is 0 or 2. In another class of this embodiment, q is 0. In another class of this embodiment, q is 1. In another class of this embodiment, q is 2.

In one embodiment, ring A is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrazolyl, thiazolyl, isoxazolyl, or benzo[d]isoxazolyl. In a class of this embodiment, ring A is pyrimidinyl, pyridinyl, pyrazinyl, thiazolyl, isoxazolyl, pyrrolyl, or pyrazolyl, or benzo[d]isoxazolyl. In another class of this embodiment, ring A is pyridinyl, pyrazinyl, thiazolyl, isoxazolyl, pyrrolyl, or pyrazolyl, or benzo[d]isoxazolyl. In another class of this embodiment, ring A is pyridinyl, pyrazinyl, thiazolyl, isoxazolyl, pyrrolyl, or pyrazolyl. In another class of this embodiment, ring A is benzo[d]isoxazolyl. In another class of this embodiment, ring A is phenyl. In another class of this embodiment, ring A is pyrimidinyl. In another class of this embodiment, ring A is pyridinyl. In another class of this embodiment, ring A is pyrazinyl. In another embodiment, ring A is pyrazolyl. In another embodiment, ring A is thiazolyl. In another embodiment, ring A is isoxazolyl. In another embodiment, ring A is benzo[d]isoxazolyl.

In one class of this embodiment, R² is hydrogen.

In one subclass of this class, R¹ is a bond. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₁₋₆)alkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is -O-(C₁₋₆)alkyl-. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₃₋₆)cycloalkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₁₋₆)alkyl or -O-(C₁₋₆)alkyl-. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one class of this embodiment, R² is hydroxy.

In one subclass of this class, R¹ is a bond. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R^1 is (C_{1-6}) alkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C_{1-2}) alkyl.

In one subclass of this class, R^1 is $-O-(C_{1-6})$ alkyl-. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C_{1-2}) alkyl.

5 In one subclass of this class, R^1 is (C_{3-6}) cycloalkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C_{1-2}) alkyl.

In one subclass of this class, R^1 is (C_{1-6}) alkyl or $-O-(C_{1-6})$ alkyl-. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C_{1-2}) alkyl.

In one class of this embodiment, R^2 is COOH.

10 In one subclass of this class, R^1 is (C_{1-6}) alkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is a bond.

In one subclass of this class, R^1 is ethyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is a bond.

In one subclass of this class, R^1 is a bond. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C_{1-2}) alkyl.

15 In one subclass of this class, R^1 is (C_{1-6}) alkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C_{1-2}) alkyl.

In one subclass of this class, R^1 is $-O-(C_{1-6})$ alkyl-. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C_{1-2}) alkyl.

20 In one subclass of this class, R^1 is (C_{3-6}) cycloalkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C_{1-2}) alkyl.

In one subclass of this class, R^1 is (C_{1-6}) alkyl or $-O-(C_{1-6})$ alkyl-. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C_{1-2}) alkyl.

In one class of this embodiment, R^2 is hydroxyisoxazole or triazole. In one class of this embodiment, R^2 is hydroxyisoxazole. In one class of this embodiment, R^2 is triazole.

In one class of this embodiment, R^2 is $C(O)NH_2$, $C(O)NHC_{1-6}$ alkyl, $C(O)NHC_{3-6}$ cycloalkyl, $C(O)NHC_{2-5}$ cycloheteroalkyl, $C(O)NH$ -aryl, $C(O)NH$ -heteroaryl, SO_2C_{1-6} alkyl, SO_2C_{3-6} cycloalkyl, SO_2C_{2-5} cycloheteroalkyl, SO_2 -aryl, or SO_2 -heteroaryl.

In one subclass of this class, R^1 is a bond. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C_{1-2}) alkyl.

30 In one subclass of this class, R^1 is (C_{1-6}) alkyl. In one sub-subclass of this subclass, X is a

bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is -O-(C₁₋₆)alkyl-. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₃₋₆)cycloalkyl. In one sub-subclass of this subclass,
5 X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one class of this embodiment, R² is C(O)NH₂, C(O)NHC₁₋₆alkyl, C(O)NHcyclopropyl, C(O)NH-cyclobutyl, C(O)NH-cyclopentyl, C(O)NH-cyclohexyl, C(O)NH-oxetane, C(O)NH-tetrahydrofuran, C(O)NH-tetrahydropyran, C(O)NH-pyrrolidine, C(O)NH-piperidine, C(O)NH-phenyl, C(O)NH-thiazole, C(O)NH-oxazole, C(O)NH-imidazole,
10 C(O)NH-furan, C(O)NH-thiophene, C(O)NH-pyridine, C(O)NH-pyrazine, C(O)NH-pyrimidine, SO₂C₁₋₆alkyl, SO₂cyclopropyl, SO₂cyclobutyl, SO₂cyclopentyl, SO₂cyclohexyl, SO₂-oxetane, SO₂-tetrahydrofuran, SO₂-tetrahydropyran, SO₂-pyrrolidine, SO₂-piperidine, SO₂-phenyl, SO₂-thiazole, SO₂-oxazole, SO₂-imidazole, SO₂-furan, SO₂-thiophene, SO₂-pyridine, SO₂-pyrazine or SO₂-pyrimidine.

15 In one subclass of this class, R¹ is a bond. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₁₋₆)alkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is -O-(C₁₋₆)alkyl-. In one sub-subclass of this subclass, X
20 is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₃₋₆)cycloalkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₁₋₆)alkyl or -O-(C₁₋₆)alkyl-. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

25 In one class of this embodiment, R² is hydrogen, hydroxy, COOH or tetrazole. In one subclass of this embodiment, R² is hydroxy, COOH or tetrazole.

In one subclass of this class, R¹ is a bond. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₁₋₆)alkyl. In one sub-subclass of this subclass, X is a
30 bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is -O-(C₁₋₆)alkyl-. In one sub-subclass of this subclass, X

is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₃₋₆)cycloalkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₁₋₆)alkyl or -O-(C₁₋₆)alkyl-. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one class of this embodiment, R² is COOH or tetrazole.

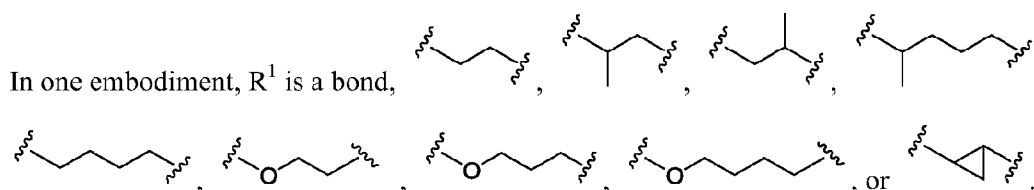
In one subclass of this class, R¹ is a bond. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₁₋₆)alkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is -O-(C₁₋₆)alkyl-. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₃₋₆)cycloalkyl. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.

In one subclass of this class, R¹ is (C₁₋₆)alkyl or -O-(C₁₋₆)alkyl-. In one sub-subclass of this subclass, X is a bond. In one sub-subclass of this subclass, X is (C₁₋₂)alkyl.



In one embodiment, R² is hydrogen. In one class of this embodiment, R¹ is a bond. In one class of this embodiment, R¹ is (C₁₋₆)alkyl. In one class of this embodiment, R¹ is -O-(C₁₋₆)alkyl-. In one class of this embodiment, R¹ is (C₃₋₆)cycloalkyl.

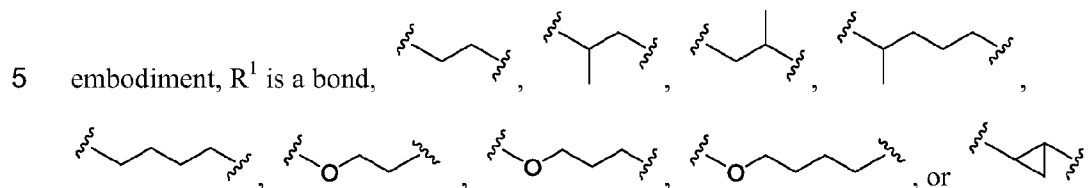
In one embodiment, R² is hydroxy. In one class of this embodiment, R¹ is a bond. In one class of this embodiment, R¹ is (C₁₋₆)alkyl. In one class of this embodiment, R¹ is -O-(C₁₋₆)alkyl-. In one class of this embodiment, R¹ is (C₃₋₆)cycloalkyl.

In one embodiment, R² is COOH. In one class of this embodiment, R¹ is a bond. In one class of this embodiment, R¹ is (C₁₋₆)alkyl. In one class of this embodiment, R¹ is -O-(C₁₋₆)alkyl-. In one class of this embodiment, R¹ is (C₃₋₆)cycloalkyl.

In one class of this embodiment, R² is hydroxyisoxazole or triazole. In one class of this embodiment, R² is hydroxyisoxazole. In one class of this embodiment, R² is triazole.

In one class of this embodiment, R^2 is tetrazolyl. In one subclass of this class, R^1 is a bond. In one subclass of this class, R^1 is (C_{1-6}) alkyl. In one subclass of this class, R^1 is $-O-(C_{1-6})$ alkyl-. In one subclass of this class, R^1 is (C_{3-6}) cycloalkyl.

In one embodiment, R^2 is hydrogen, hydroxy, COOH, or tetrazolyl. In one class of this



In one embodiment, X is bond, (C_{1-2}) alkyl, or halo (C_{1-2}) alkyl. In one embodiment, X is bond, or CH_2 .

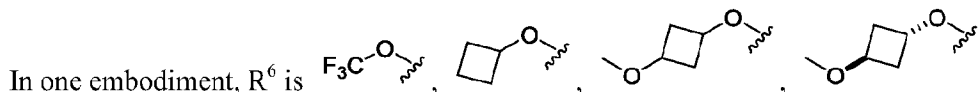
In one embodiment, R^2 is hydrogen, hydroxy, COOH, or tetrazole. In one embodiment, R^2 is hydroxy, COOH, or tetrazole. In one embodiment, R^2 is COOH. In one embodiment, R^2 is tetrazole.

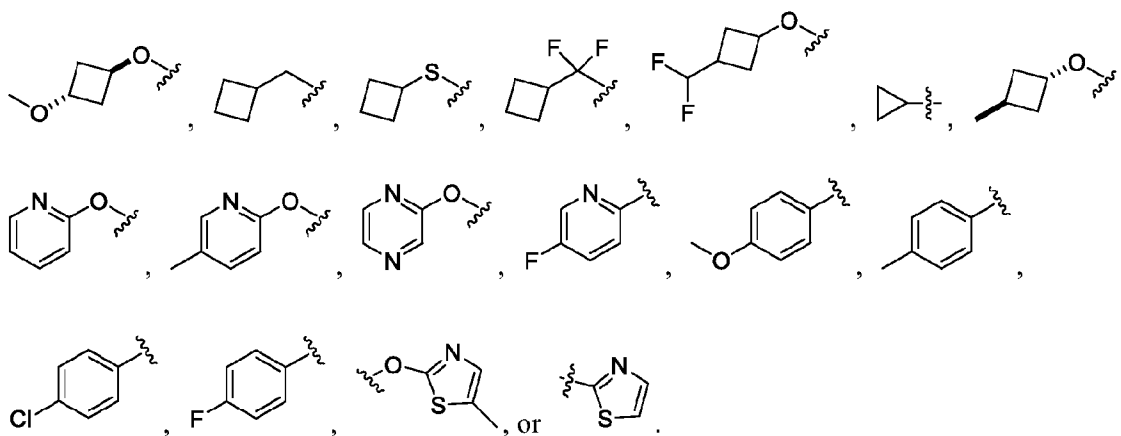
In one embodiment, R^3 is hydrogen, halo, cyano, or (C_{1-3}) alkyl. In one embodiment, R^3 is hydrogen, fluoro, chloro, or methyl. In one class of this embodiment, R^3 is hydrogen. In one class of this embodiment, R^3 is fluoro. In one class of this embodiment, R^3 is chloro. In one class of this embodiment, R^3 is fluoro or chloro. In one class of this embodiment, R^3 is methyl.

In one embodiment, R^3 is hydrogen, F or CH_3 .

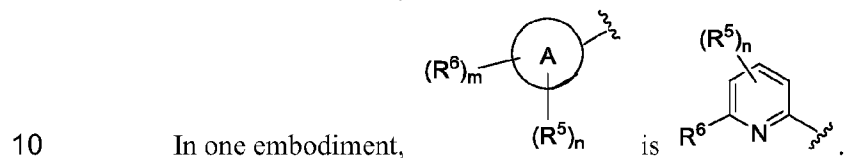
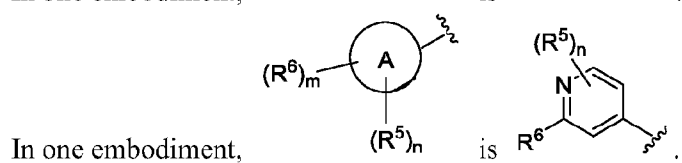
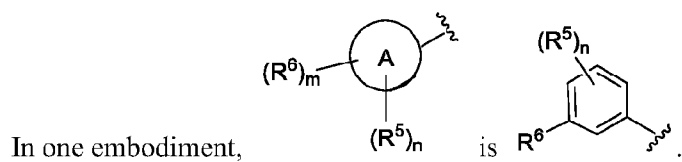
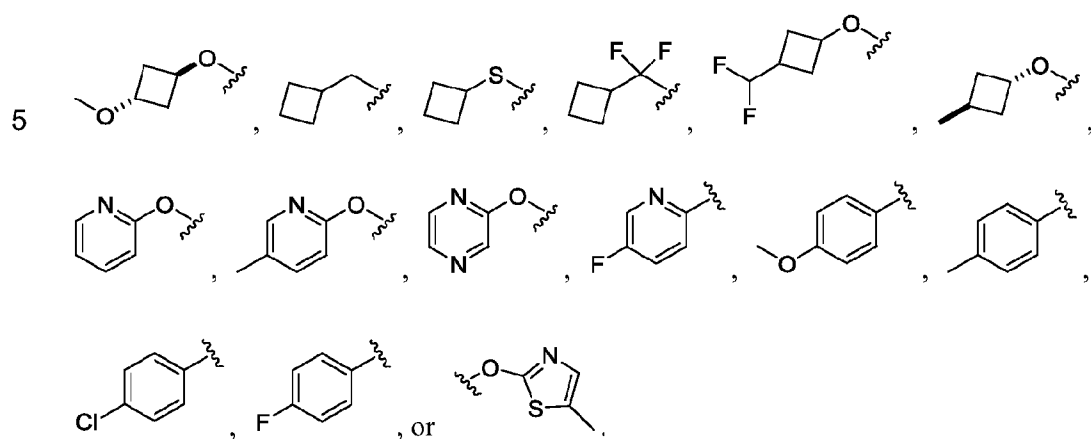
In one embodiment R^4 is hydrogen, (C_{1-3}) alkyl, halo (C_{1-3}) alkyl, or halo. In one embodiment R^4 is hydrogen, or R^4 is (C_{1-3}) alkyl. In one embodiment R^4 is hydrogen, or CH_3 . In one embodiment, R^4 is hydrogen. In one embodiment, R^4 is (C_{1-3}) alkyl. In one embodiment, R^4 is halo (C_{1-3}) alkyl. In one embodiment, R^4 is halo. In one embodiment, R^4 is hydrogen, fluoro, or methyl. In one embodiment R^4 is hydrogen.

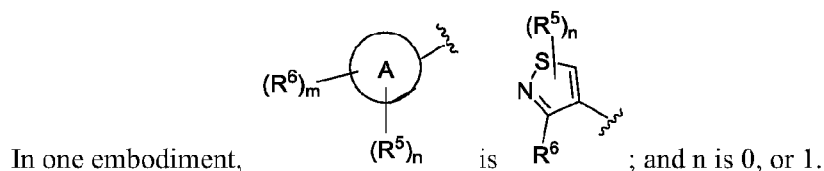
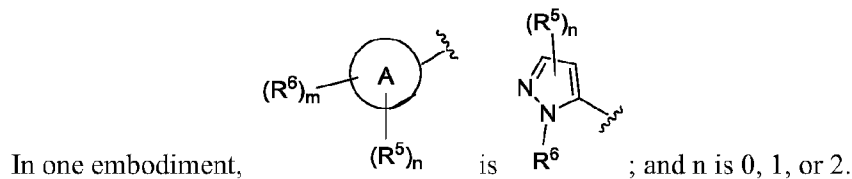
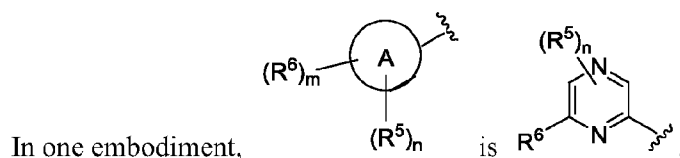
In one embodiment, R^5 is cyano, (C_{1-3}) alkyl, halo (C_{1-3}) alkyl, (C_{1-3}) alkoxy, halo (C_{1-3}) alkoxy, or halo. In one embodiment, R^5 is $-CN$, $-CH_3$, $-CF_3$, $-CHF_2$, $-OCH_3$, $-OCF_3$, Cl, or F. In one embodiment, R^5 is methoxy, fluoro, chloro, difluoromethyl, trifluoromethyl, methyl, or cyano. In one embodiment, R^5 is cyano, (C_{1-3}) alkyl, halo (C_{1-3}) alkyl, (C_{1-3}) alkoxy, halo (C_{1-3}) alkoxy, or halo. In one embodiment, R^5 is $-CN$, $-CH_3$, $-OCH_3$, Cl, or F.





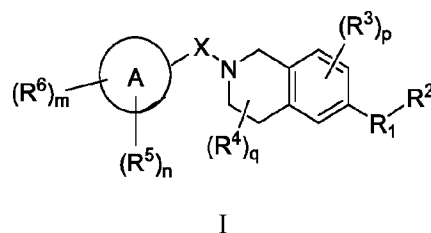
In one embodiment, R⁶ is 





In another embodiment of the present invention, the invention relates to compounds of

5 structural formula I:



wherein:

X is

- 10 (1) a bond, or
(2) (C₁₋₂)alkyl;

ring A is

- (1) aryl,
(2) 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently
15 selected from N, O and S, or
(3) 9- or 10-membered fused heteroaryl containing 1, 2, or 3 heteroatoms
independently selected from N, O, and S;

R¹ is

- (1) bond,
20 (2) (C₁₋₆)alkyl,

(3) -O-(C₁₋₆)alkyl-, or

(4) (C₃₋₆)cycloalkyl;

R² is

(1) hydrogen,

5 (2) hydroxy,

(3) COOH, or

(4) tetrazole;

R³ is

(1) hydrogen,

10 (2) halogen, or

(3) (C₁₋₃)alkyl;

R⁴ is

(1) hydrogen, or

(2) (C₁₋₃)alkyl;

15 R⁵ is

(1) cyano,

(2) (C₁₋₃)alkyl,

(3) halo(C₁₋₃)alkyl,

(4) (C₁₋₃)alkoxy, or

20 (5) halogen;

R⁶ is

(1) halo(C₁₋₃)alkoxy,

(2) halo(C₁₋₃)alkyl,

(3) (C₃₋₆)cycloalkyl,

25 (4) (C₃₋₆)cycloalkyl-O-,

(5) (C₃₋₆)cycloalkyl-S-,

(6) (C₃₋₆)cycloalkyl-(C₁₋₂)alkyl-,

(7) phenyl,

(8) 5- to 6-membered heteroaryl-O- wherein the heteroaryl contains 1, 2, or 3

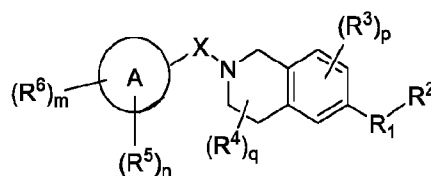
30 heteroatoms independently selected from N, O and S, or

(9) 5- to 6-membered heteroaryl- wherein the heteroaryl contains 1, 2, or 3

heteroatoms independently selected from N, O and S,
 wherein alkyl, cycloalkyl, phenyl and heteroaryl are unsubstituted or substituted with 1-3
 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and
 halogen;

5 or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, the invention relates to compounds of
 structural formula I



I

10 wherein:

X is a bond;

ring A is aryl;

R¹ is (C₁₋₆)alkyl;

R² is COOH,

15 R³ is

(1) hydrogen, or

(2) halogen;

R⁴ is hydrogen;

R⁵ is

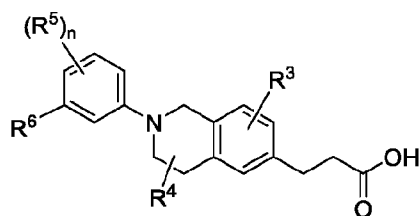
20 (1) cyano, or

(2) halogen;

R⁶ is (C₃₋₆)cycloalkyl-O-, wherein cycloalkyl is unsubstituted or substituted with 1-3
 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and
 halogen;

25 or a pharmaceutically acceptable salt thereof.

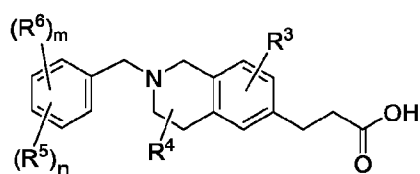
In one embodiment, the invention relates to compounds of formula I-A:



I-A

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^4 , R^5 , R^6 and n are as previously defined. In one class of this embodiment, R^3 , and R^4 are each hydrogen.

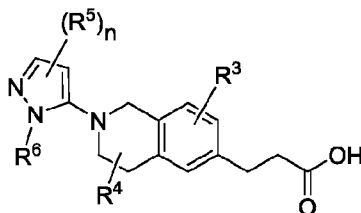
5 In one embodiment, the invention relates to compounds of formula I-B:



I-B

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^4 , R^5 , R^6 and n are as previously defined. In one class of this embodiment, R^3 , and R^4 are each hydrogen.

10 In one embodiment, the invention relates to compounds of formula I-C:

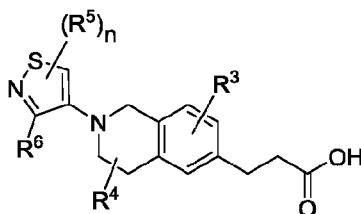


I-C

or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl unsubstituted or substituted with (C_{1-3}) alkyl, (C_{1-3}) alkoxy, or halo; and n is 0, 1 or 2; and R^3 , R^4 , R^5 are as previously defined.

15 In one class of this embodiment, R^3 , and R^4 are each hydrogen.

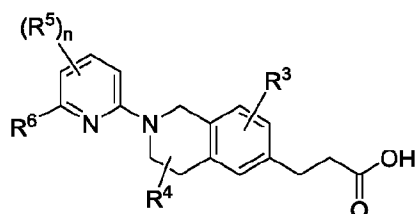
In one embodiment, the invention relates to compounds of formula I-D:



I-D

or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl unsubstituted or substituted with (C_{1-3}) alkyl, (C_{1-3}) alkoxy, or halo; and n is 0 or 1; and R^3 , R^4 , R^5 are as previously defined. In one class of this embodiment, R^3 , and R^4 are each hydrogen.

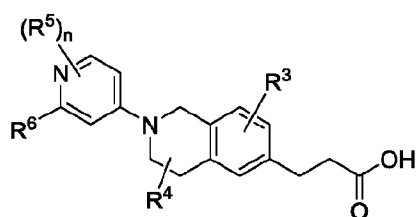
5 In one embodiment, the invention relates to compounds of formula I-E:



I-E

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^4 , R^5 , R^6 and n are as previously defined. In one class of this embodiment, R^3 , and R^4 are each hydrogen.

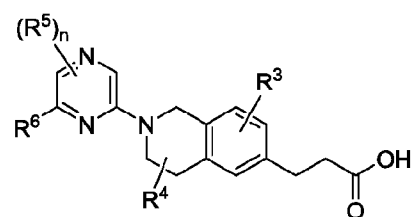
10 In one embodiment, the invention relates to compounds of formula I-F:



I-F

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^4 , R^5 , R^6 and n are as previously defined. In one class of this embodiment, R^3 , and R^4 are each hydrogen.

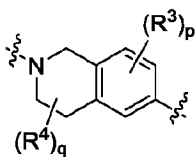
15 In one embodiment, the invention relates to compounds of formula I-G:



I-G

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^4 , R^5 , R^6 and n are as previously defined. In one class of this embodiment, R^3 , and R^4 are each hydrogen.

In the compounds of formulas I, I-A, I-B, I-C, I-D, I-E, I-F, and I-G, the R^4 substituent is substituted on the piperidine ring of the 1,2,3,4-tetrahydroisoquinoline ring, and the R^3 substituent is substituted on the phenyl of the 1,2,3,4-tetrahydroisoquinoline ring, as shown below:



5

The present invention also relates to a GPR120 function regulating agent containing a compound represented by formulas I to I-G or a pharmaceutically acceptable salt thereof as an active ingredient. Particularly, the present invention relates to a GPR120 agonist containing a compound represented by formulas I to I-G or a pharmaceutically acceptable salt thereof as an active ingredient.

10

The present invention also relates to an agent for treating and/or preventing diabetes, obesity, hyperlipidemia, NASH, or an inflammation related disorder, containing a compound represented by formulas I to I-G or a pharmaceutically acceptable salt thereof, as an active ingredient.

15

Furthermore, the present invention relates to a pharmaceutical composition containing the compound represented by formulas I to I-G and a pharmaceutically acceptable carrier.

The present also relates a compound represented by formulas I to I-G for use as a medicament.

The present invention relates to the use of a compound represented by formulas I to I-G or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating a condition selected from the group consisting of diabetes, hyperlipidemia, obesity, NASH, and inflammation related disorders.

20

The present invention relates to the treatment of a condition selected from the group consisting of diabetes, hyperlipidemia, obesity, NASH, and inflammation related disorders comprising administering to an individual in need of such treatment a pharmaceutical composition comprising the compound represented by formulas I to I-G.

25

A compound according to an embodiment of the present invention or the pharmaceutically acceptable salt thereof has a strong GPR120 function regulating action, particularly an agonist

action, and may be useful for treating and/or preventing diabetes, obesity, hyperlipidemia, NASH, or an inflammation related disorder.

The invention is described herein in detail using the terms defined below unless otherwise specified.

5 "Alkyl", as well as other groups having the prefix "alk", such as alkoxy, and the like, means carbon chains which may be linear or branched, or combinations thereof, containing the indicated number of carbon atoms. 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, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl and the
10 like.

"Alkoxy" refers to an alkyl group linked to oxygen.

"Aryl" refers to phenyl or naphthyl.

"Halo" is halogen; halo and halogen include fluorine, chlorine, bromine and iodine.

"Cycloalkyl" means a saturated cyclic hydrocarbon radical having the number of carbon
15 atoms designated if no number of atoms is specified, 3-7 carbon atoms are intended, forming 1-3 carbocyclic rings that are fused. "Cycloalkyl" also includes monocyclic rings fused to an aryl group in which the point of attachment is on the non-aromatic portion. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl and the like.

20 "Haloalkyl" include mono- substituted as well as multiple halo substituted alkyl groups, up to perhalo substituted alkyl. For example, trifluoromethyl is included.

"Haloalkoxy" and "haloalkyl-O" are used interchangeably and refer to halo substituted alkyl groups linked through the oxygen atom. Haloalkoxy include mono-halo substituted alkoxy groups as well alkoxy groups substituted with multiple halo substituents, up to perhalo
25 substituted alkoxy. For example, trifluoromethoxy is included.

"Heterocyclyl", "heterocycle", "heterocyclic" or "cycloheteroalkyl" refers to nonaromatic cyclic 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. Examples of heterocyclyl groups include: piperidine, piperazine, morpholine, pyrrolidine, tetrahydrofuran, azetidine, oxirane, or aziridine, and the like.
30

"Heteroaryl" refers to aromatic cyclic ring structures in which one or more atoms in the

ring, the heteroatoms(s), is an element other than carbon. Heteroatoms are typically O, S, or N atoms. Examples of heteroaryl groups include: pyridine, pyrimidinyl, pyrrole, pyridazine, isoxazole, indole, or imidazole.

“Fused heteroaryl” refers to a heteroaryl group fused to an aryl or heteroaryl group.

5 Examples of fused heteroaryl groups include benzo[d]oxazolyl, or benzo[d]isoxazolyl.

In the compounds described herein, 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 predominantly found in nature. The present invention is meant to include
10 all suitable isotopic variations of the compounds of the formulas described herein. For example, different isotopic forms of hydrogen (H) include protium (1H) and deuterium (2H). 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.

15 Isotopically-enriched compounds within the formulas described herein 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.

The individual tautomers of the compounds of the formulas described herein, as well as
20 mixture thereof, are encompassed with compounds of the formulas described herein. Tautomers are defined as compounds that undergo rapid proton shifts from one atom of the compound to another atom of the compound. Some of the compounds described herein may exist as tautomers with different points of attachment of hydrogen. Such an example may be a ketone and its enol form known as keto-enol tautomers.

25 Compounds of the formulas described herein may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active amine or acid as a resolving agent or on a chiral HPLC column.

30 Alternatively, any enantiomer of a compound of the formulas described herein may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known

configuration.

It is generally preferable to administer compounds of the present invention as enantiomerically pure formulations. Racemic mixtures can be separated into their individual enantiomers by any of a number of conventional methods. These include chiral chromatography, derivatization with a chiral auxiliary followed by separation by chromatography or crystallization, and fractional crystallization of diastereomeric salts.

Compounds described herein may contain an asymmetric center and may thus exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereomers. When bonds to the chiral carbon are depicted as straight lines in the 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. The present invention includes all such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers. Except where otherwise specified, the formulae encompassing compounds of the present invention are shown without a definitive stereochemistry at certain positions. The present invention therefore may be understood to include all stereoisomers of compounds of formulas I to I-G and pharmaceutically acceptable salts thereof.

Diastereoisomeric pairs of enantiomers may be separated by, for example, fractional crystallization from a suitable solvent, and the pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid or base as a resolving agent or on a chiral HPLC column. Further, any enantiomer or diastereomer of a compound of formulas I to I-G may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Furthermore, the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Solvates, and in particular, the hydrates of the compounds of the structural formulas described herein are also included in the present invention.

Compounds of the present invention are potent agonists of the GPR120 receptor. These compounds and pharmaceutically acceptable salts thereof are modulators of the receptor known

as GPR120, and are therefore useful in the treatment of diseases that are modulated by GPR120 ligands and agonists. Many of these diseases are summarized below. Said compounds may be used for the manufacture of a medicament for treating one or more of diseases or conditions, including, without limitation:

- 5 (1) noninsulin dependent diabetes mellitus (type 2 diabetes);
- (2) hyperglycemia;
- (3) metabolic syndrome/ syndrome X;
- (4) obesity;
- (5) ischemia and myocardial infarction;
- 10 (6) neurological disorders such as Alzheimer's disease, schizophrenia, and
impaired cognition;
- (7) hypercholesterolemia;
- (8) hypertriglyceridemia (elevated levels of triglyceride-rich-lipoproteins);
- (9) mixed or diabetic dyslipidemia;
- 15 (10) low HDL cholesterol;
- (11) high LDL cholesterol;
- (12) Hyperapobetalipoproteinemia;
- (13) atherosclerosis;
- (14) inflammation related disorders;
- 20 (15) type 1 diabetes;
- (16) insulin resistance;
- (17) fatty liver; and
- (18) non-alcoholic steatohepatitis (NASH).

Because the compounds are agonists of the GPR120 receptor, the compounds may be
25 useful for lowering glucose, lipids, and insulin resistance and increasing insulin sensitivity in
diabetic patients and in non-diabetic patients who have impaired glucose tolerance and/or are in
a pre-diabetic condition. The compounds may be useful to ameliorate hyperinsulinemia, which
often occurs in diabetic or pre-diabetic patients, by modulating the swings in the level of serum
glucose that often occurs in these patients. The compounds may be useful for treating or
30 reducing insulin resistance. The compounds may be useful for increasing insulin sensitivity. The
compounds are useful for treating or preventing gestational diabetes.

Additionally, by keeping hyperglycemia under control, the compounds may be useful to delay or for preventing vascular restenosis and diabetic retinopathy.

The compounds of this invention may be useful in improving or restoring β -cell function, so that they may be useful in treating type 1 diabetes or in delaying or preventing a
5 patient with type 2 diabetes from needing insulin therapy.

The compounds of this invention may be useful in treating inflammation related disorders such as obesity, diabetes, NASH, cancer, and cardiovascular disease.

The compounds, compositions, and medicaments as described herein may be further useful for reducing the risks of adverse sequelae associated with metabolic syndrome, or
10 Syndrome X, and in reducing the risk of developing atherosclerosis, delaying the onset of atherosclerosis, and/or reducing the risk of sequelae of atherosclerosis. Sequelae of atherosclerosis include angina, claudication, heart attack, stroke, and others.

The compounds may be useful for reducing appetite and body weight in obese subjects and may therefore be useful in reducing the risk of co-morbidities associated with obesity such
15 as hypertension, atherosclerosis, diabetes, and dyslipidemia.

By elevating levels of active GLP-1 in vivo, the compounds are useful in treating neurological disorders such as Alzheimer's disease, multiple sclerosis, and schizophrenia.

One aspect of the invention provides a method for the treatment and control of mixed or diabetic dyslipidemia, hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels,
20 hyperlipidemia, NASH, and/or hypertriglyceridemia, which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of the formulas described herein or a pharmaceutically acceptable salt thereof. The compound may be used alone or advantageously may be administered with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor (e.g., simvastatin, atorvastatin, rosuvastatin and
25 the like). The compound may also be used advantageously in combination with other lipid lowering drugs such as cholesterol absorption inhibitors (e.g., stanol esters, sterol glycosides or azetidinones such as ezetimibe), ACAT inhibitors (e.g., avasimibe), CETP inhibitors (e.g. anacetrapib), niacin, bile acid sequestrants, microsomal triglyceride transport inhibitors, and bile acid reuptake inhibitors. Such combination treatments are useful for the treatment or control of
30 conditions such hypercholesterolemia, atherosclerosis, hyperlipidemia, hypertriglyceridemia, dyslipidemia, high LDL, and low HDL.

Another aspect of the invention provides a method for the treatment and control of obesity or metabolic syndrome, which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound having the formulas described herein or a pharmaceutically acceptable salt thereof. The compound may be used alone or
5 advantageously may be administered with an anti-obesity agent, such as a lipase inhibitor (e.g., orlistat) or a monoamine neurotransmitter uptake inhibitor (e.g., sibutramine or phentermine). The compound may also be used advantageously in combination with CB-1 inverse agonists or antagonists (e.g., rimonabant).

The present invention further relates to a method of treating hyperglycemia, diabetes or
10 insulin resistance in a mammalian patient in need of such treatment which comprises administering to said patient a compound in accordance with the formulas described herein or a pharmaceutically acceptable salt thereof in an amount that is effective to treat hyperglycemia, diabetes or insulin resistance.

Yet another aspect of the invention that is of interest relates to a method of treating
15 atherosclerosis in a mammalian patient in need of such treatment, comprising administering to said patient a compound in accordance with a compound in accordance with the formulas described herein or a pharmaceutically acceptable salt thereof in an amount that is effective to treat atherosclerosis.

Yet another aspect of the invention that is of interest relates to a method of delaying the
20 onset of one of the aforementioned conditions and disorders where insulin resistance is a component in a mammalian patient in need thereof, comprising administering to the patient a compound in accordance with the formulas described herein or a pharmaceutically acceptable salt thereof in an amount that is effective to delay the onset of said condition.

Yet another aspect of the invention that is of interest relates to a method of reducing the
25 risk of developing one of the aforementioned conditions and disorders where insulin resistance is a component in a mammalian patient in need thereof, comprising administering to the patient a compound in accordance with the formulas described herein or a pharmaceutically acceptable salt thereof in an amount that is effective to reduce the risk of developing said condition.

Yet another aspect of the invention that is of interest relates to a method of treating a
30 condition or reducing the risk of developing a condition or delaying the onset of a condition selected from the group consisting of (1) hyperglycemia, (2) impaired glucose tolerance, (3)

- insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) pancreatitis, (15) abdominal obesity, (16) neurodegenerative disease, (17) retinopathy, (18) nephropathy, (19) neuropathy, (20) Syndrome X, (21) hypertension, (22) fatty liver, (23) non-alcoholic steatohepatitis (NASH) and other conditions and disorders where insulin resistance is a component, in a mammalian patient in need of such treatment, comprising administering to the patient a compound in accordance with the formulas described herein or a pharmaceutically acceptable salt thereof in an amount that is effective to treat said condition, and a compound selected from the group consisting of:
- 10 (a) DPP-IV inhibitors (e.g., sitagliptin, alogliptin, omarigliptin, linagliptin, vildagliptin, trelagliptin);
 - (b) insulin sensitizers selected from the group consisting of (i) PPAR agonists and (ii) biguanides;
 - (c) insulin and insulin mimetics (e.g., insulin degludec, insulin glargine, insulin lispro);
 - 15 (d) sulfonylureas and other insulin secretagogues;
 - (e) α -glucosidase inhibitors;
 - (f) glucagon receptor antagonists;
 - (g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists (e.g., dulaglutide, exenatide, semaglutide, albiglutide, liraglutide, lixisenatide, taspoglutide);
 - 20 (h) GIP, GIP mimetics, and GIP receptor agonists;
 - (i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists;
 - (j) cholesterol lowering agents selected from the group consisting of
 - (i) HMG-CoA reductase inhibitors, (ii) sequestrants, (iii) nicotinic alcohol, nicotinic acid and salts thereof, (iv) PPAR α agonists, (v) PPAR α / γ dual agonists (e.g.,
 - 25 aleglitazar), (vi) inhibitors of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, and (viii) anti-oxidants;
 - (k) PPAR δ agonists;
 - (l) SGLT inhibitors (e.g., empagliflozin, dapagliflozin, canagliflozin, BI-10773, tofogliflozin, ipragliflozin, LX-4211, PF-4971729, remogliflozin, TS-071, ertugliflozin);
 - 30 (m) antiobesity compounds;
 - (n) ileal bile acid transporter inhibitors;

(o) anti-inflammatory agents excluding glucocorticoids;

(p) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;

(q) antihypertensives including those acting on the angiotensin or renin systems, such as angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists or renin inhibitors, (e.g., lisinopril, losartan); and

(r) GPR-40 agonists;

said compounds being administered to the patient in an amount that is effective to treat said condition.

For dosing purposes, any suitable route of administration may be employed for providing a mammal, especially a human, with an effective amount of a compound of the present invention. Dosage forms may include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Most preferably, compounds of the formulas described herein or a pharmaceutically acceptable salt thereof are administered orally. The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating or controlling diabetes mellitus or other diseases for which compounds of the formulas described herein are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 1 milligram to about 350 milligrams. For a particularly potent compound, the dosage for an adult human may be as low as 0.1 mg. The dosage regimen may be adjusted within this range or even outside of this range to provide the optimal therapeutic response. Oral administration will usually be carried out using tablets or capsules. Examples of doses in tablets and capsules are 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 12 mg, 15 mg, 20 mg, 25

mg, 50 mg, 100 mg, 200 mg, 350 mg, 500 mg, 700 mg, 750 mg, 800 mg and 1000 mg. Other oral forms may also have the same or similar dosages.

Another aspect of the invention that is of interest is a pharmaceutical composition comprised of a compound of the formulas described herein or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention comprise a compound of the formulas described herein or a pharmaceutically acceptable salt as an active ingredient, as well as a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

Salts of basic compounds encompassed within the term "pharmaceutically acceptable salt" refer to non-toxic salts of the compounds described herein which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts of basic compounds described herein include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, edetate, edisylate, estolate, esylate, formate, fumarate, gluceptate, gluconate, glutamate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, palmitate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate. Furthermore, where the compounds described herein 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. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, cyclic 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, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

5 A pharmaceutical composition may also comprise a prodrug, or a pharmaceutically acceptable salt thereof, if a prodrug is administered.

The compositions are typically suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the particular active
10 ingredient selected. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art.

In practical use, compounds of the formulas described herein, or the pharmaceutically acceptable salts thereof can be combined as the active ingredient in intimate admixture with the pharmaceutical carrier according to conventional pharmaceutical compounding techniques.
15 The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and
20 solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most
25 advantageous oral dosage form. Solid pharmaceutical carriers are therefore typically employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations typically comprise at least about 0.1 percent of active compound, the remainder of the composition being the carrier. The percentage of active compound in these compositions may, of course, be varied and is conveniently between about 2 percent to about 60
30 percent of the weight of the dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be delivered.

Alternatively, the active compound can be administered intranasally as, for example, in the form of liquid drops or a spray.

The tablets, capsules and the like also typically contain a binder. Examples of suitable binders include gum tragacanth, acacia, gelatin and a synthetic or semisynthetic starch derivative, such as hydroxypropylmethylcellulose (HPMC); excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and in some instances, a sweetening agent such as sucrose, lactose or saccharin. When the dosage form employed is a capsule, it may contain, in addition to the components described above, a liquid carrier such as fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. Syrups and elixirs typically contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl or propylparabens as a preservative, a dye and a flavoring such as cherry or orange flavor.

The compound of the formulas described herein or a pharmaceutically acceptable salt thereof may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water, saline or another biocompatible vehicle, suitably mixed with a surfactant, buffer, and the like. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in an oil. Under ordinary conditions of storage and use, these preparations can also contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions and dispersions, and sterile powders for the extemporaneous preparation of sterile injectable solutions and dispersions. The preparation should be prepared under sterile conditions and be fluid to the extent that easy syringability exists. It should be sufficiently stable under the conditions of manufacture and storage and preserved against the growth of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and suitable oils.

Combination Therapy

The compounds of the present invention are further useful in methods for the prevention or treatment of the aforementioned diseases, disorders and conditions in combination with other therapeutic agents.

The compounds of the present invention may be used in combination with one or more other
5 drugs in the treatment, prevention, suppression or amelioration of diseases or conditions for which compounds of formulas I to I-G or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of formulas I to I-G. When a compound of formulas I to I-G is used contemporaneously with
10 one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of formulas I to I-G is preferred. However, the combination therapy may also include therapies in which the compound of formulas I to I-G and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients
15 may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of formulas I to I-G.

Examples of other active ingredients that may be administered separately or in the same pharmaceutical composition in combination with a compound of the formulas described herein
20 include, but are not limited to:

(1) dipeptidyl peptidase-IV (DPP-4) inhibitors (e.g., sitagliptin, alogliptin, omarigliptin, linagliptin, vildagliptin, trelagliptin);

(2) insulin sensitizers, including (i) PPAR γ agonists, such as the glitazones (e.g. pioglitazone, AMG 131, MBX2044, mitoglitazone, lobeglitazone, IDR-105, rosiglitazone, and
25 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 02/08188, WO 2004/019869, WO 2004/020409, WO
30 2004/020408, and WO 2004/066963); and (4) PPAR γ partial agonists; (ii) biguanides, such as metformin and its pharmaceutically acceptable salts, in particular, metformin hydrochloride, and

- extended-release formulations thereof, such as Glumetza™, Fortamet™, and GlucophageXR™; and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors (e.g., ISIS-113715 and TTP814);
- (3) insulin or insulin analogs (e.g., insulin detemir, insulin glulisine, insulin degludec, insulin glargine, insulin lispro and inhalable formulations of each);
- 5 (4) leptin and leptin derivatives and agonists;
- (5) amylin and amylin analogs (e.g., pramlintide);
- (6) sulfonylurea and non-sulfonylurea insulin secretagogues (e.g., tolbutamide, glyburide, glipizide, glimepiride, mitiglinide, meglitinides, nateglinide and repaglinide);
- (7) α -glucosidase inhibitors (e.g., acarbose, voglibose and miglitol);
- 10 (8) glucagon receptor antagonists (e.g., MK-3577, MK-0893, LY-2409021 and KT6-971);
- (9) 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
- 15 once-weekly formulations thereof);
- (10) LDL cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (e.g., simvastatin, lovastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, pitavastatin and rosuvastatin), (ii) bile acid sequestering agents (e.g., colestilan, colestimide, colesevalam hydrochloride, colestipol, cholestyramine, and dialkylaminoalkyl derivatives of a cross-linked
- 20 dextran), (iii) inhibitors of cholesterol absorption, (e.g., ezetimibe), and (iv) acyl CoA:cholesterol acyltransferase inhibitors, (e.g., avasimibe);
- (11) HDL-raising drugs, (e.g., niacin and nicotinic acid receptor agonists, and extended-release versions thereof);
- (12) antiobesity compounds;
- 25 (13) 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;
- (14) antihypertensive agents, such as ACE inhibitors (e.g., lisinopril, enalapril, ramipril, captopril, quinapril, and tandolapril), A-II receptor blockers (e.g., losartan, candesartan,
- 30 irbesartan, olmesartan medoxomil, valsartan, telmisartan, and eprosartan), renin inhibitors (e.g., aliskiren), beta blockers, and calcium channel blockers;

- (15) glucokinase activators (GKAs) (e.g., AZD6370);
- (16) 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);
- (17) CETP inhibitors (e.g., anacetrapib, and torcetrapib);
- 5 (18) 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);
- (19) inhibitors of acetyl CoA carboxylase-1 or 2 (ACC1 or ACC2);
- (20) AMP-activated Protein Kinase (AMPK) activators;
- (21) other agonists of the G-protein-coupled receptors: (i) GPR-109, (ii) GPR-119 (e.g.,
- 10 MBX2982 and PSN821), and (iii) GPR-40 (e.g., TAK875);
- (22) SSTR3 antagonists (e.g., such as those disclosed in WO 2009/001836);
- (23) neuromedin U receptor agonists (e.g., such as those disclosed in WO 2009/042053, including, but not limited to, neuromedin S (NMS));
- (24) SCD inhibitors;
- 15 (25) GPR-105 antagonists (e.g., such as those disclosed in WO 2009/000087);
- (26) SGLT inhibitors (e.g., ASP1941, SGLT-3, empagliflozin, dapagliflozin, canagliflozin, BI-10773, PF-04971729, remogliflozin, TS-071, tofogliflozin, ipragliflozin, ertugliflozin, and LX-4211);
- (27) inhibitors of acyl coenzyme A:diacylglycerol acyltransferase 1 and 2 (DGAT-1 and
- 20 DGAT-2);
- (28) inhibitors of fatty acid synthase;
- (29) inhibitors of acyl coenzyme A:monoacylglycerol acyltransferase 1 and 2 (MGAT-1 and MGAT-2);
- (30) agonists of the TGR5 receptor (also known as GPBAR1, BG37, GPCR19,
- 25 GPR131, and M-BAR);
- (31) ileal bile acid transporter inhibitors;
- (32) PACAP, PACAP mimetics, and PACAP receptor 3 agonists;
- (33) PPAR agonists;
- (34) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;
- 30 (35) IL-1b antibodies, (e.g., XOMA052 and canakinumab); and
- (36) bromocriptine mesylate and rapid-release formulations thereof.

