

COMPOSITIONS AND METHODS OF USE TO TREAT 12-LIPOXYGENASE (12-LOX) MEDIATED DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/509,699, filed June 22, 2023, which is incorporated herein by reference in its entirety.

FIELD

[0002] The present disclosure provides compounds and compositions thereof for use in treating diseases, such as diseases mediated by 12-lipoxygenase (12-LOX). The disclosure further provides compounds and compositions thereof for the treatment of heparin-induced thrombocytopenia (HIT), type 1 diabetes (T1D), lupus (SLE), and lupus nephritis.

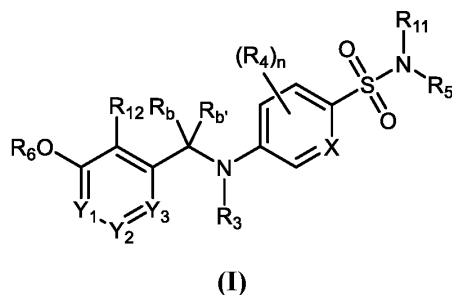
BACKGROUND

[0003] Regulation of platelet function is essential for the prevention and treatment of cardiovascular atherothrombotic events, such as coronary artery disease and stroke. While current antiplatelet drugs effectively inhibit platelet function and prevent thrombotic complications, these treatments often increase the risk of unwanted bleeding. Therefore, there is an unmet need for the identification of novel antiplatelet targets that block unnecessary platelet activation in disease conditions and reverse platelet inhibition with a minimal risk of bleeding. Platelet adhesion and aggregation at the site of vascular injury are essential for maintaining normal hemostasis and preventing blood loss. However, the same processes can also lead to the development of arterial thrombosis and vessel occlusion when the integrity of the vessel wall is compromised by rupture of an atherosclerotic plaque. Excessive platelet activation and aggregation may lead to the formation of occlusive thrombi and result in severe consequences, such as myocardial infarction, ischemic stroke, and pulmonary embolism, which are the predominant causes of morbidity and mortality worldwide. Antiplatelet therapy is considered a gold standard for its effectiveness in preventing aberrant platelet activation and pivotal in the treatment of cardiovascular atherothrombotic events to reduce morbidity and mortality. Currently approved antiplatelet therapies inhibit platelet function by targeting platelet enzymes, receptors, and glycoproteins. Although these therapeutic approaches limit platelet function, they often result in a concomitant increased risk of bleeding. Therefore, a need exists for the identification of novel antiplatelet therapeutic targets that limit bleeding.

[0004] 12-lipoxygenase (12-LOX) is an enzyme that oxidizes fatty acids, generates proinflammatory metabolites and has been implicated in a myriad of diseases including heparin-induced thrombocytopenia (HIT), type 1 diabetes (T1D), lupus (SLE), and lupus nephritis. As such, there is a need to develop therapies for these diseases.

SUMMARY

[0005] In some embodiments, the present disclosure provides a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

X is N or CR₄;

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R_b and R_{b'} are each independently H, F, or CH₃, or R_b and R_{b'} taken together with the carbon atom to which they are attached form a cyclopropyl;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, or R₃ and Y₃ taken together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl;

R₄ is each independently hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is each independently hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

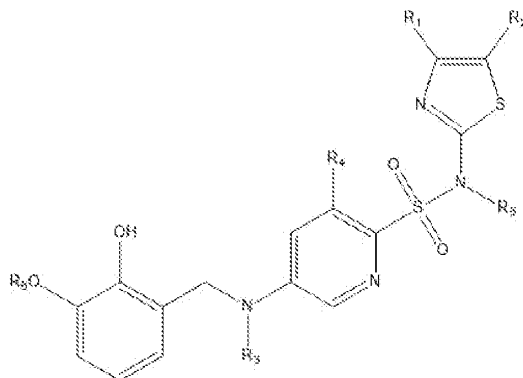
R₁₀ is hydrogen or halogen;

R₁₁ is C₆-C₁₂ aryl or 5- to 14-membered heteroaryl, each of which is substituted with one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, aryl, -(C₁-C₃ alkylene)-aryl, C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl), 3- to 14-membered heterocyclyl, and -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl); and

n is 1 or 2,

with the proviso that when X is CR₄, at least one R₄ is not H.

[0006] Further provided herein is a compound of Formula (Ia)



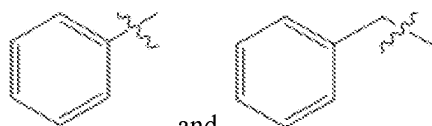
(Ia)

or a pharmaceutically acceptable salt thereof,

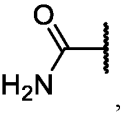
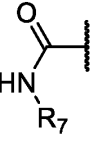
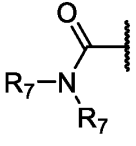
wherein

R₁ is H, C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, or C₁-C₃-alkylene-C₆-C₁₄-aryl, each of which is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or 3- to 14-membered heterocyclic ring;

R₂ is H, CN, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₂-C₆ alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₁-C₃-alkylene-C₃-C₈-cycloalkyl, substituted or unsubstituted C₃-C₈-cycloalkylene-C₁-C₃-alkyl, C₁-C₃-alkylene-C₆-C₁₄-aryl, substituted or unsubstituted C₆-C₁₄ aryl and aralkyl



including and , substituted or unsubstituted 3- to 14-membered heterocyclic ring including pyrazolyl, pyridinyl, pyrimidinyl, oxetanyl, and

imidazolyl, or amide including , , and , wherein R₇ is independently selected from C₁-C₃ alkyl, C₃-C₈ cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 3- to 14-membered heterocyclic ring, including pyrazolyl, pyridinyl, pyrimidinyl, oxetanyl, and imidazolyl;

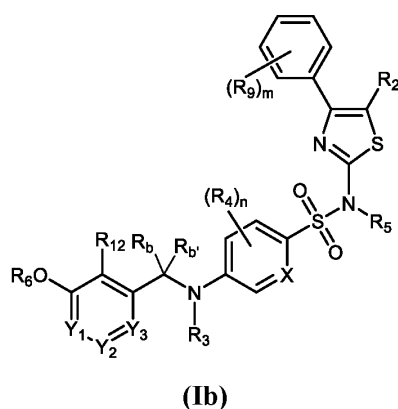
R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₄ is hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl; and

R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl.

[0007] Further provided herein is a compound of Formula (Ib):



or a pharmaceutically acceptable salt thereof,

wherein

X is N or CR₄;

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R_b and R_{b'} are each independently H, F, or CH₃, or R_b and R_{b'} taken together with the carbon atom to which they are attached form a cyclopropyl;

R₂ is a halogen or a substituted or unsubstituted group selected from the group consisting of 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl), C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), phenyl, and -(C₁-C₃ alkylene)-phenyl;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, or R₃ and Y₃ taken together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl;

R₄ is each independently hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₉ is each independently halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy or 3- to 14-membered heterocyclic ring;

R₁₀ is hydrogen or halogen;

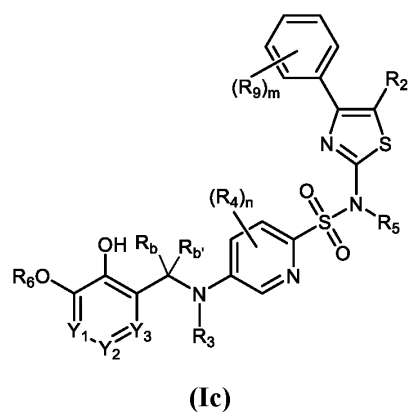
R₁₂ is halogen, -OH, or -OR₆;

m is 0, 1, 2, or 3; and

n is 1 or 2,

with the proviso that when X is CR₄, at least one R₄ is not H.

[0008] Further provided herein is a compound of Formula (Ic):



or a pharmaceutically acceptable salt thereof,

wherein

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R_b and R_{b'} are each independently H, F, or CH₃, or R_b and R_{b'} taken together with the carbon atom to which they are attached form a cyclopropyl;

R₂ is a substituted or unsubstituted group selected from the group consisting of 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl), C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), phenyl, and -(C₁-C₃ alkylene)-phenyl;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₄ is hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

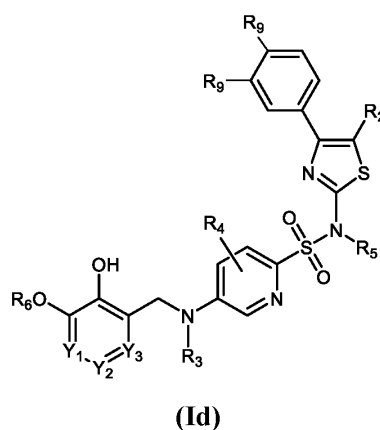
R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₉ is each independently halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy or 3- to 14-membered heterocyclic ring;

R₁₀ is hydrogen or halogen; and

m is 0, 1, 2, or 3.