Of particular interest are dipeptidyl peptidase-IV (DPP-4) inhibitors that can be used in combination with compounds of the present invention. Such inhibitors include, without limitation, sitagliptin (disclosed in US Patent No. 6,699,871), omarigliptin, SYR-472, teneligliptin, KRP104, TS021, AMG222, SK0403, LC15-0444, vildagliptin, saxagliptin, alogliptin, melogliptin, linagliptin, and pharmaceutically acceptable salts thereof, and fixed-dose combinations of these compounds with metformin hydrochloride, pioglitazone, rosiglitazone, simvastatin, atorvastatin, rosuvastatin, ertugliflozin, ipragliflozin, or a sulfonylurea.

Antiobesity compounds that can be combined with compounds of formulas I to I-G include topiramate; zonisamide; naltrexone; phentermine; bupropion; the combination of bupropion and naltrexone; the combination of bupropion and zonisamide; the combination of topiramate and phentermine; fenfluramine; dexfenfluramine; sibutramine; lipase inhibitors, such as orlistat and cetilistat; melanocortin receptor agonists, in particular, melanocortin-4 receptor agonists; CCK-1 agonists; melanin-concentrating hormone (MCH) receptor antagonists; neuropeptide Y₁ or Y₅ antagonists (such as MK-0557); CB1 receptor inverse agonists and antagonists (such as rimonabant and taranabant); β_3 adrenergic receptor agonists; ghrelin antagonists; bombesin receptor agonists (such as bombesin receptor subtype-3 agonists); and 5-hydroxytryptamine-2c (5-HT_{2c}) agonists, such as lorcaserin. For a review of anti-obesity compounds that can be combined with compounds of the present invention, see S. Chaki et al., "Recent advances in feeding suppressing agents: potential therapeutic strategy for the treatment of obesity," Expert Opin. Ther. Patents, 11: 1677-1692 (2001); D. Spanswick and K. Lee, "Emerging antiobesity drugs," Expert Opin. Emerging Drugs, 8: 217-237 (2003); J.A. Fernandez-Lopez, et al., "Pharmacological Approaches for the Treatment of Obesity," Drugs, 62: 915-944 (2002); and K.M. Gadde, et al., "Combination pharmaceutical therapies for obesity," Exp. Opin. Pharmacother., 10: 921-925 (2009).

In another aspect of the invention, a pharmaceutical composition is disclosed which comprises one or more of the following agents:

- (a) a compound of structural formulas I to I-G;
- (b) one or more compounds selected from the group consisting of:

- (1) dipeptidyl peptidase-IV (DPP-4) inhibitors;

- (2) insulin sensitizers, including (i) PPAR γ agonists, such as the glitazones (e.g. AMG 131, MBX2044, mitoglitazone, lobeglitazone, IDR-105, pioglitazone, rosiglitazone, and balaglitazone) and

- other PPAR ligands, including (1) PPAR α / γ dual agonists, such as ZYH1, YYH2, chiglitazar, GFT505, muraglitazar, aleglitazar, sodelglitazar, and naveglitazar, (2) PPAR α agonists, such as fenofibric acid derivatives (e.g., gemfibrozil, clofibrate, ciprofibrate, fenofibrate and bezafibrate), (3) selective PPAR γ modulators (SPPAR γ M's), and (4) PPAR γ partial agonists; (ii) biguanides, such as metformin and its
- 5 pharmaceutically acceptable salts, in particular, metformin hydrochloride, and extended-release formulations thereof, such as Glumetza®, Fortamet®, and GlucophageXR®; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, such as ISI-113715, and TTP814;
- (3) sulfonylurea and non-sulfonylurea insulin secretagogues, (e.g., tolbutamide, glyburide, glipizide, glimepiride, mitiglinide, and meglitinides, such as nateglinide and repaglinide);
- 10 (4) α -glucosidase inhibitors (e.g., acarbose, voglibose and miglitol);
- (5) glucagon receptor antagonists;
- (6) LDL cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (e.g., lovastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, pitavastatin, and rosuvastatin), (ii) bile acid sequestering agents (e.g., colestilan, cholestyramine, colestimide, colesevelam hydrochloride,
- 15 colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) inhibitors of cholesterol absorption, (e.g., ezetimibe), and (iv) acyl CoA:cholesterol acyltransferase inhibitors (e.g., avasimibe);
- (7) HDL-raising drugs, such as niacin or a salt thereof and extended-release versions thereof;
- (8) antiobesity compounds;
- (9) agents intended for use in inflammatory conditions, such as aspirin, non-steroidal
- 20 anti-inflammatory drugs (NSAIDs), glucocorticoids, and selective cyclooxygenase-2 (COX-2) inhibitors;
- (10) antihypertensive agents, such as ACE inhibitors (e.g., enalapril, lisinopril, ramipril, captopril, quinapril, and tandolapril), A-II receptor blockers (e.g., losartan, candesartan, irbesartan, olmesartan medoxomil, valsartan, telmisartan, and eprosartan), renin inhibitors (e.g., aliskiren), beta
- 25 blockers (e.g., calcium channel blockers);
- (11) glucokinase activators (GKAs) (e.g., AZD6370);
- (12) inhibitors of 11 β -hydroxysteroid dehydrogenase type 1 (e.g., such as those disclosed in U.S. Patent No. 6,730,690; WO 03/104207; and WO 04/058741);
- (13) inhibitors of cholesteryl ester transfer protein (CETP), (e.g., torcetrapib and anacetrapib);
- 30 (14) 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);

- (15) inhibitors of acetyl CoA carboxylase-1 or 2 (ACC1 or ACC2);
- (16) AMP-activated Protein Kinase (AMPK) activators;
- (17) agonists of the G-protein-coupled receptors: (i) GPR-109, (ii) GPR-119 (e.g., MBX2982, and PSN821), and (iii) GPR-40;
- 5 (18) SSTR3 antagonists (e.g., such as those disclosed in WO 2009/011836);
- (19) neuromedin U receptor agonists (e.g., such as those disclosed in WO2009/042053, including, but not limited to, neuromedin S (NMS));
- (20) inhibitors of stearoyl-coenzyme A delta-9 desaturase (SCD);
- (21) GPR-105 antagonists (e.g., such as those disclosed in WO 2009/000087);
- 10 (22) inhibitors of glucose uptake, such as sodium-glucose transporter (SGLT) inhibitors and its various isoforms, such as SGLT-1; SGLT-2 (e.g., ASP1941, TS071, BI10773, tofogliflozin, LX4211, canagliflozin, dapagliflozin, ertugliflozin, ipragliflozin and remogliflozin; and SGLT-3);
- (23) inhibitors of acyl coenzyme A:diacylglycerol acyltransferase 1 and 2 (DGAT-1 and DGAT-2);
- 15 (24) inhibitors of fatty acid synthase;
- (25) inhibitors of acyl coenzyme A:monoacylglycerol acyltransferase 1 and 2 (MGAT-1 and MGAT-2);
- (26) agonists of the TGR5 receptor (also known as GPBAR1, BG37, GPCR19, GPR131, and M-BAR);
- 20 (28) bromocriptine mesylate and rapid-release formulations thereof, and
- (29) IL-1b antibodies (e.g., XOMA052, and canakinumab); and
- (c) a pharmaceutically acceptable carrier.

When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention may be employed. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will

generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200.

Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

- 5 In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

ABBREVIATIONS

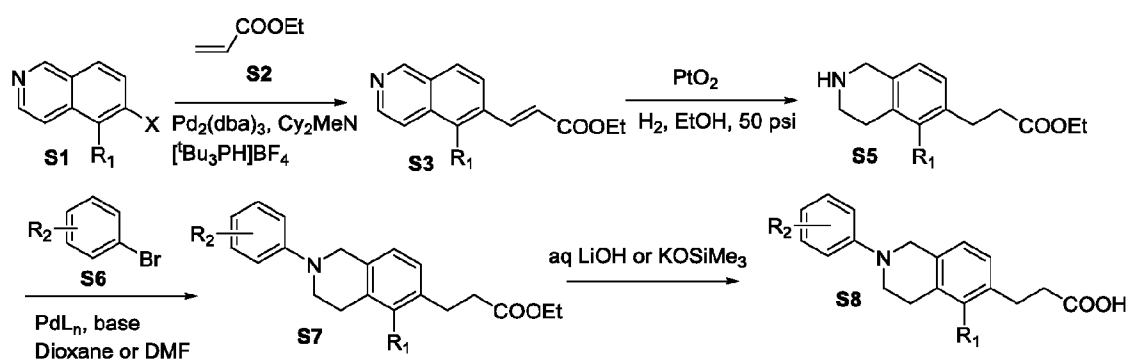
- 10 The following abbreviations may be used in the synthetic schemes or Examples:
 ACN is acetonitrile; AcOH is acetic acid; Ac₂O is acetic anhydride; anhyd. or anhydr. is anhydrous; aq. is aqueous; Ar is aryl; BINAP is (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl); (BOC)₂O is Boc anhydride or di-*tert*-butyl dicarbonate; *n*-BuLi is *n*-butyl lithium; *tert*-BuOH or *t*-BuOH is *tert*-butanol; (*t*-Bu)₃PHBF₄ is tri-*tert*-butylphosphine tetrafluoroborate *t*-Busphos
 15 precatalyst is chloro(2-ditert-butyl-2',6'-dimethoxy-1,1'-biphenyl)[2-(2-aminoethyl-phenyl)]palladium(II)dichloromethane adduct; Bu₄NI is tetrabutyl ammonium iodide; ^tBuOK is potassium *tert*-butoxide; °C is degree Celsius; CataCXium A is di(1-adamantyl)-*n*-butylphosphine; CDCl₃ is deuterated chloroform; CD₃OD is deuterated methanol; Celite™ is diatomaceous earth; conc. is concentrated; d is day or days; DAST is diethylaminosulfur
 20 trifluoride; DCM is dichloromethane; DEA is N,N-diisopropylethylamine; DEAD is diethyl azodicarboxylate; DIAD is diisopropyl azodicarboxylate; DIBAL is diisobutylaluminum hydride; DIEA is diisopropylethylamine; DMA is N,N-dimethylacetamide; DMF is dimethylformamide; DMP is Dess-Martin periodinane; DMS is dimethyl sulfide; DMSO is dimethylsulfoxide; Et is ethyl; EA or EtOAc is ethyl acetate; EtOH is ethanol; Et₂Zn is diethylzinc; g is grams; Et₃N is
 25 triethylamine; Et₃SiH is triethylsilane; iPrOH is isopropyl alcohol; g is gram; G2 Ru Phos is chloro(2-dicyclohexylphosphino-2',6-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II); G2 X Phos is chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II); G418 is Geneticin, an aminoglycoside antibiotic; h is hour; HATU is 1-[Bis(dimethylamino)-
 30 methylene]-1H-1,2,3-triazolo-[4,5-b]pyridinium 3-oxide-hexa-fluorophosphate); HPLC is high performance liquid chromatography; KHMDS is potassium hexamethyldisilazide; KOTMS

- is potassium trimethylsiloxide; LAH is lithium aluminum hydride; LDA is lithium diisopropylamide; LHMDs or LiHMDs is lithium bis(trimethylsilyl)amide; LiTMP is lithium tetramethylpiperidide; M is molar; m-CPBA or mCPBA is meta-chloroperoxybenzoic acid; Me is methyl; MeCN is acetonitrile; MeI is methyl iodide; MeOH is methanol; mg is milligram;
- 5 MHz is megaHertz; min is minute(s); mmol is millimoles; ml or mL is milliliter; mPa is millipascal; N is normal; nBuLi is n-butyllithium; NBS is N-bromosuccinimide; NCS is N-chlorosuccinimide; NMP is N-methylpyrrolidone; NMR is nuclear magnetic resonance; PCC is pyridinium chlorochromate; Pd-C or Pd/C is palladium(0) on carbon; PdCl₂(dtbpf) is [1,1'-Bis(di-*tert*-butylphosphino)-ferrocene]di-chloropalladium(II); PE is petroleum ether;
- 10 Pd(PPh₃)₄ is tetrakis(triphenyl-phosphine)palladium(0); Pd(OAc)₂ is palladium (II) acetate; Pd₂(dba)₃ is tris(dibenzylideneacetone)dipalladium(0); Pd(OH)₂/C is palladium(II)hydroxide on carbon; PPh₃ is triphenyl phosphine; prep is preparative; Prep-HPLC is preparative high performance liquid chromatography; psi is pounds per square inch; PTLC or prep tlc is preparative thin layer chromatography; rac is racemic; rt or RT or r.t. is room temperature;
- 15 RuPhos precatalyst is 2-dicyclohexylphosphino-2',6'-diisopropoxy-biphenyl; sat. or satd. Is saturated; soln. is solution; SelectFluor is 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]-octane bis(tetrafluoroborate); SFC is supercritical fluid chromatography; SPHOS precatalyst is 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl; TBAB is tetrabutylammonium bromide; TBAF is tetra-n-butylammonium fluoride; TBAI is tetra-n-butylammonium iodide; TEA is
- 20 triethylamine; Tf₂O is triflic anhydride or tri-fluoromethanesulfonic anhydride; TFA is trifluoroacetic acid; TFAA is trifluoroacetic anhydride; THF is tetrahydrofuran; TIPS-Cl is triisopropyl silylchloride; TLC is thin layer chromatography; TMP is tetramethylpiperidine; TMSCl or TMS-Cl is trimethylsilyl chloride; TRIXIEPHOS is 2-Di-t-butylphosphino-1,1'-binaphthyl; PTLC or prep-TLC is preparative thin layer chromatography; XantPhos is X; and
- 25 XPHOS, XPhos or Xphos precatalyst is 2-dicyclohexylphosphino-2'4'6'-triisopropylbiphenyl.

GENERAL SCHEMES

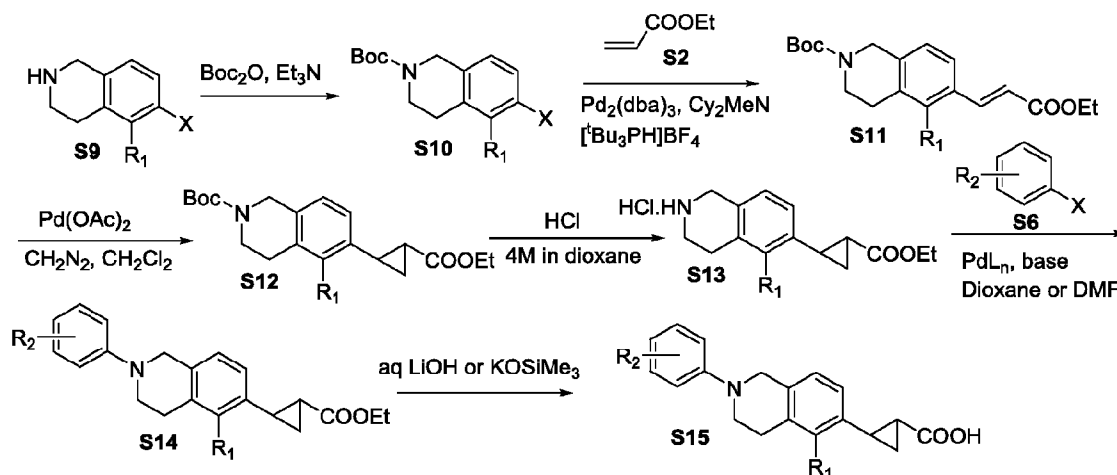
- The compounds of the invention can be prepared using the synthetic schemes described herein as well as any of several alternate methods which will be apparent to a chemist skilled in
- 30 the art.

Scheme 1



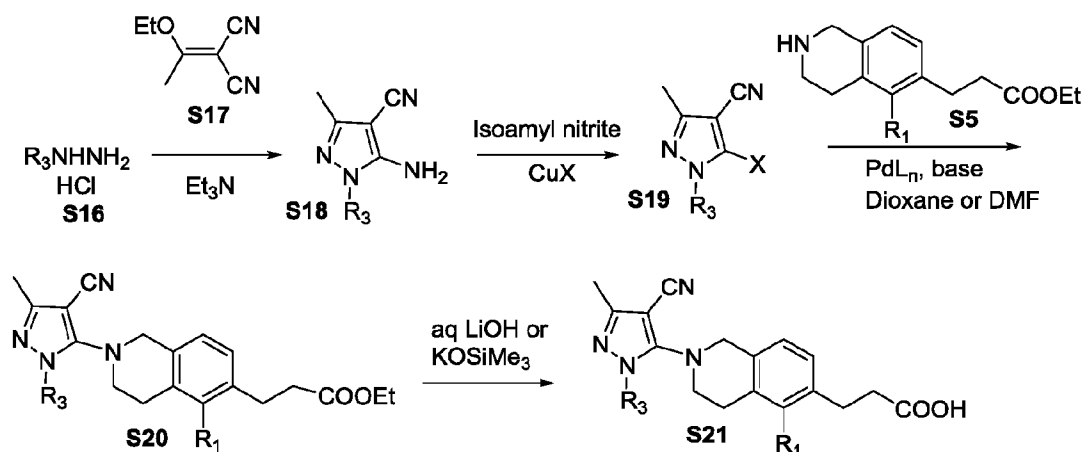
- 5 S8 can be obtained by first reacting the 6-halo-isoquinoline derivative S1 with the ethyl acrylate using a palladium catalyst to give S3, which is selectively reduced by hydrogenation with platinum oxide catalysis to yield the ethyl tetrahydroisoquinoline-6-yl-propanoate S5. S5 can be coupled with an aryl halide S6 with a palladium catalyst to give S7. The acid S8 is obtained after treatment of S7 with LiOH or KOSiMe₃.

Scheme 2



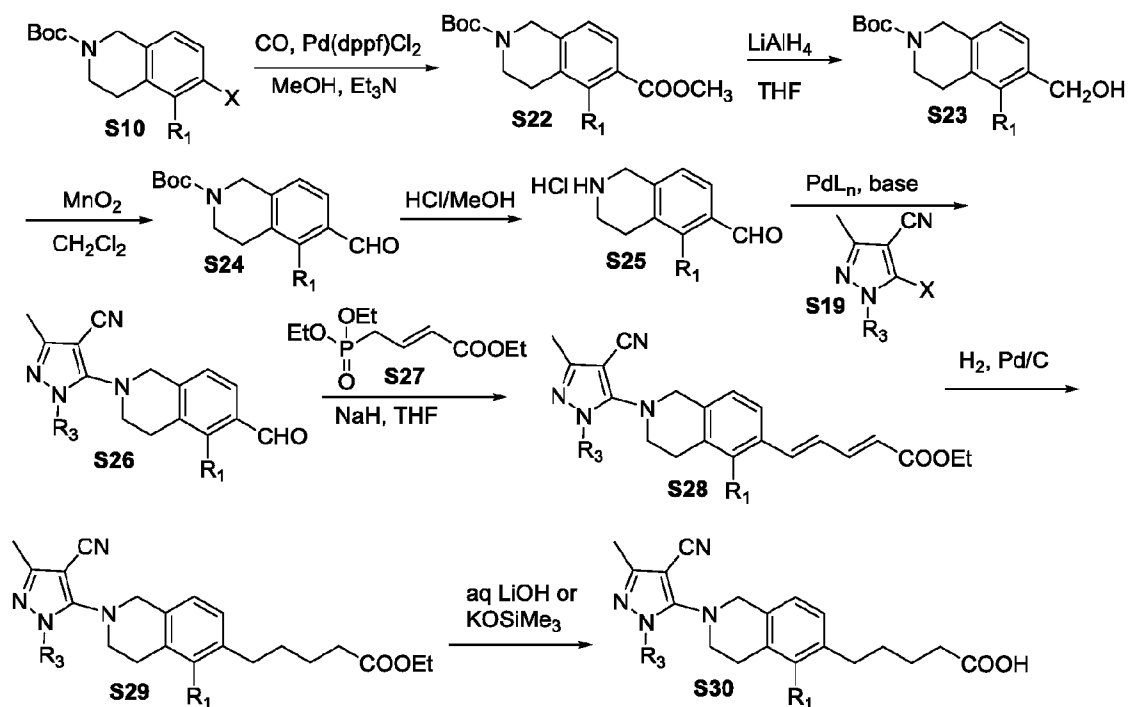
- S15 can be obtained by protecting the 6-halo-tetrahydroisoquinoline S9 at the amino group with a Boc group to give S10. The Boc protected compound S10 can further be treated with ethyl acrylate S2 in the presence of a palladium catalyst to give alkene S11. Alkene S11 can be treated under cyclopropanation conditions with diazomethane in the presence of palladium acetate to give the cyclopropyl compound S12. The Boc group is then removed under acidic conditions to give S13 as the hydrochloric acid salt. S13 is then coupled with the aryl halide S6 in the presence of a palladium catalyst to give S14. S14 can be treated with LiOH or KOSiMe₃ to give the acid S15.

Scheme 3



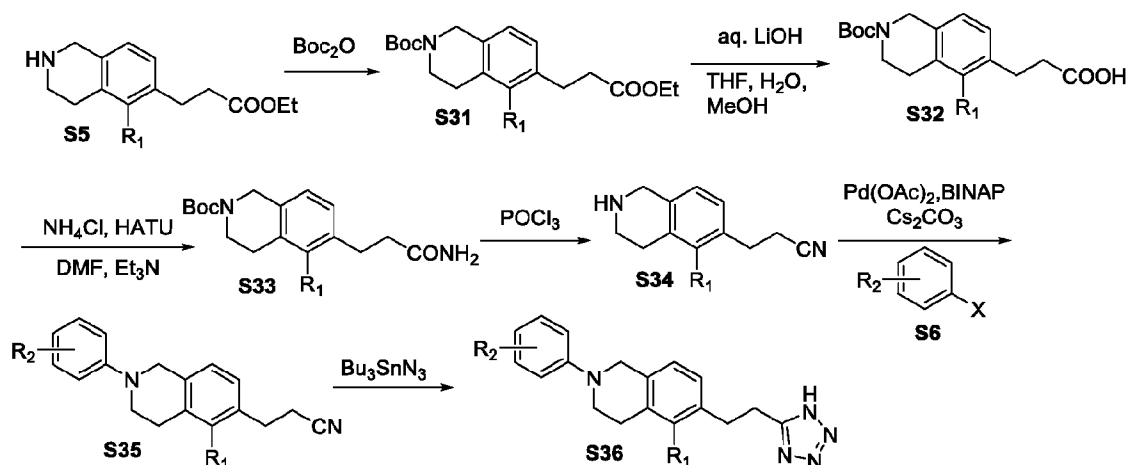
S21 can be obtained by first reacting the substituted hydrazine S16 with 2-(1-ethoxyethylidene)malononitrile S17 under basic conditions to give amino-pyrazolyl S18. S18 can be treated with an isoamyl nitrite in the presence of a copper (I) halide to give the halo-pyrazolyl compound S19. S19 and S5 can be coupled in the presence of a palladium catalyst to give S20, and S20 can be deprotected with LiOH or KOSiMe₃ to give S21.

Scheme 4



S30 can be obtained by reacting S10 with carbon monoxide and MeOH in the presence of a palladium catalyst to give S22. The ester S22 can be reduced in the presence of LiAlH₄ to give the alcohol S23, which may be oxidized to the aldehyde in the presence of MnO₂ to give S24. The Boc group can be removed using acidic conditions to give the amine S25. Then amine S25 and S19 can be coupled in the presence of a palladium catalyst to give S26. S27 after treatment with NaH can be activated to react with S26 to give the diene S28. The diene S28 can be reduced in the presence of hydrogen and palladium on carbon to give the alkane S29. S30 can be obtained after treatment of S29 with either LiOH or KOSiMe₃.

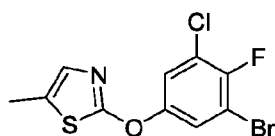
Scheme 5



- 5 S36 can be obtained by first treating S5 with Boc_2O to give the Boc protected compound S31. S31 can be treated with LiOH to give acid S32. S32 can be treated in peptide coupling conditions in the presence of NH_4Cl to give amide S33. The amide S33 can be reduced in the presence of POCl_3 to give the deprotected cyano compound S34. S34 and S6 can be coupled in the presence of a palladium catalyst to give S35. S35 can be treated with Bu_3SnN_3 to give the tetrazolyl compound S36.
- 10

INTERMEDIATE 1

2-(3-Bromo-5-chloro-4-fluorophenoxy)-5-methylthiazole



- 15 Step A. (3-Chloro-4-fluorophenoxy)triisopropylsilane: To a solution of 3-chloro-4-fluorophenol (20.0 g, 136 mmol) in DMF (100 mL) was added 1H-imidazole (9.29 g, 136 mmol) and chlorotriisopropylsilane (26.3 g, 136 mmol), and the mixture was stirred at 10°C for 18 h. The

mixture was diluted with water (500 mL) and extracted with EtOAc (3x150 mL). The separated organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The resulting residue was purified via silica gel chromatography (PE) to afford the the title compound.

Step B. (3-Bromo-5-chloro-4-fluorophenoxy)triisopropylsilane: To a soln. of

- 5 2,2,6,6-tetramethylpiperidine (5.60 g, 39.6 mmol) in THF (80 mL) was added 2.5 M n-BuLi (16 mL, 40.0 mmol) dropwise at -78°C under N₂. The reaction mixture was stirred for 1 h, then the mixture was allowed to warm to 0°C and stirred for 10 min. The reaction was cooled back to -78°C, and (3-chloro-4-fluorophenoxy)triisopropylsilane (10.0 g, 33.0 mmol) in THF (40 mL) was added dropwise at -78°C, and the mixture was stirred at -78°C for 2 h. Br₂ (7.91 g, 49.5
- 10 mmol) was added, then the mixture was stirred at -78°C for another 2 h. The mixture was quenched by addition of satd. aq. NH₄Cl (50 mL), diluted with water (100 mL), and extracted with EtOAc (3x150 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE) to afford the title compound.

Step C. 3-Bromo-5-chloro-4-fluorophenol: To a soln. of (3-bromo-5-chloro-4-

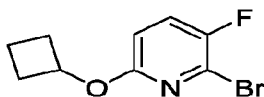
- 15 fluorophenoxy)triisopropylsilane (10.40 g, 27.2 mmol) in THF (120 mL) was added TBAF (33 mL, 33.0 mmol), and the mixture was stirred at 20°C for 1 h. Then the mixture was diluted with water (150 mL) and extracted with EtOAc (150 mLx3). The organic layer was separated, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE:EtOAc=50:1) to afford the title compound.

- 20 Step D. 2-(3-Bromo-5-chloro-4-fluorophenoxy)-5-methylthiazole: A mixture of 3-bromo-5-chloro-4-fluorophenol (500 mg, 2.218 mmol), 2-bromo- 5-methylthiazole (434 mg, 2.440 mmol) and Cs₂CO₃ (1.08 g, 3.33 mmol) in NMP (6 mL) was stirred under microwave irradiation at 150°C for 30 min. The mixture was extracted with EtOAc (20 mLx3), and the organic layer was washed with water (15 mL). The organic layer was dried (Na₂SO₄) and
- 25 concentrated *in vacuo*. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250*21.2 mm*4 μm) column using water (0.2% TFA) and ACN as eluents (Mobile phase A: water (0.2% TFA), Mobile phase B: ACN, Detector wavelength: 220 nm) followed by concentration *in vacuo* to obtain the title compound.

- ¹H NMR (400 MHz, CDCl₃) δ 7.43 (dd, *J*=4.89, 2.93 Hz, 1 H) 7.34 (dd, *J*=5.48, 2.74 Hz, 1 H)
- 30 6.91 (s, 1 H) 2.38 (s, 3 H).

INTERMEDIATE 2

2-Bromo-6-cyclobutoxy-3-fluoropyridine



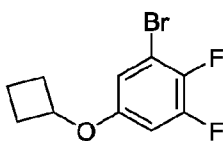
Step A. 2-Cyclobutoxy-5-fluoropyridine: To a suspension of NaH (1.25 g, 31.30 mmol) in THF (30 mL) was added cyclobutanol (2.25 g, 31.30 mmol) at rt in one portion, and the mixture was stirred at ~25°C for 10 min, followed by the dropwise addition of 2,5-difluoropyridine (3.00 g, 26.10 mmol). The above suspension was stirred at rt for 1 h. The mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL). The organic layer was collected, washed with brine (10 mL), dried over anhyd. Na₂SO₄, filtered, and then concentrated *in vacuo* to afford the title compound. *m/z* 168.2 [M+H]⁺

Step B. 2-Cyclobutoxy-5-fluoropyridine 1-oxide: To a soln. of 2-cyclobutoxy-5-fluoropyridine (1.20 g, 7.18 mmol) in DCM (20 mL) was added *m*-CPBA (2.47 g, 14.36 mmol) at rt in one portion, and the mixture was stirred at ~25°C for 36 h. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography (PE:EtOAc from 2:1 to DCM:EtOAc 5:1) to afford the title compound. *m/z* 184.1 [M+H]⁺

Step C. 2-Bromo-6-cyclobutoxy-3-fluoropyridine: To a soln. of 2-cyclobutoxy-5-fluoropyridine-1-oxide (400 mg, 2.18 mmol) in toluene (5 mL) was added phosphoryl tribromide (689 mg, 2.40 mmol) in one portion, and the mixture was stirred at 100°C for 1 h. The mixture was added to a satd. aq. NaHCO₃ soln. (10 mL), and then extracted with EtOAc (10 mL). The organic layer was concentrated *in vacuo*, and the remaining residue was purified by silica gel PTLC (PE) to afford the title compound. *m/z*=245.8 [M+H]⁺

INTERMEDIATE 3

1-Bromo-5-cyclobutoxy-2,3-difluorobenzene



Step A. 4,5-Difluoro-2-nitrophenol: To a soln. of 3,4-difluorophenol (40.00 g, 307 mmol) in AcOH (100 mL) was added dropwise a soln. of fuming nitric acid (18.0 ml, 431 mmol) in AcOH (60 mL) maintaining the temperature below 50°C. Then the reaction mixture was stirred

at 16°C for 2 h. The reaction mixture was poured into water (200 mL) and the solid separating out was filtered. The solid was dissolved in dichloromethane (200 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to give the title compound which was used directly in the next step.

- 5 Step B. Cyclobutoxy-4,5-difluoro-2-nitrobenzene: To a soln. of 4,5-difluoro-2-nitrophenol (45.00 g, 257 mmol) in DMF (200 mL) was added bromocyclobutane (69.4 g, 514 mmol), mono(4-(tributylammonio)butan-1-ylum) monoiodide (95 g, 257 mmol) and Cs₂CO₃ (84 g, 257 mmol). Then the reaction mixture was stirred at 90°C for 16 h. Water (1.5 L) was added, and the mixture was extracted with EtOAc (300 mL×3). The resulting organic layer was concentrated
- 10 *in vacuo*. The crude product was purified by silica gel chromatography (PE to PE/EtOAc=50:1 to 40:1) to give the title compound.

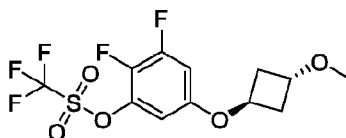
- Step C. 2-Cyclobutoxy-4,5-difluoroaniline: To a soln. of 1-cyclobutoxy-4,5-difluoro-2-nitrobenzene (5.00 g, 21.82 mmol) in MeOH (60 mL) and water (6 mL) was added NH₄Cl (11.67 g, 218 mmol) and iron (6.09 g, 109 mmol). Then the reaction mixture was stirred at 90°C
- 15 for 16 h. The reaction mixture was filtered, and water (50 mL) was added to the filtrate. The filtrate was extracted with EtOAc (30 mL×2), and the organic layer was concentrated *in vacuo* to give the crude product which was used without further purification.

- Step D. 2-Bromo-6-cyclobutoxy-3,4-difluoroaniline: To a soln. of 2-cyclobutoxy-4,5-difluoroaniline (2.30 g, 11.55 mmol) in AcOH (50 mL) was added Br₂ (0.68 mL, 13.28 mmol).
- 20 Then the reaction mixture was stirred at 14°C for 16 h. A satd. aq. solution of Na₂S₂O₃ (30 mL) was added, and the mixture was extracted with EtOAc (50 mL). The organic layer was separated and concentrated *in vacuo*. The crude product was purified by PTLC (PE/EtOAc=10:1) to give the title compound.

- Step E. 1-Bromo-5-cyclobutoxy-2,3-difluorobenzene: To a soln. of 2-bromo-6-cyclobutoxy-3,4-difluoroaniline (450 mg, 1.618 mmol) in THF (3 mL) was added isopentyl nitrite (380 mg, 3.24 mmol). Then the reaction mixture was stirred at 70°C for 16 h. The mixture was concentrated *in vacuo*. Water (30 mL) was added, and the mixture was extracted with EtOAc (30 mL×2). The organic layer was concentrated *in vacuo*, and the resulting crude product purified by silica gel TLC (PE/EtOAc=10:1) to give title compound. ¹H NMR (400 MHz, CDCl₃)
- 25 δ 6.74 (d, *J*=2.0 Hz, 1 H), 6.58-6.61 (m, 1 H), 4.53-4.58 (m, 1 H), 2.43-2.45 (m, 2 H), 2.12-2.17 (m, 2 H), 1.84-1.87 (m, 2 H), 1.65-1.71 (m, 2 H).
- 30

INTERMEDIATE 4

2,3-Difluoro-5-((1R,3R)-3-methoxycyclobutoxy)phenyl trifluoromethanesulfonate



Step A: 1-(Benzyloxy)-5-((1R,3R)-3-(benzyloxy)cyclobutoxy)-2,3-difluorobenzene: To a solution of 3-(benzyloxy)-4,5-difluorophenol (2.50 g, 10.58 mmol), 3-(benzyloxy) cyclobutanol (2.07 g, 11.64 mmol) and PPh₃ (4.16 g, 15.88 mmol) in THF (50 mL) was added DIAD (2.9 mL, 14.82 mmol) dropwise with stirring at 0°C under N₂. After the addition was complete, the reaction mixture was stirred at 70°C for an additional 18 h under N₂. The solvent was removed *in vacuo*, and the residue was purified via silica gel chromatography (PE:EtOAc=50:1 to 20:1) to afford the title compound.

Step B. 2,3-Difluoro-5-(3-hydroxycyclobutoxy)phenol: To a solution of 1-(benzyloxy)-5-((1R,3R)-3-(benzyloxy)cyclobutoxy)-2,3-difluorobenzene (1.50 g, 3.78 mmol) in MeOH (50 mL) was added 10% Pd-C (600 mg, 2.82 mmol). Then the mixture was stirred at rt for 18 h under H₂ (50 Psi). The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE:EtOAc=1:1) to afford the title compound.

Step C: 3-(3-(Benzyloxy)-4,5-difluorophenoxy)cyclobutanol: To a suspension of 2,3-difluoro-5-((1R,3R)-3-hydroxycyclobutoxy) phenol (1.00 g, 4.63 mmol) and K₂CO₃ (1.279 g, 9.25 mmol) in acetone (30 mL) was added (bromomethyl)benzene (0.87 g, 5.09 mmol) dropwise with stirring at rt. Then the mixture was stirred at rt for 48 h. After removing the solvent *in vacuo*, the residue was diluted with water (30 mL), extracted with EtOAc (30 mLx3). The organic layer was dried over anhyd. Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EtOAc=2:1) to afford title compound.

Step D. 1-(Benzyloxy)-2,3-difluoro-5-((1R,3R)-3-methoxycyclobutoxy)benzene: To a soln. of (1R,3R)-3-(3-(benzyloxy)-4,5-difluorophenoxy)cyclobutan-1-ol from step C (380 mg, 1.241 mmol) in dry DMF (10 mL) was added NaH (60 mg, 1.5 mmol) (60 % in oil) in portions at 0°C. After 1 h, MeI (528 mg, 3.72 mmol) was added dropwise at 0°C. Then the mixture was stirred for 18 h with gradual warming to rt. Water (~10 mL) was added to quench the reaction, and the

mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 20 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EtOAc=10:1) to afford the title compound.

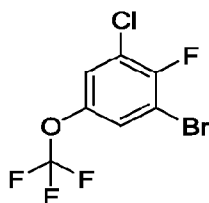
Step E. *Cis* 2,3-Difluoro-5-(-3-methoxycyclobutoxy)phenol: To a soln. of

- 5 1-(benzyloxy)-2,3-difluoro-5-((1*R*,3*R*)-3-methoxycyclobutoxy)benzene (310 mg, 0.968 mmol) in MeOH (30 mL) was added 10% Pd-C (50 mg, 0.235 mmol). Then the mixture was stirred at rt for 2 h under H₂ (40 PSI). The mixture was filtered, and the filtrate was concentrated *in vacuo* to give the title compound.

- Step F. 2,3-Difluoro-5-((1*r*, 3*r*)-3-methoxycyclobutoxy)phenyl trifluoromethane sulfonate: To a soln. of 2,3-difluoro-5-((1*r*,3*r*)-3-methoxycyclobutoxy)phenol (200 mg, 0.869 mmol) in DCM (5 mL) was added pyridine (89 mg, 1.129 mmol) and trifluoromethanesulfonic anhydride (319 mg, 1.129 mmol) dropwise with stirring at 0°C. Then the mixture was stirred at rt for 3 h. Water (10 mL) was added, and the mixture was extracted with DCM (20 mLx2). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EtOAc=20:1) to afford the title compound. ¹H NMR (400 MHz, CDCl₃) δ 6.65 (ddd, *J*=11.05, 5.77, 2.74 Hz, 1 H) 6.52-6.56 (m, 1 H) 4.73-4.79 (m, 1 H) 4.10-4.16 (m, 1 H) 3.28 (s, 3 H) 2.37-2.50 (m, 4 H).

INTERMEDIATE 5

- 20 1-Bromo-3-chloro-2-fluoro-5-(trifluoromethoxy)benzene

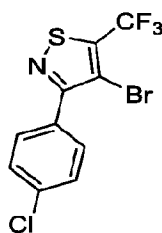


- Step A. 1-Bromo-2-fluoro-4-nitro-5-(trifluoromethoxy)benzene: To a soln. of 2-bromo-1-fluoro-4-(trifluoromethoxy)benzene (10.0 g, 38.6 mmol) in ACN (150 mL) was added nitronium tetrafluoroborate (5.38 g, 40.5 mmol) at 0°C, and the mixture was stirred at 0-18°C for 16 h. The reaction mixture was extracted with EtOAc (3x200 mL), and washed with water (2x150 mL) and brine (2 x 150 mL). The organic layer was dried over anhyd. Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (PE:EtOAc=20:1 to 5:1) to give the title compound.

- Step B. 4-Bromo-5-fluoro-2-(trifluoromethoxy)aniline: To a stirred soln. of 1-bromo-2-fluoro-4-nitro-5-(trifluoromethoxy)benzene (4.0 g, 13.16 mmol) in MeOH (20 mL) and water (2 mL) was added NH_4Cl (7.04 g, 132 mmol) and iron (2.204 g, 39.5 mmol). The mixture was stirred at 50°C for 18 h. The mixture was washed with water (2x30 mL) and
- 5 extracted with EtOAc (2x50 mL). The extract was dried over by Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE:EtOAc=10:1) to give the title compound.
- Step C. 4-Bromo-2-chloro-3-fluoro-6-(trifluoromethoxy)aniline: To a stirred soln. of 4-bromo-5-fluoro-2-(trifluoromethoxy)aniline (750 mg, 2.74 mmol) in ACN (30 mL) was added
- 10 1-chloropyrrolidine-2,5-dione (365 mg, 2.74 mmol) and the mixture was stirred at 50°C for overnight (18 h). The mixture was washed with water (2x10 mL) and extracted with EtOAc (2x30 mL). The organic layer was dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE:EtOAc=50 :1 to 30:1) to give the title compound.
- 15 Step D. 1-Bromo-3-chloro-2-fluoro-5-(trifluoromethoxy)benzene: To a stirred soln. of 4-bromo-2-chloro-3-fluoro-6-(trifluoromethoxy)aniline (300 mg, 0.973 mmol) in THF (5 mL) was added isopentyl nitrite (228 mg, 1.945 mmol), and the mixture was stirred at 50°C for 4 h. The mixture was washed with water (2x10 mL) and extracted with EtOAc (2x30 mL). The combined organic layer was dried over anhyd. Na_2SO_4 , filtered and concentrated *in vacuo*. The
- 20 residue was purified by TLC (PE:EtOAc=10:1) to give the title compound.

INTERMEDIATE 6

4-bromo-3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazole



- 25 Step A. 5-(4-chlorophenyl)-1,3,4-oxathiazol-2-one. To a solution of 4-chlorobenzamide (3.0 g, 17.35 mmol) in toluene (10 ml) was added carbonochloridic hypochlorous thioanhydride (4.55

g, 34.7 mmol) at ~20°C. Then the mixture was stirred overnight (~18 h) at 100°C. The resulting mixture was concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (EtOAc/PE=1:20) to give the title compound.

Step B- ethyl 3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazole-4-carboxylate: Into a 100 mL sealed tube was placed 5-(4-chlorophenyl)-1,3,4-oxathiazol-2-one (2.2g, 9.78 mmol), ethyl 4,4,4-trifluorobut-2-ynoate (2.437 g, 14.67 mmol) and 1,3-dichlorobenzene (20 ml). The resulting solution was stirred for 18 h at 130°C. The mixture was stirred at 150°C for 5 h. The resulting mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (PE) to give the title compound.

10 Step C. 3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazole-4-carboxylic acid: To a solution of ethyl 3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazole-4-carboxylate (2.6 g, 6.58 mmol) in THF (10 mL) and water (5 mL) was added LiOH hydrate (0.829 g, 19.75 mmol). Then the mixture was stirred at rt for 18 h. After acidification with 1N HCl to pH=2, the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/PE =
15 10:1 to 1:1) to give the title compound.

Step D. tert-butyl (3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-yl) carbamates: To a mixture of 3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazole-4- carboxylic acid (600 mg, 1.755 mmol) and Et₃N (195 mg, 1.931 mmol) in t-BuOH (20 ml) was added diphenylphosphoryl azide (531 mg, 1.931 mmol) at rt. Then the mixture was refluxed for 3 h. The reaction mixture was
20 concentrated *in vacuo*, and the residue was partitioned between EtOAc (30 mL) and H₂O (30 mL). The organic layer was washed with brine (30 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc/PE 1:20) to give the title compound.

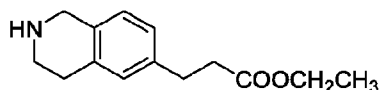
Step E. 3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-amine: To a solution of *tert*-butyl
25 (3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-yl)carbamate (590 mg, 1.246 mmol) in EtOAc (10 ml) was added HCl/EtOAc (3 ml, 4 M in dioxane) at rt. Then the mixture was stirred rt (under an N₂ atmosphere) for 18 h. The mixture was concentrated *in vacuo* to give crude product. To the crude product was added EtOAc (20 mL) and water (20 mL) basified with saturated Na₂CO₃ to pH=7~8. Then the mixture extracted with EtOAc (2x10 mL). The organic
30 layer was washed with brine (20 mL), dried over anhydrous MgSO₄, filtered and concentrated *in*

vacuo. The residue was purified by silica gel column chromatography (EtOAc/PE= 20:1) to give the title compound.

Step F. 4-bromo-3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazole: To a solution of 3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-amine (50 mg, 0.161 mmol) in MeCN (2 mL) was added CuBr₂ (72 mg, 0.322 mmol) and *tert*-butyl nitrite (37 mg, 0.359 mmol) at 0°C, and the mixture was stirred at 0°C for 30 min. The mixture was concentrated *in vacuo* and washed with water (10 mL), and extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL) and concentrated *in vacuo* to give the crude product, which was purified by silica gel chromatography (PE:EtOAc=50:1) to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.78 (d, *J*=8.41 Hz, 2 H) 7.49 (d, *J*=8.41 Hz, 2 H).

INTERMEDIATE 7

Ethyl 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate

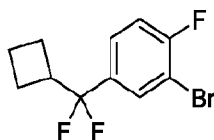


Step A. (E)-ethyl 3-(isoquinolin-6-yl)acrylate: To a solution of 6-bromoisoquinoline (10.0 g, 48.06 mmol) in dry 1,4-dioxane (100 ml) was added tri-*tert*-butylphosphonium tetrafluoroborate (1.4g, 4.8 mmol), ethyl acrylate (7.22 g, 72.10 mmol) and *N*-cyclohexyl-*N*-methylcyclohexanamine (28.17 g, 144.19 mmol). Then the mixture was degassed for 5 min with N₂, and Pd₂(dba)₃ (3.5 g, 4.8 mmol) was added. The mixture was stirred at 100°C for 18 h under a N₂ atmosphere. The mixture was extracted with EtOAc (2 x 200 mL), washed with brine (500 mL), dried (Na₂SO₄), and then purified by chromatography (PE:EtOAc=20:1 to 10:1) to give the title compound.