[0009] Further provided herein is a compound of Formula (Id):



or a pharmaceutically acceptable salt thereof,

wherein

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R₂ is a substituted or substituted group selected from the group consisting of 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl), C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), phenyl, and -(C₁-C₃ alkylene)-phenyl;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₄ is hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

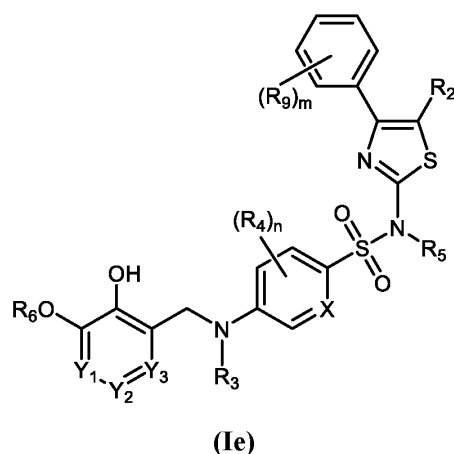
R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₉ is each independently F, Cl, CF₃, CHF₂, CH₂F, cyclopropyl, or oxetanyl; and

R₁₀ is hydrogen or halogen.

[0010] Further provided herein is a compound of Formula (Ie):

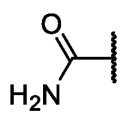


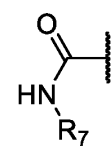
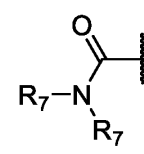
or a pharmaceutically acceptable salt thereof,
wherein

X is C-R₄ or N;

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R₂ is H, CN, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₂-C₆ alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₁-C₃-alkylene-C₃-C₈-cycloalkyl, substituted or unsubstituted C₃-C₈-cycloalkylene-C₁-C₃-alkyl, substituted or unsubstituted C₁-C₃-alkylene-C₆-C₁₄-aryl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted 3- to 14-membered heterocyclic ring, substituted or unsubstituted 5- to 14-membered heteroaryl, substituted or unsubstituted -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclic ring), substituted or unsubstituted -(C₁-C₃ alkylene)-(5- to

14-membered heteroaryl), or amide selected from the group consisting of ,

, and , wherein R₇ is independently selected from C₁-C₃ alkyl, C₃-C₈ cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted 4- to 6-membered heterocyclic ring, or 5- or 6-membered heteroaryl;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₄ is H, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₉ is each independently halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy or 3- to 14-membered heterocyclic ring;

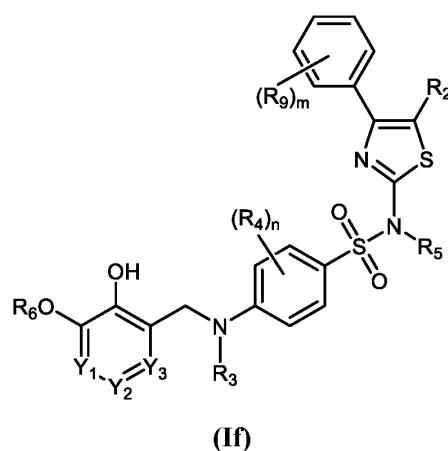
R₁₀ is hydrogen or halogen; and

m is 0, 1, 2, or 3; and

n is 1 or 2,

with the proviso that at least one of R₁₀ is not H or at least one of Y₁, Y₂, and Y₃ is N.

[0011] Further provided herein is a compound of Formula (If):



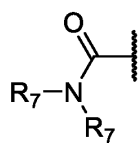
or a pharmaceutically acceptable salt thereof,

wherein

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R₂ is H, CN, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₂-C₆ alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₁-C₃-alkylene-C₃-C₈-cycloalkyl, substituted or unsubstituted C₃-C₈-cycloalkylene-C₁-C₃-alkyl, substituted or unsubstituted C₁-C₃-alkylene-C₆-C₁₄-aryl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted 3- to 14-membered heterocyclic ring, 5- to 14-membered heteroaryl, substituted or unsubstituted -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclic ring), substituted or unsubstituted -(C₁-C₃ alkylene)-(5- to 14-membered

heteroaryl), or amide selected from the group consisting of , , and



, wherein R₇ is independently C₁-C₃ alkyl, C₃-C₈ cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted 4- to 6-membered heterocyclic ring, or 5- or 6-membered heteroaryl;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₄ is CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₉ is each independently halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy or 3- to 14-membered heterocyclic ring;

R₁₀ is hydrogen or halogen;

m is 0, 1, 2, or 3; and

n is 1 or 2.

[0012] In some embodiments, the compound of the formulas disclosed herein is not a compound disclosed in WO2023/122494. In some embodiments, the compound of the formulas disclosed herein is not a compound disclosed in Table A.

[0013] Further provided herein is a pharmaceutical composition comprising any one of the compounds disclosed herein and one or more pharmaceutically acceptable carriers or excipients.

[0014] Further provided herein is a method of treating a disease or condition mediated by 12-lipoxygenase (12-lox), comprising administering to a subject in need thereof an effective amount of any one of the compounds disclosed herein or any one of the compositions disclosed herein.

DETAILED DESCRIPTION

Definitions

[0015] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein.

[0016] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the

Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0017] The articles "a" and "an" are used in this disclosure to refer to one or more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0018] The term "and/or" is used in this disclosure to mean either "and" or "or" unless indicated otherwise.

[0019] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[0020] As used herein, the term "bivalent C_{1 to n} saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0021] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C₃-C₈ hydrocarbon that is saturated or that contains one or more units of unsaturation but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0022] The term, "hydrogen" as used here when referring to an atomic substituent, means a covalent hydrogen atom, as in, -H.

[0023] “Alkyl” or “alkyl group” refers to a fully saturated, straight or branched hydrocarbon chain having from one to twelve carbon atoms, and which is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 12 are included. An alkyl comprising up to 12 carbon atoms is a C₁-C₁₂ alkyl, an alkyl comprising up to 10 carbon atoms is a C₁-C₁₀ alkyl, an alkyl comprising up to 6 carbon atoms is a C₁-C₆ alkyl and an alkyl comprising up to 5 carbon atoms is a C₁-C₅ alkyl. A C₁-C₅ alkyl includes C₅ alkyls, C₄ alkyls, C₃ alkyls, C₂ alkyls and C₁ alkyl (*i.e.*, methyl). A C₁-C₆ alkyl includes all moieties described above for C₁-C₅ alkyls but also includes C₆ alkyls. A C₁-C₁₀ alkyl includes all moieties described above for C₁-C₅ alkyls and C₁-C₆ alkyls, but also includes C₇, C₈, C₉ and C₁₀ alkyls. Similarly, a C₁-C₁₂ alkyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkyls. Non-limiting examples of C₁-C₁₂ alkyl include methyl, ethyl, *n*-propyl, *i*-propyl, *sec*-propyl, *n*-butyl, *i*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, *t*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl, and *n*-dodecyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0024] Alkyl may be generally lower alkyl, or C₁-C₆ alkyl. Examples of a C₁-C₆ alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, isopentyl, neopentyl, and isohexyl.

[0025] “C₁-C₃ alkyl” refers to a straight or branched chain saturated hydrocarbon containing 1-3 carbon atoms. Examples of a C₁-C₃ alkyl group include, but are not limited to, methyl, ethyl, propyl and isopropyl.

[0026] “C₁-C₅ alkyl” refers to a straight or branched chain saturated hydrocarbon containing 1-5 carbon atoms. Examples of a C₁-C₅ alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, isopentyl and neopentyl.

[0027] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, *i.e.*, $-(CH_2)_n-$, wherein *n* is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0028] “Alkenyl” or “alkenyl group” refers to a straight or branched hydrocarbon chain having from two to twelve carbon atoms and having one or more carbon-carbon double bonds. Each alkenyl group is attached to the rest of the molecule by a single bond. Alkenyl group comprising any number of carbon atoms from 2 to 12 are included. An alkenyl group comprising up to 12 carbon atoms is a C₂-C₁₂ alkenyl, an alkenyl comprising up to 10 carbon