Step B. ethyl 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate: To a solution of (E)-ethyl 3-(isoquinolin-6-yl)acrylate (9.0 g, 39.60 mmol) in EtOH (150 ml) was added platinum (IV) oxide (0.899 g, 3.96 mmol). The reaction mixture was stirred under hydrogen (50 PSI) at 60°C for 5 h. The reaction mixture was cooled to rt, the mixture was filtered, and the filtrate was concentrated *in vacuo* to give the title compound. *m/z* 234.3 [M + H]⁺.

INTERMEDIATE 8

2-Bromo-4-(cyclobutyldifluoromethyl)-1-fluorobenzene



Step A: 3-Bromo-4-fluoro-N-methoxy-N-methylbenzamide: To a soln. of DIEA (4.78 ml, 27.4 mmol), 3-bromo-4-fluorobenzoic acid (2.0 g, 9.13 mmol) and N,O- dimethylhydroxylamine hydrochloride (0.891 g, 9.13 mmol) in DMF (25 ml) was added HATU (3.47 g, 9.13 mmol) at 0°C, and the mixture was stirred 18 h (0°C → rt). The mixture was poured into water (100 mL), extracted with EtOAc (3x200 mL), washed with water (5x50 mL) and brine (2x50 mL). The organic soln. was dried over Na₂SO₄, the salt was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EtOAc=20:1 to 5:1) to give the title compound. *m/z* 264.0 [M+H]⁺.

Step B. (3-Bromo-4-fluorophenyl)(cyclobutyl)methanone: To a suspension of magnesium (0.538 g, 22.13 mmol) in THF (20 ml) was added I₂ (0.028 g, 0.111 mmol) at 40°C, the mixture was stirred at 40°C for 10 min, and then bromocyclobutane (2.99 g, 22.13 mmol) was added dropwise with stirring at 10°C (N₂ atmosphere). After the addition was complete, the reaction mixture was stirred at 40°C for additional 2 h. The above soln. was added dropwise to a soln. of 3-bromo-4-fluoro-N-methoxy-N- methylbenzamide (2.9 g, 11.07 mmol) in THF (30 mL) at 0°C (under N₂ atmosphere). The mixture was stirred for 16 h (0°C-rt). The reaction mixture was poured into ice water (20 mL), and the mixture was extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine (2 x 20 mL) and then dried over anhyd. Na₂SO₄. The organic layer was filtered and concentrated *in vacuo* to give crude product. The crude product was purified by silica gel column chromatography (PE/DCM=100:1 to 5:1) to give compound the title compound.

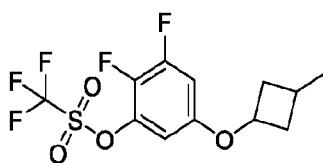
Step C. 2-bromo-4-(cyclobutyldifluoromethyl)-1-fluorobenzene: To a soln. of (3-bromo-4-fluorophenyl)(cyclobutyl)methanone (300 mg, 1.167 mmol) in DAST (3.0 ml, 16.27 mmol) was added dropwise MeOH (7.58 μl, 0.187 mmol) with stirring at 0°C (under N₂ atmosphere). After the addition was complete, the reaction mixture was stirred at 80°C for

additional 3 days. The reaction mixture was cooled to rt, and poured into sat. Na_2CO_3 (10 mL). Then the mixture was extracted with PE ($\sim 20 \text{ mL} \times 2$). The combined organic layers were washed with brine ($\sim 10 \text{ mL} \times 2$), dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give crude product. The crude product was purified by PTLC (PE) to give the title compound. ^1H

5 NMR (400 MHz, CDCl_3) δ 7.66 (d, $J=5.5 \text{ Hz}$, 1H), 7.37 (br. s., 1H), 7.15 (t, $J=8.4 \text{ Hz}$, 1H), 3.03-2.85 (m, 1H), 2.27-2.11 (m, 2H), 2.05-1.77 (m, 4H).

INTERMEDIATE 9

2,3-Difluoro-5-(3-methylcyclobutoxy)phenyl trifluoromethanesulfonate



10

Step A. 1-(benzyloxy)-5-(3-(bromomethyl)cyclobutoxy)-2,3-difluoro-benzene: To a stirred soln. of (3-(3-(benzyloxy)-4,5-difluorophenoxy)cyclobutyl)methanol (800 mg, 2.498 mmol) and CBr_4 (1.24 g, 3.75 mmol) in DMF (8 mL) was added PPh_3 (982 mg, 3.75 mmol) portionwise at 0°C . Then the reaction mixture was stirred at rt for 2 h. The mixture was diluted with water (50 mL)

15 and extracted with EtOAc ($2 \times 30 \text{ mL}$). The organic layer was concentrated *in vacuo*, and the crude product was purified by silica gel chromatography (PE/EtOAc=40:1) to give the title compound.

Step B. 1-(benzyloxy)-2,3-difluoro-5-(3-methylcyclobutoxy)benzene: To a stirred soln. of 1-(benzyloxy)-5-(3-(bromomethyl)cyclobutoxy)-2,3-difluorobenzene (580 mg, 1.51 mmol) in

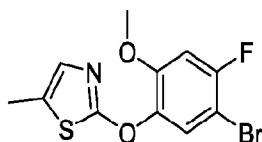
20 DMF (8 mL) was added NaBH_4 (115 mg, 3.03 mmol). Then the reaction mixture was placed under N_2 and stirred at rt for 18 h. The reaction was quenched with satd. aq. of NH_4Cl (20 mL), extracted with EtOAc ($20 \text{ mL} \times 2$), washed with water (100 mL), and the organic layer was concentrated *in vacuo*. The crude product was purified by silica gel chromatography (PE/EtOAc=5:1) to give the title compound.

25 Step C. 2,3-difluoro-5-(3-methylcyclobutoxy)phenol: A mixture of 1-(benzyloxy)-2,3-difluoro-5-(3-methylcyclobutoxy)benzene (390 mg, 1.28 mmol) and 10% Pd-C (100 mg, 0.094 mmol) in MeOH (50 mL) was stirred under hydrogen (40 PSI) at rt for 2 h. The mixture was filtered and concentrated *in vacuo* to give the crude title compound.

Step D. 2,3-difluoro-5-(3-methylcyclobutoxy)phenyl trifluoromethanesulfonate: To a stirred soln. of 2,3-difluoro-5-(3-methylcyclobutoxy)phenol (200 mg, 0.934 mmol) in DCM (5 mL) was added pyridine (96 mg, 1.214 mmol) and trifluoromethanesulfonic anhydride (342 mg, 1.214 mmol) dropwise at 0°C. Then the reaction mixture was warmed to rt for 5 h. The solvent was evaporated *in vacuo*, and the resulting mixture was diluted with water (20 mL) and extracted with EtOAc (20 mLx2). The organic layer was concentrated *in vacuo*, and the crude product was purified by silica gel chromatography (PE/EtOAc=10:1) to give the title compound.

INTERMEDIATE 10

10 2-(5-Bromo-4-fluoro-2-methoxyphenoxy)-5-methylthiazole

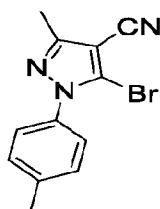


Step A. 5-Bromo-4-fluoro-2-methoxyphenol: To a soln. of 4-fluoro-2-methoxyphenol (2.0 g, 14.07 mmol) in MeCN (40 mL) was added NBS (2.63 g, 14.78 mmol) at 0°C, and the mixture was stirred at rt for 18 h. After removing the solvent *in vacuo*, the residue was extracted with EtOAc (60 mL) and water (60 mL). The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE:EtOAc=100:1) to afford the title compound.

Step B. 2-(5-Bromo-4-fluoro-2-methoxyphenoxy)-5-methylthiazole: A mixture of 2-bromo-5-methylthiazole (300 mg, 1.68 mmol), 5-bromo-4-fluoro-2-methoxyphenol (410 mg, 1.85 mmol) and K₂CO₃ (466 mg, 3.37 mmol) in DMF (10 mL) was stirred at 120°C for 18 h. The mixture was diluted with water (200 mL) and extracted with EtOAc 3 x 20 mL). The organic layer was dried and concentrated *in vacuo*. The residue was purified via prep-HPLC to afford the title compound. *m/z* 319 [M+H]⁺.

25 INTERMEDIATE 11

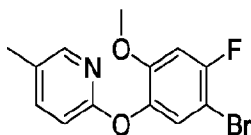
5-Bromo-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile



- Step A. 5-Amino-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile: To a soln. of p-tolylhydrazine hydrochloride (50 g, 315 mmol) in EtOH (400 ml) was added TEA (132 ml, 946 mmol), and the reaction mixture was stirred at rt for 40 min. Then 2-(1-ethoxyethylidene)- malononitrile (38.6 g, 284 mmol) was added slowly at 0°C, and the reaction mixture was stirred at 25°C for 12 h. The reaction mixture was partitioned between EtOAc (200 mL) and water (200 mL), and the separated organic layer was washed with brine (200 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*, and the resulting residue was purified by silica gel chromatography (PE/EtOAc 5:1 to 1:1) to give the title compound. *m/z* 213.2 [M+H]⁺.
- Step B. 5-Bromo-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile: To a soln. of 5-amino-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile (10 g, 47.1 mmol) and CuBr (10.14 g, 70.7 mmol) in MeCN (100 mL) was added isopentyl nitrite (11.04 g, 94 mmol) dropwise. The reaction mixture was stirred at 25°C under a N₂ atmosphere for 2 h. The reaction mixture was partitioned between EtOAc (60 mL) and water (60 mL), and the separated organic layer was washed with brine (60 mL). The organic layer was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (PE/EtOAc 15:1-10:1) to give the title compound. *m/z* 276.1 [M+H]⁺.

INTERMEDIATE 12

- 2-(5-bromo-4-fluoro-2-methoxyphenoxy)-5-methylpyridine



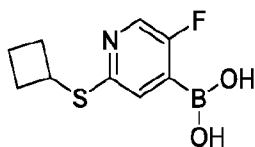
- Step A. 2-(5-bromo-4-fluoro-2-methoxyphenoxy)-5-methyl-3-nitropyridine: A mixture of 2-chloro-5-methyl-3-nitropyridine (2 g, 10.5 mmol), 5-bromo-4-fluoro-2-methoxyphenol (2.56 g, 10.5 mmol) and K₂CO₃ (4.8 g, 34.8 mmol) in DMF (20 mL) was stirred at rt overnight. The mixture was poured into cold water (100 mL) and extracted with EtOAc (3x50 mL). The

combined organic layers were washed with brine, and the organic layer was concentrated *in vacuo*. The resulting residue was stirred with PE (10 mL) for 30 min., and the solid that separated was filtered off to give the title compound.

- Step B. 2-(5-bromo-4-fluoro-2-methoxyphenoxy)-5-methylpyridin-3-amine: To a mixture of
 5 2-(5-bromo-4-fluoro-2-methoxyphenoxy)-5-methyl-3-nitropyridine (2.7 g, 7.56 mmol) and iron powder (1.7 g, 30.4 mmol) in EtOH (25 mL) was added a soln. of NH₄Cl (1.0 g, 18.9 mmol) in water (3 mL) dropwise at 55-60°C. After addition, the mixture was heated to reflux for 3 h. The reaction mixture was filtered through CeliteTM, and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc (20 mL), and the organic layer was washed with water (10 mL)
 10 and brine (10 mL). The organic layer was concentrated *in vacuo* to give the title compound.
- Step C: 2-(5-bromo-4-fluoro-2-methoxyphenoxy)-5-methylpyridine: To the soln. of 2-(5-bromo-4-fluoro-2-methoxyphenoxy)-5-methylpyridin-3-amine (2.0 g, 6.1 mmol) in THF (20 mL) was added dropwise a soln. of isopentyl nitrite (1.4 g, 12.2 mmol) in THF (3 mL) at rt under N₂. Then the reaction mixture was heated to reflux for 3 h. The reaction mixture was
 15 concentrated *in vacuo*, and the resulting residue was purified by silica gel chromatography (PE:EA=20:1) to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.93 (s, 1 H) 7.48-7.56 (m, 1 H) 7.30 (d, *J*=7.04 Hz, 1 H) 6.77-6.92 (m, 2 H) 3.71-3.81 (m, 3 H) 2.28 (s, 3 H).

INTERMEDIATE 13

- 20 (2-(Cyclobutylthio)-5-fluoropyridin-4-yl)boronic acid



- Step A. 5-Fluoropyridine-2-thiol: Prepared from 5-fluoropyridin-2-ol according to the procedure described in US 2012/0309796.
- Step B. 2-(Cyclobutylthio)-5-fluoropyridine: A reaction vial was charged with Cs₂CO₃ (652 mg, 2.00 mmol) and 5-fluoro-2-thiopyridone (129 mg, 1 mmol). The vial was sealed and flushed
 25 with N₂. Dry DMF (5 mL) and bromocyclobutane (113 μl, 1.200 mmol) were added via syringe. The tube was heated (50 °C) for 2 h. The mixture was diluted with EtOAc (20 mL) and washed with water (2x10 mL). The organic layer was washed with brine (5 mL), dried over MgSO₄,

filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 30% EtOAc/hexanes) to give the title compound. m/z 184.50 $[M+H]^+$

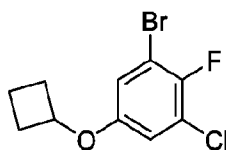
Step C. (2-(Cyclobutylthio)-5-fluoropyridin-4-yl)boronic acid: A three-necked round-bottom flask was charged with a soln. of diisopropylamine (0.097 ml, 0.682 mmol) in dry THF (2 ml).

- 5 The solution was cooled to -20°C and 2.5 M n-BuLi (0.262 ml, 0.655 mmol) was added. The soln was stirred for 10 min and then warmed to 0°C for 10 min. The soln. was cooled to -78°C and a soln. of 2-(cyclobutylthio)-5-fluoropyridine (100 mg, 0.546 mmol) from step B in dry THF (3 ml) was added dropwise. The mixture was stirred for 1 h, followed by the addition of trimethyl borate (0.305 ml, 2.73 mmol). The mixture was gradually warmed to rt and stirred for
- 10 4 h. The reaction was quenched by addition of aq. 1 M HCl (10 mL), and the mixture was stirred for 10 min. The product was extracted with EtOAc (2x15 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was used for next step without further purification. m/z 228.17 $[M+H]^+$

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INTERMEDIATE 14

1-Bromo-3-chloro-5-cyclobutoxy-2-fluorobenzene



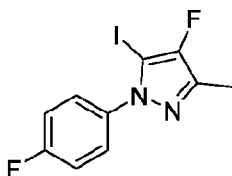
- Step A. 2-chloro-4-cyclobutoxy-1-fluorobenzene: To a soln. of 3-chloro-4- fluorophenol (5 g, 34.12 mmol) in DMF (50 mL) was added bromocyclobutane (9.21 g, 68.24 mmol), Bu_4NI
- 20 (12.60 g, 34.12 mmol) and Cs_2CO_3 (11.12 g, 34.12 mmol). Then the mixture was stirred at 90°C for 18 h. The mixture was extracted with EtOAc (3 x 100 mL) and water (600 mL), and the organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE) to afford the title compound.

- Step B. 1-bromo-3-chloro-5-cyclobutoxy-2-fluorobenzene: To a soln. of 2,2,6,6-tetramethyl- piperidine (0.845 g, 5.98 mmol) in THF (20 mL) was added dropwise n-BuLi (2.5 M, 2.4 mL, 6.00 mmol) at -78°C under N_2 . After 20 min, the mixture was allowed to warm to 0°C and stirred for 10 min. Then 2-Chloro-4-cyclobutoxy-1- fluorobenzene (1.0 g, 4.98 mmol) in THF (5
- 25 mL) was added dropwise to the mixture at -78°C . The mixture was stirred at -78°C for 40 min.

Then bromine (1.195 g, 7.48 mmol) was added, and the mixture was stirred at -78 °C for 40 min. The mixture was quenched with satd. aq. NH₄Cl (10 mL), and extracted with EtOAc (3x30 mL) and water (20 mL). The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE) to afford the title compound. ¹HNMR (400 MHz, CDCl₃, ppm): δ 1.63-1.72 (m, 1 H) 1.85 (q, *J*=10.30 Hz, 1 H) 2.07-2.17 (m, 2 H) 2.37-2.47 (m, 2 H) 4.53 (quin, *J*=6.95 Hz, 1 H) 6.77 (dd, *J*=5.28, 2.93 Hz, 1 H) 6.87 (dd, *J*=4.89, 2.93 Hz, 1 H).

INTERMEDIATE 15

4-Fluoro-1-(4-fluorophenyl)-5-iodo-3-methyl-1H-pyrazole



Step A. 1-(4-Fluorophenyl)-3-methyl-1H-pyrazol-5-amine: To a soln. of (4-fluorophenyl)-hydrazine hydrochloride (30.0 g, 185 mmol) in EtOH (100 mL) was added Et₃N (56.0 g, 554 mmol) and 2-(ethoxymethylene)malononitrile (23.66 g, 194 mmol). After the addition was complete, the reaction mixture was stirred 70°C for 15 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. Then the mixture was extracted with EtOAc (2x100mL). The combined organic layer was washed with brine, and then dried over Na₂SO₄, filtered and concentrated *in vacuo* to give crude product. The crude product was purified by silica gel column chromatography (PE/EtOAc 10:1 to 5:1) to give the title compound.

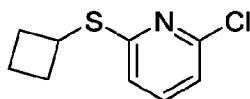
Step B. 4-fluoro-1-(4-fluorophenyl)-3-methyl-1H-pyrazol-5-amine: To a soln. of 1-(4-fluorophenyl)-3-methyl-1H-pyrazol-5-amine (10.0 g, 52.3 mmol) in THF (50 mL) was added Selectfluor® (18.53 g, 52.3 mmol). After the addition was complete, the mixture was stirred at rt for 15 h. The reaction was concentrated *in vacuo*, and the mixture was extracted with EtOAc (2 x 50 mL). The organic layer was washed with brine, then dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by silica gel column chromatography (PE/EtOAc 30:1 to 10:1) to give the title compound.

Step C. 4-fluoro-1-(4-fluorophenyl)-5-iodo-3-methyl-1H-pyrazole: To a soln. of 4-fluoro-

1-(4-fluorophenyl)-3-methyl-1H-pyrazol-5-amine (2.0 g, 9.56 mmol) in MeCN (30 mL) was added isobutyl nitrite (2.465 g, 23.90 mmol) and CuI (3.64 g, 19.12 mmol). After the addition was complete, the mixture was stirred at 60°C for 1 h. The reaction mixture was cooled to rt, filtered, and concentrated *in vacuo*. Then the mixture was extracted with EtOAc (50 mLx2). The combined organic layer was washed with brine, and then dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the crude product. The crude product was purified by silica gel column chromatography (PE/EtOAc 30:1 to 10:1) to give the title compound. m/z 321.0 [M+H]⁺

INTERMEDIATE 16

2-Chloro-6-(cyclobutylthio)pyridine

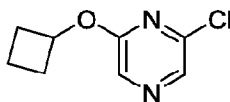


Step A: 6-chloropyridine-2-thiol: To a mixture of 6-chloropyridin-2-ol (2.00 g, 15.44 mmol) and Lawesson's reagent (6.56 g, 16.21 mmol) was added THF (50 mL), and the soln. was stirred at about 80°C overnight under a N₂ atmosphere. The soln. was concentrated *in vacuo* to give the crude product which was purified by silica gel chromatography (PE:EtOAc=6:1) to afford the title compound.

Step B: 2-chloro-6-(cyclobutylthio)pyridine: To a mixture of 6-chloropyridine-2-thiol (270 mg, 1.85 mmol) in DMF (3 mL) was added bromocyclobutane (250 mg, 1.85 mmol) and Cs₂CO₃ (725 mg, 2.23 mmol). Then the soln. was stirred at 100°C about 2 h. The soln. was treated with H₂O (20 mL) and extracted with EtOAc (10 mLx3). The combined organic layer was washed with brine (10 mL), and then dried over anhyd. Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (PE:EtOAc=20:1) to afford the title compound. ¹H NMR (400 MHz, CDCl₃) ppm 7.40 (t, *J*=7.83 Hz, 1H), 6.96 (dd, *J*=7.83, 2.74 Hz, 1H), 4.30 (quin, *J*=7.92 Hz, 1H), 2.49-2.62 (m, 2H), 2.00-2.19 (m, 4H).

INTERMEDIATE 17

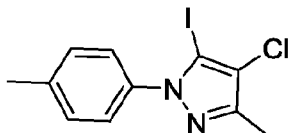
2-Chloro-6-cyclobutoxypyrazine



To a suspension of NaH (322 mg, 8.05 mmol) in THF (10 ml) was added cyclobutanol (581 mg, 8.05 mmol), and the mixture was stirred at rt for 15 min. To this soln. was added 2,6-dichloropyrazine (1 g, 6.71 mmol), and the mixture was stirred at 50°C for 18 h. The soln. was diluted with H₂O (20 mL), and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford crude product. The residue was purified by silica gel chromatography (PE) to give the title compound. ¹H NMR (400 MHz, CDCl₃) ppm 8.09 (d, *J*=16.82 Hz, 2H), 5.17 (q, *J*=7.34 Hz, 1H), 2.43-2.52 (m, 2H), 2.10-2.20 (m, 2H), 1.86 (q, *J*=10.30 Hz, 1H), 1.62-1.75 (m, 1H).

INTERMEDIATE 18

4-Chloro-5-iodo-3-methyl-1-(p-tolyl)-1H-pyrazole

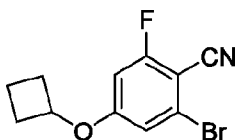


Step A: 4-Chloro-3-methyl-1-(p-tolyl)-1H-pyrazol-5-amine: To a soln. of 3-methyl-1-(p-tolyl)-1H-pyrazol-5-amine (3.0 g, 16.02 mmol, synthesized using similar conditions as described for the fluoro intermediate 15) in MeCN (50 mL) was added NCS (2.35 g, 17.62 mmol), and the mixture was stirred at rt (~25 °C) for 18 h. Then the solvent evaporated *in vacuo*, and the resulting residue was desolved in EtOAc (100 mL), washed with H₂O (60 mL×3) and brine (60 mL), The organic layer was concentrated *in vacuo* and purified by silica gel chromatography (PE:EtOAc=10:1) to give the title compound. *m/z* 221.6 [M+H]⁺.

Step B: 4-Chloro-5-iodo-3-methyl-1-(p-tolyl)-1H-pyrazole: To a soln. of 4-chloro-3-methyl-1-(p-tolyl)-1H-pyrazol-5-amine (2.5 g, 11.28 mmol) in MeCN (50 mL) was added CuI (6.44 g, 33.84 mmol) and isopentyl nitrite (3.30 g, 28.19 mmol) at 0°C. Then the reaction mixture was stirred under reflux for 3 h. The solvent was evaporated *in vacuo*, and the residue was dissolved in EtOAc (100 mL). The organic layer was washed with H₂O (60 mL×3) and brine (60 mL). Then the organic layer was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (PE:EtOAc=50:1) to give the title compound. *m/z* 332.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.34 (s, 3 H), 2.40 (s, 3 H), 7.23-7.28 (m, 3 H), 7.29-7.37 (m, 2 H).

INTERMEDIATE 19

2-Bromo-4-cyclobutoxy-6-fluorobenzonitrile



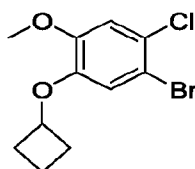
- Step A. 1-Bromo-3-cyclobutoxy-5-fluorobenzene: To a soln. of 3-bromo-5-fluorophenol (3.0 g, 15.71 mmol) in DMF (15 mL) was added bromocyclobutane (4.24 g, 31.41 mmol), Bu₄NI (5.80 g, 15.71 mmol) and Cs₂CO₃ (5.12 g, 15.71 mmol). Then the mixture was stirred at 90 °C overnight. The mixture was extracted with EtOAc (90 mL) and water (300 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE) to afford the title compound.
- Step B. 2-Bromo-4-cyclobutoxy-6-fluorobenzaldehyde: To a soln. of 2,2,6,6-tetramethylpiperidine (692 mg, 4.90 mmol) in THF (10 mL) was added n-BuLi (2.5 M, 1.96 mL, 4.90 mmol) at -78 °C under N₂. After 30 min, 1-bromo-3-cyclobutoxy-5-fluorobenzene (1 g, 4.08 mmol) in THF (5 mL) was added dropwise at -78 °C under N₂. Then the mixture was stirred at -78 °C for 40 min. DMF (447 mg, 6.12 mmol) was added, and the mixture was stirred at -78 °C for 1 h. The reaction was quenched with saturated NH₄Cl soln., acidified to pH 1-2 with 6 N HCl, then partitioned with EtOAc (30 mL) and water (20 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified via silica gel (PE:EtOAc=100:1) to afford the title compound.
- Step C. (E)-2-Bromo-4-cyclobutoxy-6-fluorobenzaldehyde oxime: To a soln. of 2-bromo-4-cyclobutoxy-6-fluorobenzaldehyde (700 mg, 2.56 mmol) in EtOH (10 mL), was added NH₂OH (aq., 50% w/w, 340 mg, 5.13 mmol). Then the mixture was stirred at 100 °C for 2 h. After cooling to rt, the mixture was poured onto ice and stirred for 30 min. The resulting suspension was filtered, and the cake was dried to afford the title compound. m/z 288 [M+H]⁺.
- Step D: 2-Bromo-4-cyclobutoxy-6-fluorobenzonitrile: To a soln. of (E)-2-bromo-4-cyclobutoxy-6-fluorobenzaldehyde oxime (650 mg, 2.26 mmol) in DMF (5 mL) was added POCl₃ (865 mg, 5.64 mmol) dropwise at 0 °C. Then the mixture was allowed to warm to rt and stirred for 4 h. The mixture was poured into water, and the mixture was stirred for 1 h. The mixture was extracted with EtOAc (30 mL) and water (100 mL). The organic layer was dried

(Na_2SO_4) and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE:EtOAc=50:1) to afford the title compound. ^1H NMR (400 MHz, CDCl_3 , ppm): δ 1.70-1.78 (m, 1 H) 1.89-1.97 (m, 1 H) 2.15-2.25 (m, 2 H) 2.48 (d, $J=7.43$ Hz, 2 H) 4.61-4.68 (m, 1 H) 6.57 (d, $J=10.56$ Hz, 1 H) 6.92 (br. s., 1 H).

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INTERMEDIATE 20

1-Bromo-2-chloro-5-cyclobutoxy-4-methoxybenzene

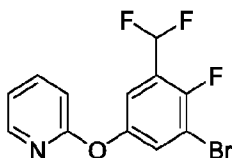


- Step A. 4-chloro-1-cyclobutoxy-2-methoxybenzene: To a soln. of 4-chloro-2-methoxyphenol (5.0 g, 31.5 mmol) in 50 mL of DMF was slowly added bromocyclobutane (8.50 g, 63.0 mmol), Cs_2CO_3 (20.52 g, 63.0 mmol) and Bu_4NI (11.64g, 31.6 mmol). The mixture was stirred at 90°C overnight. The mixture was diluted with water (400 mL), extracted with EtOAc (100 mL), and concentrated *in vacuo*. The resulting residue was purified by silica gel flash column chromatography (Petroleum ether:ethyl acetate=100:1) to give the title compound.
- Step B: 1-bromo-2-chloro-5-cyclobutoxy-4-methoxybenzene: To a soln. of 4-chloro-1-cyclobutoxy-2-methoxybenzene (2 g, 9.49 mmol) in MeCN (20 mL) was slowly added NBS (1.832 g, 10.44 mmol). The mixture was stirred at rt for overnight. The mixture was extracted with EtOAc (100 mL), and the organic layer was washed with H_2O (50 mL $\times$ 3), and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (Petroleum ether:ethyl acetate=100:1) to afford the title compound. ^1H NMR (400 MHz, CDCl_3) ppm 6.91 (d, $J=8.78$ Hz, 2 H) 4.61 (quin, $J=7.15$ Hz, 1 H) 3.84 (s, 3 H) 2.42-2.52 (m, 2 H) 2.17-2.29 (m, 2 H) 1.87 (q, $J=10.29$ Hz, 1 H) 1.64-1.75 (m, 1 H).

INTERMEDIATE 21

2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)pyridine

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Step A. 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)benzaldehyde: To a stirred soln. of 2,2,6,6-tetramethylpiperidine (18.06 g, 0.13 mol) in THF (250 mL) in a three necked round bottom flask was added n-BuLi (2.5 M, 51.1 mL, 0.13 mmol) dropwise at -78 °C over 0.5 h.

5 Then the mixture was stirred at 0°C for 0.5 h. A solution of (3-bromo-4- fluorophenoxy)-triisopropylsilane (37.0 g, 0.11 mmol) in THF (300 mL) was added to the above mixture dropwise at -78 °C over 0.5 h. The mixture was stirred for 1 h, and then DMF (15.57 g, 213 mmol) was added. The mixture was diluted with water (300 mL) and extracted with EtOAc (2x100 mL). The organic layer was collected, washed with brine, dried over anhydrous Na₂SO₄,

10 filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (PE:EtOAc from 20:1 to 1:1) to afford 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy) benzaldehyde and 3-bromo-2-fluoro-5-hydroxybenzaldehyde.

Step B-3-bromo-5-(difluoromethyl)-4-fluorophenol: To a stirred solution of 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)benzaldehyde (22.00 g, 58.60 mmol) in DCM (200 mL) was added DAST (11.62 ml, 88.00 mmol) dropwise at 0°C, and the resulting mixture was allowed to warm to rt for 2 h with stirring. The mixture was poured into a diluted NaHCO₃ solution to adjust the pH of the mixture to about pH 5, then diluted with water (100 mL), extracted with DCM (100 mL). The organic layer was collected, washed with brine, dried over anhydrous

20 Na₂SO₄, and filtered. The organic layer was concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (PE:EtOAc from 20:1 to 5:1) to give the title compound.

Step C-3-bromo-5-(difluoromethyl)-4-fluorophenol: A mixture of (3-bromo-5-(difluoromethyl)-4-fluorophenoxy)triisopropylsilane (10.0 g, 25.2 mmol) and TBAF (7.90 g, 30.2 mmol) in THF (50 ml) was stirred at 15°C for 2 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL). The organic layer was collected, washed with brine, dried over anhydrous Na₂SO₄, and filtered, and the concentrated *in vacuo*. The crude product

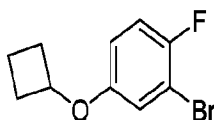
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was purified by silica gel column chromatography (PE:EtOAc from 10:1 to 3:1) to afford the title compound.

Step D-2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)pyridine: A mixture of 2-fluoropyridine (200 mg, 2.06 mmol) and 3-bromo-5-(difluoromethyl)-4-fluorophenol (596 mg, 2.47 mmol), Cs₂CO₃ (1.34 g, 4.12 mmol) in NMP (5 mL) was heated at 140 °C under microwave irradiation for 1 h. The mixture was diluted with water (20 mL), and extracted with EtOAc (20 mL). The organic layer was collected, washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was further purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm), followed by concentration (below 50 °C) to afford the title compound.

INTERMEDIATE 22

2-Bromo-4-cyclobutoxy-1-fluorobenzene



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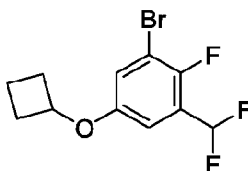
To a soln. of 3-bromo-4-fluorophenol (50.0 g, 262 mmol) in DMF (400 mL) was added bromocyclobutane (38.9 g, 288 mmol), TBAI (48.3 g, 131 mmol) and Cs₂CO₃ (102 g, 314 mmol). The mixture was stirred at 90°C for 12 h. The reaction mixture was diluted with water (1 L) and extracted with the mixture of PE:EtOAc=4:1 (3 x 1L). The organic layer was concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography (PE) to give the title compound. ¹H-NMR (400 MHz, CDCl₃) ppm 6.97-7.03 (m, 2 H) 6.70-6.73 (m, 1 H) 4.53-4.60 (m, 1 H) 2.43-2.46 (m, 2 H) 2.14-2.17 (m, 2 H) 1.80-1.91 (m, 1 H) 1.60-1.73 (m, 1 H).

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INTERMEDIATE 23

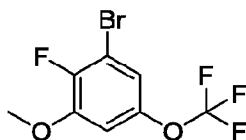
1-Bromo-5-cyclobutoxy-3-(difluoromethyl)-2-fluorobenzene



- Step A. 3-Bromo-5-cyclobutoxy-2-fluorobenzaldehyde: To a soln. of 2,2,6,6-tetramethylpiperidine (3.46 g, 24.48 mmol) in THF (50 mL) was added 2.5 M nBuLi (9.8 mL, 24.48 mmol) dropwise at -78°C under N₂. After 30 min, 2-bromo-4-cyclobutoxy-1-fluorobenzene (5.0 g, 20.4 mmol) in THF (15 mL) was added dropwise at -78°C. Then the mixture was stirred at -78°C for 1 h. DMF (2.237 g, 30.6 mmol) was added dropwise at -78°C, and the mixture was stirred for another 1 h. The reaction was quenched with satd. aq. NH₄Cl soln. (10 mL), and the mixture was extracted with EtOAc (3x50 mL) and water (30 mL). The organic layer was dried with anhyd. Na₂SO₄ and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE) to afford the title compound.
- Step B. 1-Bromo-5-cyclobutoxy-3-(difluoromethyl)-2-fluorobenzene: To a soln. of 3-bromo-5-cyclobutoxy-2-fluorobenzaldehyde (1.00 g, 3.66 mmol) in DCM (20 mL), was added DAST (2.4 mL, 18.16 mmol) dropwise at 0°C. Then the mixture was stirred at 19°C for 2 h. The mixture was quenched with water (5 mL) and extracted with DCM (20 mLx2) and water (15 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE) to afford the title compound. ¹H-NMR (400 MHz, CDCl₃) δ 1.66-1.77 (m, 1 H) 1.83-1.95 (m, 1 H) 2.09-2.24 (m, 2 H) 2.39-2.53 (m, 2 H) 4.55-4.66 (m, 1 H) 6.67-7.01 (m, 2 H) 7.10 (br. s., 1 H).

INTERMEDIATE 24

- 1-Bromo-2-fluoro-3-methoxy-5-(trifluoromethoxy)benzene



Step A. 2-fluoro-5-(trifluoromethoxy)phenol: To a stirred soln. of (2-fluoro-5-(trifluoromethoxy)phenyl)boronic acid (13.40 g, 60 mmol) in anhyd. EtOH (20 mL) was added dropwise 30% H₂O₂ (10.2 mL, 90 mmol) at 0-5 °C, and the reaction mixture was stirred for 3 h. The

reaction was quenched with a satd. soln. of $\text{Na}_2\text{S}_2\text{O}_3$, and concentrated *in vacuo*. The resulting residue was dissolved in DCM (30 mL), and the soln. was washed with brine (10 mLx2). The organic layer was concentrated *in vacuo* to give the title compound.

Step B. 1-Fluoro-2-methoxy-4-(trifluoromethoxy)benzene: To a stirred suspension of

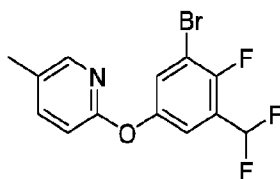
- 5 2-fluoro-5-(trifluoromethoxy)phenol (5.00 g, 25 mmol) and K_2CO_3 (5.20 g, 38 mmol) in DMF (10 mL) was added MeI dropwise at rt. The reaction mixture was stirred for 18 h at rt, then poured into water (100 mL), and extracted with DCM (20 mLx3). The organic layer was washed with brine (20 mL) and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (PE:EtOAc=10:1) to give the title compound.

- 10 Step C. 1-Bromo-2-fluoro-3-methoxy-5-(trifluoromethoxy)benzene: To a soln. of 2,2,6,6-tetramethylpiperidine (3.40 g, 24 mmol) in anhyd. THF (30 mL) was added dropwise 2.5 M n-BuLi (9.0 mL, 23 mmol) at -78°C under N_2 . After the addition, the reaction mixture was stirred at -75°C for 30 minutes. Then a soln. of 1-fluoro-2-methoxy-4-(trifluoromethoxy)-
- 15 benzene (4.0 g, 19 mmol) in THF (10 mL) was added dropwise to the reaction mixture at -78°C . After the addition, the reaction mixture was stirred for 2 h at -78°C , and Br_2 (3.70 g, 23 mmol) was added dropwise to the reaction mixture while maintaining at -78°C . The reaction mixture was allowed to stir for 1 h at -75°C , and the reaction was quenched with satd. aq. NH_4Cl (5 mL). The mixture was washed with with brine (20 mL), and the organic layer was concentrated *in vacuo*. The resulting residue was purified by reverse phase HPLC on a GILSON 281 instrument
- 20 fitted with a Phenomenex Synergi C18 (250 x21.2 mm x 4 μm) using water (0.2% Formic acid) and ACN as eluents (Mobile phase A: water (0.2 % Formic acid), Mobile phase B: ACN, Detective wavelength: 220 nm) followed by concentration *in vacuo* to obtain the title compound.
- ^1H NMR (400 MHz, CDCl_3) ppm: 7.04 (br. s., 1 H) 6.79 (d, $J=4.30$ Hz, 1 H) 3.91 (s, 3 H).

25

INTERMEDIATE 25

2-(3-Bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-methylpyridine



Step A. 2-(3-Bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-methyl-3-nitropyridine: A mixture

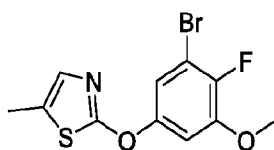
of 2-chloro-5-methyl-3-nitropyridine (300 mg, 1.74 mmol) and 3-bromo-5-(difluoromethyl)-4-fluorophenol (503 mg, 2.09 mmol) and Cs_2CO_3 (850 mg, 2.61 mmol) in DMF (10 mL) was stirred at 15 °C for 2 h. The mixture was diluted with water (20 mL), and extracted with PE:EtOAc (1:1, 2 x 10 mL). The organic layer was collected, washed with brine, dried over anhyd. Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (PE: EtOAc from 100:1 to 1:1) to afford the title compound. m/z 377.1 $[\text{M}+\text{H}]^+$

Step B. 2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-methylpyridin-3-amine: A mixture of 2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-methyl-3-nitropyridine (550 mg, 1.46 mmol), zinc (286 mg, 4.38 mmol), and NH_4Cl (390 mg, 7.29 mmol) in a mixture of MeOH (10 ml) and water (1 mL) was heated at 60°C for 3 h. The suspension was diluted with DCM (20 ml) and filtered through silica gel. The filtrate was concentrated *in vacuo*, and the mixture was diluted with water (10 mL) and extracted with DCM (20 mL). The organic layer was collected, washed with brine, dried over anhyd. Na_2SO_4 , filtered, then concentrated under *in vacuo* to afford the title compound. $m/z=348.1$ $[\text{M}+\text{H}]^+$.

Step C. 2-(3-Bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-methylpyridine: A mixture of 2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-methylpyridin- 3-amine (500 mg, 1.44 mmol) and isopentyl nitrate (384 mg, 2.88 mmol) in THF (10 mL) was heated under reflux for 2 h. After cooling to rt, the mixture was diluted with water (20 mL), and extracted with EtOAc (15 mLx2). The organic layer was collected, washed with brine, dried over anhyd. Na_2SO_4 , filtered, then concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (PE:EtOAc from 20:1 to 10:1) to afford the title compound. m/z 333.1 $[\text{M}+\text{H}]^+$.

INTERMEDIATE 26

25 2-(3-Bromo-4-fluoro-5-methoxyphenoxy)-5-methylthiazole



Step A. 3-Bromo-2-fluoro-5-(((triisopropylsilyl)oxy)phenol: To a stirred soln. of

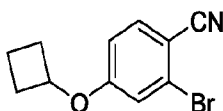
- 2,2,6,6-tetramethylpiperidine (2.5 g, 17.2 mmol) in anhyd. THF (30 mL) was added dropwise n-BuLi (7.0 mL, 17.2 mmol) below -75°C under N₂. The reaction mixture was stirred for 30 min. Then a soln. of (3-bromo-4-fluorophenoxy) triisopropylsilane (5.0 g, 14.4 mmol) in THF (5 mL) was added dropwise to the reaction mixture below -75°C. After the addition, the reaction
- 5 mixture was stirred for 2 h maintaining at -75°C. Trimethyl borate (1.80 g, 17.2 mmol) was added dropwise to the reaction mixture below -75°C. Then the reaction mixture was stirred for 1 h. The reaction mixture was warmed to rt to give a soln. of crude dimethyl (3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)phenyl)boronate. Then, 30% NaOH (4 mL, 28.8 mmol) was added to the soln. with stirring at rt. The reaction mixture was cooled in an ice-bath, and 30%
- 10 H₂O₂ (3.3 mL, 28.8 mmol) was added dropwise to the mixture. After the addition, the reaction was warmed to rt and stirred for 10 h. The reaction mixture was acidified to pH~4 with 3 N HCl and extracted with EtOAc (3 X 30 mL). The combined organic layers were washed with brine and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE/EtOAc 20:1) to give the title compound.
- 15 Step B. (3-Bromo-4-fluoro-5-methoxyphenoxy)triisopropylsilane: To a stirred suspension of 3-bromo-2-fluoro-5-((thiisopropylsilyl)oxy)phenol (3.3 g, 9 mmol) and K₂CO₃ (1.50 g, 11 mmol) in DMF (10 mL), cooled by an ice water bath, was added dropwise MeI (2.60 g, 18 mmol). After the addition, the reaction mixture was stirred for 3 h at ~16°C. The reaction mixture was poured into water (100 mL) and extracted with PE (2x10 mL). The combined organic layers
- 20 were washed with brine, concentrated *in vacuo* to give crude product.
- Step C. 3-Bromo-4-fluoro-5-methoxyphenol: To a stirred soln. of (3-bromo-4-fluoro-5-methoxyphenoxy) triisopropylsilane (3.10 g, 8.2 mmol) in THF (10 mL) was added dropwise 1 M TBAF (9.8 mL, 9.8 mmol) at ~16°C. The reaction mixture was stirred at ~16°C for 3 h and concentrated *in vacuo*. The resulting residue was dissolved in DCM (20 mL), and the organic
- 25 layer was separated and washed with brine. The organic layer was then concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (PE:EtOAc=10:1) to give the title compound.
- Step D. 2-(3-Bromo-4-fluoro-5-methoxyphenoxy)-5-methylthiazole: To a soln. of 3-bromo-4-fluoro-5-methoxyphenol (663 mg, 3 mmol) and 2-bromo- 5-methylthiazole (587 mg, 3.3 mmol) in NMP (5 mL) was added Cs₂CO₃ (1.20 g, 3.6 mmol) in one portion. The reaction
- 30

vessel was sealed and heated by microwave irradiation at 150°C for 3 h. The reaction mixture was poured into cold water (50 mL) and extracted with DCM (3 x 10 mL). The combined layers were combined and washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EtOAc=10:1) to afford the title compound. ¹H

5 NMR (400 MHz, CDCl₃) δ ppm 7.06 (dd, *J*=4.70, 2.74 Hz, 1 H) 6.82-6.92 (m, 2 H) 3.89 (s, 3 H) 2.38 (s, 3 H).

INTERMEDIATE 27

2-Bromo-4-cyclobutoxybenzonitrile



10

Step A. 2-Bromo-4-hydroxybenzonitrile: To a soln. of 2-bromo-4-methoxybenzonitrile (1 g, 4.72 mmol) in MeCN (40 mL) was added NaI (2.12 g, 14.15 mmol) and TMSCl (1.54 g, 14.15 mmol). Then the mixture was stirred at 80°C overnight. Then the mixture was concentrated *in vacuo* and poured into water basified with Na₂CO₃. The mixture was extracted with EtOAc. The

15 aq. layer was acidified with HCl and extracted with EtOAc. The organic layer was washed with brine, dried (Na₂SO₄), and concentrated *in vacuo* to give the title compound.

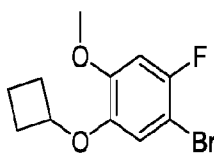
Step B. 2-Bromo-4-cyclobutoxybenzonitrile: To a soln. of 2-bromo-4-hydroxybenzonitrile (110 mg, 0.56) in DMF (40 mL) was added bromocyclobutane (150 mg, 1.11 mmol), Bu₄NI (205 mg, 0.56 mmol) and Cs₂CO₃ (181 mg, 0.56 mmol). The reaction mixture was stirred at 90°C

20 overnight. The mixture was washed with water, extracted with EtOAc, and the separated organic layer was washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (PE:EA=20:1) to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ: 7.54 (d, *J*=8.61 Hz, 1H), 7.08 (d, *J*=1.96 Hz, 1H), 6.81 (dd, *J*=8.80, 2.15 Hz, 1H), 4.67 (t, *J*=7.24 Hz, 1H), 2.40-2.54 (m, 2H), 2.19 (ddd, *J*=9.88, 7.53, 2.54 Hz, 2H), 1.91 (d,

25 *J*=10.56 Hz, 1H), 1.66-1.81 (m, 1H).

INTERMEDIATE 28

1-bromo-5-cyclobutoxy-2-fluoro-4-methoxybenzene

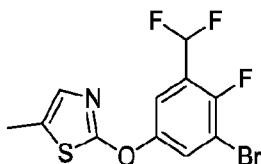


Step A. 1-cyclobutoxy-4-fluoro-2-methoxybenzene: To a solution of compound 4-fluoro-2-methoxyphenol (1 g, 7 mmol) and bromocyclobutane (1.13 g, 8.4 mmol) in DMF (5 mL) was added Cs₂CO₃ (3.4 g, 10.6 mmol) at rt. The mixture was stirred at 80°C for 12 h. The mixture was concentrated *in vacuo* and extracted with EtOAc (40 mL). The organic layer was concentrated *in vacuo*, and the crude product was purified by silica gel column (PE:EA=100:1) to give the title compound.

Step B. 1-bromo-5-cyclobutoxy-2-fluoro-4-methoxybenzene: To a solution of compound 1-cyclobutoxy-4-fluoro-2-methoxybenzene (1 g, 5.2 mmol) in MeCN (10 mL) was added NBS (1.02 g, 5.8 mmol) at 0°C. The mixture was stirred at rt for 12 h. Water (50 mL) was added to the mixture, and the mixture was extracted with EtOAc (40 mL). The organic layer was concentrated *in vacuo*, and the crude product was purified by silica gel chromatography (PE:EA=100:1) to give the title compound.

INTERMEDIATE 29

2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-methylthiazole



Step A. 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)benzaldehyde: To a stirred solution of 2,2,6,6-tetramethylpiperidine (18.06 g, 0.13 mol) in THF (250 mL) was added n-BuLi (2.5 M, 51.1 mL, 0.13 mol) dropwise at -78 °C over 0.5 h. The mixture was stirred at 0°C for 0.5 h. Then a solution of 3-bromo-4-fluorophenoxytriisopropylsilane (37.0 g, 0.11 mmol) in THF (300 mL) was added to the above mixture dropwise at -78°C over 0.5 h. The mixture was stirred for 1 h, and DMF (15.57 g, 213 mmol) was added. The mixture was diluted with water (300 mL), and extracted with EtOAc (2x 100 mL). The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was

purified by silica gel column chromatography (PE:EtOAc from 20:1 to 1:1) to afford 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)benzaldehyde and 3-bromo-2-fluoro-5-hydroxybenzaldehyde.

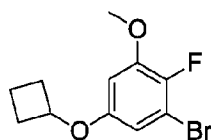
Step B. 3-bromo-5-(difluoromethyl)-4-fluorophenoxy)triisopropylsilane: To a stirred solution of 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)benzaldehyde (22.00 g, 58.60 mmol) in DCM (200 mL) was added dropwise DAST (11.62 mL, 88.00 mmol) at 0°C. The resulting mixture was warmed to rt for 2 h. The mixture was pouring into diluted NaHCO₃ solution until the pH was 5. Water (100 mL) was added and the mixture was extracted with DCM (100 mL). The organic layer was separated, washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EtOAc 20:1 to 5:1) to afford the title compound.

Step C: 3-bromo-5-(difluoromethyl)-4-fluorophenol: A mixture of (3-bromo-5-(difluoromethyl)-4-fluorophenoxy)triisopropylsilane (10.0 g, 25.2 mmol) and TBAF (7.90 g, 30.2 mmol) in THF (50 mL) was stirred at 15°C for 2 h. The mixture was diluted with water (50 mL), and extracted with EtOAc (50 mL). The organic layer was collected, washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (PE:EtOAc from 10:1 to 3:1) to afford the title compound.

Step D. 2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-methylthiazole: A mixture of 2-bromo-5-methylthiazole (300 mg, 1.68 mmol), 3-bromo-5-(difluoromethyl)-4-fluorophenol (487 mg, 2.02 mmol) and Cs₂CO₃ (1.09 g, 3.37 mmol) in DMF (5 mL) was irradiated by microwave at 160°C for 0.5 h. The mixture was diluted with water (20 mL), and extracted with EtOAc (2 x 10 mL). The organic layer was collected, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The residue was further purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 µm) using water (0.2% Formic acid) and MeCN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detective wavelength: 220 nm), followed by concentration (below 50 °C) to afford the title compound.

INTERMEDIATE 30

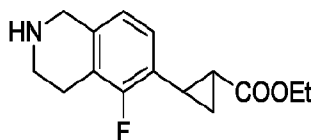
1-Bromo-5-cyclobutoxy-2-fluoro-3-methoxybenzene



- Step A. 3-bromo-5-cyclobutoxy-2-fluorophenol: To a solution of TMP (5.9 g, 41.6 mmol) in anhydrous THF (5 mL) was added dropwise 2.5 M *n*-BuLi (17 mL, 41.6 mmol) at between -78 and -75°C under nitrogen. After the addition the reaction mixture was stirred at -75°C for 30 min. Then a solution of 2-bromo-4-cyclobutoxy-1-fluorobenzene (8.5 g, 34.6 mmol) in THF (10 mL) was added dropwise to the reaction mixture at -75°C. The reaction mixture was stirred for 1 h at -75°C. Then a solution of trimethyl borate (4.3 g, 41.6 mmol) in THF (5 mL) was added dropwise to the reaction mixture while maintaining at -75°C. After the addition, the reaction mixture was allowed to stir for 1 h at -75°C. Then reaction mixture was allowed to warm to rt.
- 10 Then 30% aq. NaOH (11 mL, 68.7 mmol) was added to the solution with stirring at rt. The reaction mixture cooled by ice-bath, and 30% hydrogen peroxide (8 mL, 68.7 mmol) was slowly added dropwise. After addition, the reaction mixture was warmed to the rt and stirred for 10 h. The reaction mixture was acidified to pH=4 with 3 N HCl and extracted with EtOAc (30 mLx3). The organic layer was washed with brine and concentrated *in vacuo*. The residue was purified
- 15 by silica gel chromatography (PE:EtOAc 20 :1) to give the title compound.
- Step B. 1-bromo-5-cyclobutoxy-2-fluoro-3-methoxybenzene: To a suspension of 3-bromo-5-cyclobutoxy-2-fluorophenol (8.0 g, 30.6 mmol) and K₂CO₃ (8.5 g, 61.2 mmol) in DMF (25 mL), cooled by an ice bath, was added dropwise MeI (20.0 g, 141.0 mmol). After the addition, the reaction mixture was stirred for 12 h at rt. The reaction mixture was poured into
- 20 cold water (100 mL) and extracted with DCM (30 mLx3). The organic layer was rinsed with brine and concentrated *in vacuo*. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and MeCN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: MeCN, Detective wavelength: 220 nm) followed by concentration (below 50
- 25 °C) to obtain the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.47 (d, *J*=4.02 Hz, 1 H) 6.39-6.45 (m, 1 H) 4.56 (quin, *J*=7.15 Hz, 1 H) 3.85 (s, 3 H) 2.39-2.51 (m, 2 H) 2.07-2.21 (m, 2 H) 1.87 (q, *J*=10.21 Hz, 1 H) 1.64-1.77 (m, 1 H).

INTERMEDIATE 31

Ethyl-2-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate

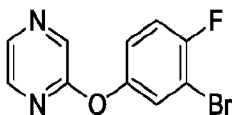


- Step A. *Tert*-butyl-6-bromo-5-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate. To a solution of 6-bromo-5-fluoro-1,2,3,4-tetrahydroisoquinoline (1.8 g, 7.82 mmol) in DCM (30 mL) was added Boc_2O (2.0 mL, 8.61 mmol) in one portion with stirring at $\sim 26^\circ\text{C}$. Then the reaction mixture was stirred at $\sim 26^\circ\text{C}$ for an additional 18 h. The reaction mixture was concentrated *in vacuo* to give the crude product which was purified by silica gel column chromatography (PE/EtOAc 40:1-20:1) to give the title compound.
- Step B. (*E*)-*tert*-butyl-6-(3-ethoxy-3-oxoprop-1-en-1-yl)-5-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate. To a solution of *tert*-butyl 6-bromo-5-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.2 g, 6.66 mmol) in dry 1,4-dioxane (20 mL) was added tri-*tert*-butyl phosphonium tetrafluoroborate (0.387 g, 1.333 mmol), *N*-cyclohexyl-*N*-methylecyclohexanamine (1.952 g, 9.99 mmol), and ethyl acrylate (0.800 g, 8.00 mmol) with stirring at $\sim 26^\circ\text{C}$. The mixture was degassed for 5 min with N_2 , and $\text{Pd}_2(\text{dba})_3$ (203 mg, 0.221 mmol) was added. The mixture was stirred at 100°C for 18 h under a N_2 atmosphere. The mixture was cooled to rt and diluted with EtOAc (20 mL). The organic layer was filtered, and the filtrate was concentrated *in vacuo* to give the residue which was purified by silica gel chromatography (PE:EtOAc=20:1 to 10:1) to afford the title compound.
- Step C. *Tert*-butyl 6-(2-(ethoxycarbonyl)cyclopropyl)-5-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate. To a solution of (*E*)-*tert*-butyl-6-(3-ethoxy-3-oxoprop-1-en-1-yl)-5-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (5.1 g, 14.60 mmol) and palladium acetate (0.328 g, 1.460 mmol) in dry DCM/ether (1:2, 450 mL) was added CH_2N_2 (117 mL, 58.4 mmol) in diethyl ether at 0°C over a period of 2 h. Then the reaction mixture was slowly warmed to rt and stirred for 18 h. The reaction was quenched by addition of AcOH (10 mL). The resulting mixture was washed with water (200 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. The

- crude product was purified by silica gel column chromatography (PE/EtOAc 30:1-10:1) to give *tert*-butyl 6-(2-(ethoxycarbonyl)cyclopropyl)-5-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate. ¹H NMR (400 MHz, CDCl₃) δ 6.82-6.73 (m, 2H), 4.51 (br.s., 2H), 4.16 (q, *J*=7.0 Hz, 2H), 3.61 (br. s., 2H), 2.77 (br. s., 2H), 2.63-2.58 (m, 1H), 1.89-1.84 (m, 1H), 1.58-1.53 (m, 1H), 1.33-1.28 (m, 1H), 1.28-1.23 (m, 3H). The two enantiomers were separated by SFC using the following conditions: Instrument: MG-II, Column: Chiralpak AD 250×30mm I.D., 5μm, Mobile phase: Supercritical CO₂/A (0.1%NH₃/H₂O)=85/15 at 60 mL/min, A= MeOH+HEP (1:1), Column Temp: 38°C Nozzle Pressure: 100Bar , Nozzle Temp: 60°C Evaporator Temp: 20°C, Trimmer Temp: 25°C. Wavelength: 220 nm Peak 1 (ee 97.0% fast eluting) and Peak 2 (ee 97.7% slow eluting) were obtained from the racemate. (*Peak1*) ¹H NMR (400 MHz, CDCl₃) δ 6.82-6.75 (m, 2H), 4.53 (br.s., 2H), 4.17 (d, *J*=7.0 Hz, 2H), 3.63 (br. s., 2H), 2.79 (br. s., 2H), 2.65-2.59 (m, 1H), 1.91-1.85 (m, 1H), 1.60-1.56 (m, 1H), 1.48 (s, 9H), 1.36-1.30 (m, 1H), 1.30-1.26 (m, 3H); (*Peak2*) ¹H NMR (400 MHz, CDCl₃) δ 6.83-6.74 (m, 2H), 4.53 (br. s., 2H), 4.18 (q, *J*=7.2 Hz, 2H), 3.63 (br. s., 2H), 2.79 (br. s., 2H), 2.62 (t, *J*=9.8 Hz, 1H), 1.91-1.86 (m, 1H), 1.58 (d, *J*=4.3 Hz, 1H), 1.48 (s, 9H), 1.35-1.31 (m, 1H), 1.30-1.26 (m, 3H)
- Step E. Ethyl 2-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropane- carboxylate. To a solution of *tert*-butyl 6-(2-(ethoxycarbonyl)cyclopropyl)-5-fluoro-3,4- dihydroisoquinoline-2(1H)-carboxylate (500 mg, 1.376 mmol) in DCM (6 mL) was added TFA (3 mL, 38.9 mmol) dropwise with stirring at ~26°C. The solvent was removed *in vacuo*. The residue was purified by cation ion exchange column chromatography (1 M NH₃-MeOH) to afford the title compound.

INTERMEDIATE 32

2-(3-bromo-4-fluorophenoxy)pyrazine



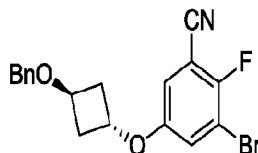
To a stirred solution of 2-fluoropyrazine (1g, 10.20 mmol) in DMSO (12 mL) was added 3-bromo-4-fluorophenol (1.95 g, 10.21 mmol), and K₂CO₃ (2.82 g, 20.39 mmol). The reaction mixture was stirred at 75°C for 15 h. The mixture was filtered, and the filtrate was diluted with

brine (50 mL). The filtrate was extracted with EtOAc (2x100 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the title compound. m/z 270.9 (M+2+H)⁺.

5

INTERMEDIATE 33

5-((1R,3R)-3-(benzyloxy)cyclobutoxy)-3-bromo-2-fluorobenzonitrile



Step A. (3-bromo-4-fluorophenoxy)triisopropylsilane: TIPS-Cl (33.3 mL, 157 mmol) was added to a stirred mixture of 3-bromo-4-fluorophenol (30 g, 157 mmol) and imidazole (10.69 g, 157 mmol) in DMF (150 mL) at rt, and the mixture was stirred at rt for 12 h. The mixture was diluted with EtOAc (300 mL), washed with water (2 x 800 mL), dried (Na₂SO₄), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE) to give the title compound.

Step B. 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)benzaldehyde: To a solution of 2,2,6,6-tetramethylpiperidine (4.64 g, 32.8 mmol) in THF (50 mL) was added *n*-BuLi (13 mL, 32.5 mmol, 2.5 M in hexane) dropwise at -78 °C under N₂. After 30 min, the mixture was allowed to warm to 0°C and stirred for 10 min. Then (3-bromo-4-fluorophenoxy)triisopropylsilane (10 g, 27.4 mmol) in THF (30 mL) was added dropwise at -78 °C, and the mixture was stirred at -78°C for 1.5 h. DMF (3.00 g, 41.0 mmol) was added, and the mixture was stirred at -78°C for 40 min. The reaction was quenched by the addition of satd. NH₄Cl solution (50 mL). Then the mixture was extracted with EtOAc (150 mLx2). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (EtOAc:petroleum ether 1:100 to 1:50) to give the title compound.

Step C: 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)benzaldehyde oxime: To a solution of 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)benzaldehyde (7.60 g, 19.24 mmol) in EtOH (80 mL) was added hydroxylamine (2.54 g, 38.5 mmol) (50% in water). The mixture was stirred at 80°C

for 5 h and cooled to rt. The mixture was poured onto water (100 mL), and the mixture was stirred for 30 min. The mixture was concentrated *in vacuo*, and the residue was extracted with DCM (3x50 mL) and water (30 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EtOAc=50:1) to afford the title compound. *m/z* 390.0 [M+H]⁺.

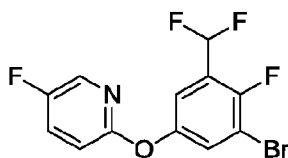
Step D. 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)benzonitrile: To a solution of 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)benzaldehyde oxime (7.30 g, 18.35 mmol) in DMF (80 mL) was added POCl₃ (7.03 g, 4.27 mL, 45.9 mmol) dropwise at 0°C. The mixture was stirred at rt for 15 h. The mixture was poured into water (800 mL), and the mixture was stirred for 1 h. The mixture was extracted with EtOAc (2x150 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE) to afford the title compound.

Step E: 3-bromo-2-fluoro-5-hydroxybenzonitrile. TBAF (10 mL, 10.00 mmol) (1 M in THF) was added to a stirred mixture of 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy) benzonitrile (4.0 g, 9.67 mmol) in THF (20 mL) at rt. The mixture was stirred at rt 20°C for 2 h. The mixture was concentrated *in vacuo*, and the residue was diluted with EtOAc (30 mL) and washed with water (20 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc: PE 1:2) to give the title compound.

Step F. 5-((1*r*,3*r*)-3-(benzyloxy)cyclobutoxy)-3-bromo- 2-fluorobenzonitrile. To a solution of 3-bromo-2-fluoro-5-hydroxybenzonitrile (1.00 g, 4.40 mmol), (1*S*,3*S*)-3-(benzyloxy)cyclobutanol (0.862 g, 4.84 mmol) and PPh₃ (1.730 g, 6.60 mmol) in THF (15 mL) was added DIAD (1.197 mL, 6.16 mmol) dropwise with stirring at 0°C under a N₂ atmosphere. After the addition was complete, the reaction mixture was stirred at ~70°C for additional 15 h under a N₂ atmosphere. The solvent was removed *in vacuo*. The resulting residue was purified via silica gel chromatography (PE:EtOAc=100:1 to 50:1) to afford the title compound. ¹HNMR δ (CDCl₃, 400 MHz, ppm): 7.29-7.41 (m, 5 H) 7.22 (dd, *J*=5.40, 2.98 Hz, 1 H) 6.88-6.95 (m, 1 H) 4.76-4.85 (m, 1 H) 4.43-4.49 (m, 2 H) 4.29-4.37 (m, 1 H) 2.49-2.60 (m, 2 H) 2.36-2.46 (m, 2 H).

INTERMEDIATE 34

2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-fluoropyridine



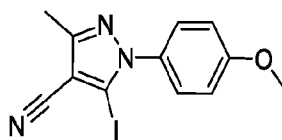
Step A: 2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-fluoro-3-nitropyridine. A mixture of 2-chloro-5-fluoro-3-nitropyridine (300 mg, 1.69 mmol) and 3-bromo-5-(difluoromethyl)-4-fluorophenol (491 mg, 2.03 mmol), Cs₂CO₃ (554 mg, 1.69 mmol) in DMF (10 mL) was stirred at 15°C for 2 h. The mixture was diluted with water (20 mL), extracted with PE:EtOAc (1:1, 2 x 10 mL). The organic layer was separated and washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (DCM) to yield the title compound.

Step B: 2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-fluoropyridin-3-amine. A mixture of 2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-fluoro-3-nitro pyridine (600 mg, 1.574 mmol), zinc (309 mg, 4.72 mmol) and NH₄Cl (421 mg, 7.87 mmol) in water (1 mL) and MeOH (10 mL) was heated at 60°C for 6 h. The mixture was diluted with DCM (20 mL) and filtered through silica gel. The filtrate was concentrated *in vacuo*. Water (10 mL) was added to the residue, and the mixture was extracted with DCM (20 mL). The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo* to afford the title compound.

Step C: 2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-fluoropyridine: A mixture of 2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)-5-fluoro pyridin-3-amine (500 mg, 1.42 mmol) and isopentyl nitrate (379 mg, 2.85 mmol) in THF (10 mL) was heated at 66°C for 2 h. After cooling the mixture to rt, the mixture was diluted with water (20 mL), and extracted with EtOAc (2x15 mL). The organic layer was collected, washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (PE:EtOAc from 20:1 to 10:1) to afford the title compound.

INTERMEDIATE 35

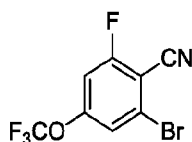
5-Iodo-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbonitrile



- Step A: 5-amino-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbonitrile: To a solution of (4-methoxyphenyl)hydrazine hydrochloride (50 g, 286.32 mmol) in EtOH (400 mL) was added Et₃N (31.87 g, 314.96 mmol), and the mixture was stirred for 10 min. Then 2-(1-ethoxy-ethylidene)malononitrile (38.98 g, 286.32 mmol) was added portionwise. The reaction mixture was stirred at rt overnight. Then the reaction mixture was filtered, and the filtrate was extracted with EtOAc (3 x 200 mL). The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (DCM to MeOH:DCM =1:20) to give the title compound.
- Step B: 5-Iodo-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbonitrile. To a solution of 5-amino-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbonitrile (30 g, 131.6 mmol) in CH₂I₂ (105.78 g, 394.74 mmol) was added isopentyl nitrite (46.18 g, 394.74 mmol) dropwise at 0°C. The reaction mixture was stirred at 90°C for 2 h. The precipitate was filtered off, washed with water and extracted with DCM (3x100 mL). The extract was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE:EA=4:1) to give the title compound.

INTERMEDIATE 36

2-bromo-6-fluoro-4-(trifluoromethoxy)benzonitrile



- Step A. 1-bromo-2-fluoro-5-nitro-4-(trifluoromethoxy)benzene: To a solution of 1-bromo-2-fluoro-4-(trifluoromethoxy)benzene (5.00 g, 19.31 mmol) in MeCN (20 mL) was added NO₂BF₄ (2.69 g, 20.27 mmol) in portions keeping the temperature between -40 to -30 °C. The mixture was stirred at between -40°C to -30°C for 2 h. Then the mixture was allowed to warm to rt and stirred for 18 h. The mixture was poured into ice, and extracted with EtOAc (3x30 mL). The combined organic layers were dried over Na₂SO₄, filtrated and concentrated *in*

vacuo. The residue was purified on silica gel (PE:EtOAc=80:1 to 50:1) to afford the title compound.

Step B. 5-bromo-4-fluoro-2-(trifluoromethoxy)aniline: To a solution of 1-bromo-2-fluoro-5-nitro-4-(trifluoromethoxy)benzene (2.00 g, 6.58 mmol) in MeOH (30 mL) and water (3 mL)

- 5 was added Fe (1.837 g, 32.9 mmol) and NH₄Cl (1.760 g, 32.9 mmol). The mixture was stirred at 75°C for 4 h. The mixture was filtered, and the solvent was removed *in vacuo*. The residue was extracted with DCM (3x30 mL) and water (3x30 mL). The organic layer was dried over Na₂SO₄, filtrated and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE:EtOAc) to afford the title compound.

- 10 Step C: 3-bromo-5-(difluoromethyl)-4-fluorophenol: To a solution of 5-bromo-4-fluoro-2-(trifluoromethoxy)aniline (520 mg, 1.898 mmol) in DMA (5 mL) was added dicyanozinc (134 mg, 1.139 mmol), zinc (10 mg, 0.153 mmol), dppf (105 mg, 0.190 mmol) and Pd₂(dba)₃ (87 mg, 0.095 mmol). Then the reaction mixture was stirred and irradiated by microwave at 160°C for 30 min. Water (50 mL) was added to the mixture, and the mixture was
- 15 extracted with EtOAc (20 mL×3). The organic layer was concentrated *in vacuo*, and the crude product was purified by silica gel chromatography (PE/EtOAc=10:1 to 5:1) to give the title compound.

Step D. 3-amino-2-bromo-6-fluoro-4-(trifluoromethoxy)benzonitrile: To a solution of 5-amino-2-fluoro-4-(trifluoromethoxy)benzonitrile (370 mg, 1.681 mmol) in DMF (10 mL), was

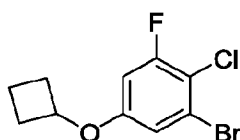
20 added 1-bromopyrrolidine-2,5-dione (299 mg, 1.681 mmol). The mixture was stirred at rt for 2 h. The reaction mixture was extracted with EtOAc (3x30 mL) and water (80 mL), and the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE: EtOAc=10:1) to afford the title compound.

Step E. 3-amino-2-bromo-6-fluoro-4-(trifluoromethoxy)benzonitrile: To a solution of

- 25 3-amino-2-bromo-6-fluoro-4-(trifluoromethoxy)benzonitrile (220 mg, 0.736 mmol) in THF (5 mL) was added isopentyl nitrite (172 mg, 1.471 mmol). Then the mixture was stirred at 70°C for 18 h. The mixture was concentrated *in vacuo*, and the resulting residue was extracted with EtOAc (3x20 mL) and water (20 mL). The organic layer was dried over Na₂SO₄, filtrated and concentrated. The residue was purified by silica gel PTLC (PE:EtOAc=10:1) to afford the title
- 30 compound. ¹HNMR (CD₃OD, 400 MHz, ppm) δ: 7.68 (s, 1 H) 7.51 (d, *J*=9.39 Hz, 1 H).

INTERMEDIATE 37

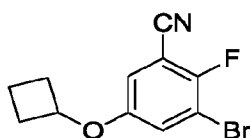
1-bromo-2-chloro-5-cyclobutoxy-3-fluorobenzene



- Step A. 1-bromo-3-cyclobutoxy-5-fluorobenzene. To a solution of 3-bromo-5-fluorophenol (10.00 g, 52.4 mmol) in DMF (50 mL) was added bromocyclobutane (14.14 g, 105 mmol), Bu₄NI (19.34 g, 52.4 mmol) and Cs₂CO₃ (17.06 g, 52.4 mmol). Then the mixture was stirred at 90°C for 18 h. The mixture was diluted with water (400 mL) and extracted with EtOAc (3 x 80 mL). The organic layer was dried and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE) to afford the title compound.
- Step B. 1-bromo-2-chloro-5-cyclobutoxy-3-fluorobenzene. To a solution of 1-bromo-3-cyclobutoxy-5-fluorobenzene (2.00 g, 8.16 mmol) in DMF (15 mL) was added 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione (0.626 g, 2.69 mmol). Then the mixture was stirred at 50°C for 3 h. The mixture was poured into water (30 mL) and extracted with EtOAc (3x30 mL). The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC on a Shimadzu pump LC-8A instrument fitted with a SYNERGI (250 x 50 x 10µm) using water (0.1% TFA) and MeCN as eluents (Mobile phase A: water (0.1 % TFA), Mobile phase B: MeCN, Detective wavelength: 220 nm), followed by concentration (below 50 °C) to afford the title compound. ¹HNMR (CDCl₃, 400 MHz, ppm) δ, 1.66-1.76 (m, 1 H) 1.89 (q, *J*=10.30 Hz, 1 H) 2.10-2.22 (m, 2 H) 2.40-2.51 (m, 2 H) 4.58 (quin, *J*=7.04 Hz, 1 H) 6.60 (dd, *J*=10.17, 2.35 Hz, 1 H) 6.90 (br. s, 1 H).

INTERMEDIATE 38

3-bromo-5-cyclobutoxy-2-fluorobenzonitrile



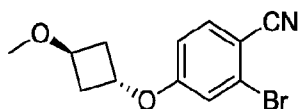
- Step A. 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)benzaldehyde. To a solution of 3-bromo-5-cyclobutoxy-2-fluorobenzaldehyde (Intermediate 23, step A, 1.00 g, 3.66 mmol) in

EtOH (20 mL) was added NH₂OH (0.484 g, 7.32 mmol), and the mixture was stirred at reflux for 5 h. After cooling to rt, the mixture was poured onto ice, and the mixture was stirred for 30 min. The mixture was concentrated *in vacuo*, and the residue was extracted with DCM (3x30 mL) and water (30 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound. *m/z* 289.0 *m/z* [M+H]⁺.

Step B. 3-bromo-5-(difluoromethyl)-4-fluorophenoxy)triisopropylsilane. To a solution of (Z)-3-bromo-5-cyclobutoxy-2-fluorobenzaldehyde oxime (950 mg, 3.30 mmol) in DMF (5 mL) was added POCl₃ (1.77 g, 11.54 mmol) dropwise at 0 °C. Then the mixture was stirred at 20°C for 18 h. The mixture was poured into water and stirred for 1 h, and the solid that formed was filtered. The solid was dissolved in DCM (30 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound. ¹HNMR (CDCl₃ 400 MHz, ppm), δ: 1.68-1.79 (m, 1 H) 1.91 (q, *J*=10.30 Hz, 1 H) 2.09-2.23 (m, 2 H) 2.39-2.52 (m, 2 H) 4.58 (quin, *J*=6.95 Hz, 1 H) 6.90-6.96 (m, 1 H) 7.24 (dd, *J*=5.09, 2.74 Hz, 1 H).

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INTERMEDIATE 39

2-bromo-4-((1*r*,3*r*)-3-methoxycyclobutoxy)benzonitrile

Step A. (1*S*,3*S*)-3-((tert-butyldimethylsilyl)oxy)cyclobutanol: To a stirred solution of 3-((tert-butyldimethylsilyl)oxy)cyclobutanone (5.0 g, 0.025 mol) in MeOH (60 mL) was added sodium tetrahydridoborate (1.5 g, 0.040 mol) at 0°C. The resulting mixture was allowed to warm to rt and stirred for an additional 2 h. Then the mixture was cooled to rt, and the reaction was quenched with ice-water and saturated sodium sulfate solution (10 mL). The mixture was filtered, and the filtrate was concentrated *in vacuo* to afford crude product. Water (100 mL) was added to the crude product and the mixture was extracted with EtOAc (3x50 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound.

25

Step B. 2-bromo-4-((1*R*,3*R*)-3-((tert-butyldimethylsilyl)oxy)cyclobutoxy) benzonitrile: To a stirred solution of (1*S*,3*S*)-3-((tert-butyldimethylsilyl)oxy)cyclobutanol (0.14 g, 0.69 mmol) in THF (8 mL) was added PPh₃ (0.25 g, 0.95 mmol), 2-bromo-4-hydroxybenzonitrile (0.15 g, 0.76

mmol) at 0°C. DEAD (0.15 g, 0.86 mmol) was added dropwise to the reaction mixture under a N₂ atmosphere. The resulting mixture was stirred at 60°C for 16 h. The mixture was cooled to rt and water (20 mL) was added. The mixture was extracted with EtOAc (3x15 mL), and the organic layer was dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (PE/EtOAc=50:1) to give the title compound.

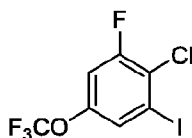
Step C. 2-bromo-4-((1R,3R)-3-hydroxycyclobutoxy)benzonitrile: To a stirred solution of 2-bromo-4-((1R,3R)-3-((tert-butyldimethylsilyl)oxy)cyclobutoxy)benzonitrile (120 mg, 0.31 mmol) in THF (5 mL) was added TBAF (110 mg, 0.42 mmol) at rt, and the mixture was stirred for 3 h under a N₂ atmosphere. Water (15 mL) was added to the mixture, and the mixture was extracted with EtOAc (3x8 mL). The organic layer was dried (Na₂SO₄), and concentrated *in vacuo* to afford crude product. The crude product was purified by silica gel chromatography (MeOH/DCM=1:50) to give the title compound.

Step D. 2-bromo-4-((1R,3R)-3-methoxycyclobutoxy)benzonitrile: To a stirred solution of 2-bromo-4-((1R,3R)-3-hydroxycyclobutoxy)benzonitrile (65 mg, 0.24 mmol) in THF was added NaH (60% in mineral oil, 12 mg, 0.30 mmol) at rt, and the mixture was stirred for 30 min. Then MeI (37 mg, 0.26 mmol) was added, and the mixture was stirred for 16 h. Water (15 mL) was added, and the mixture was extracted with EtOAc (3x10 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to afford crude product. The crude product was purified by silica gel chromatography (PE/EtOAc=18:1 to 10:1 as eluent) to give the title compound.

¹H-NMR (400 MHz, CDCl₃) δ ppm: 2.29-2.46 (m, 4 H), 3.21 (s, 3 H), 4.00-4.13 (m, 1 H), 4.71-4.82 (m, 1 H), 6.68-6.80 (m, 1 H), 6.95-7.02 (m, 1 H), 7.48 (d, *J*=8.60 Hz, 1 H).

INTERMEDIATE 40

2-chloro-1-fluoro-3-iodo-5-(trifluoromethoxy)benzene



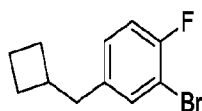
Step A. 2-fluoro-6-iodo-4-(trifluoromethoxy)aniline: To a solution of 2-fluoro-4-(trifluoromethoxy)aniline (1.00 g, 5.13 mmol) in EtOH (20 mL) was added Ag₂SO₄ (1.598 g, 5.13 mmol) and I₂ (1.301 g, 5.13 mmol). The mixture was stirred at rt for 1 h, and the mixture

was filtered, and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE:EtOAc=80:1 to 40:1) to afford the title compound.

Step B. 2-chloro-1-fluoro-3-iodo-5-(trifluoromethoxy)benzene: To a solution of 2-fluoro-6-iodo-4-(trifluoromethoxy)aniline (300 mg, 0.935 mmol) and CuCl₂ (251 mg, 1.869 mmol) in MeCN (20 mL) was added tert-butyl nitrite (193 mg, 1.869 mmol) at 0°C. The mixture was stirred at rt for 2 h, and the mixture was concentrated *in vacuo*. Water (30 mL) was added, and the mixture was extracted with EtOAc (3 x 30 mL). The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified via silica gel chromatography (PE:EtOAc=50:1) to afford the title compound. ¹H NMR (CD₃OD, 400 MHz, ppm): 7.73 (br s., 1 H) 7.40 (dd, *J*=9.16, 1.88 Hz, 1 H).

INTERMEDIATE 41

2-bromo-4-(cyclobutylmethyl)-1-fluorobenzene



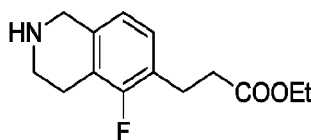
Step A. 3-bromo-4-fluoro-*N*-methoxy-*N*-methylbenzamide. To a solution of DIEA (4.78 mL, 27.4 mmol), 3-bromo-4-fluorobenzoic acid (2.0 g, 9.13 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (0.891 g, 9.13 mmol) in DMF (25 mL) was added HATU (3.47 g, 9.13 mmol) at 0°C, and the mixture while stirring was allowed to gradually warm to rt. The mixture was stirred at rt for 18 h. Water (100 mL) was added, and the mixture was extracted with EtOAc (3 x 200 mL) and washed with brine (2x50 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (PE:EtOAc=20:1~5:1) to give the title compound. *m/z* 264.0 [M+H]⁺.

Step B:(3-bromo-4-fluorophenyl)(cyclobutyl)methanone: To a suspension of magnesium (0.538 g, 22.13 mmol) in THF (20 mL) was added I₂ (0.028 g, 0.111 mmol) at 40°C, and the mixture was stirred at 40 °C for 10 min. Then bromocyclobutane (2.99 g, 22.13 mmol) was added dropwise with stirring at 10°C (under a N₂ atmosphere). After the addition was complete, the reaction mixture was stirred at 40 °C for 2 h. The above solution was added dropwise to a solution of 3-bromo-4-fluoro-*N*-methoxy-*N*-methylbenzamide (2.9 g, 11.07 mmol) in THF (30

- mL) at 0°C (under a N₂ atmosphere). The mixture was stirred at rt for 16 h. The reaction mixture was poured into ice water (20 mL), and the mixture was extracted with EtOAc (30 mL×2). The combined organic layer was washed with brine (20 mL×2), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give crude product. The crude product was purified by silica gel column chromatography using (PE/DCM=100:1-5:1) to give the title compound.
- 5 Step C. 2-bromo-4-(cyclobutylmethyl)-1-fluorobenzene. To a solution of (3-bromo-4-fluorophenyl)(cyclobutyl)methanone (125 mg, 0.486 mmol) in TFA (2 mL) was added triethylsilane (170 mg, 1.459 mmol) dropwise at 0 °C. The mixture was stirred at 0°C and gradually allowed to warm to rt, and the mixture was stirred for 16 h. The mixture was poured
- 10 into aq. NaOH (30%, 50 mL), and the mixture was extracted with DCM (3x300 mL), washed with water (2x150 mL), and brine (2 x150 mL). The organic layer was dried (Na₂SO₄), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EtOAc=200:1~50:1) to give the crude product. ¹H NMR (400 MHz, CDCl₃) δ 8.12 (dd, *J*=2.0, 6.7 Hz, 1H), 7.84 (ddd, *J*=1.8, 4.7, 8.4 Hz, 1H), 7.19 (t, *J*= 8.2 Hz, 1H), 3.94
- 15 (quin, *J*=8.4 Hz, 1H), 2.47-2.25 (m, 4H), 2.18-2.03 (m, 1H), 1.98-1.86 (m, 1H).

INTERMEDIATE 42

Ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate

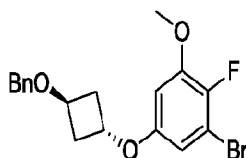


- 20 Step A. (E)-ethyl 3-(6-chloroquinolin-2-yl)acrylate: To a solution of 6-bromo-5-fluoroisoquinoline (210 mg, 0.929 mmol) in dry 1,4-dioxane (10 mL) was added tri-*tert*-butylphosphonium tetrafluoroborate (51 mg, 0.176 mmol), dicyclohexylamine (253 mg, 1.394 mmol), and ethyl acrylate (112 mg, 1.115 mmol). The mixture was degassed for 5 min with N₂. Then Pd₂(dba)₃ (85 mg, 0.093 mmol) was added to the mixture, and the mixture was
- 25 stirred at 100°C for 18 h under a N₂ atmosphere. The mixture was diluted with EtOAc (20 mL), and the mixture was filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel chromatography (PE:EtOAc=20:1 to 3:1) to afford the title compound.
- Step B. Ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate To a solution of

(E)-ethyl 3-(5-fluoroisoquinolin-6-yl)acrylate (220 mg, 0.897 mmol) in MeOH (20 mL) was added platinum(IV) oxide (40 mg, 0.176 mmol). The reaction mixture was stirred under a hydrogen atmosphere (50 psi) at 30 °C for 5 h. The reaction mixture was cooled to rt and filtered. The filtrate was concentrated *in vacuo* to give the title compound, which was used in the next step without further purification. ¹HNMR (400 MHz, CDCl₃) δ 7.02-6.91 (m, 1H), 6.73 (d, *J*=7.4 Hz, 1H), 4.12 (q, *J*=7.0 Hz, 2H), 3.97 (s, 2H), 3.13 (t, *J*=6.1 Hz, 2H), 2.92 (t, *J*=7.6 Hz, 2H), 2.73 (t, *J*=5.7 Hz, 2H), 2.60 (t, *J*=7.6 Hz, 2H), 1.24 (t, *J*=7.0 Hz, 3H).

INTERMEDIATE 43

5-((1*r*,3*r*)-3-(benzyloxy)cyclobutoxy)-1-bromo-2-fluoro-3-methoxybenzene



Step A. (3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)phenyl)boronic acid: To a solution of 2,2,6,6-tetramethylpiperidine (6.10 g, 43.2 mmol) in THF (150 ml) was added n-BuLi (2.5 M, 17.27 ml, 43.2 mmol) at -78 °C. The mixture was stirred at -78 °C for 0.5 h, and then warmed to rt and stirred for 1 h. The mixture was extracted with EtOAc (100 mLx2), washed with water (1 L), and dried (Na₂SO₄). The organic layer was concentrated *in vacuo* to give the crude product, which was used in the next step without further purification.

Step B. 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)phenol: To a solution of (3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)phenyl)boronic acid (17.15 g, 43.8 mmol) in THF (150 ml) was added NaH (11.69 g, 88 mmol) (30%). Then H₂O₂ (9.94 g, 88 mmol) (30%) was added at 0 °C. The mixture was stirred at 15 °C for 16 h, then diluted with aqueous saturated Na₂SO₃ (100 mL) and stirred for 0.5 h. The mixture was extracted with EtOAc (2 x100 mL), washed with water (500 mL), dried (Na₂SO₄), filtered, concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE:EtOAc = 50:1 to 20:1) to give the title compound.

Step C. (3-bromo-4-fluoro-5-methoxyphenoxy)triisopropylsilane: To a solution of 3-bromo-2-fluoro-5-((triisopropylsilyl)oxy)phenol (8.0 g, 22.02 mmol) and K₂CO₃ (6.09 g, 44.0

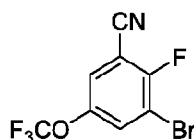
mmol) in DMF (50 ml) was added MeI (11.834 g, 83 mmol) at 0°C. The mixture was stirred at 15°C for 16 h. Aq. saturated Na₂S₂O₃ (100 mL) was added, and the mixture was extracted with EtOAc (50 mL x2), washed with water (500 mL), dried (Na₂SO₄), filtered, concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE:EtOAc = 50:1 to 20:1) to give the title compound.

Step D. 3-bromo-4-fluoro-5-methoxyphenol: To a solution of (3-bromo-4-fluoro-5-methoxyphenoxy)triisopropylsilane (5.0 g, 13.25 mmol) in THF (50 ml) was added TBAF (13.25 ml, 13.25 mmol, 1 M in THF). The mixture was stirred at 25°C for 2 h. Water (100 mL) was added, and the mixture was extracted with EtOAc (2x50 mL). The organic layer was washed with water (200 mL), dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE:EtOAc = 10:1 to 5:1) to give the title compound.

Step E. 5-((1R,3R)-3-(benzyloxy)cyclobutoxy)-1-bromo-2-fluoro-3-methoxy benzene: To a stirred solution of 3-bromo-4-fluoro-5-methoxyphenol (0.546 g, 2.469 mmol), (1S,3S)-3-(benzyloxy)cyclobutanol (0.4 g, 2.244 mmol) and PPh₃ (0.883 g, 3.37 mmol) in THF (15 mL) was added DEAD (0.569 mL, 3.59 mmol) dropwise at 0°C. Then the reaction mixture was placed under a nitrogen atmosphere and stirred at 80°C for 15 h. The solvent was removed *in vacuo*, and the resulting residue was purified by silica gel chromatography (PE/EtOAc=20:1 to 10:1) to give the title compound. ¹H NMR (400 MHz, CDCl₃) ppm δ 2.38-2.48 (m, 2 H) 2.48-2.59 (m, 2 H) 3.87 (s, 3 H) 4.30-4.40 (m, 1 H) 4.75-4.88 (m, 1 H) 6.42 (dd, *J*=6.65, 2.64 Hz, 1 H) 6.44-6.47 (m, 1 H) 7.30-7.42 (m, 5 H).

INTERMEDIATE 44

3-bromo-2-fluoro-5-(trifluoromethoxy)benzonitrile



Step A. 1-bromo-2-fluoro-4-nitro-5-(trifluoromethoxy)benzene: To a solution of 2-bromo-1-fluoro-4-(trifluoromethoxy)benzene (10.0 g, 38.6 mmol) in CH₃CN (150 mL) was added nitronium tetrafluoroborate (5.38 g, 40.5 mmol) at 0°C, and the mixture was stirred at 0~18

°C for 16 h. The mixture was poured into water (50 mL) and extracted with EtOAc (200 mL x 3). The organic layer was washed with water (150 mLx2) and brine (150 mLx2), dried (Na₂SO₄), and filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel chromatography (PE:EtOAc=20:1~5:1) to give the title compound.

5 Step B. 4-bromo-5-fluoro-2-(trifluoromethoxy)aniline: To a stirred solution of 1-bromo-2-fluoro-4-nitro-5-(trifluoromethoxy)benzene (4.0 g, 13.16 mmol) in MeOH (20 mL) and water (2 mL) was added NH₄Cl (7.04 g, 132 mmol) and iron (2.204 g, 39.5 mmol). The mixture was stirred at 50°C for 18 h. The mixture was extracted with EtOAc (2x50 mL) and water (2x30 mL), and the organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*.

10 The residue was purified by silica gel chromatography (PE:EtOAc=10:1) to give the title compound.

Step C. 4-amino-3-bromo-2-fluoro-5-(trifluoromethoxy)benzonitrile. To a stirred solution of 4-amino-2-fluoro-5-(trifluoromethoxy)benzonitrile (0.76 g, 3.45 mmol) in CH₃CN (30 mL) was added NBS (0.615 g, 3.45 mmol), and the mixture was stirred at rt for 2 h. The mixture was

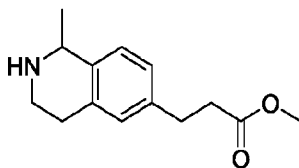
15 diluted with water (60 mL) and extracted with EtOAc (2x50 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EtOAc=30:1) to give the title compound.

Step D. 3-bromo-2-fluoro-5-(trifluoromethoxy)benzonitrile: To a stirred solution of 2-amino-5-bromo-6-fluoro-3-(trifluoromethoxy)benzonitrile (330 mg, 1.104 mmol) in THF (10 mL) was added isopentyl nitrite (388 mg, 3.31 mmol), and the mixture was stirred at 50°C for 24 h. The mixture was washed with water (2x10 mL) and extracted with EtOAc (2x30 mL). The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by silica gel PTLC (PE:EtOAc=10:1) to give the title compound.

25

INTERMEDIATE 45

methyl 3-(1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate



Step A-6-bromo-3,4-dihydroisoquinoline: To a solution of 6-bromo-1,2,3,4-tetrahydro- iso-

quinoline (15.00 g, 71.1 mmol) in DCM (160 mL) was added activated MnO₂ (77.84 g, 859.7 mmol). The mixture was stirred for 18 h at rt and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (PE:EtOAc =20:1 to 5:1) to afford the title compound.

- 5 Step B-6-bromo-1-methyl-1,2,3,4-tetrahydroisoquinoline: To a solution of 6-bromo-3,4-dihydroisoquinoline (2.50 g, 11.9 mmol) in dry THF (50 ml) was added BF₃·Et₂O (9.0 ml, 71.0 mmol) at -78 °C in a N₂ atmosphere. After stirring for 5 min at -78°C, MeMgBr (4.26 g, 35.7 mmol) was added. The mixture was warmed to rt and stirred 18 h. The mixture was cooled to 0°C, and water was added to quench the reaction. The mixture was extracted with EtOAc (100 mL×2). The organic layer was washed with brine, dried (Na₂SO₄), and concentrated *in vacuo* to afford the title compound, which was used in the next step without further purification.

- Step C. *tert*-butyl 6-bromo-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate: To a solution of 6-bromo-1-methyl-1,2,3,4-tetrahydroisoquinoline (1.50 g, 6.63 mmol) in DCM (15 ml) was added TEA (1.8 ml, 13.2 mmol), followed by (Boc)₂O (2.2 g, 9.95 mmol). The mixture was stirred for 1h at rt, and the mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EtOAc= 30:1) to afford the title compound.