atoms is a C₂-C₁₀ alkenyl, an alkenyl group comprising up to 6 carbon atoms is a C₂-C₆ alkenyl and an alkenyl comprising up to 5 carbon atoms is a C₂-C₅ alkenyl. A C₂-C₅ alkenyl includes C₅ alkenyls, C₄ alkenyls, C₃ alkenyls, and C₂ alkenyls. A C₂-C₆ alkenyl includes all moieties described above for C₂-C₅ alkenyls but also includes C₆ alkenyls. A C₂-C₁₀ alkenyl includes all moieties described above for C₂-C₅ alkenyls and C₂-C₆ alkenyls, but also includes C₇, C₈, C₉ and C₁₀ alkenyls. Similarly, a C₂-C₁₂ alkenyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkenyls. Non-limiting examples of C₂-C₁₂ alkenyl include ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, 9-decenyl, 1-undecenyl, 2-undecenyl, 3-undecenyl, 4-undecenyl, 5-undecenyl, 6-undecenyl, 7-undecenyl, 8-undecenyl, 9-undecenyl, 10-undecenyl, 1-dodecenyl, 2-dodecenyl, 3-dodecenyl, 4-dodecenyl, 5-dodecenyl, 6-dodecenyl, 7-dodecenyl, 8-dodecenyl, 9-dodecenyl, 10-dodecenyl, and 11-dodecenyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0029] The term “alkenylene” refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0030] “Alkynyl” or “alkynyl group” refers to a straight or branched hydrocarbon chain having from two to twelve carbon atoms, and having one or more carbon-carbon triple bonds. Each alkynyl group is attached to the rest of the molecule by a single bond. Alkynyl group comprising any number of carbon atoms from 2 to 12 are included. An alkynyl group comprising up to 12 carbon atoms is a C₂-C₁₂ alkynyl, an alkynyl comprising up to 10 carbon atoms is a C₂-C₁₀ alkynyl, an alkynyl group comprising up to 6 carbon atoms is a C₂-C₆ alkynyl and an alkynyl comprising up to 5 carbon atoms is a C₂-C₅ alkynyl. A C₂-C₅ alkynyl includes C₅ alkynyls, C₄ alkynyls, C₃ alkynyls, and C₂ alkynyls. A C₂-C₆ alkynyl includes all moieties described above for C₂-C₅ alkynyls but also includes C₆ alkynyls. A C₂-C₁₀ alkynyl includes all moieties described above for C₂-C₅ alkynyls and C₂-C₆ alkynyls, but also includes C₇, C₈, C₉ and C₁₀ alkynyls. Similarly, a C₂-C₁₂ alkynyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkynyls. Non-limiting examples of C₂-C₁₂ alkenyl

include ethynyl, propynyl, butynyl, pentynyl and the like. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[0031] The term “alkynylene” refers to a bivalent alkynyl group. A substituted alkynylene chain is a polymethylene group containing at least one triple bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0032] Alkyloxy and alkoxy can be used interchangeably and generally refer to lower alkoxy, or C₁-C₆ alkoxy. Examples of a C₁-C₆ alkoxy group include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, isopropoxy, isobutoxy, sec-butoxy, tert-butoxy, isopentoxy, neopentoxy, and isohexoxy. Alkoxy is generally alkyl covalently bonded to oxygen.

[0033] Halogen may be F, Cl, Br or I.

[0034] Haloalkyl may be generally lower haloalkyl, or C₁-C₆ haloalkyl, or C₁-C₃ alkyl. Examples of C₁-C₃ haloalkyl include -CH₂F, -CHF₂, -CF₃, -CH₂Cl, -CHCl₂, -CCl₃, -CF₂CF₃, -CF₂CF₂H, and -CH₂CF₃.

[0035] Haloalkyloxy and haloalkoxy may be used interchangeably and generally refer to a lower haloalkyl, e.g., C₁-C₆ haloalkyl or C₁-C₃ haloalkyl, bonded to oxygen. Examples of C₁-C₃ haloalkoxy include -OCH₂F, -OCHF₂, -OCF₃, -OCH₂Cl, -OCHCl₂, -OCCl₃, -OCF₂CF₃, -OCF₂CF₂H, and -OCH₂CF₃.

[0036] “C₃-C₈ cycloalkyl” means monocyclic saturated carbon rings containing 3-8 carbon atoms. Examples of a C₃-C₈ cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctanyl.

[0037] Heterocycloalkyl means monocyclic saturated carbon rings taken from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctanyl wherein a heteroatom, e.g., nitrogen, oxygen, or sulfur, is bonded to two carbons in the ring.

[0038] As used herein, the term “cyclopropylenyl” refers to a bivalent cyclopropyl group of



the following structure:

[0039] The term “halogen” or “halo” refers to a covalently bonded halogen atom, such as, -F, -Cl, -Br, or -I. The term “fluorine” as used herein refers to a covalently bonded fluorine atom as in, -F. As used herein, the same is applicable for chlorine (-Cl), bromine (-Br), and iodine (-I).