- Step D. (*E*)-*tert*-butyl 6-(3-methoxy-3-oxoprop-1-en-1-yl)-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate: To a solution of *tert*-butyl 6-bromo-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.50 g, 4.60 mmol) in dioxane (15 mL) was added *N,N*-dicyclohexylmethylamine (1.34 g, 6.86 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (0.13 g, 0.45 mmol). The final mixture was degassed for 5 min with N₂. Then Pd₂(dba)₃ (0.21 g, 0.229 mmol) and methyl acrylate (1.98 g, 23.00 mmol) were added. The final mixture was heated to 110 °C and stirred overnight in a N₂ atmosphere. The mixture was diluted with EtOAc (20 mL), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EA=40:1 to 20:1) to afford the title compound. m/z 317.0 [M-16]⁺.

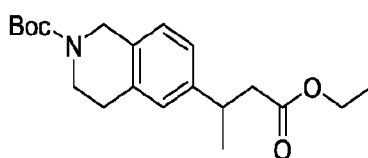
- Step E *tert*-butyl 6-(3-methoxy-3-oxopropyl)-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate: To a solution of (*E*)-*tert*-butyl 6-(3-methoxy-3-oxoprop-1-en-1-yl)-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (700 mg, 2.112 mmol) in MeOH (15 ml) was added Pd-C (70 mg, 0.66 mmol). The mixture was stirred overnight at 22°C in a H₂

atmosphere (45 PSI). The mixture was filtered, and the filtrate was concentrated *in vacuo* to afford the title compound.

Step F. methyl 3-(1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate: To a solution of *tert*-butyl 6-(3-methoxy-3-oxopropyl)-1-methyl-3,4-dihydro-iso-quinoline-2(1H)-carboxylate (350 mg, 1.05 mmol) in DCM (10 mL) was added HCl (4.0 M dioxane solution, 3 mL). The mixture was stirred for 1 h at rt, and concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL), and Cs₂CO₃ was added to adjust the pH to pH 8-9. Then the mixture was concentrated *in vacuo* to afford the title compound, which was used in the next step without further purification.

INTERMEDIATE 46

tert-butyl 6-(4-ethoxy-4-oxobutan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate



Step A. (E)-*tert*-butyl 6-(4-ethoxy-4-oxobut-2-en-2-yl)-3,4-dihydroisoquinoline-

2(1H)-Carboxylate: To a solution of *tert*-butyl 6-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.0 g, 6.41 mmol) and (E)-ethyl but-2-enoate (1.462 g, 12.81 mmol) in dioxane (20 ml) was added tri-*tert*-butylphosphonium tetrafluoroborate (0.186 g, 0.641 mmol) and Pd₂(dba)₃ (0.117 g, 0.128 mmol) followed by the addition of N-cyclohexyl- N-methylcyclohexanamine (1.502 g, 7.69 mmol). The reaction was stirred at 100°C under a N₂ atmosphere for 12 h. The reaction mixture was partitioned between EtOAc (50 mL) and water (50 mL), and the organic layer was washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (PE/EtOAc 30:1 to 10:1) to give the title compound.

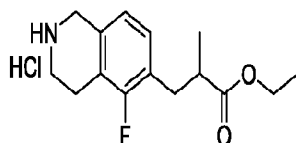
Step B. *tert*-butyl 6-(4-ethoxy-4-oxobutan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate: To a mixture of (E)-*tert*-butyl 6-(4-ethoxy-4-oxobut-2-en-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (400 mg, 1.158 mmol) in MeOH (10 ml) was added Pd-C (40 mg, 0.038 mmol), and the mixture was stirred at rt under a H₂ atmosphere (30 psi) for

50 min. The mixture was filtered and concentrated *in vacuo* to afford the title compound. m/z 348.2 $[M+H]^+$. ^1H NMR (400 MHz, CDCl_3) δ 7.05 (s, 1 H) 7.00 (s, 1 H) 4.54 (s, 2 H) 4.09 (q, $J=7.04$ Hz, 2 H) 3.64 (br. s., 2 H) 3.24 (dq, $J=14.38, 7.08$ Hz, 1 H) 2.81 (br. s., 2 H) 2.49-2.63 (m, 2 H) 1.49 (s, 9 H) 1.29 (d, $J=7.04$ Hz, 3 H) 1.20 (t, $J=7.24$ Hz, 3 H).

- 5 Step C. *tert*-butyl 6-(4-ethoxy-4-oxobutan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate: *Tert*-butyl 6-(4-ethoxy-4-oxobutan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (350 mg) was purified by SFC (Column: Chiral Pak WHELK-O1, $5\mu\text{m}$, Daicel Chemical Industries, Ltd $250\times 30\text{mm}$ I.D. Mobile phase A: Supercritical CO_2 , Mobile phase B: EtOH (contained 0.1% ETOA), A:B = 75:25 at 60 mL/min, Column Temp: 38°C , Wavelength: 220 nm, Nozzle Pressure: 100 Bar Nozzle Temp: 60°C) to afford *tert*-butyl 6-(4-ethoxy-4-oxobutan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate and *tert*-butyl 6-(4-ethoxy-4-oxobutan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate. m/z 348.2 $[M+H]^+$.

INTERMEDIATE 47

- 15 ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanoate hydrochloride



- Step A. *tert*-butyl 6-(3-ethoxy-3-oxopropyl)-5-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate: To a solution of ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (Intermediate 7, 1.0 g, 3.98 mmol) in DCM (20 mL) were added Et_3N (0.6 mL, 4.30 mmol) and BOC_2O (1.1 mL, 4.74 mmol) with stirring at 0°C (under a N_2 atmosphere). The mixture was stirred at $\sim 26^\circ\text{C}$ overnight (~ 18 h). The solvent was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (PE/EtOAc = 20:1~5:1) to give the title compound.

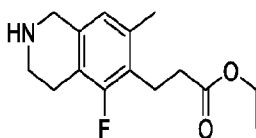
- Step B. *tert*-butyl 6-(3-ethoxy-2-methyl-3-oxopropyl)-5-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate: To a solution of *tert*-butyl 6-(3-ethoxy-3-oxopropyl)-5-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.3 g, 0.854 mmol) in anhydrous THF (10 mL) with stirring at -78°C was added KHMDS (1.3 mL, 1.300 mmol) in THF dropwise. The mixture was stirred at -78°C for 30 min, and MeI (0.182 g, 1.281 mmol) was added. The mixture was stirred for an

additional 30 min at -78°C, and the mixture was gradually warmed to rt for 18 h. The reaction was quenched with water (10 mL), and the mixture was extracted with EtOAc (2x20 mL). The organic phase was concentrated *in vacuo* to give crude product, which was purified by silica gel column chromatography (EtOAc/PE 1:20~1:10) to give the title compound.

- 5 Step C. *tert*-butyl ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methyl- propanoate: To a solution of *tert*-butyl 6-(3-ethoxy-2-methyl-3-oxopropyl)-5- fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (500 mg, 1.368 mmol) in dioxane (10 mL) was added a solution of 4 M HCl in dioxane (5 mL), and the mixture was stirred at 24°C for 18 h. The mixture was concentrated *in vacuo* to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ
- 10 ppm 6.92 (t, *J*=7.63 Hz, 1 H) 6.71 (*d*, *J*=8.22 Hz, 1 H) 4.06-4.12 (m, 2 H) 3.96 (s, 2 H) 3.12 (t, *J*=6.06 Hz, 2 H) 2.96 (*d*, *J*=6.65 Hz, 1 H) 2.72 (br. s., 4 H) 1.16-1.23 (m, 6 H).

INTERMEDIATE 48

ethyl 3-(5-fluoro-7-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate



15

- Step A. 3-bromo-2-fluoro-4-methylbenzaldehyde. To a stirred solution of 2-bromo-1-fluoro-3-methylbenzene (9.0 g, 47.6 mmol) in THF (150 mL) was added LDA (26.2 mL, 52.4 mmol) at -70 °C under a nitrogen atmosphere. The mixture was stirred for 1 h at -70°C, then DMF (4.5 g, 61.6 mmol) was added to the mixture. The mixture was allowed to warm to rt and
- 20 stirred for 2 h. The reaction was quenched by addition of NH₄Cl solution (10 mL) and extracted with EtOAc (2x30 mL). The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo* to give a residue. The residue was purified by silica gel column chromatography (PE:EtOAc =20:1) to give the title compound.

- Step B. (*E*)-methyl 3-(3-bromo-2-fluoro-4-methylphenyl)acrylate: To a stirred solution of ethyl
- 25 2-(diethoxyphosphoryl)acetate (5.34 g, 23.82 mmol) in THF (80 mL) was added NaH (1.0 g, 25.00 mmol). The resulting solution was stirred at rt for 30 min. Then 3-bromo-2- fluoro-4-methylbenzaldehyde (4.7 g, 21.66 mmol)) in THF (20 mL) was added dropwise, and the mixture was stirred at rt for 2 h. The reaction was quenched with NH₄Cl solution (5 mL), the

resulting mixture was extracted with EtOAc (100 mLx2). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to give a residue. The residue was purified by silica gel column chromatography (EtOAc:PE=1:15) to give the title compound.

Step C. (*E*)-3-(3-bromo-2-fluoro-4-methylphenyl)acrylic acid: To a solution of (*E*)-methyl

- 5 3-(3-bromo-2-fluoro-4-methylphenyl)acrylate (12.0 g, 43.9 mmol) in THF (20 ml), MeOH (20 ml) and water (10 ml) was added LiOH hydrate (3.69 g, 88 mmol). The mixture was stirred at 15°C for 16 h. The mixture was diluted with water (200 mL) and aqueous HCl (6N, 15 mL) to adjust the pH to ~4. The mixture was then extracted with EtOAc (2 x 100 mL), and the organic layer was washed with water (200 mL), dried over anhydrous Na₂SO₄, and concentrated *in*
10 *vacuo* to give the crude title compound, which was used in next step without further purification.

Step D (*E*)-3-(3-bromo-2-fluoro-4-methylphenyl)acryloyl chloride: To a solution of (*E*)-3-(3-bromo-2-fluoro-4-methylphenyl)acrylic acid (4.5 g, 16.50 mmol) in THF (30 mL) was added oxalyl chloride (2.304 g, 18.15 mmol) and DMF (0.005 mL). The mixture was stirred at 18°C for 2 h. The mixture was concentrated *in vacuo* to give the crude title compound, which
15 was used in next step without further purification.

- Step E. (*E*)-3-(3-bromo-2-fluoro-4-methylphenyl)acryloyl azide: To a solution of sodium azide (1.44 g, 22.15 mmol) in dioxane (8 mL) and water (5 mL) was added (*E*)-3-(3-bromo-2-fluoro-4-methylphenyl)acryloyl chloride (4.58 g, 16.50 mmol) in dioxane (10 mL) dropwise at 0°C. The mixture was stirred at 0°C for 1 h, and water (100 mL) was added. The mixture was
20 extracted with diethyl ether (3 x 30 mL), and organic layer was washed with sat. aqueous of NaHCO₃ (2 x 30 mL) and brine (50 mL), dried over Na₂SO₄, and filtered. The organic layer was concentrated *in vacuo* at a temperature of less than 40°C behind a protective screen to afford the title compound.

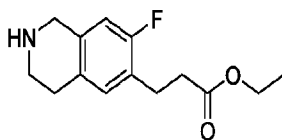
- Step F. 6-bromo-5-fluoro-7-methylisoquinolin-1(2H)-one: A solution of (*E*)-3-(3-bromo-2-fluoro-4-methylphenyl)acryloyl azide (4.69 g, 16.51 mmol) in diphenyl ether (20 mL) was
25 stirred at 250°C for 3 h. The mixture was cooled to 20°C and diluted with cyclohexane (40 mL). The precipitate was filtered and dried to give the title compound. *m/z* 255.9 (M+H)⁺.

- Step G. 6-bromo-1-chloro-5-fluoro-7-methylisoquinoline: 6-bromo-5-fluoro-7-methylisoquinolin-1(2H)-one (0.65 g, 2.54 mmol) was dissolved in POCl₃ (10.29 mL, 110 mmol), and
30 the mixture was stirred at 110°C for 2 h. The reaction mixture was concentrated *in vacuo*, and

- the concentrate was poured into water (20 mL). The water layer was extracted with EtOAc (2 x30 mL), and the organic layer was washed with aqueous saturated NaHCO₃ solution. The organic layer was washed with brine (20 mLx2), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give crude product. The crude product was purified by silica gel column chromatography (PE/EtOAc 10:1) to give the title compound. *m/z* 276.0(M+H)⁺.
- Step H. 6-bromo-5-fluoro-7-methylisoquinoline. To a solution of 6-bromo-1-chloro-5-fluoro-7-methylisoquinoline (350 mg, 1.275 mmol) in AcOH (5 ml) and hydrochloric acid, 37% (1 ml) was added tin (454 mg, 3.82 mmol). The mixture was stirred at 60°C for 0.5 h. The mixture was diluted with water (100 mL), and the mixture was extracted with EtOAc (2 x 50 mL). The organic layer was washed with water (200 mL), dried over anhydrous Na₂SO₄, filtered, concentrated *in vacuo*, and the residue was purified by silica column chromatography (PE:EtOAc=50:1 to 20:1) to give the title compound. *m/z* 240.1 [M + H]⁺.
- Step I. (*E*)-ethyl 3-(5-fluoro-7-methylisoquinolin-6-yl)acrylate. To a solution of 6-bromo-5-fluoro-7-methylisoquinoline (180 mg, 0.750 mmol) in dry 1,4-dioxane (10 ml) was added tri-*tert*-butylphosphonium tetrafluoroborate (22 mg, 0.076 mmol), ethyl acrylate (120 mg, 1.2 mmol) and *N*-cyclohexyl-*N*-methylcyclohexanamine (439 mg, 2.249 mmol). Then the mixture was degassed for 5 min with N₂, and Pd₂(dba)₃ (137 mg, 0.150 mmol) was added to the mixture. The mixture was heated to 100 °C and stirred for 18 h in a N₂ atmosphere. The mixture was diluted with water (100 mL) and extracted with EtOAc (2x50 mL). The organic layer was washed with water (200 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE:EtOAc=50:1 to 20:1) to give the title compound. *m/z* 260.3 [M+H]⁺.
- Step J. ethyl 3-(5-fluoro-7-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate. To a solution of (*E*)-ethyl 3-(5-fluoro-7-methylisoquinolin-6-yl)acrylate (0.2 g, 0.771 mmol) in EtOH (15 ml) was added platinum(IV) oxide (0.035 g, 0.154 mmol). The reaction mixture was stirred under a hydrogen atmosphere (50 PSI) at 50°C for 5 h. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give the title compound. *m/z* 266.1 [M+H]⁺.

INTERMEDIATE 49

- ethyl 3-(7-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate



- Step A. 2-(3-bromo-4-fluorophenyl)acetamide: To a solution of 2-(3-bromo-4-fluorophenyl)-acetic acid (5.0 g, 21.46 mmol), NH_4Cl (1.262 g, 23.60 mmol) and DIPEA (11.3 ml, 64.7 mmol) in DMF (50 ml) was stirred at $\sim 15^\circ\text{C}$ for 15 min. Then HATU (8.16 g, 21.46 mmol) was added at 15°C , and the mixture was stirred at 15°C for 5 h. The reaction was quenched with water (100 mL), and the mixture was extracted with DCM (3x80 mL). The organic layer was washed with water (3x30 mL) and brine (3x30 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel chromatography (PE:EtOAc=5:1 to 1:1) to give the title compound.
- 10 Step B. 2-(3-bromo-4-fluorophenyl)ethanamine: To a solution of 2-(3-bromo-4-fluorophenyl)acetamide (3.0 g, 12.93 mmol) in THF (25 mL) was added dropwise $\text{BH}_3 \cdot \text{THF}$ (24 mL, 24.00 mmol) at 0°C . The mixture was stirred at 70°C for 16 h. The mixture was cooled to 0°C , and water (2 mL) and conc. HCl solution (8 mL) were added to the mixture. The reaction mixture was stirred at 70°C for 10 min, then cooled to rt. Then the mixture was poured into
- 15 NaOH aqueous solution (4 N, 25 mL). The mixture was extracted with EtOAc (3x50 mL), and the organic layer was washed with water (5 x20 mL) and brine (2x20 mL), dried over Na_2SO_4 , filtered, and the filtrate was concentrated *in vacuo* to give crude title compound, which was used in the next step without further purification.
- Step C. N-(3-bromo-4-fluorophenethyl)-2,2,2-trifluoroacetamide: To a solution of
- 20 2-(3-bromo-4-fluorophenyl)ethanamine (1.5 g, 6.88 mmol) and TEA (1.4 ml, 10.04 mmol) in THF (20 ml) was added TFAA (1.1 mL, 7.79 mmol) at 0°C , and the mixture was stirred at $0\sim 19^\circ\text{C}$ for 3 h. The mixture was poured into aq. NaHCO_3 (2 M, 10 mL), and the mixture was extracted with EtOAc (3x30 mL), washed with water (2x10 mL), and brine (2 x10 mL). The organic layer was dried over Na_2SO_4 , and filtered, and the filtrate was concentrated *in vacuo*.
- 25 The residue was purified by silica gel chromatography (PE:EtOAc=20:1~5:1) to give the title compound.
- Step D. 1-(6-bromo-7-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone. To a solution of concentrated sulfuric acid (2.5 ml, 46.9 mmol) in AcOH (10 ml) was added

N-(3-bromo-4-fluoro-phenethyl)-2,2,2-trifluoroacetamide (1.2 g, 3.82 mmol) and formaldehyde (0.229 g, 7.64 mmol), and the mixture was stirred at 20°C for 24 h. The mixture was poured into ice water (100 mL), and the mixture was extracted with EtOAc (3x30 mL). The organic layer was washed with water (2x20 mL) and brine (2x20 mL), dried over Na₂SO₄, filtered, and the
5 filtrate was concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (PE:EtOAc=20:1~5:1) to give 1-(6-bromo-7-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)- 2,2,2-trifluoroethanone and 1-(8-bromo-7-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone.

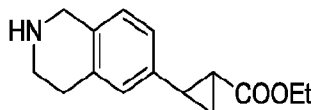
Step E. (E)-ethyl 3-(7-fluoro-2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)acrylate: To a solution of 1-(8-bromo-7-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone (250 mg, 0.767 mmol), and 1-(6-bromo-7-fluoro-3,4-dihydro-isoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone (500 mg, 1.533 mmol) in dry 1,4-dioxane (10 ml) was added tri-*tert*-butylphosphonium tetrafluoroborate (45 mg, 0.155 mmol), ethyl acrylate (246 mg, 2.453 mmol), and *N*-cyclohexyl-*N*-methylcyclohexanamine (899 mg, 4.60 mmol). Then the
10 mixture was degassed for 5 min with N₂, and Pd₂(dba)₃ (281 mg, 0.307 mmol) was added. The mixture was then heated to 100°C and stirred for 18 h in a N₂ atmosphere. EtOAc (100 mL) was added, and the mixture was filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (PE:EtOAc=20:1 to 10:1) to afford the crude title compound. The mixture was purified by SFC to give title compound.

Step F: ethyl 3-(7-fluoro-2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate: To a solution of (E)-ethyl-3-(7-fluoro-2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)acrylate (500 mg, 1.448 mmol) in EtOH (20 mL) was added Pd-C (15 mg, 0.141 mmol). The mixture was stirred at 45°C under H₂ (30 psi) for 2 h. The mixture was filtered, washed with EtOH (10 mL), and the filtrate was concentrated *in vacuo* to give the
25 crude title compound.

Step G. ethyl 3-(7-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate. To a solution of ethyl 3-(7-fluoro-2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (200 mg, 0.576 mmol) in EtOH (10 mL) was added K₂CO₃ (239 mg, 1.728 mmol). The mixture was stirred at 15°C for 12 h, and the mixture was cooled to rt and diluted with EtOAc (20 mL). The
30 organic layer was washed with water (2x20 mL), dried with Na₂SO₄, and concentrated *in vacuo* to give the crude title compound.

INTERMEDIATE 50

Ethyl 2-(1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate



Step A. Tert-butyl 6-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate. To a solution of
 5 6-bromo-1,2,3,4-tetrahydroisoquinoline (19.17 g, 90.39 mmol) in DCM (200 mL) was added
 TEA (18.29 g, 180.77 mmol) and Boc₂O (23.67 g, 108.46 mmol) at 0°C. After the completion
 of the addition, the mixture was stirred at ~ 25°C for 15 h. Water (300 mL) was added, and the
 mixture was extracted with EtOAc (3x100 mL). The organic layer was dried over Na₂SO₄ and
 concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography
 10 (PE: EtOAc = 50:1 to 10:1) to give the title compound.

Step B. 6-(3-ethoxy-3-oxoprop-1-en-1-yl)-3,4-dihydroisoquinoline-2(1H)- carboxylate. To a
 solution of tert-butyl 6-bromo-3,4-dihydroisoquinoline-2(1H)- carboxylate (11.30 g, 36.20
 mmol) in dioxane (100 mL) was added ethyl acrylate (7.25 g, 72.39 mmol), (*t*-Bu)₃PHBF₄ (2.10
 g, 72.40 mmol), CH₃N(C₆H₄)₂ and Pd₂(dba)₃ (3.3 g, 3.62 mmol). Then the mixture was stirred at
 15 100°C under N₂ for 15 h. After the reaction mixture was cooled to rt, and water (200 mL) was
 added. The mixture was extracted with EtOAc (3x100 mL), and the organic layer was washed
 with brine, dried (Na₂SO₄), filtered, concentrated *in vacuo*. The resulting residue was purified by
 silica gel column chromatography (PE:EtOAc=50:1 to 10:1) to give the title compound.

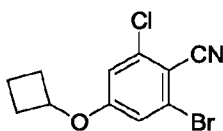
Step C. Tert-butyl 6-(2-(ethoxycarbonyl)cyclopropyl)-3,4-dihydro-isoquino- line-2(1H)-
 20 carboxylate. To a solution of tert-butyl 6-(3-ethoxy-3-oxoprop-1- en-1-yl)-3,4-dihydro-
 isoquinoline-2(1H)-carboxylate (6.3 g, 19.01 mmol) and Pd(OAc)₂ (0.43 g, 1.90 mmol) in DCM
 (200 mL) and diethyl ether (400 mL) was added diazomethane in diethyl ether (250 mL, 125
 mmol) at 0°C under a N₂ atmosphere. Then the reaction mixture was slowly warmed to rt and
 stirred for 15 h. The reaction mixture was quenched with AcOH (20 mL), washed with brine
 25 (100 mL), and the organic layer was concentrated *in vacuo*. The crude product was purified by
 silica gel column chromatography to give the title compound.

Step D. Ethyl 2-(1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate. To a solution of
 tert-butyl 6-(2-(ethoxycarbonyl)cyclopropyl)-3,4-dihydroisoquinoline-2(1H)- carboxylate (2.00

g, 5.79 mmol) in dioxane (5 mL) was added HCl-dioxane (4 M, 5 mL). Then the mixture was stirred at ~25°C for 2 h, and then concentrated *in vacuo*. The residue was purified by cation ion exchange column chromatography (1 M NH₃-MeOH) to afford the title compound. ¹H NMR (400 MHz, CD₃OD) δ 6.90-6.97 (m, 1 H), 6.81-6.90 (m, 2 H), 4.14 (q, *J*=7.30 Hz, 2 H), 3.89 (s, 2 H), 3.00-3.07 (m, 2 H), 2.78 (t, *J*=5.87 Hz, 2 H), 2.35-2.43 (m, 1 H), 1.80-1.88 (m, 1 H), 1.48 (s, 1 H), 1.31-1.35 (m, 1 H), 1.21-1.29 (m, 3 H).

INTERMEDIATE 51

2-bromo-6-chloro-4-cyclobutoxybenzonitrile



10

Step A 2-Chloro-4-cyclobutoxy-1-nitrobenzene. To a stirred solution of NaH (3.42 g, 85 mmol) in DMF (50 mL) was added dropwise cyclobutanol (6.16 g, 85 mmol), and the solution was stirred at 20 °C for about 5 minutes. Then 2-chloro-4-fluoro-1-nitrobenzene (10.00g, 57.0 mmol) was added to the reaction, and the reaction was stirred for 18 h at room temperature.

15 Saturated NH₄Cl aqueous solution (100 mL) and EtOAc (100 mL) were added to the reaction. The organic layer was separated and washed with saturated NH₄Cl aqueous solution (100 mL×4), dried over sodium sulfate and concentrated to give the title compound.

Step B 2-Chloro-4-cyclobutoxyaniline. To a solution of 2-chloro-4-cyclobutoxy-1-nitrobenzene (11.20 g, 49.2 mmol) in MeOH (100 mL) was added Raney Ni (0.42g, 4.92 mmol) at 20 °C under an argon atmosphere. Then the reaction mixture was stirred at 20 °C for 1 h under 50 psi of H₂ atmosphere. The mixture was filtered and the filtrate was concentrated and purified on silica gel (PE/EtOAc =10:1-2:1) to afford the title compound.

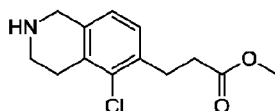
25 Step C 2-Bromo-6-chloro-4-cyclobutoxyaniline. To a stirred solution of 2-chloro-4-cyclobutoxyaniline (8.95 g, 45.3 mmol) in DCM (150 mL) was added bromine (2.449 mL, 47.5 mmol) by syringe at 0 °C. The solution was stirred at 0 °C for about 4 h, then aqueous saturated Na₂S₂O₃ (20 mL) and water (100 mL) were added dropwise. The resulting mixture was further stirred at room temperature for 5 min. Then the organic layer was separated, washed with brine (100 mL x2), dried over sodium sulfate and concentrated. The resulting residue was purified by flash chromatography (PE:EA = 100:1) to give the title compound.

Step D 1-Bromo-3-chloro-5-cyclobutoxy-2-iodobenzene. To a stirred solution of 2-bromo-6-chloro-4-cyclobutoxyaniline (5.50 g, 19.89 mmol) and copper(I) iodide (5.68 g, 29.8 mmol) in acetonitrile (40 mL) at 65 °C was added dropwise isopentyl nitrite (4.66 g, 39.8 mmol). The reaction was stirred at 65 °C for about 20 min, then cooled to room temperature. Then water (50 mL) and EtOAc (50 mL) were added to the reaction mixture. The organic layer was separated, washed with water (50 mL×2) and brine (50 mL×2), dried over sodium sulfate and filtered. The filtrate was concentrated and purified by flash chromatography (petroleum ether) to afford the title compound.

Step E 2-Bromo-6-chloro-4-cyclobutoxybenzonitrile. To a stirred solution of 1-bromo-3-chloro-5-cyclobutoxy-2-iodobenzene (4.30 g, 11.10 mmol) in DMF (25 mL) was added cyanocopper (1.988 g, 22.20 mmol). The reaction was stirred at 110 °C overnight (18 h), then cooled to room temperature and poured into 30 mL of saturated aqueous NH₄Cl. The resulting mixture was stirred for about 5 min, then 30 mL of EtOAc were added, and the mixture was stirred 5 min. Then the organic layer was separated, washed with brine (60 mL×2), dried over sodium sulfate and filtered. The filtrate was concentrated and purified by flash chromatography (PE: EtOAc=40:1) to give partially purified crude product. The crude product was further purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250*21.2 mm*4 μm) using water (0.2% Formic acid) and acetonitrile as eluents (Mobile phase A water (0.2% Formic acid), Mobile phase B acetonitrile, Detective wavelength: 220 nm) to give the title compound.

Intermediate 52

methyl 3-(5-chloro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate



Step A 1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide. 6-methoxy-1,2,3,4-tetrahydroisoquinoline (10.0 g, 61.3 mmol) was dissolved in 48 % HBr (40 mL, 354 mmol). The reaction was stirred at 100 °C for 15 h, then evaporated *in vacuo* to give the title compound, which was used directly in the next step without further purification.

Step B *tert*-butyl 6-hydroxy-3,4-dihydroisoquinoline-2(1H)-carboxylate. To a solution of 1,2,3,4-tetrahydroisoquinolin-6-ol hydrobromide (10 g) in H₂O (100 mL) was added a solution of triethylamine (20 mL, 143 mmol) and di-*tert*-butyl dicarbonate (10.43 g, 47.8 mmol) in THF (30 mL) dropwise. The reaction mixture was stirred at 25 °C for 15 h. Then the reaction mixture
5 was evaporated *in vacuo* to give the crude product, which was purified by silica gel (SiO₂, PE:EtOAc from 100:1 to 10:1) to afford the title compound.

Step C *tert*-butyl-5-chloro-6-hydroxy-3,4-dihydroisoquinoline-2(1H)-carboxylate.

Sulfonyl dichloride (3.28 g, 24.27 mmol) was added dropwise to a stirred mixture of *tert*-butyl 6-hydroxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (5.5 g, 22.06 mmol) in acetic acid (50
10 mL) at room temperature (~25 °C), and the mixture was stirred at room temperature (~25 °C) for 1.5 h. Then the mixture was concentrated. The resulting residue was dissolved in anhydrous DMF (50.0 mL), and Et₃N (9.22 mL, 66.2 mmol) and BOC-Anhydride (6.15 mL, 26.5 mmol) were added. Then the mixture was stirred at room temperature (25 °C) for 3 h, then concentrated *in vacuo*. Water (50 mL) was added to the residue and the mixture was extracted
15 with ethyl acetate (50 mL x 3). The combined organic layers were washed with aqueous ammonium chloride (30 mL), dried over Na₂SO₄, and filtered. The filtrate was evaporated under reduced pressure to give a residue, which was purified by column chromatography on silica gel (SiO₂), eluting with EA/PE= 1:20-1:5 to give the title compound.

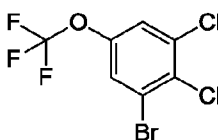
Step D *tert*-butyl-5-chloro-6-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydroisoquinoline
20 -2(1H)-carboxylate. To a stirred solution of *tert*-butyl 5-chloro-6-hydroxy-3,4-dihydroisoquinoline-2(1H) carboxylate (1.4g, 4.93 mmol) in CH₂Cl₂ (20 mL) was added pyridine (1.171 g, 14.8 mmol) and trifluoromethanesulfonic anhydride (2.09 g, 7.40 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature (20 °C) and stirred for 30 min. Then the solvent was removed by rotary evaporation, and the resulting mixture was
25 diluted with water (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were evaporated, and the resulting crude product was purified on silica gel (SiO₂, PE/EtOAc=20:1-10:1) to give the title compound.

Step E *tert*-butyl-6-(3-(*tert*-butoxy)-3-oxopropyl)-5-chloro-3,4-dihydroisoquinoline-2
(1H)-carboxylate. To a solution of *tert*-butyl 5-chloro-6-(((trifluoromethyl)sulfonyl)oxy)-3,4-
30 dihydroisoquinoline-2(1H)-carboxylate (0.92 g, 2.1 mmol) in toluene (20 ml) and H₂O (2 ml)

was added potassium 3-trifluoroboropropionate *tert*-butyl ester (0.49 g, 2.1 mmol) and sodium carbonate (0.66 g, 6.3 mmol), followed by the addition of G2Ruphos (75 mg, 0.1 mmol) under a N₂ atmosphere. The reaction mixture was stirred at 90°C for 12h, then poured into water (10 mL) and extracted with EA (30 mL×3). The combined organic layers were washed with water (10 mL×3), and dried over Na₂SO₄. After filtration and concentration, the resulting residue was purified by *prep*-HPLC (acid) to give the title compound.

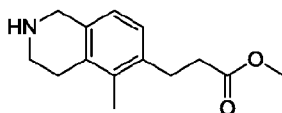
Step F methyl 3-(5-chloro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate. To a solution of *tert*-butyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate (395 mg, 1 mmol) in MeOH (10 mL) was added HCl-MeOH (5 mL, 3M). The mixture was stirred at 70°C for 4 h, then the reaction mixture was cooled to room temperature and concentrated to give the title compound. MS (ESI) *m/z*: 254 [M+H⁺]

Intermediate 53

1-bromo-2,3-dichloro-5-(trifluoromethoxy)benzene

1-bromo-2,3-dichloro-5-(trifluoromethoxy)benzene. A suspension of copper(II) chloride (403 mg, 3.00 mmol) and *tert*-butyl nitrite (309 mg, 3.00 mmol) in anhydrous MeCN (15 mL) was warmed to 65°C. Then a solution of 2-bromo-6-chloro-4-(trifluoromethoxy)aniline (870 mg, 3.00 mmol) in anhydrous MeCN (5 mL) was added dropwise. The reaction mixture was stirred for 1h at 65°C, then allowed to cool to 25°C and poured into 1 M HCl (15 mL). The acidic mixture was neutralized with saturated NaHCO₃ and aqueous ammonia (35%, 5 mL). The mixture was extracted with DCM (25 mL) and then washed with aqueous ammonia (17.5%, 20 mL) and brine (2 x 20 mL). The resulting crude product was purified by column (SiO₂, eluting with PE) to give the title compound.

Intermediate 54

methyl 3-(5-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate

Step A *tert*-butyl 5-methyl-6-oxo-3,4,6,7,8,8a-hexahydroisoquinoline-2(1H)-carboxylate. To a solution of *N*-Boc-4-piperidone (19.8 g, 9.92 mol) in toluene (400 ml) was added pyrrolidine (10.9 g, 1.55 equiv). The reaction was heated to reflux for 2 h and the water was removed by azeotropic distillation. The reaction was then concentrated *in vacuo* and cooled to 20 °C. Toluene (100 mL) was added to the residue, followed by a slurry of hydroquinone (64 mg, 0.5 mol %) in toluene (3 mL). The reaction was cooled to 10 °C, and ethyl vinyl ketone (8.30 g, 0.99 eq) was added. The solution was heated to 40 °C for 1 h and then heated to 105 °C for 18 h, before being cooled to 26~28 °C. The organic layer was washed with saturated NH₄Cl solution, followed by water (100 mL). The organic phase was concentrated to give a toluene solution, which was used directly in the next reaction.

Step B *tert*-butyl 5-methyl-6-((triethylsilyl)oxy)-3,4,8,8a-tetrahydroisoquinoline-2(1H)-carboxylate. To a solution of *tert*-butyl 5-methyl-6-oxo-3,4,6,7,8,8a-hexahydroisoquinoline-2(1H)-carboxylate (700 mg, 2.64 mmol) in THF (10 mL) was added LiHMDS (2 mL, 4 mmol) at 0 °C for 0.2 h. The reaction mixture was stirred at 0 °C for 5 h, then poured into ice water (30 mL) and extracted with EA (40 mL). The organic layer was washed with brine (20 mL), and dried over Na₂SO₄. After filtration, the solvent was concentrated to afford the title compound, which used in the next step without further purification.

Step C *tert*-butyl 6-hydroxy-5-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate. To a solution of *tert*-butyl 5-methyl-6-((triethylsilyl)oxy)-3,4,8,8a-tetrahydroisoquinoline-2(1H)-carboxylate (750 mg, 1.581 mmol) in THF (10 mL) was added Pd(OAc)₂ (426 mg, 1.897 mmol) at 10 °C. The reaction mixture was stirred at 20 °C for 10h, Then potassium formate (199 mg, 2.371 mmol) in water (0.5 mL) was added, and the mixture was stirred at 20 °C for 2 h. TBAF (0.790 ml, 0.790 mmol) was added to the reaction and the reaction was stirred at 20 °C for 2 h, then poured into ice water (30 mL) and extracted with EA (40 mL*2). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na₂SO₄. After filtration and concentration, the resulting residue was purified by flash chromatography (SiO₂), eluting with 0-20% EA in PE to give the title compound.

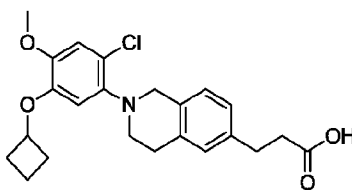
Step D *tert*-butyl 5-methyl-6-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate. To a solution of *tert*-butyl-6-hydroxy-5-methyl-3,4-dihydro-isoquinoline-2(1H)-carboxylate (230 mg, 0.873 mmol), pyridine (0.21 mL, 2.6 mmol) in DCM (5 mL) was added TiF_2O (0.18 mL, 1 mmol) at -35°C for 0.2 h. The mixture was stirred at -35°C for 1 h, then poured into ice HCl (0.5N, 10 mL) and extracted with EA (20 mL*2). The combined organic layers were washed with NaHCO_3 (10 mL) and brine (20 mL). After filtration, the filtrate was concentrated to give the title compound, which was used in the next step without further purification.

Step E *tert*-butyl-6-(3-(*tert*-butoxy)-3-oxopropyl)-5-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate. To a solution of *tert*-butyl 5-methyl-6-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.8 g, 4.55 mmol), potassium 3-trifluoroborate-propionate *tert*-butyl ester (3.22 g, 13.66 mmol), Na_2CO_3 (1.45 g, 13.66 mmol) in water (2 mL) and toluene (20 mL) was added G2-Ru-Phos (0.354 g, 0.455 mmol). The mixture was stirred at 100°C for 10 h, then the solvent was removed under reduced pressure. The resulting mixture was purified by *prep*-HPLC (TFA) to afford the title compound.

Step F methyl 3-(5-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate. The mixture of *tert*-butyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.2 g, 3.2 mmol) in HCl-MeOH (4M, 15 mL, 60 mmol) was stirred at 65°C for 10 h, then the solvent was removed under reduced pressure to give the title compound, which was used in the next step without further purification. MS (ESI) m/z : 254.1 $[\text{M}+\text{H}^+]$

EXAMPLE 1

3-(2-(2-chloro-5-cyclobutoxy-4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoic acid

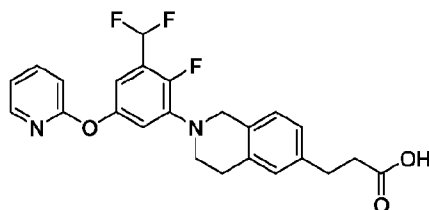


Step A. Methyl-3-(2-(2-chloro-5-cyclobutoxy-4-methoxyphenyl)-1,2,3,4-tetra-hydro-isoquinolin-6-yl)propanoate: Methyl-3-(1,2,3,4-tetrahydro-isoquinolin-

- 6-yl)-propanoate (100 mg, 0.456 mmol), 1-bromo-2-chloro-5-cyclobutoxy-4-methoxybenzene (Intermediate 20, 146 mg, 0.502 mmol), Cs₂CO₃ (297 mg, 0.912 mmol), Xantphos (53 mg, 0.092 mmol) and Pd₂(dba)₃ (42 mg, 0.046 mmol) in 1,4-dioxane (5 mL) were stirred at 90°C for 18 h under a N₂ atmosphere. The mixture was diluted with water (15 mL), extracted with EtOAc (3x20 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified via silica gel PTLC (PE:EtOAc=5:1) to afford the title compound. *m/z* 430.1 [M+1]⁺.
- Step-B. 3-(2-(2-chloro-5-cyclobutoxy-4-methoxyphenyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)propanoic acid: To a solution of methyl 3-(2-(2-chloro-5-cyclobutoxy-4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (60 mg, 0.140 mmol) in THF (4 mL) and water (2 mL), was added LiOH hydrate (12 mg, 0.286 mmol). Then the mixture was stirred at ~17°C for 2 h. After acidification to pH 2-3, the solvent was removed *in vacuo*. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 column (250x21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration (below 50 °C) *in vacuo* to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ 6.98-7.08 (m, 3H), 6.91 (s, 1H), 6.56 (s, 1H), 4.55 (q, *J*=7.14 Hz, 1H), 4.18 (s, 2H), 3.94 (s, 3H), 3.33 (t, *J*=7.48 Hz, 2H), 2.90-2.99 m, 4H), 2.68 (t, *J*=7.63 Hz, 2H), 2.28-2.38 (m, 2H), 2.18-2.26 (m, 2H), 1.82-1.84 (m, 1H), 1.60-1.68 (m, 1H); *m/z* =416.1 [M+1]⁺.

EXAMPLE 2

3-(2-(3-(difluoromethyl)-2-fluoro-5-(pyridin-2-yloxy)phenyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)propanoic acid



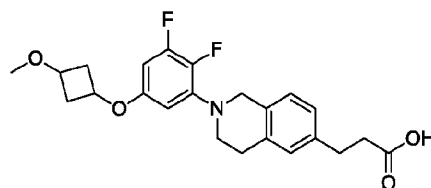
25

Step A. Methyl 3-(2-(3-(difluoromethyl)-2-fluoro-5-(pyridin-2-yloxy)phenyl)-

- 1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate: To a stirred solution of methyl 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (100 mg, 0.456 mmol) in 1,4-dioxane (3 mL) was added 2-(3-bromo-5-(difluoromethyl)-4-fluorophenoxy)pyridine (Intermediate 21, 160 mg, 0.502 mmol), 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (39 mg, 0.092 mmol) and
- 5 Cs₂CO₃ (223 mg, 0.684 mmol). The mixture was degassed with N₂, and Pd₂(dba)₃ (42 mg, 0.046 mmol) was added. The mixture was heated to 100°C and stirred for 18 h. The reaction mixture was diluted with EtOAc (5 mL) and filtered. The filtrate was concentrated *in vacuo* to afford the crude title compound, which was used in the next step without further purification.
- Step B. 3-(2-(3-(difluoromethyl)-2-fluoro-5-(pyridin-2-yloxy)phenyl)-1,2,3,4-
- 10 tetrahydroisoquinolin-6-yl)propanoic acid: To a stirred solution of methyl 3-(2-(3-(difluoromethyl)-2-fluoro-5-(pyridin-2-yloxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (80 mg, crude) in THF (5 mL) was added LiOH·H₂O (40 mg, 0.953 mmol) and water (2.5 mL). The mixture was stirred for 5 h at rt, and HCl (3N) was added to adjust the mixture to pH = 2-3. Then the mixture was diluted with EtOAc (20 mL). The organic layer was separated,
- 15 dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration (below 50 °C) *in vacuo* to afford the title compound. ¹H-NMR (400 MHz, CDCl₃) δ 8.19 (d, *J*=7.6 Hz, 1H), 7.72 (t, *J*=6.8 Hz, 1H), 7.02-6.91 (m, 4H), 6.89-6.76 (m, 1H), 4.28 (m, 2H), 3.46 (t, *J*=5.6 Hz, 2H), 2.97-2.90 (m, 2H), 2.69-2.65 (m, 2H); *m/z* = 443.0 [M+1]⁺.
- 20

EXAMPLE 3

- 3-(2-(2,3-difluoro-5-(3-methoxycyclobutoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-
- 25 propanoic acid (trans)

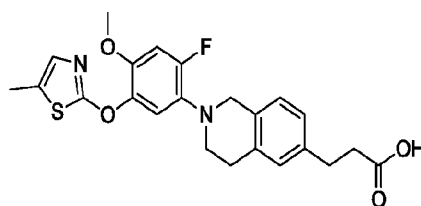


- Step A. Ethyl 3-(2-(2,3-difluoro-5-(3-methoxycyclobutoxy)phenyl)-1,2,3,4-

- tetrahydroisoquinolin-6-yl)propanoate (trans): To a solution of ethyl 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (84 mg, 0.359 mmol) in 1,4-dioxane (5 mL) was added 2,3-difluoro-5-(3-methoxycyclobutoxy)phenyl trifluoromethanesulfonate (Intermediate 4, 130 mg, 0.359 mmol), Cs₂CO₃ (351 mg, 1.077 mmol), XPhos (35 mg, 0.073 mmol) and Pd₂(dba)₃ (33 mg, 0.036 mmol). The mixture was stirred at 90°C for 15 h under a N₂ atmosphere. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water (20 mL) and extracted with EtOAc (3x30 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EtOAc=20:1 to 5:1) to afford the title compound. *m/z* 446.2 [M+1]⁺.
- Step-B- 3-(2-(2,3-difluoro-5-(3-methoxycyclobutoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid (trans): To a solution of ethyl 3-(2-(2,3-difluoro-5-(3-methoxycyclobutoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (20 mg, 0.045 mmol) in THF (2 mL), MeOH (2 mL) and Water (1 mL) was added LiOH hydrate (4 mg, 0.095 mmol). The mixture was stirred at rt for 2 h. After acidification with 1N HCl to pH=2, the solvent was removed *in vacuo*. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration (below 50 °C) *in vacuo* to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ7.05 (s, 2 H), 7.00 (s, 1 H), 6.12-6.22 (m, 2 H), 4.63 - 4.70 (m, 1 H), 4.29 (s, 2 H), 4.08-4.14 (m, 1 H), 3.48 (t, *J*=5.67 Hz, 2 H), 3.28 (s, 3 H), 2.87-2.97 (m, 4 H), 2.64-2.72 (m, 2 H), 2.32-2.39 (m, 4 H); *m/z* =418.1 [M+1]⁺.

EXAMPLE 4

- 3-(2-(2-fluoro-4-methoxy-5-((5-methylthiazol-2-yl)oxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid

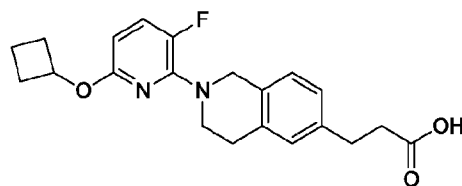


Step A. Methyl 3-(2-(2-fluoro-4-methoxy-5-((5-methylthiazol-2-yl)oxy)phenyl)-

- 1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate: To a solution of methyl 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (100 mg, 0.456 mmol) in dioxane (4.00 mL) was added 2-(5-bromo-4-fluoro-2-methoxyphenoxy)-5-methylthiazole (Intermediate 10, 214 mg, 0.673 mmol), Cs₂CO₃ (446 mg, 1.368 mmol), 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (40 mg, 0.094 mmol) and Pd₂(dba)₃ (42 mg, 0.046 mmol). Then the reaction mixture was placed under nitrogen and stirred at 100°C for 24 h. The mixture was concentrated *in vacuo*, and water (30 mL) was added to the residue. The mixture was extracted with EtOAc (30 mL×2), and the organic layer was concentrated *in vacuo*. The resulting crude product was purified by silica gel PTLC (PE/EtOAc=5:1) to give the title compound.
- Step B. 3-(2-(2-fluoro-4-methoxy-5-((5-methylthiazol-2-yl)oxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid: To a solution of methyl 3-(2-(2-fluoro-4-methoxy-5-((5-methylthiazol-2-yl)oxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (30 mg, 0.066 mmol) in THF (1 mL), MeOH (1 mL) and water (0.5 mL) was added LiOH hydrate (14 mg, 0.334 mmol). Then the reaction mixture was stirred at rt for 2 h. The mixture was acidified with HCl (0.25 mL, 6 N) and concentrated *in vacuo*. The crude product as purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration *in vacuo* to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ 6.94-7.04 (m, 4 H), 6.78-6.86 (m, 2 H), 4.19 (s, 2 H) 3.79 (s, 3 H), 3.35 (t, *J*=5.48 Hz, 2 H), 2.88-3.00 (m, 4 H), 2.62-2.70 (m, 2 H), 2.33 (s, 3 H); *m/z* =443.1 [M+1]⁺

EXAMPLE 5

3-(2-(6-cyclobutoxy-3-fluoropyridin-2-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoic acid



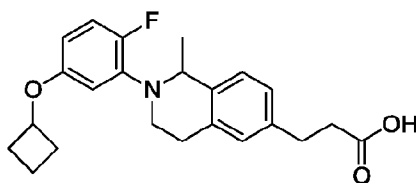
Step A. (methyl 3-(2-(6-cyclobutoxy-3-fluoropyridin-2-yl)-1,2,3,4-tetrahydroiso-

- quinolin-6-yl)propanoate: To a solution of 2-bromo-6-cyclobutoxy-3-fluoropyridine (Intermediate 2, 150 mg, 0.61 mmol) and ethyl 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (Intermediate 7, 142 mg, 0.61 mmol) in 1,4-dioxane (10 ml) was added Cs₂CO₃ (397 mg, 1.22 mmol) and XPhos precatalyst (45.0 mg, 0.06 mmol), and the mixture was stirred at 90°C for 18 h under a N₂ atmosphere. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL). The organic layer was collected, washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under *in vacuo*. The residue was purified by silica gel column chromatography (PE:EtOAc from 10:1 to 1:1) to afford the title compound.
- Step B. 3-(2-(6-cyclobutoxy-3-fluoropyridin-2-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid: A mixture of ethyl 3-(2-(6-cyclobutoxy-3-fluoropyridin-2-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (80 mg, 0.20 mmol) and LiOH hydrate (20 mg, 0.47 mmol) in THF (4 mL) and water (2 mL) was stirred at rt for 1 h. The mixture was acidified with 1 N HCl (10 mL) to pH=~6, and extracted with EtOAc (20 mL). The organic layer was separated, washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was further purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm), followed by concentration (below 50 °C) *in vacuo* to afford the title compound. ¹H NMR (400 MHz, CD₃OD) δ 7.16 (d, *J*=3.6 Hz, 1H), 7.13 (s, 1H), 7.08 (d, *J*=8.0 Hz, 1H), 7.03 (d, *J*=8.0 Hz, 1H), 6.01 (dd, *J*=1.6, 8.4 Hz, 1H), 5.02-4.95 (m, 1H), 4.61 (s, 2H), 3.78 (t, *J*=6.0 Hz, 2H), 2.96-2.92 (m, 4H), 2.69-2.66 (m, 2H), 2.42-2.40 (m, 2H), 2.18-2.14 (m, 2H), 1.82-1.81 (m, 1H), 1.70-1.69 (m, 1H); *m/z* =371.0 [M+1]⁺.

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EXAMPLE 6

3-(2-(5-cyclobutoxy-2-fluorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoic acid



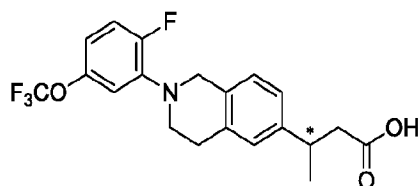
- Step A. methyl 3-(2-(5-cyclobutoxy-2-fluoro-4-nitrophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate: To a solution of methyl 3-(1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (Intermediate 45, 250 mg, 1.07 mmol) was added 1-cyclobutoxy-4,5-difluoro-2-nitrobenzene (Intermediate 3 Step B, 319 mg, 1.39 mmol) and Cs₂CO₃ (698 mg, 2.14 mmol). The mixture was heated at 150°C and stirred for 3 h. Then the reaction mixture was cooled to rt and EtOAc (20 mL) was added. The mixture was washed with brine, dried over Na₂SO₄ and evaporated *in vacuo*. The residue was purified by silica gel PTLC (PE:EtOAc=4:1) to afford the title compound.
- Step B. Methyl 3-(2-(4-amino-5-cyclobutoxy-2-fluorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate: To a solution of methyl 3-(2-(5-cyclobutoxy-2-fluoro-4-nitrophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (180 mg, 0.41 mmol) in MeOH (10 ml) was added Fe powder (114 mg, 2.03 mmol), NH₄Cl (109 mg, 2.03 mmol) and water (1 mL). The mixture was heated to reflux and stirred overnight. The mixture was filtered, and the filtrate was concentrated *in vacuo* to afford the title compound, which was taken to next step without further purification.
- Step C. methyl 3-(2-(5-cyclobutoxy-2-fluorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate: To a solution of methyl 3-(2-(4-amino-5-cyclobutoxy-2-fluorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (150 mg, 0.36 mmol) in dry THF (5 ml) was added isopentyl nitrite (128 mg, 1.09 mmol). The mixture was heated to reflux for 3 h. The reaction mixture was concentrated *in vacuo* to give the crude title compound, which was taken to next step without further purification.
- Step D. 3-(2-(5-cyclobutoxy-2-fluorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid: To a solution of methyl 3-(2-(5-cyclobutoxy-2-fluorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (150 mg, 0.38 mmol) in THF (3 ml) was added LiOH·H₂O (38 mg, 0.91 mmol) and water (1.5 ml). The final mixture was stirred overnight at rt. Then HCl (3 N aqueous solution) was added to adjust the pH to 2 - 3. The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength:

220 nm.) to afford the title compound. m/z 384.1 $[M + H]^+$. ^1H -NMR (400 MHz, $CDCl_3$) δ : 7.06 (m, 2 H), 6.96 (s, 1 H), 6.89 (m, 1 H), 4.75 (m, 1 H), 4.52 (m, 1 H), 3.47 (m, 1 H), 2.92-3.12 (m, 3 H), 2.66-2.75 (m, 3 H), 2.33 (m, 2 H), 2.17-2.25 (m, 2 H), 1.84 (m, 1 H), 1.81 (m, 1 H), 1.34 (d, $J=6.8$ Hz, 3 H).

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EXAMPLE 7

3-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)butanoic acid



Step A. ethyl 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)butanoate hydrochloride (slow eluting): To a solution of tert-butyl 6-(4-ethoxy-4-oxobutan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (92 mg, 0.265 mmol) in MeOH (3 ml) was added 4 M HCl (1 mL, 4.0 mmol) and stirred 15°C for 1 h. The mixture was concentrated *in vacuo*, to give the crude product which was used directly in the next step without further purification. m/z 247.1 $[M + H]^+$.

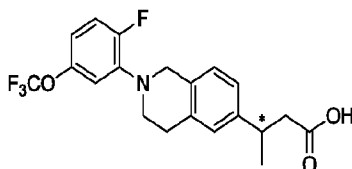
Step B. ethyl 3-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-butanoate: To a solution of ethyl 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)butanoate hydrochloride from the previous step (65 mg, 0.255 mmol) and 2-bromo-1-fluoro-4-(trifluoromethoxy)benzene (66 mg, 0.255 mmol) in dioxane (3 mL) was added XANTPHOS (25 mg, 0.043 mmol) and $Pd_2(dba)_3$ (49 mg, 0.054 mmol), followed by the addition of Cs_2CO_3 (138 mg, 0.423 mmol). The reaction mixture was stirred at 100°C under a N_2 atmosphere for 12 h. The reaction mixture was partitioned between EtOAc (50 mL) and water (50 mL), and the organic layer was washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude title compound was used in the next step without further purification. m/z 426.1 $[M+H]^+$.

Step C. 3-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)butanoic acid: To a solution of ethyl 3-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)butanoate (20 mg, 0.047 mmol) in THF-MeOH- H_2O (2:2:1 2.5 mL) was added LiOH hydrate (2 mg, 0.048 mmol) at 25°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was acidified

with diluted 1 M HCl until pH <5 . The reaction mixture was partitioned between EtOAc (20 mL) and water (20 mL), and the separated organic layer was washed with brine (20 mL). The organic layer was concentrated *in vacuo*. The crude product was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μ m) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm), followed by concentration (below 50 °C) *in vacuo* to give the title compound. ¹HNMR (400 MHz, CDCl₃) δ : 7.00-7.09 (m, 4 H) 6.83 (d, *J*=6.65 Hz, 1 H) 6.77 (d, *J*=8.22 Hz, 1 H) 4.28 (s, 2 H) 3.46 (t, *J*=5.67 Hz, 2 H) 3.21-3.30 (m, 1 H) 3.00 (t, *J*=5.48 Hz, 2 H) 2.56-2.72 (m, 2 H) 1.32 (d, *J*=6.65 Hz, 3 H). MS *m/z* 397. 1 [M + H]⁺.

EXAMPLE 8

3-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)-butanoic acid

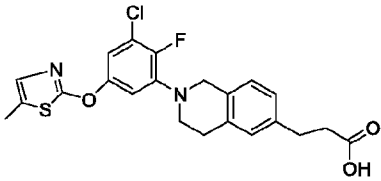
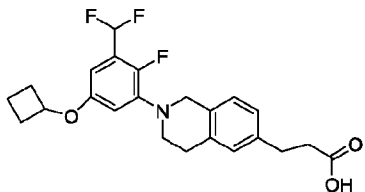


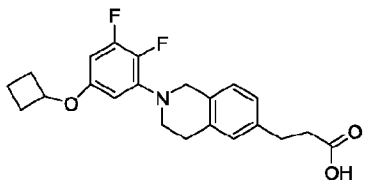
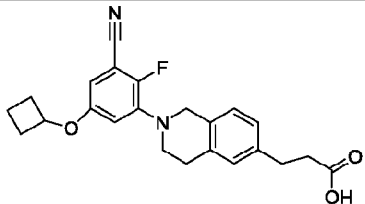
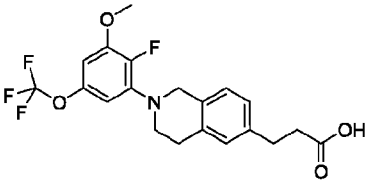
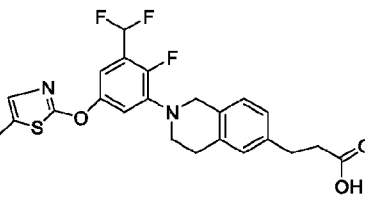
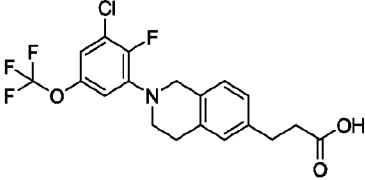
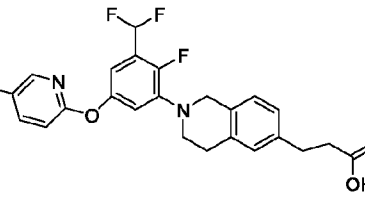
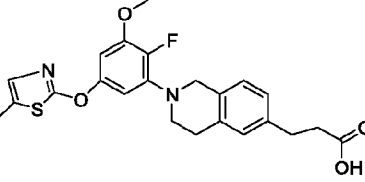
- Step A-ethyl 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)butanoate hydrochloride (slow eluting): To a solution of tert-butyl 6-(4-ethoxy-4-oxobutan-2-yl)-3,4-dihydro isoquinoline-2(1H)- carboxylate (92 mg, 0.265 mmol, slower eluting) in MeOH (3 mL) was added 4M HCl (1 mL, 4.00 mmol) and stirred 15°C for 1 h. The mixture was evaporated *in vacuo*, to give the crude title compound which was used in the next step without further purification. *m/z* 247.1 [M+H]⁺.
- Step B. Ethyl-3-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydro- isoquino- lin-6-yl)butanoate: To a solution of ethyl 3-(1,2,3,4- tetrahydroisoquinolin-6- yl)butanoate hydrochloride (65 mg, 0.229 mmol) and 2-bromo-1-fluoro-4-(trifluoro- methoxy)benzene (71 mg, 0.274 mmol) in dioxane (3 ml) was added XANTPHOS (3 mg, 0.005 mmol), Pd₂(dba)₃ (49 mg, 0.054 mmol) and Cs₂CO₃ (149 mg, 0.458 mmol). The the mixture stirred at 100°C under N₂ atmosphere for 12 h. The reaction mixture was partitioned between EtOAc (50 mL) and water (50 mL), and the organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude title compound was used in the next step without further purification. *m/z* 426.1 [M+H]⁺.

Step C. 3-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)butanoic acid (peak 2): To a solution of crude ethyl 3-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)butanoate (20 mg, 0.047 mmol) in THF-MeOH-H₂O (2:2:1, 2.5 mL) was added LiOH hydrate (2 mg, 0.048 mmol) at 25°C, and the mixture was stirred at 25 °C for 2 h. The mixture was concentrated *in vacuo*, and the resulting residue was acidified with diluted 1 M HCl until pH <5. The reaction mixture was partitioned between EtOAc (20 mL) and water (20 mL), and the organic layer was washed with brine (20 mL). The organic layer was concentrated *in vacuo*, and the crude product was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration (below 50 °C) *in vacuo* to obtain the title compound. ¹HNMR (400 MHz, ppm) δ: 7.06 (s, 2 H) 7.00-7.05 (m, 2 H) 6.83 (d, *J*=7.04 Hz, 1 H) 6.77 (d, *J*=8.61 Hz, 1 H) 4.27 (s, 2 H) 3.45 (t, *J*=5.67 Hz, 2 H) 3.25 (br. s., 1 H) 2.99 (t, *J*=5.28 Hz, 2 H) 2.67 (br. s., 2 H) 1.32 (d, *J*=5.87 Hz, 3 H); *m/z* 397. 1 [M+H]⁺.

The examples in Table 1 were prepared from the appropriate starting materials described previously or commercially available starting materials available using procedures described in Examples 1-8.

Table 1

Example	Structure	Name	[M+H] ⁺
9		3-(2-(2-chloro-5-[(5-methyl-1,3-thiazol-2-yl)oxy]phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	447.0
10		3-(2-(2-[5-(cyclobutyloxy)-3-(difluoromethyl)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	420.1

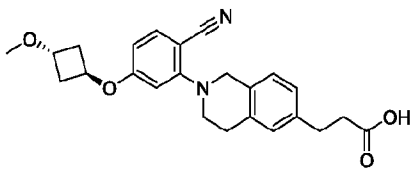
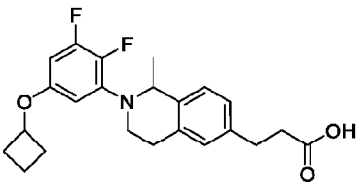
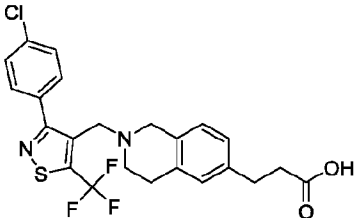
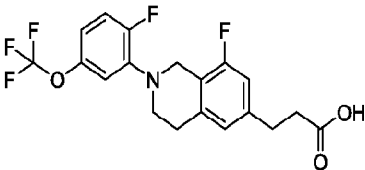
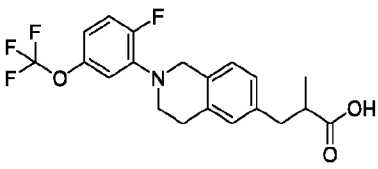
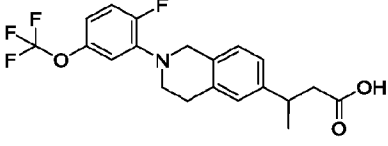
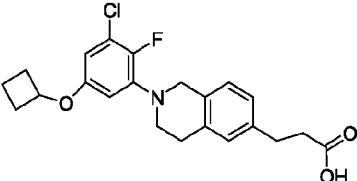
Example	Structure	Name	[M+H] ⁺
11		3-{2-[5-(cyclobutyloxy)-2,3-difluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	388.1
12		3-{2-[3-cyano-5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	395.1
13		3-{2-[2-fluoro-3-methoxy-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	413.1
14		3-(2-{3-(difluoromethyl)-2-fluoro-5-[(5-methyl-1,3-thiazol-2-yl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	463.1
15		3-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	418.0
16		3-(2-{3-(difluoromethyl)-2-fluoro-5-[(5-methylpyridin-2-yl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	457.1
17		3-(2-{2-fluoro-3-methoxy-5-[(5-methyl-1,3-thiazol-2-yl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	443.2

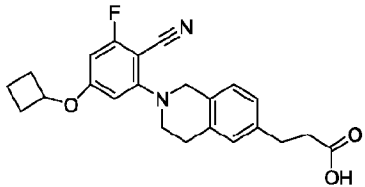
Example	Structure	Name	[M+H] ⁺
18		3-{2-[5-(cyclobutyloxy)-2-fluoro-3-methoxyphenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	400.1
19		3-{2-[5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	370.1
20		3-(2-{2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	418.1
21		3-(2-{2-fluoro-4-methoxy-5-[(5-methyl-1,3-thiazol-2-yl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	443.1
22		3-{2-[4-chloro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	410.1
23		3-{2-[5-(cyclobutylmethyl)-2-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	386.2
24		3-{2-[2-chloro-5-(cyclobutyloxy)-4-methoxyphenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	416.1
25		3-{2-[6-(cyclobutyloxy)-3-fluoropyridin-2-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	371.0

Example	Structure	Name	[M+H] ⁺
26		3-{2-[2-(cyclobutylsulfanyl)-5-fluoropyridin-4-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	387.1
27		3-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	384.3
28		3-(2-{2-fluoro-4-methoxy-5-[(5-methylpyridin-2-yl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	437.1
29		3-{2-[6-fluoro-3-(trifluoromethyl)-1,2-benzisoxazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	409.0
30		3-{7-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	402.1
31		3-{2-[5-(cyclobutyloxy)-2-fluoro-4-methoxyphenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	400.1
32		3-{2-[5-(cyclobutyloxy)-2,3-difluorophenyl]-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	402.1
33		3-{2-[2-fluoro-5-(pyrazin-2-yloxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	394.1

Example	Structure	Name	[M+H] ⁺
34		3-(2-{3-cyano-2-fluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	425.4
35		3-(2-{3-(difluoromethyl)-2-fluoro-5-[(5-fluoropyridin-2-yl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	461.1
36		3-{2-[5-(cyclobutyloxy)-2-fluorophenyl]-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	384.2
37		3-{2-[2-chloro-5-(cyclobutyloxy)-3-fluorophenyl]-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	418.1
38		3-{2-[6-(cyclobutylsulfanyl)pyridin-2-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	369.1
39		3-{2-[5-(cyclobutyloxy)-2-fluorophenyl]-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	384.1
40		3-{2-[3,5-dichloro-4-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	

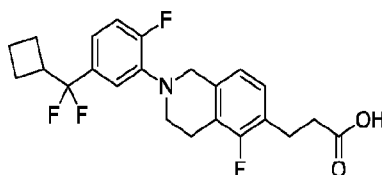
Example	Structure	Name	[M+H] ⁺
41		3-{2-[6-(cyclobutyloxy)pyrazin-2-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	354.1
42		3-{2-[2-cyano-5-(cyclobutyloxy)-4-methoxyphenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	407.2
43		3-{2-[4-cyano-1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	417.3
44		3-{2-[2-cyano-3-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	409.1
45		3-{2-[2-chloro-5-(cyclobutyloxy)-3-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	404.1
46		3-{2-[2-cyano-5-(cyclobutyloxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	395.1
47		3-{2-[4-fluoro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	394.2

Example	Structure	Name	[M+H] ⁺
48		3-(2-{2-cyano-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoic acid	407.2
49		3-{2-[5-(cyclobutyloxy)-2,3-difluorophenyl]-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid	402.1
50		3-(2-{[3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-yl]methyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	481.1
51		3-{8-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid	402.1
52		3-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-2-methylpropanoic acid	398.1
53		3-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}butanoic acid	398.1
54		3-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	404.1

Example	Structure	Name	[M+H] ⁺
55		3-{2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	395.0

EXAMPLE 56

3-(2-(5-(cyclobutyldifluoromethyl)-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid



5

Step A. Ethyl-3-(2-(5-(cyclobutyldifluoromethyl)-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate. To a solution of ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (Intermediate 42, 100 mg, 0.398 mmol) in 1,4-dioxane (5 mL), were added 2-bromo-4-(cyclobutyldifluoromethyl)-1-fluorobenzene (111 mg, 0.398 mmol), Cs₂CO₃ (389 mg, 1.194 mmol) and X-Phos precatalyst (30 mg, 0.041 mmol), then the mixture was stirred at 90 °C for 18 h under N₂. After completion of the reaction according to TLC (PE:EtOAc = 10 :1), the solvent was removed under reduced pressure. The residue was diluted with water (20 mL), and extracted with EtOAc (2 x 30 mL). The organic layer was dried over Na₂SO₄, filtrated and concentrated. The residue was purified by silica gel chromatography (PE:EtOAc=30:1) to afford the title compound. *m/z* =450.2 [M+1]⁺.

15

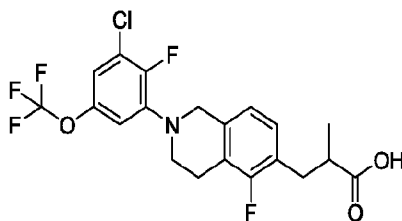
Step-B. 3-(2-(5-(cyclobutyldifluoromethyl)-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid. To a solution of ethyl 3-(2-(5-(cyclobutyldifluoromethyl)-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (60 mg,

0.133 mmol) in THF (2 mL), MeOH (2 mL) and water (1 mL), was added LiOH hydrate (12 mg, 0.286 mmol), then the mixture was stirred at r.t. (ca. 27 °C) for 2 h. After acidification with 1N HCl to pH=0.02, the solvent was removed under reduced pressure. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration (below 50 °C) to obtain the title compound. ¹H NMR (400 MHz, CDCl₃) δ 6.98 - 7.12 (m, 4 H), 6.86 (d, *J*=7.83 Hz, 1 H), 4.27 (s, 2 H), 3.44 (t, *J*=5.87 Hz, 2 H), 2.87 - 3.03 (m, 5 H), 2.69 (t, *J*=7.63 Hz, 2 H), 2.15 - 2.25 (m, 2 H), 1.85 - 1.99 (m, 4 H); *m/z* =422.1 [M+1]⁺.

10

EXAMPLE 57

3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-methylpropanoic acid



15 Step A. ethyl 3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanoate: To a solution of ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methyl propanoate (Intermediate 47, 300 mg, 1.131 mmol) in THF (10 mL) were added 1-bromo-3-chloro-2-fluoro-5- (trifluoromethoxy)-benzene (Intermediate 5, 398 mg, 1.357 mmol), sodium 2-methylpropan- 2-olate (1.1 mL, 2.200 mmol, 2 M, THF solution) and t-Buxphos-precatalyst (116 mg, 0.170 mmol)) at rt. Then the reaction mixture was placed under nitrogen atmosphere and stirred at 40 °C for 15 h. The mixture was diluted with water (25 mL), extracted with EtOAc (40 mL× 2), and the organic layer was evaporated. The crude product was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water 20 (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile 25

phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration (below 50 °C) to obtain the title compound.

Step B. tert-butyl ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methyl- propanoate: To a solution of ethyl 3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)- phenyl)-

5 5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanoate (300 mg, 0.565 mmol) in THF (6 mL) and water (3 mL) was added LiOH hydrate (119 mg, 2.83 mmol). The reaction mixture was stirred at rt for 4 h. The mixture was acidified to pH~2 with HCl (2 mL, 1 N), extracted with EtOAc (20 mL×2), and the organic layer was evaporated to give the title compound, which was used directly in next step without further purification.

10 Step C. 3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydro-isoquinolin-6-yl)-2-methylpropanoyl chloride. To a solution of 3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4 -tetrahydroisoquinolin-6-yl)-2-methylpropanoic acid (250 mg, 0.365 mmol) in DCM (10 mL) was added SOCl₂ (0.5ml, 6.85 mmol) with stirring at -78°C. The mixture was placed under a N₂ atmosphere and stirred at
15 overnight (~18 h). The reaction mixture was concentrated *in vacuo* to give the title compound, which was directly used in the next step without further purification.

Step D. (4R)-4-benzyl-3-(3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanoyl)oxazolidin-2-one. To a solution of
(R)-4-benzyloxazolidin-2-one (91 mg, 0.513 mmol) in THF (10 mL) was added NaH (28 mg,
20 0.700 mmol) (60% in NaH) with stirring at 0°C. The mixture was placed under N₂ atmosphere and stirred at rt for about 30 min. Then a solution of 3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydro- isoquinolin-6-yl)-2-methylpropanoyl chloride (160 mg, 0.342 mmol) in THF (2 mL) was added dropwise at rt. The mixture was stirred at rt for about 2 h. The reaction mixture was diluted with water (10 mL) and EtOAc (15
25 mL), and was stirred for about 10 min at rt (15 °C). Then the organic layer was separated and washed with water (2 x 10 mL), brine (2 x 10 mL), dried (Na₂SO₄) and filtered. The filtrate was concentrated to give crude product, which was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile
30 phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration (below 50 °C) to obtain the title compound.

Step E. (4R)-4-benzyl-3-(3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanoyl)oxazolidin-2-one.

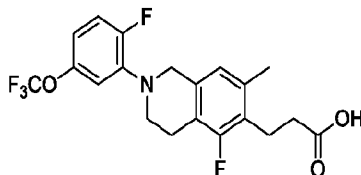
(4R)-4-benzyl-3-(3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanoyl)oxazolidin-2-one (90 mg, 0.145 mmol) was separated by SFC-HPLC on Chiralpak AD-3 150×4.6mm I.D., 3µm Mobile phase: A: CO₂ B:methanol (0.05% DEA) Gradient: from 5% to 40% of B in 5.0 min and hold 40% for 2.5 min, then 5% of B for 2.5 min Flow rate: 2.5mL/min Column temperature: 35 °C Wavelength: 220nm to give (4R)-4-benzyl-3-(3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanoyl)oxazolidin-2-one and (4R)-4-benzyl-3-(3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanoyl)oxazolidin-2-one.

Step F. 3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanoic acid. To a solution of (4R)-4-benzyl-3-(3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanoyl)oxazolidin-2-one (30 mg, 0.046 mmol) in THF (4 mL) and water (2 mL) at 0 °C was added dropwise a solution of lithium peroxide prepared by adding H₂O₂ (0.065 mL, 0.741 mmol) to LiOH hydrate (6 mg, 0.143 mmol) in water (0.2 mL). The reaction mixture was stirred for 0 °C for 1 h and then quenched with saturated aqueous Na₂SO₃ (0.5 mL). The mixture was diluted with water (10 mL) and acidified with 1 N HCl to pH=2, and extracted with EtOAc (2 x 10 mL). The EtOAc extracts were combined, washed with brine (5 mL), dried over anhydrous MgSO₄, and concentrated. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 µm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm), followed by concentration (below 50°C) to obtain the title compound. *m/z* 450.2 [M+H]⁺, ¹H NMR (400 MHz, CD₃OD) δ ppm 7.05 (t, *J*=7.63 Hz, 1 H) 7.00 (br. s., 1 H) 6.87-6.94 (m, 2 H) 4.26 (s, 2 H) 3.46 (t, *J*=5.67 Hz, 2 H) 2.95 (d, *J*=6.06 Hz, 1 H) 2.87-2.93 (m, 2 H) 2.66-2.74 (m, 2 H) 1.12 (d, *J*=6.26 Hz, 3 H).

EXAMPLE 58

3-(5-fluoro-2-(2-fluoro-5-(trifluoromethoxy)phenyl)-7-methyl-1,2,3,4-tetra-

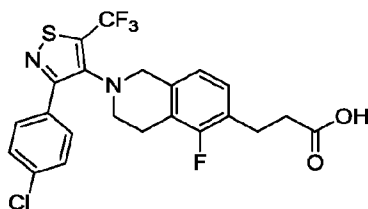
hydroisoquinolin-6-yl)propanoic acid



- Step A. ethyl 3-(5-fluoro-2-(2-fluoro-5-(trifluoromethoxy)phenyl)-7-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate. To a solution of ethyl 3-(5-fluoro-7-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (Intermediate 48, 100 mg, 0.377 mmol) and 2-bromo-1-fluoro-4-(trifluoromethoxy)benzene (117 mg, 0.452 mmol) in dioxane (3 mL) were added Xphos-precatalyst (32 mg, 0.039 mmol) and Cs₂CO₃ (368 mg, 1.131 mmol). The mixture was stirred at 90 °C for 16 h. Then water (100 mL) was added. The mixture was extracted with EtOAc (2x50 mL), washed with water (200 mL), dried over anhydrous Na₂SO₄ filtered, concentrated *in vacuo* and purified by silica gel column chromatography (PE/EtOAc=50:1 to 20:1) to give the title compound. ESI MS *m/z* 444.1 [M + H]⁺.
- Step B. 3-(5-fluoro-2-(2-fluoro-5-(trifluoromethoxy)phenyl)-7-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid. To a solution of ethyl 3-(5-fluoro-2-(2-fluoro-5-(trifluoromethoxy)phenyl)-7-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (127 mg, 0.286 mmol) in THF (6 ml) and water (3 ml) was added LiOH hydrate (12 mg, 0.286 mmol). The mixture was stirred at 20 °C for 2 h, then acidified with HCl (6 N, about 3 mL). The mixture was extracted with EtOAc (2 x 20 mL), washed with water (20 mL), dried over anhydrous Na₂SO₄, and evaporated. The crude product was purified with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm.) followed by concentration to obtain the title compound. ¹H NMR (400 MHz, CDCl₃) ppm δ 2.33 (s, 3 H) 2.55 - 2.64 (m, 2 H) 2.91 (t, *J*=5.51 Hz, 2 H) 2.98 (t, *J*=7.83 Hz, 2 H) 3.44 (t, *J*=5.84 Hz, 2 H) 4.22 (s, 2 H) 6.74 (s, 1 H) 6.76 - 6.85 (m, 2 H) 7.04 (dd, *J*=11.80, 8.71 Hz, 1 H); ESI MS *m/z* 416.1 [M + H]⁺

EXAMPLE 59

3-(2-(3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid

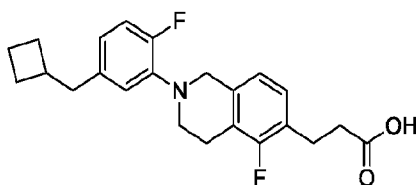


Step A. Ethyl 3-(2-(3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate A solution of ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (53 mg, 0.211 mmol), 4-bromo-3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazole (60 mg, 0.175 mmol) in dioxane (1.00 mL) was treated with Xantphos (30 mg, 0.035 mmol) and Cs_2CO_3 (170 mg, 0.525 mmol), and then heated at 100 °C for 16 h. The mixture was concentrated under reduced pressure to give a residue, which was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH_3CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH_3CN , Detector wavelength: 220 nm) followed by concentration (below 50 °C) to obtain the title compound.

Step B. 3-(2-(3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid. To a solution of ethyl 3-(2-(3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (1 mg, 1.950 μmol) in THF (1 ml), EtOH (1 ml) and water (0.5 ml), was added LiOH hydrate (1 mg, 0.024 mmol). The mixture was stirred at 30 °C for 15 h. After acidification with 1N HCl to pH=2, the solvent was removed under reduced pressure. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250*21.2 mm*4 μm) using water (0.2% Formic acid) and CH_3CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH_3CN , Detector wavelength: 220 nm) followed by concentration (below 50 °C) to obtain the title compound. m/z 485.1 $[\text{M}+\text{H}]^+$; ^1H NMR (400 MHz, CDCl_3) δ ppm 7.80 (d, $J=8.60$ Hz, 2 H) 7.25 (d, $J=8.38$ Hz, 2 H) 6.90-6.98 (m, 1 H) 6.58 (d, $J=7.94$ Hz, 1 H) 4.05 (s, 2 H) 3.30 (t, $J=5.51$ Hz, 2 H) 2.88-2.95 (m, 2 H) 2.75 - 2.83 (m, 2 H) 2.61-2.68 (m, 2 H).

EXAMPLE 60

3-(2-(5-(cyclobutylmethyl)-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid

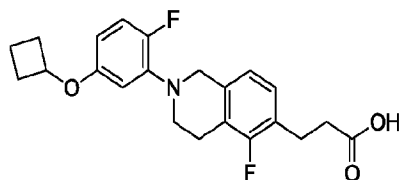


Step A-ethyl 3-(2-(5-(cyclobutylmethyl)-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate: To a solution of ethyl 3-(5-fluoro-1,2,3,4-tetrahydro-isoquinolin-6-yl)propanoate (100 mg, 0.398 mmol) in dioxane (6 mL) was added 2-bromo-4-(cyclobutylmethyl)-1-fluorobenzene (Intermediate 41, 97 mg, 0.398 mmol), Cs₂CO₃ (389 mg, 1.194 mmol) and XPHOS-precatalyst (32 mg, 0.041 mmol). The reaction mixture was placed under a N₂ atmosphere and heated to 90°C for 18 h. The solvent was removed *in vacuo* and the resulting mixture was diluted with water (20 mL) and extracted with EtOAc (2x20mL), dried, filtered and the concentrated *in vacuo*. The crude product was purified by silica gel chromatography (PE/EtOAc=40:1) to give the title compound. *m/z* 414.1[M + H]⁺.

Step-B. 3-(2-(5-(cyclobutylmethyl)-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid. To a solution of ethyl 3-(2-(5-(cyclobutylmethyl)-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (80 mg, 0.193 mmol) in THF (4 mL) and water (2 mL) was added LiOH hydrate (40 mg, 0.953 mmol). Then the reaction mixture was stirred at rt for 18 h. The mixture was acidified to pH~2 with HCl (0.7 mL, 1 N) and concentrated *in vacuo*. The crude product was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration to give the title compound. ¹HNMR (400 MHz, ppm) δ 7.04 (t, *J*=7.65 Hz, 1 H), 6.97 (dd, *J*=12.05, 8.28 Hz, 1 H), 6.80 - 6.91 (m, 3 H), 4.25 (s, 2 H), 3.42 (t, *J*=5.90 Hz, 2 H), 2.89-3.00 (m, 5 H), 2.69 (t, *J*=7.78 Hz, 2 H), 2.02 - 2.09 (m, 2 H), 1.76 - 1.84 (m, 2 H), 1.66-1.73 (m, 2 H), 1.50-1.60 (m, 2 H). *m/z* 386.2 [M + H]⁺.

EXAMPLE 61

3-(2-(5-(cyclobutoxy-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoic acid



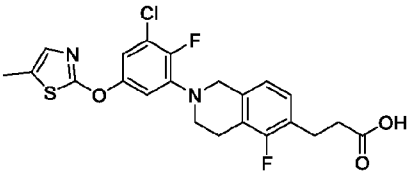
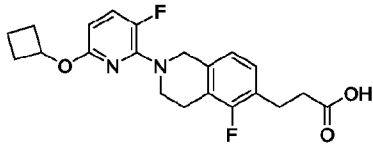
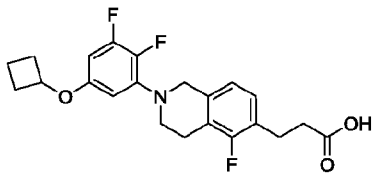
- Step A-(E)-ethyl 3-(6-chloroquinolin-2-yl)acrylate: To a solution of 6-bromo-5-fluoroisoquinoline (210 mg, 0.929 mmol) in dry 1,4-dioxane (10 ml) was added tri-*tert*-butylphosphonium tetrafluoroborate (51 mg, 0.176 mmol), dicyclohexylamine (253 mg, 1.394 mmol), and ethyl acrylate (112 mg, 1.115 mmol). Then the mixture was degassed for 5 min with N₂. Then Pd₂(dba)₃ (85 mg, 0.093 mmol) was added. The final mixture was heated to 100°C and stirred for 18 h in a N₂ atmosphere. The reaction mixture was diluted with EtOAc (20 mL). The solid was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE/EtOAc= 20:1 to 3:1) to afford the title compound.
- Step B. ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate. To a solution of (*E*)-ethyl 3-(5-fluoroisoquinolin-6-yl)acrylate (220 mg, 0.897 mmol) in MeOH (20 ml) was added platinum (IV) oxide (40 mg, 0.176 mmol). The reaction mixture was stirred under 50 psi of hydrogen atmosphere at 30°C for 5 hours. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give the title compound.
- Step C. Ethyl 3-(2-(5-cyclobutoxy-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydro- isoquinolin-6-yl)propanoate. To a solution of ethyl 3-(5-fluoro-1,2,3,4-tetrahydro- isoquinolin-6-yl)propanoate (100 mg, 0.398 mmol) in 1,4-dioxane (5 ml) was added 2-bromo-4-cyclobutoxy-1-fluorobenzene (117 mg, 0.478 mmol), Cs₂CO₃ (194 mg, 0.597 mmol), XANTPHOS (46 mg, 0.080 mmol) and Pd₂(dba)₃ (36 mg, 0.039 mmol). Then the reaction mixture was placed under nitrogen and stirred for 20 min at 100°C under microwave. The mixture was concentrated *in vacuo*, then water (10 mL) was added and extracted with EtOAc (2 x10 mL). The combined organic layers were concentrated *in vacuo*, and the crude product was purified by silica gel preparative TLC (PE/EtOAc=2:1) to give the title compound.
- Step D. 3-(2-(5-cyclobutoxy-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydro- isoquinolin-6-yl)propanoic acid: To a solution of ethyl 3-(2-(5-cyclobutoxy-2- fluoro-phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (20 mg, 0.048 mmol) in THF (2.00 mL), MeOH (2.00 mL) and water (1.00 mL) was added LiOH (6 mg, 0.251 mmol). Then the reaction mixture

was stirred at rt for 3 h. The mixture was acidified with HCl (0.5 mL, 6 N) and concentrated *in vacuo*. The crude product was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μ m) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ 6.97 (t, *J*=7.4 Hz, 1H), 6.86 (dd, *J*=8.8, 11.9 Hz, 1H), 6.76 (d, *J*=7.8 Hz, 1H), 6.45-6.38 (m, 1H), 6.28-6.21 (m, 1H), 4.52-4.44 (m, 1H), 4.16 (s, 2H), 3.35 (t, *J*=5.7 Hz, 2H), 2.94-2.80 (m, 4H), 2.61 (t, *J*=7.0 Hz, 2H), 2.37-2.28 (m, 2H), 2.11-2.01 (m, 2H), 1.77 (d, *J*=10.2 Hz, 1H), 1.64-1.56 (m, 1H). *m/z* = 388.1 [M + H]⁺.

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The examples in Table 2 were prepared from the appropriate starting materials described previously or commercially available starting materials available using procedures described in Examples 56-61.

15 Table 2

Example	Structure	Name	[M+H] ⁺
62		3-(2-{3-chloro-2-fluoro-5-[(5-methyl-1,3-thiazol-2-yl)oxy]phenyl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	465.0
63		3-{2-[6-(cyclobutyl)oxy]-3-fluoropyridin-2-yl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	389.1
64		3-{2-[5-(cyclobutyl)oxy]-2,3-difluorophenyl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	406.1

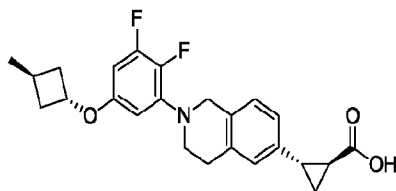
Example	Structure	Name	[M+H] ⁺
65		3-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	436.0
66		3-(2-{2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	436.1
67		3-(2-{5-[cyclobutyl(difluoro)methyl]-2-fluorophenyl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	422.1
68		3-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}-2-methylpropanoic acid	450.0
69		3-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}-2-methylpropanoic acid	450.1
70		3-{5-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-7-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	416.1
71		3-{2-[4-chloro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	428.1

Example	Structure	Name	[M+H] ⁺
72		3-{5-chloro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroiso-quinolin-6-yl}propanoic acid	418.1
73		3-{2-[3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-yl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid	485.1
74		3-{2-[5-(cyclobutylmethyl)-2-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	386.2
75		3-[2-(5-{[3-(difluoromethyl)cyclobutyl]oxy}-2,3-difluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl]-propanoic acid	456.1
76		3-{2-[2-cyano-5-(cyclobutyloxy)-phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	395.1
77		3-{5-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-2-methylpropanoic acid	416.1
78		3-{2-[2-cyano-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	409.1

Example	Structure	Name	[M+H] ⁺
79		3-(2-(2-cyano-5-cyclobutoxy-3-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methylpropanoic acid	425.1
80		3-{5-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	402.0
81		3-{2-[5-(cyclobutyloxy)-2-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	388.1
82		3-{2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	395.0

EXAMPLE 83

(1S,2S)-2-(2-(2,3-difluoro-5-((1R,3S)-3-methylcyclobutoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid



5

Step A. (1S,2S)-ethyl 2-(2-(2,3-difluoro-5-((1R,3S)-3-methylcyclobutoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate. To a solution of 2,3-difluoro-5-((1R,3R)-3-methylcyclobutoxy)phenyl trifluoromethanesulfonate (200 mg, 0.578 mmol) in dioxane (4 mL) were added (1S,2S)-ethyl 2-(1,2,3,4-tetrahydroisoquinolin-6-yl)-cyclopropanecarboxylate (156 mg, 0.635 mmol), Cs₂CO₃ (565 mg, 1.733 mmol) and RUPHOS precatalyst (94 mg, 0.116 mmol). After the addition was complete, the mixture was stirred under argon at 90°C for 15 h. The reaction mixture was filtered, washed with water (2 x 20 mL),

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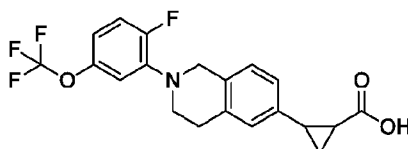
extracted with EtOAc (3 x 20 mL). The combined organic layers were evaporated *in vacuo* to give crude product, which was further purified by silica gel preparative TLC (PE:EtOAc=10:1 as elute) to give the title compound. ESI MS m/z =442.1 $[M+1]^+$.

Step B. (1S,2S)-2-(2-(2,3-difluoro-5-((1r,3S)-3-methylcyclobutoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid. To a solution of (1S,2S)-ethyl 2-(2-(2,3-difluoro-5-((1r,3S)-3-methylcyclobutoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-cyclopropanecarboxylate (20 mg, 0.045 mmol) in MeOH (2 mL), THF (2mL) and water (1 mL) was added LiOH hydrate (10 mg, 0.238 mmol) and stirred at rt for 15 h. The mixture was acidified by the diluted hydrochloride acid (1N) to pH~2. The mixture was concentrated *in vacuo* to give crude product. The crude product was further purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μ m) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm), then concentrated on a lyophilizer to afford the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.04 (d, J =7.78 Hz, 1 H), 6.88 - 6.98 (m, 2 H), 6.12 - 6.24 (m, 2 H), 4.66 (t, J =6.15 Hz, 1 H), 4.27 (s, 2 H), 3.45 (t, J =5.77 Hz, 2 H), 2.94 (t, J =5.52 Hz, 2 H); 2.53 - 2.63 (m, 1 H), 2.40 - 2.52 (m, 1 H), 2.25 - 2.34 (m, 2 H), 2.02 - 2.10 (m, 2 H), 1.89 (dt, J =8.34, 4.49 Hz, 1 H), 1.65 (dt, J =9.54, 4.77 Hz, 1 H), 1.36 - 1.45 (m, 1 H), 1.19 (d, J =7.03 Hz, 3 H); ESI MS m/z =414.1.

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EXAMPLE 84

2-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-cyclopropanecarboxylic acid



Step A. *tert*-butyl 6-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate: To a stirred solution of *tert*-butyl 6-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.5 g, 4.80 mmol) in THF (30 mL) was added 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (0.740 g, 4.80 mmol), triphenylphosphine (1.260 g, 4.80 mmol) and potassium 2-methyl- propan-2-olate (0.027 g, 0.240 mmol). The mixture was stirred at 67°C for 24 h. The mixture was washed with water (2 x

10 mL) and extracted with EtOAc (2 x30 mL). The extract was dried over by Na₂SO₄ filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE:EtOAc=20 :1) to give the title compound.

Step B. 6-vinyl-1,2,3,4-tetrahydroisoquinoline hydrochloride. A solution of *tert*-butyl

- 5 6-vinyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (970 mg, 3.74 mmol) in HCl-EtOAc (10 mL) was stirred at rt for 1 h. The mixture was then evaporated under reduce pressure to give the crude title compound.

Step C. 2-(2-fluoro-5-(trifluoromethoxy)phenyl)-6-vinyl-1,2,3,4-tetrahydro- isoquinoline. To a stirred solution of 6-vinyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (732 mg, 3.74 mmol) in

- 10 1,4-dioxane (30 mL) was added 2-bromo-1- fluoro-4-(trifluoromethoxy)benzene (969 mg, 3.74 mmol), Cs₂CO₃ (2438 mg, 7.48 mmol), XANTPHOS (433 mg, 0.748 mmol) and Pd₂(dba)₃ (343 mg, 0.374 mmol). The mixture was stirred at 90°C for 18 h. The mixture was washed with water (10 mLx2) and extracted with EtOAc(30 mLx2). The extract was dried over by Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography
15 (PE:EtOAc=40 :1) to give the title compound.

Step D. ethyl 2-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydro- isoquinolin-6-yl)cyclopropanecarboxylate. To a solution of 2-(2-fluoro-5-(trifluoro- methoxy)phenyl)-6-vinyl-1,2,3,4-tetrahydroisoquinoline (60 mg, 0.178 mmol) in DCM (10 mL) was added CuI (7 mg, 0.037 mmol) and the mixture was stirred for 5 min. Then ethyl

- 20 2-diazoacetate (61 mg, 0.535 mmol) in DCM (10 mL) was added dropwise slowly and the reaction was stirred at rtfor overnight (18 h). The mixture was washed with water (10 mLx2) and extracted with DCM (30 mLx2). The extract was dried over by Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel PTLC (PE:EtOAc=10 :1) to give the title compound.

- 25 Step E. 2-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid: To a stirred solution of ethyl 2-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate (30 mg, 0.071 mmol) in THF (4 mL) and water (2 mL) was added LiOH·H₂O (6 mg, 0.143 mmol) and the mixture was stirred at rt for 2 h. The mixture was diluted with water and extracted with
30 EtOAc (2x30 mL). The extract was dried (Na₂SO₄) filtered, and concentrated *in vacuo*. The

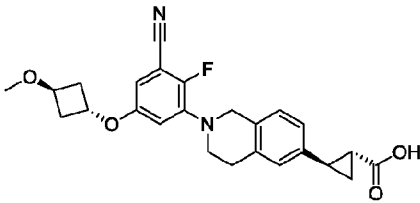
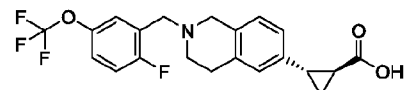
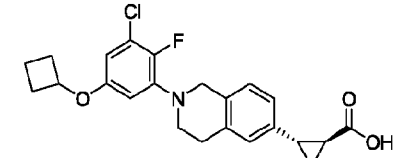
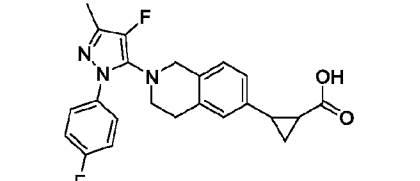
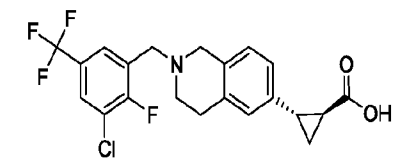
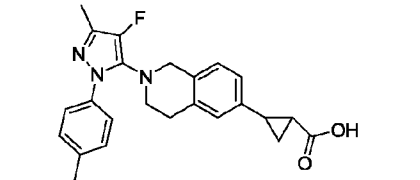
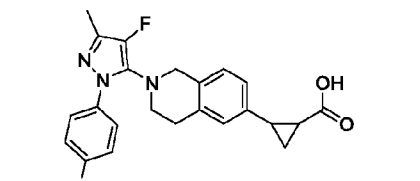
residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μ m) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration (below 50 °C) to give the title compound.

- 5 ¹HNMR (400 MHz, CDCl₃) δ (400 MHz, ppm): 7.00 - 7.10 (m, 2 H) 6.90 - 6.98 (m, 2 H) 6.83 (d, *J*=6.65 Hz, 1 H) 6.78 (d, *J*=8.61 Hz, 1 H) 4.28 (s, 2 H) 3.46 (t, *J*=5.67 Hz, 2 H) 2.98 (t, *J*=5.09 Hz, 2 H) 2.59 (br. s., 1 H) 1.91 (br. s., 1 H) 1.62 - 1.71 (m, 1 H) 1.41 (d, *J*=3.52 Hz, 1 H). *m/z* 369.1 [M + H]⁺.

- 10 The examples in Table 3 were prepared from the appropriate starting materials described previously or commercially available starting materials available using procedures described in Examples 83-81.

Table 3

Example	Structure	IUPAC Name	[M+H] ⁺
85		(1R,2R)-2-{2-[5-(cyclobutyloxy)-2,3-difluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropane-1-carboxylic acid	400.1
86		(1R,2R)-2-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropane-1-carboxylic acid	416.1
87		(1R,2R)-2-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropane-1-carboxylic acid	396.1
88		(1S,2S)-2-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropane-1-carboxylic acid	396.1

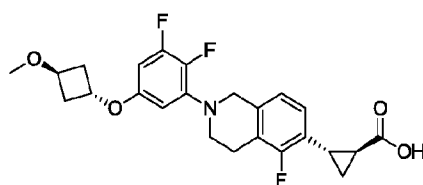
89		(1R,2R)-2-(2-(3-cyano-2-fluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid	437.2
90		(1S,2S)-2-{2-[2-fluoro-5-(trifluoromethoxy)benzyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropane carboxylic acid	410.4
91		(1S,2S)-2-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropane carboxylic acid	416.1
92		2-{2-[4-fluoro-1-(4-fluorophenyl)-3-methyl-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid	410.1
93		(1S,2S)-2-{2-[3-chloro-2-fluoro-5-(trifluoromethyl)benzyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid	428.1
94		2-{2-[4-fluoro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid	406.2
95		2-{2-[4-fluoro-1-(4-fluorophenyl)-3-methyl-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid	410.1

96		2-{2-[4-fluoro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid	406.2
97		(1S,2S)-2-(2-{2-cyano-3-methoxy-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid	449.2
98		(1S,2S)-2-(2-{2,3-difluoro-5-[(trans-3-methylcyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)-cyclopropanecarboxylic acid	414.1
99		(1R,2R)-2-(2-{2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)-cyclopropanecarboxylic acid	430.2
100		(1S,2S)-2-(2-{2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)-cyclopropanecarboxylic acid	430.2
101		(1R,2R)-2-(2-{2,3-difluoro-5-[(trans-3-methylcyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)-cyclopropanecarboxylic acid	414.1

102		2-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid	396.1
103		(1R,2R)-2-(2-{2-cyano-3-fluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid	437.1
104		2-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid	430.1
105		2-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid	430.1

EXAMPLE 106

(1S,2S)-2-(2-(2,3-difluoro-5-((1R,3S)-3-methoxycyclobutoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid



5

Step A. (1S,2S)-ethyl 2-(2-(2,3-difluoro-5-((1R,3S)-3-methoxycyclobutoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate. To a solution of 2,3-difluoro-5-((1R,3R)-3-methoxycyclobutoxy)phenyl trifluoromethanesulfonate (200 mg, 0.552 mmol) and (1S,2S)-ethyl 2-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate (160 mg, 0.607 mmol) in 1,4-dioxane (10 ml) were added Cs₂CO₃ (540 mg, 1.656

10

mmol) and Ruphos-precatalyst (90 mg, 0.110 mmol). The mixture was stirred at 100 °C for 15 h under N₂. The mixture was filtered and concentrated *in vacuo* to give the crude product, which was purified by silica gel PTLC (PE:EA=5:1) to give the title compound. *m/z* 476.3 [M + H]⁺.

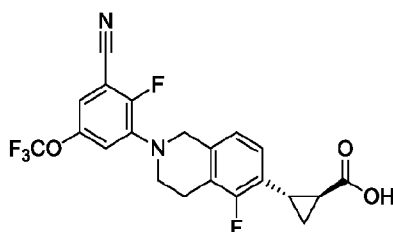
Step B. (1S,2S)-2-(2-(2,3-difluoro-5-((1*r*,3*S*)-3-methoxycyclobutoxy)phenyl)-5-fluoro-

- 5 1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid: To a solution of (1S,2S)-ethyl 2-(2-(2,3-difluoro-5-((1*r*,3*S*)-3-methoxycyclobutoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate (40 mg, 0.084 mmol) in MeOH (2 ml), THF (2 ml) and water (1 mL) was added LiOH hydrate (11 mg, 0.262 mmol), then the mixture was stirred at 20°C for 15 h. The reaction mixture was acidified with 1N HCl to pH ~ 5 and
 10 extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2 % Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2 % Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm), followed by
 15 concentration (below 50°C) to obtain the title compound. ¹H NMR (400 MHz, CDCl₃) δ 6.77-6.87 (m, 1H), 6.13-6.22 (m, 1H), 4.71 (t, *J* = 4.70 Hz, 1H), 4.24 (s, 2H), 4.07-4.14 (m, 1H), 3.45 (t, *J* = 5.48 Hz, 2H), 3.27 (s, 3 H), 2.92 (br. s., 2H), 2.71 (br. s., 1H), 2.33-2.45 (m, 4H), 1.87-1.95 (m, 1H), 1.61-1.70 (m, 1H), 1.38-1.48 (m, 1H); *m/z* = 448.2 [M + H]⁺.

20

EXAMPLE 107

(1S,2S)-2-(2-(3-cyano-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid

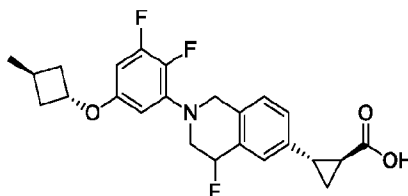


- Step A. (1S,2S)-ethyl 2-(2-(3-cyano-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate: To a solution of (1S,2S)-ethyl 2-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate (200 mg, 0.760 mmol) in 1,4-dioxane (20 mL) was added Cs₂CO₃ (495 mg, 1.519 mmol),
 25

- 3-bromo-2-fluoro-5-(trifluoromethoxy)benzonitrile (Intermediate 44, 350 mg, 1.232 mmol), $\text{Pd}_2(\text{dba})_3$ (696 mg, 0.760 mmol) and XANTPHOS (440 mg, 0.760 mmol). The mixture was stirred at 100°C under N_2 overnight (15 h). The mixture was filtered, concentrated under vacuum and dissolved with EtOAc (2 x 50 mL). The combined organic layer was washed with
- 5 brine (2 x 30 mL), and then dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give crude (1S,2S)-ethyl 2-(2-(3-cyano-2-fluoro-5-(trifluoromethoxy)-phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate. The crude product was purified by silica gel chromatography (PE/EtOAc 30:1-20:1) to give the title compound.
- Step B. (1S,2S)-2-(2-(3-cyano-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid. To a solution of (1S,2S)-ethyl
- 10 2-(2-(3-cyano-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate (88 mg, 0.189 mmol) in THF (5 mL) and water (2.5 mL) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (20 mg, 0.477 mmol) and the mixture was stirred at 20 °C for 15 h. The mixture was concentrated *in vacuo* to give crude product. The crude product was purified by
- 15 reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH_3CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH_3CN , Detector wavelength: 220 nm) followed by concentration (below 50 °C) to give the title compound. ^1H NMR (400 MHz, CH_3OD) δ ppm 7.31–7.22 (m, 2H) 6.99–6.86 (m, 2 H) 4.35 (s, 2 H) 3.54 (t, $J = 5.77$ Hz, 2 H) 3.00–2.90 (m, 2 H)
- 20 2.62–2.52 (m, 1 H) 1.90–1.75 (m, 1 H) 1.52 (dt, $J = 9.29, 4.89$ Hz, 1 H) 1.44–1.36 (m, 1 H). MS (ESI) m/z 439.1 ($\text{M} + \text{H}$) $^+$.

EXAMPLE 108

- (1S,2S)-2-(2-(2,3-difluoro-5-((1R,3S)-3-methylcyclobutoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid
- 25



Step A-(1S,2S)-ethyl 2-(2-(2,3-difluoro-5-((1R,3S)-3-methylcyclobutoxy)phenyl)-

- 5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate: To a solution of 2,3-difluoro-5-((1R,3R)-3-methylcyclobutoxy)phenyl trifluoromethanesulfonate (Intermediate 9, 200 mg, 0.578 mmol) in dioxane (5 mL) were added 2-(((1S,2S)-2-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl) cyclopropanecarbonyl)oxy)ethan-1-ylum (167 mg, 0.635 mmol),
- 5 Cs₂CO₃ (565 mg, 1.733 mmol) and RUPHOS precatalyst (94 mg, 0.116 mmol). After the addition was complete, the mixture was stirred at 90°C for 15 h. The mixture was filtered and filtrate was diluted with water (30 mL), and extracted with EtOAc (3x 30 mL). The combined organic layer was concentrated *in vacuo* and the residue was purified by silica gel PTLC (PE:EtOAc=10:1), to give the title compound. *m/z* 460.1 [M+1]⁺.
- 10 Step-B. (1S,2S)-2-(2-(2,3-difluoro-5-((1R,3S)-3-methylcyclobutoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid. To a solution of (1S,2S)-ethyl 2-(2-(2,3-difluoro-5-((1R,3S)-3-methylcyclobutoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylate (20 mg, 0.038 mmol) in MeOH (2 mL), THF (2mL) and water (1 mL) was added LiOH hydrate (10 mg, 0.238 mmol). After the addition
- 15 was complete, the mixture was stirred at rt for 15 h. The mixture was acidified by hydrochloride acid (1N) to pH~2, and concentrated *in vacuo* to give crude product, which was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm) then freeze
- 20 dried to afford the title compound. ¹H NMR (400 MHz, CDCl₃) δ 6.76-6.88 (m, 2 H), 6.14 - 6.25 (m, 2 H), 4.66 (dt, *J*=12.42, 6.11 Hz, 1 H), 4.25 (s, 2 H), 3.45 (t, *J*=5.67 Hz, 2 H), 2.89-2.97 (m, 2 H), 2.72 (t, *J*=9.78 Hz, 1 H), 2.46 (br. s., 1 H), 2.25 - 2.33 (m, 2 H), 2.03-2.10 (m, 2 H), 1.91 (dt, *J*=8.22, 4.50 Hz, 1 H), 1.66 (dt, *J*=9.29, 4.55 Hz, 1 H), 1.39-1.47 (m, 1 H), 1.13-1.23 (m, 3 H); *m/z* 432.4 [M+1]⁺.

25

The examples in Table 4 were prepared from the appropriate starting materials described previously or commercially available starting materials available using procedures described in Examples 106-108.

Table 4

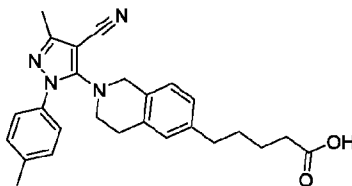
Example	Structure	Name	[M+H] ⁺
109		(1R,2R)-2-{2-[3-cyano-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropane-carboxylic acid	439.1
110		(1R,2R)-2-(2-{2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-cyclopropanecarboxylic acid	448.2
111		(1R,2R)-2-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid	448.0
112		(1R,2R)-2-(2-{2,3-difluoro-5-[(trans-3-methylcyclobutyl)oxy]phenyl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid	432.4
113		(1R,2R)-2-{5-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropane-carboxylic acid	414.1
114		(1R,2R)-2-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid	416.1

115		(1S,2S)-2-(2-(2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-cyclopropanecarboxylic acid	448.2
116		(1S,2S)-2-[2-[3-cyano-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl]cyclopropane-carboxylic acid	439.1
117		(1S,2S)-2-[2-[2-cyano-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl]cyclopropane-carboxylic acid	421.1
118		(1S,2S)-2-[5-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl]cyclopropane-carboxylic acid	414.1
119		(1S,2S)-2-[2-[2-cyano-3-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl]cyclopropane-carboxylic acid	439.0
120		(1S,2S)-2-[2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl]cyclopropane-carboxylic acid	448.0

121		(1R,2R)-2-{2-[2-chloro-3-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid	448.0
122		(1S,2S)-2-(2-{2,3-difluoro-5-[(trans-3-methylcyclobutyl)oxy]phenyl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid	432.4
123		(1R,2R)-2-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid	434.1
124		(1S,2S)-2-{2-[2-chloro-3-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid	448.0
125		(1S,2S)-2-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid	434.1
126		(1S,2S)-2-{2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid	425.1

Example 127

5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)pentanoic acid



- 5 Step A. 2-(tert-butyl) 6-methyl 3,4-dihydroisoquinoline-2,6(1H)-dicarboxylate. A stirred mixture of *tert*-butyl 6-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (21 g, 67.5 mmol) in MeOH (300 mL), was added Pd(dppf)Cl₂ (4.9 g, 6.75 mmol) and TEA (20.45 g, 202 mmol). The mixture was stirred at 110 °C for 48 h under high pressure CO (2 MPa). Then the catalyst and salt were filtered off and the filtrate was concentrated *in vacuo*, followed by purification by
- 10 silica gel chromatography (PE/EtOAc = 50:1 to 6:1) to afford the title compound.
- Step B. *tert*-butyl 6-(hydroxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate. A solution of 2-*tert*-butyl 6-methyl 3,4-dihydroisoquinoline-2,6(1H)-dicarboxylate (15 g, 51.5 mmol) in THF (80 mL) was added dropwise to a solution of LAH (2.94 g, 77.32 mmol) in THF (80 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. The mixture was quenched with H₂O,
- 15 dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE/EtOAc = 20:1~3:1) to give the title compound.
- Step C. *Tert*-butyl 6-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate. A stirred mixture of *tert*-butyl 6-(hydroxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (8.0 g, 30.4 mmol) in DCM (100 mL) was added MnO₂ (21.2 g, 243.8 mmol). The mixture was stirred under reflux for
- 20 16 h. The mixture was filtered and concentrated *in vacuo*, the crude product was purified by silica gel chromatography (PE/EtOAc = 100:1 ~ 10:1) to afford the title compound.
- Step D. 6-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate. A solution of *tert*-butyl-6-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.044 mg, 4 mmol) in HCl-MeOH (50 mL) was stirred under reflux for 16 h. The mixture was evaporated to obtain the
- 25 title compound.
- Step E. 5-(6-formyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile. To a solution of methyl 1,2,3,4-tetrahydroisoquinoline-6-carboxylate (197 mg, 1 mmol), in 1,4-dioxane was added 5-iodo-3-methyl-1-(p-tolyl)-

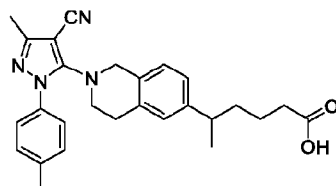
- 1H-pyrazole-4-carbonitrile (323 mg, 1 mmol), Pd₂(dba)₃ (92 mg, 0.1 mmol), XANTPHOS (173 mg, 0.3 mmol) and Cs₂CO₃ (815 mg, 3 mmol). The reaction mixture was stirred under N₂ and heated to 100°C for 15 h. The mixture was quenched with H₂O, then extracted with EtOAc, the organic layer was washed with brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by silica gel PTLC (PE:EA=3:1) to give the title compound.
- Step F. (2E,4E)-methyl 5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)penta-2,4-dienoate A stirred mixture of ethyl methyl 4-(diethoxyphosphoryl)but-2-enoate (53 mg, 0.21 mmol) in THF (2 mL) was added NaH (12 mg, 0.28 mmol) at 0 °C. The mixture was stirred for at 0°C for 45 min, and then
- 5-(6-formyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile (68 mg, 0.19 mmol) was added. The mixture was stirred at rt for 15 h. The mixture was poured into a solution of sat. NH₄Cl (10 mL) and extracted with EtOAc (10 mL × 3). The organic layer was separated, washed with brine, dried and evaporated to obtain the title compound.
- Step G. Methyl 5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)pentanoate. To a stirred mixture of (2E,4E)-methyl 5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)penta-2,4-dienoate (80 mg, 0.182 mmol) in DCM (4 mL) was added Pd/C (20 mg). The reaction was stirred under a hydrogen atmosphere at room temperature for 6 hours. Then the reaction mixture was filtered and concentrated *in vacuo* to obtain the title compound.
- Step H. 5-(6-formyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile-5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)pentanoic acid. To a solution of methyl 5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)pentanoate (70 mg, 0.160 mmol) in THF (2 mL), MeOH (2 mL) and (1 mL) was added LiOH·H₂O (44 mg, 0.8 mmol). The reaction mixture was stirred at rt overnight. The mixture was acidified with HCl, and then extracted with EtOAc. The organic layer was separated, and evaporated to give the crude product, which was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250*21.2 mm*4 μm) using water(0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detective wavelength: 220 nm.) followed by concentration (below 50°C) to obtain the title compound. ¹H

NMR (400MHz, CDCl₃) δ = 7.44 (d, J =8.2 Hz, 2H), 7.22 (d, J =8.2 Hz, 2H), 7.05-6.79 (m, 3H), 4.43 (s, 2H), 3.36 (t, J =5.9 Hz, 2H), 2.75 (t, J =5.5 Hz, 2H), 2.63 - 2.51 (m, 2H), 2.36 (d, J =11.7 Hz, 8H), 1.67 (d, J =3.1 Hz, 4H). m/z 439.2 [M + H]⁺.

5

EXAMPLE 128

5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)hexanoic acid



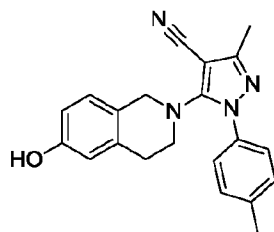
- Step A. *tert*-butyl 6-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate. To a solution of pyridine (16.22 ml, 201 mmol) and *tert*-butyl 6-hydroxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (50.0 g, 201 mmol) in DCM (600 ml), Tf₂O (33.9 ml, 201 mmol) was added dropwise at 0°C and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with DCM (800 mL), washed with water (2 x 200 mL) and brine (2 x 200 mL). The organic solution was dried, filtered, concentrated *in vacuo* and purified by silica gel chromatography (PE:EtOAc=80:1~10:1) to give the title compound.
- Step B. 1-(1,2,3,4-tetrahydroisoquinolin-6-yl)ethanone hydrochloride: To a solution of 1-(vinylloxy)butane (1.576 g, 15.73 mmol), *tert*-butyl 6-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.0 g, 2.62 mmol) in DMF (15 ml) was added Pd(OAc)₂ (0.059 g, 0.262 mmol) and 1,3-bis(diphenylphosphino)propane (0.108 g, 0.262 mmol), the mixture was stirred at 80°C for 15 h. The reaction was quenched with water (25 mL), extracted with EtOAc (3 x 45 mL). The organic layer was separated, washed with water (3 x 25 mL) and brine (3 x 25 mL), concentrated and purified by silica gel chromatography (PE:EtOAc=20:1~5:1) to give *tert*-butyl 6-acetyl-3,4-dihydroisoquinoline-2(1H)-carboxylate. A solution of *tert*-butyl 6-acetyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (0.5 g, 1.816 mmol) in HCl-MeOH (15 ml) was stirred at 20°C for 1 h. Then the reaction mixture was concentrated to give the crude title compound, which was used directly in the next step without further purification.

- Step C. 5-(6-acetyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile: A solution of potassium fluoride (0.663 g, 11.41 mmol), 5-iodo-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile (1.844 g, 5.71 mmol) and 1-(1,2,3,4-tetrahydroisoquinolin-6-yl)ethanone (1.00 g, 5.71 mmol) in DMSO (15 ml) was stirred at 110°C for 15 h. The reaction was quenched with water, extracted with EtOAc (3x30 mL). The organic layers were washed with water (2x15 mL) and brine (2x15 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (PE:EtOAc=30:1~3:1) to give the title compound.
- Step D. (2E,4E)-methyl 5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)hexa-2,4-dienoate. To a suspension of NaH (52 mg, 1.300 mmol) in THF (3 ml) was added (E)-methyl 4-(dimethoxyphosphoryl)but-2-enoate (270 mg, 1.296 mmol) at 0°C, and the mixture was stirred at 0°C for 0.5 h. Then a solution of 5-(6-acetyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile (400 mg, 1.080 mmol) in THF (3 mL) was added dropwise to the above mixture. The reaction mixture was stirred at 0~20 °C for 6 h. The reaction was quenched with a solution of sat. NH₄Cl, extracted with EtOAc (3 x25 mL). The combined organic layers were washed with water (2 x15 mL) and brine (2 x15 mL), concentrated *in vacuo* and purified by silica gel chromatography (PE:EtOAc=20:1~5:1) to give the title compound.
- Step E. (2E,4E)-5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)hexa-2,4-dienoic acid: To a solution of (2E,4E)-methyl-5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)hexa-2,4-dienoate (200 mg, 0.442 mmol) and LiOH hydrate (56 mg, 1.334 mmol) in THF (2.0 ml)/MeOH (2.0 ml)/Water (2.0 ml). The reaction mixture was stirred at 20°C for 3 h. Then the reaction mixture was concentrated to give a residue, which was diluted with HCl (1 N, 5 mL) and extracted with EtOAc (3x15 mL). The combined organic layers were washed with water (2x5 mL) and brine (2x5 mL). The organic solution was dried over Na₂SO₄, filtered, and the filtrate was concentrated to give the title compound.
- Step F. 5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)hexanoic acid. To a solution of (2E,4E)-5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)hexa-2,4-dienoic acid (180 mg, 0.410 mmol)

in MeOH (5 ml) was added Pd-C (20 mg, 0.188 mmol), and the reaction was stirred at 10°C for 15 h under H₂ balloon. The reaction mixture was filtered, the organic layer was concentrated *in vacuo* to give a residue, which was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250*21.2 mm*4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detective wavelength: 220 nm) followed by concentration to give to give the title compound as a racemic mixture. The enantiomers of 5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)-hexanoic acid (160 mg) were purified by SFC (Instrument: MG-II; Column: Chiralcel OJ 250×30mm I.D., 5μm; Mobile phase: Supercritical CO₂/MeOH (0.1%) NH₃·H₂O = 75/25 at 60 mL/min; Column Temp: 38°C; Nozzle Pressure: 100Bar; Nozzle Temp: 60°C; Evaporator Temp: 20°C; Trimmer Temp: 25 °C; Wavelength: 220nm) to yield (R)-5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroiso-quinolin-6-yl)hexanoic acid, and (S)-5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)hexanoic acid. ¹H NMR (400 MHz, CDCl₃) δ (400 MHz, ppm): 7.43 (d, *J*=8.2 Hz, 2H), 7.21 (d, *J*=8.2 Hz, 2H), 7.00 - 6.91 (m, 2H), 6.88 (s, 1H), 4.43 (s, 2H), 3.34 (t, *J*=5.7 Hz, 2H), 2.74 (t, *J*=5.3 Hz, 2H), 2.68 - 2.57 (m, 1H), 2.37 (s, 3H), 2.34 (s, 3H), 2.32 - 2.25 (m, 2H), 1.64 - 1.42 (m, 4H), 1.20 (d, *J*=7.0 Hz, 3H). ESI MS *m/z* 443.1 [M + H]⁺. ¹H NMR (400 MHz, CDCl₃) δ (400 MHz, ppm): 7.44 (d, *J*=8.2 Hz, 2H), 7.21 (d, *J*=8.2 Hz, 2H), 6.99 - 6.92 (m, 2H), 6.88 (s, 1H), 4.43 (s, 2H), 3.35 (t, *J*=5.7 Hz, 2H), 2.74 (t, *J*=5.3 Hz, 2H), 2.68 - 2.56 (m, 1H), 2.37 (s, 3H), 2.34 (s, 3H), 2.32 - 2.26 (m, 2H), 1.66 - 1.42 (m, 4H), 1.21 (d, *J*=7.0 Hz, 3H). ESI MS *m/z* 443.1 [M + H]⁺.

EXAMPLE 129

5-(6-hydroxy-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile



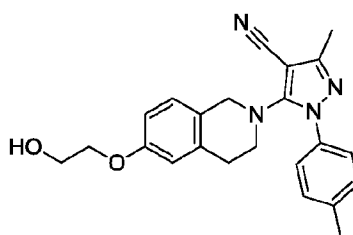
Step A. 5-(6-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-

pyrazole-4-carbonitrile. To a solution of 5-bromo-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile (Intermediate 11, 600 mg, 2.173 mmol) in DMSO (20 ml) was added 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (434 mg, 2.173 mmol), Cs₂CO₃ (1416 mg, 4.35 mmol) and CuI (414 mg, 2.173 mmol). The mixture was stirred at 140°C for 18 h. The mixture was diluted with water (2x20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE:EtOAc=50 :1 to 30:1) to yield the title compound.

Step B. 5-(6-hydroxy-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile. To a solution of 5-(6-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile (180 mg, 0.502 mmol) in DCM (20 ml) was added BBr₃ (252 mg, 1.004 mmol) dropwise at -76°C. The mixture was stirred at -76°C for 2 h. The mixture was diluted with water and extracted with EtOAc (2x30 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water(0.2% Formic acid), Mobile phase B: CH₃CN, Detective wavelength: 220 nm) followed by concentration (below 50 °C) to obtain the title compound. ¹H NMR (CDCl₃, 400 MHz, ppm): δ 7.45 (d, *J*=8.22 Hz, 2 H) 7.23 (d, *J*=8.22 Hz, 2 H) 6.90 (d, *J*=8.61 Hz, 1 H) 6.65 (d, *J*=8.22 Hz, 1 H) 6.58 (s, 1 H) 4.40 (s, 2 H) 3.30 - 3.41 (m, 2 H) 2.74 (t, *J*=5.48 Hz, 2 H) 2.31 - 2.44 (m, 6 H). ESI MS *m/z* 345.1 [M + H]⁺.

EXAMPLE 130

5-(6-(2-hydroxyethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile

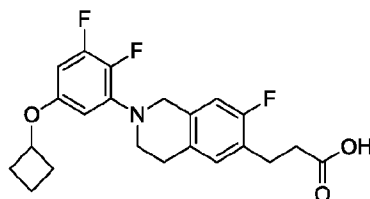


Step A. 5-(6-(2-((tert-butyl)dimethylsilyl)oxy)ethoxy)-3,4-dihydroisoquinolin-

- 2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile. To a solution of (2-bromoethoxy)(tert-butyl) dimethylsilane (34 mg, 0.142 mmol) in MeCN (20 mL) was added Cs₂CO₃ (114 mg, 0.348 mmol) and the mixture was stirred at 15 °C for 30 min. Then 5-(6-hydroxy-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile (40 mg, 0.116 mmol) was added and the mixture was stirred at 15°C for 24 h. The mixture was washed with water (2x10 mL) and extracted with EtOAc (2x30 mL). The extract was dried over by Na₂SO₄ and concentrated *in vacuo* to give the crude title compound.
- Step B. 5-(6-(2-hydroxyethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile To a stirred solution of 5-(6-(2-((tert-butyl)dimethylsilyl)oxy)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile (50 mg, 0.099 mmol) in THF (20 mL) was added TBAF (0.199 mL, 0.199 mmol) in THF (1 M), and the mixture was stirred at 15°C for 4 h. The mixture was washed with water (2x10 mL) and extracted with EtOAc (2x30 mL). The extract was dried over by Na₂SO₄ and evaporated *in vacuo*. The residue was purified by reverse phase HPLC on a GILSON 281 instrument fitted with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detector wavelength: 220 nm) followed by concentration to obtain the title compound. ¹H-NMR (400 MHz, CDCl₃) δ ppm: 7.46 (d, *J*=8.28 Hz, 2 H) 7.23 (d, *J*=8.28 Hz, 2 H) 6.96 (d, *J*=8.53 Hz, 1 H) 6.76 (dd, *J*=8.41, 2.38 Hz, 1 H) 6.67 (s, 1 H) 4.41 (s, 2 H) 4.03 - 4.10 (m, 2 H) 3.91-4.00 (m, 2 H) 3.37 (t, *J*=5.77 Hz, 2 H) 2.77 (t, *J*=5.77 Hz, 2 H) 2.39 (s, 3 H) 2.36 (s, 3 H). *m/z* 389.1 [M + H]⁺.

EXAMPLE 131

- 25 3-(2-(5-cyclobutoxy-2,3-difluorophenyl)-7-fluoro-1,2,3,4-tetrahydro-isoquinolin-6-yl)propanoic acid



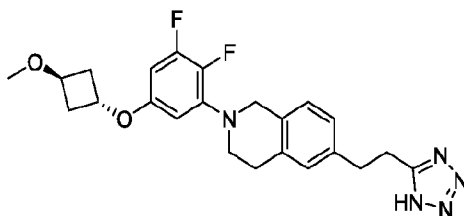
Step A. ethyl 3-(2-(5-cyclobutoxy-2,3-difluorophenyl)-7-fluoro-1,2,3,4-tetrahydro-

- isoquinolin-6-yl)propanoate. To a solution of 5-cyclobutoxy-2,3-difluorophenyl trifluoromethanesulfonate (50 mg, 0.150 mmol) in 1,4-dioxane (5 ml) was added ethyl 3-(7-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (Intermediate 49, 38 mg, 0.151 mmol), Cs₂CO₃ (147 mg, 0.451 mmol), t-buxphos (7 mg, 0.016 mmol) and Pd₂(dba)₃ (14 mg, 0.015 mmol). Then the reaction mixture was placed under nitrogen and stirred at 90°C for 16 h. The mixture was concentrated *in vacuo*, and water (10 mL) was added to the residue. The mixture was extracted with EtOAc (2 x 20 mL), and the combined organic layers were concentrated *in vacuo*. The crude product was purified by silica gel preparative TLC (PE/EtOAc=5:1) to give the title compound.
- Step B. 3-(2-(5-cyclobutoxy-2,3-difluorophenyl)-7-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid. To a solution of ethyl 3-(2-(5-cyclobutoxy-2,3-difluorophenyl)-7-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (20 mg, 0.046 mmol) in THF (2 ml), MeOH (2 ml) and water (1 ml) was added LiOH hydrate (4 mg, 0.095 mmol). The mixture was stirred at 15°C for 3 h, then acidified with HCl (6 N), and extracted with EtOAc (2 x 20 mL). The organic layer was washed with water (20 mL), dried over anhydrous Na₂SO₃, and concentrated *in vacuo* to give the crude product. The crude product was purified with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water (0.2% Formic acid), Mobile phase B: CH₃CN, Detective wavelength: 220 nm) followed by concentration to obtain title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.61-1.73 (m, 2 H) 2.13 (dd, *J*=19.96, 9.78 Hz, 2 H) 2.39 (br. s., 2 H) 2.64-2.72 (m, 2 H) 2.90 (d, *J*=5.09 Hz, 2 H) 2.92-2.98 (m, 2 H) 3.42 (t, *J*=5.67 Hz, 2 H) 4.22 (s, 2 H) 4.51 (t, *J*=7.04 Hz, 1 H) 6.20 (d, *J*= 6.26 Hz, 2 H) 6.77 (d, *J*=10.17 Hz, 1 H) 6.98 (d, *J*=7.43 Hz, 1 H). *m/z* 406.1 [M + H]⁺.

25

EXAMPLE 132

6-(2-(1H-tetrazol-5-yl)ethyl)-2-(2,3-difluoro-5-((1*r*,3*r*)-3-methoxycyclobutoxy)-phenyl)-1,2,3,4-tetrahydroisoquinoline



- Step A. *Tert*-butyl 6-(3-ethoxy-3-oxopropyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate. To a stirred solution of ethyl 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoate (Intermediate 7, 2.0 g, 8.57 mmol) in DCM (15 mL) were added (BOC)₂O (2.7 g, 12.37 mmol) and Et₃N (4.0 mL, 28.7 mmol) at rt. Then the reaction mixture was stirred at rt for 5 h. The solvent was removed under reduced pressure, and the resulting crude product was purified by silica gel column chromatography (PE:EtOAc=2:1) to give the title compound.
- Step B. 3-(2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid: To a stirred solution of *tert*-butyl 6-(3-ethoxy-3-oxopropyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.84 g, 8.52 mmol) in THF (6 mL), MeOH (3 mL) and water (2.5 mL) was added LiOH hydrate (1.7 g, 40.5 mmol) at rt (~8°C). Then the reaction mixture was stirred at rt (~8°C) for 15 h. The mixture was acidified to pH~2 with HCl (15 mL, 3 N, a.q.) and extracted with EtOAc (20 mL×2). The organic layer was removed under reduced pressure to give the crude title compound.
- Step C. *Tert*-butyl 6-(3-amino-3-oxopropyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate. To a stirred solution of 3-(2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid (2.46 g, 8.06 mmol) in DMF (10 mL) were added ammonium chloride (480 mg, 8.97 mmol), DIEA (4.2 mL, 24.05 mmol) and HATU (3.06 g, 8.06 mmol) at rt. Then the reaction mixture was stirred at rt for 15 h. The mixture was diluted with water (200 mL), extracted with EtOAc (30 mL×2), and the organic layer was concentrated *in vacuo* to give the title compound.
- Step D. 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)propanenitrile. A solution of *tert*-butyl 6-(3-amino-3-oxopropyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.4 g, 7.88 mmol) in phosphorus oxychloride (28.93 g, 189 mmol) was stirred at rt for 5 h. The mixture was poured into water (300 mL) slowly with stirring, then basified to pH~8 with saturated aqueous of NaHCO₃ (200 mL), extracted with DCM/MeOH (10:1, 50 mL×2). The organic layer was concentrated *in vacuo*. The resulting crude product was purified by silica gel column chromatography (DCM to DCM/MeOH=40:1 to 10:1) to give the title compound.
- Step E. 3-(2-(2,3-difluoro-5-((1*r*,3*r*)-3-methoxycyclobutoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanenitrile. To a solution of 3-(1,2,3,4-tetrahydroisoquinolin-6-yl)propanenitrile (100 mg, 0.537 mmol) in toluene (10 mL) were added 2,3-difluoro-5-((1*R*,3*R*)-3-methoxycyclobutoxy)phenyl trifluoromethanesulfonate (Intermediate 4, 204 mg, 0.564 mmol), Cs₂CO₃ (525 mg, 1.611 mmol), BINAP (67 mg, 0.108 mmol) and

- Pd(OAc)₂ (12 mg, 0.053 mmol) at rt. Then the reaction mixture was placed under nitrogen atmosphere and stirred at 110°C for 15 h. The solvent was removed *in vacuo*, and the resulting mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL×2). The organic layer was concentrated *in vacuo*, and the crude product was purified by silica gel PTLC (PE/EtOAc=2:1) to give the title compound. *m/z* 399.1 [M+H]⁺.
- 5 Step F 6-(2-(1H-tetrazol-5-yl)ethyl)-2-(2,3-difluoro-5-((1R,3R)-3-methoxycyclobutoxy)phenyl)-1,2,3,4-tetrahydroisoquinoline: To a solution of 3-(2-(2,3-difluoro-5-((1R,3R)-3-methoxycyclobutoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propane nitrile (50 mg, 0.125 mmol) in toluene (4 mL) was added azidotributyltin (0.2 mL, 0.730 mmol)
- 10 at rt. Then the reaction mixture was placed under a nitrogen atmosphere and stirred at 110°C for 40 h. The solvent was removed *in vacuo*, and the resulting mixture was diluted with water (10 mL), and extracted with EtOAc (10 mL×2). The organic layer was concentrated *in vacuo*, and the crude product was purified by silica gel column chromatography (DCM to DCM/MeOH=20:1), then purified by reverse phase HPLC on a GILSON 281 instrument fitted
- 15 with a Phenomenex Synergi C18 (250 x 21.2 mm x 4 μm) using water (0.2% Formic acid) and CH₃CN as eluents (Mobile phase A: water(0.2% Formic acid), Mobile phase B: CH₃CN, Detective wavelength: 220 nm) followed by concentration to give the title compound. ¹H NMR (400 MHz, MeOD) δ 7.03 - 7.08 (m, 1 H), 6.94 - 7.00 (m, 2 H), 6.23-6.32 (m, 2 H), 4.66-4.76 (m, 1 H), 4.04-4.13 (m, 1 H), 3.42 (t, *J*=5.73 Hz, 2 H), 3.19-3.27 (m, 5 H), 3.02-3.09 (m, 2 H),
- 20 2.88 (t, *J*=5.51 Hz, 2 H), 2.27 - 2.41 (m, 4 H). *m/z* 440.2 [M-H]⁺.

The examples in Table 5 were prepared from the appropriate starting materials described previously or commercially available starting materials available using procedures described in Examples 127-132.

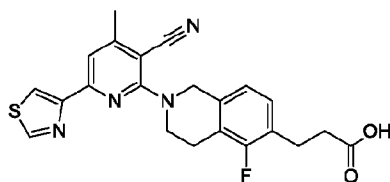
Table 5

Example	Structure	Name	[M+H] ⁺
133		5-{2-[4-cyano-1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}pentanoic acid	445.1
134		5-{2-[4-cyano-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}pentanoic acid	429.1
135		5-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}pentanoic acid	412.1
136		5-[6-(2-hydroxyethoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-methyl-1-(4-methylphenyl)-1H-pyrazole-4-carbonitrile	389.1
137		5-{2-[4-chloro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}pentanoic acid	438.2
138		5-(6-hydroxy-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(4-methylphenyl)-1H-pyrazole-4-carbonitrile	345.1
139		5-[6-(4-hydroxybutoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-methyl-1-(4-methylphenyl)-1H-pyrazole-4-carbonitrile	417.2

Example	Structure	Name	[M+H] ⁺
140		5-{2-[4-cyano-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}hexanoic acid	443.1
141		5-(3,4-dihydroisoquinolin-2(1H)-yl)-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbonitrile	345.1
142		5-{2-[4-cyano-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}hexanoic acid	443.1
143		3-(2-{[4-fluoro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]methyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid	408.2
144		5-[6-(3-hydroxypropoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-methyl-1-(4-methylphenyl)-1H-pyrazole-4-carbonitrile	403.1
145		3-{2-[5-(cyclobutyloxy)-2,3-difluorophenyl]-7-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	406.1
146		3-{2-[4-chloro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	428.1

Example 147

3-[2-(3-Cyano-4-methyl-6-thiazol-4-yl-pyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydro-isoquinolin-6-yl]-propionic acid



5 Step A Ethyl 3-(2-(6-chloro-3-cyano-4-methylpyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydro isoquinolin-6-yl)propanoate. To a solution of 2,6-dichloro-4-methylnicotinonitrile (200 mg, 1.069 mmol), ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (269 mg, 1.069 mmol) and G2-RuPHOS (41.5 mg, 0.053 mmol) in dioxane (6 ml) was added Cs₂CO₃ (697 mg, 2.139 mmol). The mixture was stirred at 90 °C for 12 h, and then water (15 ml) was added, and
10 the mixture was extracted with EA (10 mL x 2). The organic layer was separated, washed with brine (15 ml), and dried over Na₂SO₄. After filtration and concentration, the resulting residue was purified by *prep*-TLC (SiO₂, PE: EA = 5: 1) to afford the title compound.

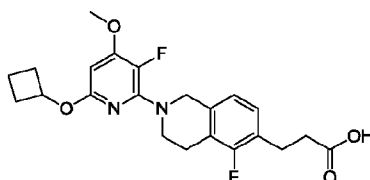
Step B : Ethyl 3-(2-(3-cyano-4-methyl-6-(thiazol-4-yl)pyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate. To a solution of ethyl 3-(2-(6-chloro-3-cyano-
15 4-methylpyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (50 mg, 0.124 mmol) and 4-(tributylstannyl)thiazole (51.2 mg, 0.137 mmol) in dioxane (3 ml) was added G2 XPhos (9.79 mg, 0.012 mmol). The mixture was stirred at 110 °C for 12 h, then quenched with 10% aqueous KF (10 ml), filtered and extracted with ethyl acetate (8 mL x 3). The organic layers were combined and washed with water (15 mL), brine (10 mL), dried over Na₂SO₄,
20 filtered and concentrated under reduced pressure to afford the title compound, which was used directly without further purification.

Step C: 3-[2-(3-Cyano-4-methyl-6-thiazol-4-yl-pyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydro-isoquinolin-6-yl]-propionic acid. To a solution of ethyl 3-(2-(3-cyano-4-methyl-6-(thiazol-4-yl)pyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (50 mg,
25 0.111 mmol) in MeOH (2 ml), THF (2 ml) and water (1 ml) was added lithium hydroxide hydrate (46.6 mg, 1.110 mmol). The mixture was stirred at 85 °C for 5 h. The resulting mixture was acidified by HCl (1 N) to pH=6-7, then extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), filtered and the

solvent was evaporated under reduced pressure. The resulting residue was purified by *prep*-HPLC (TFA) to afford the title compound. ¹H-NMR (400 MHz, METHANOL-d): 9.07 (d, *J*=1.98 Hz, 1 H), 8.37 (d, *J*=1.98 Hz, 1 H), 7.60 (s, 1 H), 7.09 - 7.16 (m, 1 H), 6.99 (d, *J*=7.94 Hz, 1 H), 4.84 (s, 2 H), 4.00 (t, *J*=5.73 Hz, 2 H), 3.04 (t, *J*=5.51 Hz, 2 H), 2.93 (t, *J*=7.61 Hz, 2 H), 2.59 (t, *J*=7.61 Hz, 2 H), 2.55 (s, 3 H).

Example 148

3-(2-(6-cyclobutoxy-3-fluoro-4-methoxypyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid



10

Step A Ethyl 3-(2-(6-cyclobutoxy-3-fluoro-4-methoxypyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate. To a solution of 2-bromo-6-cyclobutoxy-3-fluoro-4-methoxypyridine (150 mg, 0.545 mmol) and ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl) propanoate (123 mg, 0.49 mmol) in dioxane (5 ml) was added Cs₂CO₃ (354 mg, 1.09 mmol), and then G2 Ruphos (28 mg, 0.03 mmol) was added under N₂ protection. The resultant mixture was stirred at 90°C for 10 h, then quenched with H₂O (10 mL) and extracted with EA (20 mL×3). The organic layer was washed with brine (30 mL), dried over Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to afford the title compound, which was used in the next step without further purification. MS (ESI) *m/z*: 447 [M+H⁺]

15

Step B 3-(2-(6-cyclobutoxy-3-fluoro-4-methoxypyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid. To a solution of ethyl 3-(2-(6-cyclobutoxy-3-fluoro-4-methoxypyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl) propanoate (76 mg, 0.17 mmol) in MeOH (2.5 ml) and H₂O (0.5 ml) was added lithium hydroxide (20 mg, 0.85 mmol), and the resulting mixture was stirred at 18-25 °C for 6 hours. Then the reaction mixture was extracted with EA (10 mL×3). The organic layer was washed with brine (20 mL), and dried over Na₂SO₄. After filtration and concentration, the resulting residue was purified by preparative HPLC (TFA) to afford the title compound. ¹H-NMR (400 MHz, METHANOL-d₄) 7.06 (t, *J*=7.63 Hz, 1H), 6.88 (d, *J*=7.83 Hz, 1H), 5.90 (d, *J*=3.91 Hz, 1H), 4.93-5.04 (m, 1H), 4.54 (s,

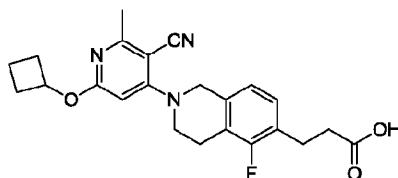
25

2H), 3.82 (s, 3H), 3.71 (t, $J=5.87$ Hz, 2H), 2.88 (t, $J=7.63$ Hz, 2H), 2.82 (t, $J=5.48$ Hz, 2H), 2.55 (t, $J=7.63$ Hz, 2H), 2.26-2.44 (m, 2H), 1.92-2.12 (m, 2H), 1.78 (q, $J=9.91$ Hz, 1H), 1.53-1.71 (m, 1H). MS (ESI) m/z : 419 $[M+H]^+$

5

Example 149

3-(2-(3-cyano-6-cyclobutoxy-2-methylpyridin-4-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid



Step A 6-chloro-2-methylpyridin-3-amine. A mixture of 6-chloro-2-methyl-3-nitropyridine (8.60 g, 50.00 mmol), NH_4Cl (27.00 g, 500.00 mmol) and Fe (14.00 g, 250.00 mmol) in MeOH (100 mL) was stirred at 80 °C for 5 h. The mixture was filtered and concentrated, and the resulting residue was purified by column chromatography (SiO_2 , eluting with PE:EA = 5:1) to afford the title compound.

Step B 4-bromo-6-chloro-2-methylpyridin-3-amine. To a solution of 6-chloro-2-methylpyridin-3-amine (4.97, 35.00 mmol) in CH_3CN (100 mL) was added NBS (6.23 g, 35.00 mmol) at 0 °C. The resulting mixture was stirred at 26 °C for 16 h, then quenched with H_2O and extracted with EtOAc (3 * 100 mL). The combined organic layers were washed with brine (200 mL), and dried over Na_2SO_4 . After filtration and concentration, the resulting residue was purified by column chromatography (SiO_2 , eluting with PE:EA = 5:1) to afford the title compound. ^1H -NMR (400MHz, chloroform- d): 7.28 (s, 1H), 4.06 (br, 2H), 2.43 (s, 3H).

Step C: 4-bromo-6-chloro-2-methylnicotinonitrile. To a solution of $CuCN$ (1.80 g, 20.09 mmol) in CH_3CN (20 mL) was added 3-methyl-1-nitrobutane (2.80 mL, 20.93 mmol). Then a solution of 4-bromo-6-chloro-2-methylpyridin-3-amine (3.70 g, 16.74 mmol) in CH_3CN (30 mL) was added to the mixture dropwise. The resulting reaction mixture was stirred at 65 °C for 16 h, then quenched with H_2O and extracted with EtOAc (3 * 50 mL). The combined organic layers were washed with brine (100 mL), and dried over Na_2SO_4 . After filtration and concentration, the resulting residue was purified by column chromatography (SiO_2 , eluting with PE:EA = 10:1) to afford the title compound.

- Step D 4-bromo-6-cyclobutoxy-2-methylnicotinonitrile. A solution of NaH (40.00 mg, 1.00 mmol) and cyclobutanol (72.00 mg, 1.00 mmol) in THF (3 mL) was cooled to -78 °C under N₂ protection. The solution was stirred at -78 °C for 30 min, and then 4-bromo-6-chloro-2-methyl-nicotinonitrile (230.00 mg, 1.00 mmol) was added. The resulting reaction mixture was stirred at 26 °C for 16 h, then quenched with H₂O and extracted with EtOAc (3 * 20 mL). The combined organic layers were washed with brine (50 mL), and dried over Na₂SO₄. After filtration and concentration, the residue was purified by column chromatography (SiO₂, eluting with PE:EA = 10:1) to afford the title compound. ¹H-NMR (400MHz, chloroform-d): 6.84 (s, 1H), 5.21-5.15 (m, 1H), 2.66 (s, 3H), 2.47-2.41 (m, 2H), 2.18-2.08 (m, 2H), 1.89-1.84 (m, 1H), 1.69-1.64 (m, 1H).
- Step E Ethyl 3-(2-(3-cyano-6-cyclobutoxy-2-methylpyridin-4-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate. A mixture of 4-bromo-6-cyclobutoxy-2-methylnicotinonitrile (40.00 mg, 0.15 mmol), ethyl 3-(5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (45.00 mg, 0.18 mmol), Cs₂CO₃ (147.00 mg, 0.45 mmol) and G2-Ruphos (6.00 mg, 0.0075 mmol) in 1,4-dioxane (5 mL) was stirred at 90 °C under N₂ for 16 h. Then the reaction was diluted with H₂O and extracted with EtOAc (10 mL*3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford the title compound, which was used in the next step without further purification. MS(ESI) m/z: 438.7 [M+H]⁺
- Step F 3-(2-(3-cyano-6-cyclobutoxy-2-methylpyridin-4-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid. A mixture of ethyl- 3-(2-(3-cyano-6-cyclobutoxy-2-methylpyridin-4-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoate (65.00 mg, 0.15 mmol) and LiOH·H₂O (126.00 mg, 3.00 mmol) in MeOH (5 mL) and H₂O (1 mL) was stirred at 26 °C for 17 h. Then the reaction solution was adjusted with 3 N HCl to pH = 7, and the reaction solution was extracted with EtOAc (20 mL*3). The combined organic layers were dried over Na₂SO₄. After filtration and concentration, the resulting residue was purified by *prep*-HPLC (Neutral) to afford the title compound. ¹H-NMR (400 MHz, chloroform-d) 7.14-7.10 (m, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.15 (s, 1H), 5.14 (t, *J* = 7.4 Hz, 1 H), 4.51 (s, 2H), 3.80 (t, *J* = 5.7 Hz, 2H), 2.99-2.89 (m, 4H), 2.59-2.54 (m, 5H), 2.45-2.43 (m, 2H), 2.14-2.09 (m, 2H), 1.85-1.68(m, 2H). MS(ESI) m/z: 410.7 [M+H]⁺

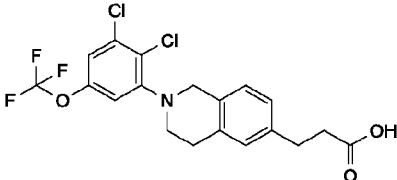
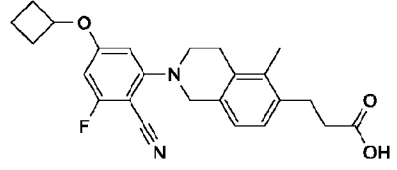
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The Examples in Table 6 were prepared from the appropriate starting materials described

previously or commercially available starting materials using procedures similar to those in the Examples above.

Table 6

Example	Structure	Name	[M+H] ⁺
150		3-{2-[3-chloro-2-cyano-5-(cyclobutyloxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	429.2
151		3-{2-[5-cyano-4-(cyclobutyloxy)-6-methylpyrimidin-2-yl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	411
152		3-{2-[5-cyano-2-(cyclobutyloxy)-6-methylpyrimidin-4-yl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	411
153		3-{5-chloro-2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	429
154		3-[2-(6-cyclopropylpyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl]propanoic acid	341.2
155		3-{2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	413.3

156		3-{2-[2,3-dichloro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	434
157		3-{2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-5-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid	409

BIOLOGICAL ASSAYS

The usefulness of the compound encompassed by formula (I) for a medicament is shown in tests described below.

Human GPR120 IP1 Assay Principle

The binding of small molecule agonists to the G-protein-coupled receptor GPR120 activates phospholipase C, and leads to the generation of inositol 1,4,5-trisphosphate (InsP3 or IP3). IP3 is subsequently de-phosphorylated to IP1, which accumulates in cells and is stable in the presence of lithium chloride.

In the present method, agonist-induced activation of the human GPR120 receptor was monitored by measuring the accumulation of IP1 in CHO-K1 cells that were stably expressing the short form of human GPR120 (Accession #NM_001195755). Following agonist addition, GPR120 activation and subsequent accumulation of IP1 was measured using a homogeneous Time Resolved Fluorescence-based ELISA commercially available from CisBio (IP-one ELISA Kit). The IP-One ELISA was a competitive immunoassay which uses IP1 labeled with HRP and a terbium cryptate-labeled anti-IP1 monoclonal antibody. Accumulation of unlabeled IP1 following GPR120 activation resulted in a loss of signal in the ELISA. The signal loss was then back calculated to IP1 concentration using an IP1 standard curve. Determination of IP1 concentration was a direct measure of GPR120 activation and was used to determine compound potency (EC50).

Generation of GPR120-Expressing Cells:

Human GPR120 stable cell-lines were generated in CHO cells. The expression plasmids were transfected using lipofectamine (Life Technologies) following manufacturer's instructions. Stable cell-lines were generated following drug selection and single cell cloning.

5

Inositol Phosphate Turnover (IP1) Assay :

The assay was performed in 384-well format. CHO cells stably expressing human GPR120 were plated at 20,000 cells per well in growth medium (DMEM/F12, 10% fetal calf serum). Cell plates were then incubated 16 hours at 37 degrees in a 5% CO₂ incubator. Measurement of Inositol Phosphate Turnover (IP1) was performed using the CisBio IP-One kit (Part number 62IPAPB). After the 16 hour incubation, the growth media was removed by centrifugation using the BlueWasher (AusWasher GUI Ver. v1.0.1.8) Protocol #21-"Light Dry" and 10 ul of stimulation buffer (prepared as described in the kit) was added to each well. In a separate plate, compounds were diluted in DMSO (200-fold over the final concentration in the assay well) and 50 nl was acoustically transferred to the appropriate well in the assay cell plate. The plates were then incubated for 60 minutes at 37 degrees in a 5% CO₂ incubator. 10 ul of detection buffer (also prepared as described in the IP-One kit) was added to each well and the plates were incubated at room temperature for 60 minutes in the dark. The plates were then read in a Perkin Elmer EnVision or equivalent reader able to measure FRET. Fluorescent ratio of emission at 665 and 620 nm was then converted to the IP1 concentration by back calculating from an IP1 standard curve prepared at the time of the assay. The data was normalized to % activity using a reference compound, and the EC₅₀ values were determined using a standard 4-parameter fit.

The compounds of the present invention, including the compounds in Examples 1-157, have EC₅₀ values $\leq$ 10,000 nanomolar (nM) in the Human GPR120 IP1 Assay described above. Specific EC₅₀ values in the Human GPR120 IP1 Assay are provided in Table I.

Table I. Specific EC₅₀ values in the Human GPR120 IP1 Assay

Example	hGPR120 EC ₅₀
1	61

2	17
3	29
4	51
5	65
6	417
7	533
8	414
9	20
10	14
11	15
12	24
13	18
14	20
15	22
16	22
17	23
18	24
19	27
20	29
21	51
22	56
23	60
24	61
25	65
26	97
27	61
28	169
29	171
30	134
31	182
32	233

33	192
34	184
35	312
36	348
37	377
38	405
39	417
40	463
41	569
42	798
43	1466
44	2365
45	2291
46	5392
47	91
48	596
49	223
50	348
51	317
52	510
53	533
54	1683
55	25
56	40
57	Isomer 1: 58; Isomer 2: 231
58	472
59	1634
60	60
61	28
62	3
63	14

64	15
65	37
66	41
67	40
68	58
69	231
70	472
71	309
72	1174
73	1634
74	60
75	358
76	845
77	5880
78	19
79	471
80	3123
81	48
82	25
83	100
84	118
85	40
86	61
87	74
88	110
89	185
90	250
91	59
92	482
93	350
94	473

95	491
96	834
97	1581
98	100
99	127
100	251
101	273
102	118
103	2999
104	4036
105	6606
106	83
107	122
108	122
109	22
110	42
111	32
112	42
113	59
114	61
115	83
116	107
117	143
118	215
119	273
120	299
121	73
122	121
123	766
124	824
125	414

126	9742
127	35
128	Isomer 1: 312; Isomer 2: 209
129	92
130	87
131	174
132	406
133	50
134	41
135	77
136	87
137	93
138	92
139	187
140	209
141	288
142	312
143	395
144	4300
145	174
146	309
147	141
148	9
149	33
150	16
151	34
152	69
153	87
154	167
155	17
156	62

157	15
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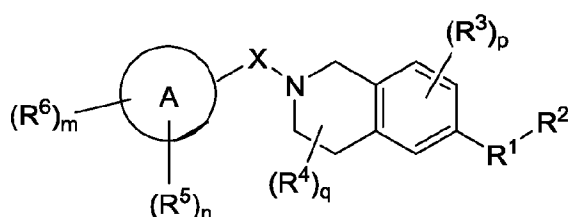
EXAMPLE OF A PHARMACEUTICAL FORMULATION

As a specific embodiment of an oral composition of a compound of the present invention, 50 mg of any of the examples is formulated with sufficient finely divided lactose to provide a
5 total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

While the invention has been described and illustrated in reference to specific embodiments thereof, various changes, modifications, and substitutions can be made therein without departing from the invention. For example, alternative effective dosages may be applicable, based upon the responsiveness of the patient being treated. Likewise, the
10 pharmacologic response may vary depending upon the particular active compound selected, formulation and mode of administration. All such variations are included within the present invention.

CLAIMS

1. A compound according to the formula I:



5

I

or a pharmaceutically acceptable salt thereof, wherein:

X is

- (1) bond,
 (2) (C₁₋₂)alkyl, or
 (3) halo(C₁₋₂)alkyl;

10

ring A is

- (1) aryl,
 (2) 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms
 independently selected from N, O and S, or
 (3) 9- or 10-membered fused heteroaryl containing 1, 2, or 3 heteroatoms
 independently selected from N, O, and S;

15

R¹ is

- (1) bond,
 (2) (C₁₋₆)alkyl,
 (3) -O-(C₁₋₆)alkyl-, or
 (4) (C₃₋₆)cycloalkyl;

20

R² is

25

- (1) hydrogen,
 (2) hydroxy,

- 5
- (3) COOH,
 - (4) tetrazole,
 - (5) hydroxyisoxazole,
 - (6) triazole,
 - (7) C(O)NH₂,
 - (8) C(O)NHC₁₋₆alkyl,
 - (9) C(O)NHC₃₋₆cycloalkyl,
 - (10) C(O)NHC₂₋₅cycloheteroalkyl,
 - (11) C(O)NH-aryl,

10

 - (12) C(O)NH-heteroaryl,
 - (13) SO₂C₁₋₆alkyl,
 - (14) SO₂C₃₋₆cycloalkyl,
 - (15) SO₂C₂₋₅cycloheteroalkyl,
 - (16) SO₂-aryl, or

15

 - (17) SO₂-heteroaryl;

R³ is

- (1) hydrogen,
- (2) halogen,

20

- (3) cyano, or
- (4) (C₁₋₃)alkyl;

R⁴ is

- (1) hydrogen,

25

- (2) (C₁₋₃)alkyl,
- (3) halo(C₁₋₃)alkyl, or
- (4) halogen;

R⁵ is

- 30
- (1) cyano,
 - (2) (C₁₋₃)alkyl,

- (3) halo(C₁₋₃)alkyl,
- (4) (C₁₋₃)alkoxy,
- (5) halo(C₁₋₃)alkoxy, or
- (6) halogen;

5

R⁶ is

- (1) (C₁₋₃)alkoxy,
 - (2) halo(C₁₋₃)alkoxy,
 - (3) halo(C₁₋₃)alkyl,
 - (4) (C₃₋₆)cycloalkyl,
 - (5) (C₃₋₆)cycloalkyl-O-,
 - (6) (C₃₋₆)cycloalkyl-S-,
 - (7) (C₃₋₆)cycloalkyl-(C₁₋₂)alkyl-,
 - (8) (C₃₋₆)cycloalkyl-halo(C₁₋₂)alkyl-,
 - (9) phenyl,
 - (10) 5- to 6-membered heteroaryl-O- wherein the heteroaryl contains 1, 2, or 3 heteroatoms independently selected from N, O and S, or
 - (11) 5- to 6-membered heteroaryl- wherein the heteroaryl contains 1, 2, or 3 heteroatoms independently selected from N, O and S,
- wherein alkyl, cycloalkyl, phenyl and heteroaryl are unsubstituted or substituted with 1-3 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and halogen;

10

15

20

n is 0, 1, 2 or 3;

25 m is 0 or 1;

p is 0, 1, 2 or 3; and

q is 0, 1, or 2.

2. The compound of Claim 1 wherein X is

30

- (1) bond, or
- (2) (C₁₋₂)alkyl;

or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1 wherein X is a bond; or a pharmaceutically acceptable salt thereof.

5

4. The compound of Claim 1 wherein ring A is phenyl, pyridine, pyrimidine, pyrazole, pyrazine, isothiazole, or benzisoxazole; or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 1 wherein R² is

10

(1) hydrogen,

(2) hydroxy,

(3) COOH, or

(4) tetrazole;

or a pharmaceutically acceptable salt thereof.

15

6. The compound of Claim 9 wherein R² is COOH; or a pharmaceutically acceptable salt thereof.

7. The compound of Claim 1 wherein R³ is

20

(1) hydrogen,

(2) halogen, or

(3) (C₁₋₃)alkyl;

or a pharmaceutically acceptable salt thereof.

8. The compound of Claim 1 wherein R³ is

25

(1) hydrogen, or

(2) halogen;

or a pharmaceutically acceptable salt thereof.

9. The compound of Claim 1 wherein R⁴ is

30

(1) hydrogen, or

(2) (C₁₋₃)alkyl;

or a pharmaceutically acceptable salt thereof.

10. The compound of Claim 1 wherein R⁴ is hydrogen; or a pharmaceutically
5 acceptable salt thereof.

11. The compound of Claim 1 wherein R⁵ is

(1) cyano,

(2) (C₁₋₃)alkyl,

10 (3) halo(C₁₋₃)alkyl,

(4) (C₁₋₃)alkoxy, or

(5) halogen;

or a pharmaceutically acceptable salt thereof.

15 12. The compound of Claim 1 wherein R⁵ is

(1) cyano, or

(2) halogen;

or a pharmaceutically acceptable salt thereof.

20 13. The compound of Claim 1 wherein R⁶ is

(1) halo(C₁₋₃)alkoxy,

(2) halo(C₁₋₃)alkyl,

(3) (C₃₋₆)cycloalkyl,

(4) (C₃₋₆)cycloalkyl-O-,

25 (5) (C₃₋₆)cycloalkyl-S-,

(6) (C₃₋₆)cycloalkyl-(C₁₋₂)alkyl-,

(7) phenyl,

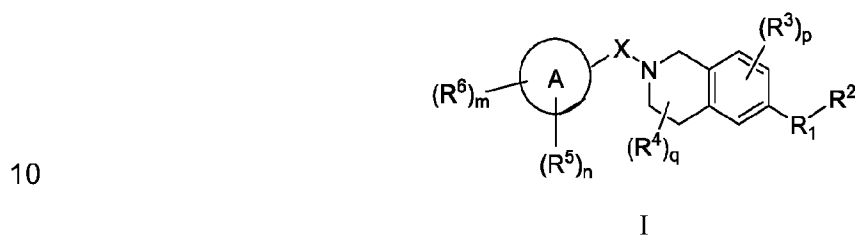
(8) 5- to 6-membered heteroaryl-O- wherein the heteroaryl contains 1, 2, or 3
heteroatoms independently selected from N, O and S, or

30 (9) 5- to 6-membered heteroaryl- wherein the heteroaryl contains 1, 2, or 3
heteroatoms independently selected from N, O and S,

wherein alkyl, cycloalkyl, phenyl and heteroaryl are unsubstituted or substituted with 1-3 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and halogen; or a pharmaceutically acceptable salt thereof.

- 5 14. The compound of Claim 1 wherein R⁶ is (C₃₋₆)cycloalkyl-O-, wherein cycloalkyl is unsubstituted or substituted with 1-3 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and halogen; or a pharmaceutically acceptable salt thereof.

15. A compound according to the formula I:



wherein:

X is

- 15 (1) a bond, or
 (2) (C₁₋₂)alkyl;

ring A is

- 20 (1) aryl,
 (2) 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from N, O and S, or
 (3) 9- or 10-membered fused heteroaryl containing 1, 2, or 3 heteroatoms independently selected from N, O, and S;

25 R¹ is

- (1) bond,
 (2) (C₁₋₆)alkyl,
 (3) -O-(C₁₋₆)alkyl-, or

(4) (C₃₋₆)cycloalkyl;

R² is

- 5 (1) hydrogen,
(2) hydroxy,
(3) COOH, or
(4) tetrazole;

R³ is

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

R⁴ is

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

R⁵ is

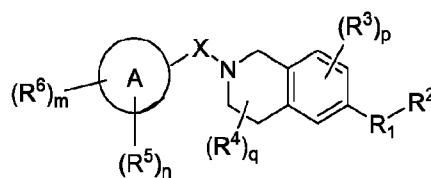
- 20 (1) cyano,
(2) (C₁₋₃)alkyl,
(3) halo(C₁₋₃)alkyl,
(4) (C₁₋₃)alkoxy, or
(5) halogen;

25 R⁶ is

- (1) halo(C₁₋₃)alkoxy,
(2) halo(C₁₋₃)alkyl,
(3) (C₃₋₆)cycloalkyl,
(4) (C₃₋₆)cycloalkyl-O-,
30 (5) (C₃₋₆)cycloalkyl-S-,
(6) (C₃₋₆)cycloalkyl-(C₁₋₂)alkyl-,

- (7) phenyl,
- (8) 5- to 6-membered heteroaryl-O- wherein the heteroaryl contains 1, 2, or 3 heteroatoms independently selected from N, O and S, or
- (9) 5- to 6-membered heteroaryl- wherein the heteroaryl contains 1, 2, or 3 heteroatoms independently selected from N, O and S,
- 5 wherein alkyl, cycloalkyl, phenyl and heteroaryl are unsubstituted or substituted with 1-3 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and halogen;
- 10 or a pharmaceutically acceptable salt thereof.

16. A compound according to the formula I:



I

15 wherein:

X is a bond;

ring A is aryl;

20

R¹ is (C₁₋₆)alkyl;

R² is COOH;

25 R³ is

- (1) hydrogen, or
- (2) halogen;

R⁴ is hydrogen;

R⁵ is

- (1) cyano, or
5 (2) halogen;

R⁶ is (C₃₋₆)cycloalkyl-O-, wherein cycloalkyl is unsubstituted or substituted with 1-3 substituents selected from (C₁₋₃)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy, halo(C₁₋₃)alkoxy, and halogen;

10

or a pharmaceutically acceptable salt thereof.

17. A compound of Claim 1 selected from the group consisting of:

- 15 1) 3-(2-(2-chloro-5-cyclobutoxy-4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoic acid;
- 2) 3-(2-(3-(difluoromethyl)-2-fluoro-5-(pyridin-2-yloxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid;
- 3) 3-(2-(2,3-difluoro-5-(3-methoxycyclobutoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoic acid;
- 20 4) 3-(2-(2-fluoro-4-methoxy-5-((5-methylthiazol-2-yl)oxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid;
- 5) 3-(2-(6-cyclobutoxy-3-fluoropyridin-2-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoic acid;
- 6) 3-(2-(5-cyclobutoxy-2-fluorophenyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoic acid;
- 25 7) 3-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)butanoic acid;
- 8) 3-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-butanoic acid;
- 30 9) 3-(2-(3-chloro-2-fluoro-5-[(5-methyl-1,3-thiazol-2-yl)oxy]phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid;

- 10) 3-{2-[5-(cyclobutyloxy)-3-(difluoromethyl)-2-fluorophenyl]-1,2,3,4-tetrahydro-
isoquinolin-6-yl}propanoic acid;
- 11) 3-{2-[5-(cyclobutyloxy)-2,3-difluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-
propanoic acid;
- 5 12) 3-{2-[3-cyano-5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetrahydroiso-
quinolin-6-yl}-propanoic acid;
- 13) 3-{2-[2-fluoro-3-methoxy-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydro-
isoquinolin-6-yl}propanoic acid;
- 14) 3-(2-{3-(difluoromethyl)-2-fluoro-5-[(5-methyl-1,3-thiazol-2-yl)oxy]phenyl}-1,2,3,4-
10 tetrahydroisoquinolin-6-yl)propanoic acid;
- 15) 3-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroiso-
quinolin-6-yl}propanoic acid;
- 16) 3-(2-{3-(difluoromethyl)-2-fluoro-5-[(5-methylpyridin-2-yl)oxy]phenyl}-1,2,3,4-tetra-
hydroisoquinolin-6-yl)propanoic acid;
- 15 17) 3-(2-{2-fluoro-3-methoxy-5-[(5-methyl-1,3-thiazol-2-yl)oxy]phenyl}-1,2,3,4-tetra-
hydroisoquinolin-6-yl)propanoic acid;
- 18) 3-{2-[5-(cyclobutyloxy)-2-fluoro-3-methoxyphenyl]-1,2,3,4-tetrahydroiso-
quinolin-6-yl}propanoic acid;
- 19) 3-{2-[5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic
20 acid;
- 20) 3-(2-{2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydro-
isoquinolin-6-yl)propanoic acid;
- 21) 3-(2-{2-fluoro-4-methoxy-5-[(5-methyl-1,3-thiazol-2-yl)oxy]phenyl}-1,2,3,4-tetra-
hydroisoquinolin-6-yl)propanoic acid;
- 25 22) 3-{2-[4-chloro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetra-
hydroisoquinolin-6-yl}propanoic acid;
- 23) 3-{2-[5-(cyclobutylmethyl)-2-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroiso-
quinolin-6-yl}propanoic acid;
- 24) 3-{2-[2-chloro-5-(cyclobutyloxy)-4-methoxyphenyl]-1,2,3,4-tetrahydroiso-
30 quinolin-6-yl}propanoic acid;
- 25) 3-{2-[6-(cyclobutyloxy)-3-fluoropyridin-2-yl]-1,2,3,4-tetrahydroisoquino-
lin-6-yl}-

- propanoic acid;
- 26) 3-{2-[2-(cyclobutylsulfanyl)-5-fluoropyridin-4-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;
- 27) 3-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;
- 5 28) 3-(2-{2-fluoro-4-methoxy-5-[(5-methylpyridin-2-yl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid;
- 29) 3-{2-[6-fluoro-3-(trifluoromethyl)-1,2-benzisoxazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 10 30) 3-{7-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 31) 3-{2-[5-(cyclobutyloxy)-2-fluoro-4-methoxyphenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 32) 3-{2-[5-(cyclobutyloxy)-2,3-difluorophenyl]-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 15 33) 3-{2-[2-fluoro-5-(pyrazin-2-yloxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 34) 3-(2-{3-cyano-2-fluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid;
- 20 35) 3-(2-{3-(difluoromethyl)-2-fluoro-5-[(5-fluoropyridin-2-yl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid;
- 36) 3-{2-[5-(cyclobutyloxy)-2-fluorophenyl]-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;
- 37) 3-{2-[2-chloro-5-(cyclobutyloxy)-3-fluorophenyl]-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 25 38) 3-{2-[6-(cyclobutylsulfanyl)pyridin-2-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;
- 39) 3-{2-[5-(cyclobutyloxy)-2-fluorophenyl]-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;
- 30 40) 3-{2-[3,5-dichloro-4-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;

- 41) 3-{2-[6-(cyclobutyloxy)pyrazin-2-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;
- 42) 3-{2-[2-cyano-5-(cyclobutyloxy)-4-methoxyphenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;
- 5 43) 3-{2-[4-cyano-1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 44) 3-{2-[2-cyano-3-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 45) 3-{2-[2-chloro-5-(cyclobutyloxy)-3-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;
- 10 46) 3-{2-[2-cyano-5-(cyclobutyloxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 47) 3-{2-[4-fluoro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 15 48) 3-(2-{2-cyano-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoic acid;
- 49) 3-{2-[5-(cyclobutyloxy)-2,3-difluorophenyl]-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;
- 50) 3-(2-{[3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-yl]methyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid;
- 20 51) 3-{8-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 52) 3-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-2-methyl-propanoic acid;
- 25 53) 3-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-butanoic acid;
- 54) 3-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;
- 55) 3-{2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-propanoic acid;
- 30 56) 3-(2-(5-(cyclobutyldifluoromethyl)-2-fluorophenyl)-5-fluoro-1,2,3,4-tetra-

- hydroisoquinolin-6-yl)propanoic acid;
- 57) 3-(2-(3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetra-
hydroisoquinolin-6-yl)-2-methylpropanoic acid;
- 58) 3-(5-fluoro-2-(2-fluoro-5-(trifluoromethoxy)phenyl)-7-methyl-1,2,3,4-tetra-
5 hydroisoquinolin-6-yl)propanoic acid;
- 59) 3-(2-(3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-yl)-5-fluoro-1,2,3,4-tetra-
hydro- isoquinolin-6-yl)propanoic acid;
- 60) 3-(2-(5-(cyclobutylmethyl)-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroiso-
quinolin-6-yl)- propanoic acid;
- 10 61) 3-(2-(5-cyclobutoxy-2-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydroisoquino-
lin-6-yl)-propanoic acid;
- 62) 3-(2-{3-chloro-2-fluoro-5-[(5-methyl-1,3-thiazol-2-yl)oxy]phenyl}-5-fluoro-1,2,3,4-
tetrahydroisoquinolin-6-yl)propanoic acid;
- 63) 3-{2-[6-(cyclobutyloxy)-3-fluoropyridin-2-yl]-5-fluoro-1,2,3,4-tetrahydro-
15 isoquinolin-6- yl}propanoic acid;
- 64) 3-{2-[5-(cyclobutyloxy)-2,3-difluorophenyl]-5-fluoro-1,2,3,4-tetrahydroiso-
quinolin-6- yl}propanoic acid;
- 65) 3-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetra-
hydroisoquinolin-6-yl}propanoic acid;
- 20 66) 3-(2-{2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-5-fluoro-1,2,3,4-tetra-
hydroisoquinolin-6-yl)propanoic acid;
- 67) 3-(2-{5-[cyclobutyl(difluoro)methyl]-2-fluorophenyl}-5-fluoro-1,2,3,4-
tetrahydroisoquinolin-6-yl)propanoic acid;
- 68) 3-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-
25 tetrahydroisoquinolin-6-yl}-2-methylpropanoic acid;
- 69) 3-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetra-
hydroisoquinolin-6-yl}-2-methylpropanoic acid;
- 70) 3-{5-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-7-methyl-1,2,3,4-tetra-
hydro- isoquinolin-6-yl}propanoic acid;
- 30 71) 3-{2-[4-chloro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-5-fluoro- 1,2,3,4-tetra-
hydroisoquinolin-6-yl}propanoic acid;

- 72) 3-{5-chloro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydro- isoquinolin-6-yl}propanoic acid;
- 73) 3-{2-[3-(4-chlorophenyl)-5-(trifluoromethyl)isothiazol-4-yl]-5-fluoro-1,2,3,4-tetrahydro-isoquinolin-6-yl}propanoic acid;
- 5 74) 3-{2-[5-(cyclobutylmethyl)-2-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydro-isoquinolin-6-yl}propanoic acid;
- 75) 3-[2-(5-{[3-(difluoromethyl)cyclobutyl]oxy}-2,3-difluorophenyl)-5-fluoro-1,2,3,4-tetra- hydroisoquinolin-6-yl]propanoic acid;
- 76) 3-{2-[2-cyano-5-(cyclobutyloxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroiso-quinolin-6-yl}propanoic acid;
- 10 77) 3-{5-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroiso-quinolin-6-yl}-2-methylpropanoic acid;
- 78) 3-{2-[2-cyano-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroiso-quinolin-6-yl}propanoic acid;
- 15 79) 3-(2-(2-cyano-5-cyclobutoxy-3-fluorophenyl)-5-fluoro-1,2,3,4-tetrahydro-isoquinolin-6- yl)-2-methylpropanoic acid;
- 80) 3-{5-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroiso-quinolin-6-yl}propanoic acid;
- 81) 3-{2-[5-(cyclobutyloxy)-2-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroiso-quinolin-6-yl} - propanoic acid;
- 20 82) 3-{2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-1,2,3,4-tetrahydroiso-quinolin-6-yl} - propanoic acid;
- 83) (1S,2S)-2-(2-(2,3-difluoro-5-((1R,3S)-3-methylcyclobutoxy)phenyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)cyclopropanecarboxylic acid;
- 25 84) 2-(2-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-cyclo- propanecarboxylic acid;
- 85) (1R,2R)-2-{2-[5-(cyclobutyloxy)-2,3-difluorophenyl]-1,2,3,4-tetrahydroiso-quinolin-6-yl}cyclopropane- carboxylic acid;
- 86) (1R,2R)-2-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetra- hydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 30 87) (1R,2R)-2-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroiso-

- quinolin-6-yl} cyclopropanecarboxylic acid;
- 88) (1S,2S)-2-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroiso-quinolin-6-yl} cyclopropanecarboxylic acid;
- 89) (1R,2R)-2-(2-{3-cyano-2-fluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl} - 1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 90) (1S,2S)-2-{2-[2-fluoro-5-(trifluoromethoxy)benzyl]-1,2,3,4-tetrahydroiso-quinolin-6-yl} cyclopropanecarboxylic acid;
- 91) (1S,2S)-2-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 92) 2-{2-[4-fluoro-1-(4-fluorophenyl)-3-methyl-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 93) (1S,2S)-2-{2-[3-chloro-2-fluoro-5-(trifluoromethyl)benzyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 94) 2-{2-[4-fluoro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 95) 2-{2-[4-fluoro-1-(4-fluorophenyl)-3-methyl-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 96) 2-{2-[4-fluoro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 97) (1S,2S)-2-(2-{2-cyano-3-methoxy-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 98) (1S,2S)-2-(2-{2,3-difluoro-5-[(trans-3-methylcyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 99) (1R,2R)-2-(2-{2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 100) (1S,2S)-2-(2-{2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 101) (1R,2R)-2-(2-{2,3-difluoro-5-[(trans-3-methylcyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 102) 2-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-cyclopropanecarboxylic acid;

- 103) (1R,2R)-2-(2-{2-cyano-3-fluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 104) 2-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 5 105) 2-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 106) (1S,2S)-2-(2-(2,3-difluoro-5-((1R,3S)-3-methoxycyclobutoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 107) (1S,2S)-2-(2-(3-cyano-2-fluoro-5-(trifluoromethoxy)phenyl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 10 108) (1S,2S)-2-(2-(2,3-difluoro-5-((1R,3S)-3-methylcyclobutoxy)phenyl)-4-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 109) (1R,2R)-2-{2-[3-cyano-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 15 110) (1R,2R)-2-(2-{2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 111) (1R,2R)-2-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 112) (1R,2R)-2-(2-{2,3-difluoro-5-[(trans-3-methylcyclobutyl)oxy]phenyl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 20 113) (1R,2R)-2-{5-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 114) (1R,2R)-2-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 25 115) (1S,2S)-2-(2-{2,3-difluoro-5-[(trans-3-methoxycyclobutyl)oxy]phenyl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)cyclopropanecarboxylic acid;
- 116) (1S,2S)-2-{2-[3-cyano-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 117) (1S,2S)-2-{2-[2-cyano-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}cyclopropanecarboxylic acid;
- 30 118) (1S,2S)-2-{5-fluoro-2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydro-

- isoquinolin-6-yl} cyclopropanecarboxylic acid;
- 119) (1S,2S)-2-{2-[2-cyano-3-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid;
- 120) (1S,2S)-2-{2-[3-chloro-2-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid;
- 5 121) (1R,2R)-2-{2-[2-chloro-3-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid;
- 122) (1S,2S)-2-(2-{2,3-difluoro-5-[(trans-3-methylcyclobutyl)oxy]phenyl}-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl) cyclopropanecarboxylic acid;
- 10 123) (1R,2R)-2-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid;
- 124) (1S,2S)-2-{2-[2-chloro-3-fluoro-5-(trifluoromethoxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid;
- 125) (1S,2S)-2-{2-[3-chloro-5-(cyclobutyloxy)-2-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid;
- 15 126) (1S,2S)-2-{2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl} cyclopropanecarboxylic acid;
- 127) 5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl) pentanoic acid;
- 20 128) 5-(2-(4-cyano-3-methyl-1-(p-tolyl)-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl) hexanoic acid;
- 129) 5-(6-hydroxy-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile;
- 130) 5-(6-(2-hydroxyethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(p-tolyl)-1H-pyrazole-4-carbonitrile;
- 25 131) 3-(2-(5-cyclobutoxy-2,3-difluorophenyl)-7-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl)-propanoic acid;
- 132) 6-(2-(1H-tetrazol-5-yl)ethyl)-2-(2,3-difluoro-5-((1R,3R)-3-methoxycyclobutoxy)-phenyl)-1,2,3,4-tetrahydroisoquinoline;
- 30 133) 5-{2-[4-cyano-1-(4-methoxyphenyl)-3-methyl-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl} pentanoic acid;

- 134) 5-{2-[4-cyano-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}pentanoic acid;
- 135) 5-{2-[2-fluoro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-pentanoic acid;
- 5 136) 5-[6-(2-hydroxyethoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-methyl-1-(4-methylphenyl)-1H-pyrazole-4-carbonitrile;
- 137) 5-{2-[4-chloro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}pentanoic acid;
- 138) 5-(6-hydroxy-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-1-(4-methylphenyl)-1H-pyrazole-4-carbonitrile;
- 10 139) 5-[6-(4-hydroxybutoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-methyl-1-(4-methylphenyl)-1H-pyrazole-4-carbonitrile;
- 140) 5-{2-[4-cyano-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}hexanoic acid;
- 15 141) 5-(3,4-dihydroisoquinolin-2(1H)-yl)-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-4-carbonitrile;
- 142) 5-{2-[4-cyano-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-1,2,3,4-tetrahydroisoquinolin-6-yl}hexanoic acid;
- 143) 3-(2-{[4-fluoro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]methyl}-1,2,3,4-tetrahydroisoquinolin-6-yl)propanoic acid;
- 20 144) 5-[6-(3-hydroxypropoxy)-3,4-dihydroisoquinolin-2(1H)-yl]-3-methyl-1-(4-methylphenyl)-1H-pyrazole-4-carbonitrile;
- 145) 3-{2-[5-(cyclobutyloxy)-2,3-difluorophenyl]-7-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 25 146) 3-{2-[4-chloro-3-methyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 147) 3-{2-[3-chloro-2-cyano-5-(cyclobutyloxy)phenyl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 148) 3-{2-[5-cyano-4-(cyclobutyloxy)-6-methylpyrimidin-2-yl]-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl}propanoic acid;
- 30 149) 3-{2-[5-cyano-2-(cyclobutyloxy)-6-methylpyrimidin-4-yl]-5-fluoro-1,2,3,4-

- tetrahydroisoquinolin-6-yl}propanoic acid;
- 150) 3-{5-chloro-2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-1,2,3,4-tetra-
hydroisoquinolin-6-yl}propanoic acid;
- 151) 3-[2-(6-cyclopropylpyridin-2-yl)-5-fluoro-1,2,3,4-tetrahydroisoquinolin-6-yl]-
5 propanoic acid;
- 152) 3-{2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-5-fluoro-1,2,3,4-tetra-
hydroisoquinolin-6-yl}propanoic acid;
- 153) 3-{2-[2,3-dichloro-5-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquino-
lin-6-yl}propanoic acid;
- 10 154) 3-{2-[2-cyano-5-(cyclobutyloxy)-3-fluorophenyl]-5-methyl-1,2,3,4-tetra-
hydroisoquinolin-6-yl}propanoic acid;
- 155) 3-{2-[6-(cyclobutyloxy)-3-fluoro-4-methoxypyridin-2-yl]-5-fluoro-1,2,3,4-
tetrahydroisoquinolin-6-yl}propanoic acid;
- 156) 3-{2-[3-cyano-6-(cyclobutyloxy)-2-methylpyridin-4-yl]-5-fluoro-1,2,3,4-
15 tetrahydroisoquinolin-6-yl}propanoic acid; and
- 157) 3-{2-[3-cyano-4-methyl-6-(1,3-thiazol-4-yl)pyridin-2-yl]-5-fluoro-1,2,3,4-
tetrahydroisoquinolin-6-yl}propanoic acid;
or a pharmaceutically acceptable salt thereof.
- 20 18. A pharmaceutical composition comprising a compound of Claim 1 in combination
with a pharmaceutically acceptable carrier.
19. A compound according to any of Claims 1-17 for use as a medicament.
- 25 20. A compound according to any of Claims 1-17 for use in the treatment of diabetes,
obesity, hyperlipidemia, or an inflammation related disorder.
21. Use of a compound of any of Claims 1-17, or a pharmaceutically acceptable salt
thereof, in the manufacture of a medicament for use in treating a condition selected from the
30 group consisting of diabetes, hyperlipidemia, obesity, and inflammation related disorders.

22. A method for the treatment of a condition selected from the group consisting of diabetes, hyperlipidemia, obesity, and inflammation related disorders comprising administering to an individual a pharmaceutical composition comprising the compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/083265

A. CLASSIFICATION OF SUBJECT MATTER

C07D 217/16(2006.01)i; C07D 401/04(2006.01)i; C07D 401/12(2006.01)i; C07D 403/04(2006.01)i; C07D 413/04(2006.01)i; C07D 417/12(2006.01)i; C07D 417/14(2006.01)i; A61K 31/4725(2006.01)i; A61P 3/04(2006.01)i; A61P 3/10(2006.01)i; A61P 3/00(2006.01)i

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)

C07D; A61K; A61P

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

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

WPI,EPDOC,CNABS,CNXT,CNKI,REGISTRY(STN),CAPLUS(STN);+isoquinolin,GPR120,protein+,receptor,diabete?, obesity,hyperlipidemia,fatty lw liver,inflammation;structure search in STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007089557 A2 (IRM LLC, ET AL.) 09 August 2007 (2007-08-09) description, paragraphs [0004]-[0005], [0007], [0021]-[0022], examples A1, C1, table 1	1-22
X	WO 2007022280 A1 (MEMORY PHARM. CORP., ET AL.) 22 February 2007 (2007-02-22) abstract, description, paragraphs [0009]-[0010], [0015], [00124]-[00125], [00210]-[00212], example 14, table 1	1-3, 5-11, 13-15, 18-22
E	WO 2016109515 A1 (FORMA THERAPEUTICS, INC.) 07 July 2016 (2016-07-07) description, example 8, intermediate 2-8	1-15, 19-20
X	WO 2013019682 A1 (TEMPERO PHARMACEUTICALS, INC., ET AL.) 07 February 2013 (2013-02-07) description, page 153, lines 16-22	1-11, 13-15, 19-20
X	WO 2008109336 A1 (JANSSEN PHARMACEUTICA N.V., ET AL.) 12 September 2008 (2008-09-12) description, example 14, step B	1-2, 4-11, 13-15, 19-20

☒ 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
 "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

03 February 2017

Date of mailing of the international search report

17 February 2017

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/083265

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005165049 A1 (HULME, CHRISTOPHER, ET AL.) 28 July 2005 (2005-07-28) description, examples 22-23	1-15, 19-20
A	WO 2004103997 A1 (PFIZER PRODUCTS INC., ET AL.) 02 December 2004 (2004-12-02) the whole document	1-22
X	BUZARD, Daniel, et al. "Discovery and characterization of potent and selective 4-oxo-4-(5-(5-phenyl-1, 2, 4-oxadiazol-3-yl)indolin-1-yl)butanoic acids as S1P1 agonists" <i>Bioorganic & Medicinal Chemistry Letters</i> , Vol. 21, 06 June 2011 (2011-06-06), ISSN: 0960-894x, pages 6013-6018, see page 6015, figure 3, compound 16	1-3, 5-11, 13-15, 18-20
X	American Chemical Society. "RN 1538454-34-0" <i>REGISTRY(STN)</i> , 06 February 2014 (2014-02-06),	1-2, 4-15, 19-20
X	American Chemical Society. "RN 1029720-61-3" <i>REGISTRY(STN)</i> , 22 June 2008 (2008-06-22),	1-2, 4-15, 19-20
X	American Chemical Society. "RN 1458775-32-0" <i>REGISTRY(STN)</i> , 15 October 2013 (2013-10-15),	1-2, 4-5, 7, 9-15, 19-20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/083265

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.: 22
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claim 22 is directed to a method of treatment of the human/animal body, but the search has been carried out and based on the use of the claimed compounds for manufacturing medicaments for treating the alleged diseases.
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.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2016/083265

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
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				WO	2007089557	A3	08 November 2007
				CA	2627682	A1	09 August 2007
				BR	PI0706782	A2	05 April 2011
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				EP	1979347	A2	15 October 2008
				RU	2008135126	A	10 March 2010
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				EP	2125741	A1	02 December 2009
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				CA	2525501	A1	02 December 2004
				US	2004248934	A1	09 December 2004
				US	6987118	B2	17 January 2006