[0040] The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” “aralkoxy,” or “aryloxyalkyl,” refers to monocyclic or bicyclic ring systems having a total of six to fourteen ring members, wherein at least one ring in the system is an aromatic hydrocarbon ring, and wherein each ring in the system contains 3 to 7 ring members. The term “aryl” may be used interchangeably with the term “aryl ring.” In certain embodiments of the present invention, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term “aryl,” as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0041] The terms “heteroaryl” and “heteroar-,” used alone or as part of a larger moiety, e.g., “heteroaralkyl,” or “heteroaralkoxy,” refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons (i.e., $4n + 2 \pi$ electrons, wherein n is 1, 2, or 3) shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term “heteroatom” refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizynyl, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar-,” as used herein, also include groups in which one or more heteroaromatic rings is fused to one or more aryl, cycloaliphatic (e.g., cycloalkyl), or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinolizynyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A heteroaryl group may be mono- or bicyclic. The term “heteroaryl” may be used interchangeably with the terms “heteroaryl ring,” “heteroaryl group,” or “heteroaromatic,” any of which terms include rings that are optionally substituted. The term “heteroaralkyl” refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0042] As used herein, the terms “heterocycle,” “heterocyclyl,” “heterocyclic radical,” and “heterocyclic ring” are used interchangeably and refer to a stable 3- to 14- membered

monocyclic or bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0043] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle," "heterocyclyl," "heterocyclic ring," "heterocyclic group," "heterocyclic moiety," and "heterocyclic radical," are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be mono- or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0044] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0045] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow

for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0046] Each optional substituent on a substitutable carbon is a monovalent substituent independently selected from halogen; $-\text{CN}$; $-(\text{CH}_2)_{0-4}\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{OR}^\circ$; $-\text{O}(\text{CH}_2)_{0-4}\text{R}^\circ$; $-\text{O}-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{OR}^\circ$; $-(\text{CH}_2)_{0-4}\text{CH}(\text{OR}^\circ)_2$; $-(\text{CH}_2)_{0-4}\text{SR}^\circ$; $-(\text{CH}_2)_{0-4}\text{Ph}$, which may be substituted with R° ; $-(\text{CH}_2)_{0-4}\text{O}(\text{CH}_2)_{0-1}\text{Ph}$ which may be substituted with R° ; $-\text{CH}=\text{CHPh}$, which may be substituted with R° ; $-(\text{CH}_2)_{0-4}\text{O}(\text{CH}_2)_{0-1}\text{-pyridyl}$ which may be substituted with R° ; $-\text{NO}_2$; $-\text{CN}$; $-\text{N}_3$; $-(\text{CH}_2)_{0-4}\text{N}(\text{R}^\circ)_2$; $-(\text{CH}_2)_{0-4}\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{R}^\circ$; $-\text{N}(\text{R}^\circ)\text{C}(\text{S})\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{NR}^\circ_2$; $-\text{N}(\text{R}^\circ)\text{C}(\text{S})\text{NR}^\circ_2$; $-(\text{CH}_2)_{0-4}\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{OR}^\circ$; $-\text{N}(\text{R}^\circ)\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{R}^\circ$; $-\text{N}(\text{R}^\circ)\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{NR}^\circ_2$; $-\text{N}(\text{R}^\circ)\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{OR}^\circ$; $-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{R}^\circ$; $-\text{C}(\text{S})\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{OR}^\circ$; $-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{SR}^\circ$; $-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{OSiR}^\circ_3$; $-(\text{CH}_2)_{0-4}\text{OC}(\text{O})\text{R}^\circ$; $-\text{OC}(\text{O})(\text{CH}_2)_{0-4}\text{SR}^\circ$; $-\text{SC}(\text{S})\text{SR}^\circ$; $-(\text{CH}_2)_{0-4}\text{SC}(\text{O})\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{NR}^\circ_2$; $-\text{C}(\text{S})\text{NR}^\circ_2$; $-\text{C}(\text{S})\text{SR}^\circ$; $-\text{SC}(\text{S})\text{SR}^\circ$; $-(\text{CH}_2)_{0-4}\text{OC}(\text{O})\text{NR}^\circ_2$; $-\text{C}(\text{O})\text{N}(\text{OR}^\circ)\text{R}^\circ$; $-\text{C}(\text{O})\text{C}(\text{O})\text{R}^\circ$; $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{R}^\circ$; $-\text{C}(\text{NOR}^\circ)\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{SSR}^\circ$; $-(\text{CH}_2)_{0-4}\text{S}(\text{O})_2\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{S}(\text{O})_2\text{OR}^\circ$; $-(\text{CH}_2)_{0-4}\text{OS}(\text{O})_2\text{R}^\circ$; $-\text{S}(\text{O})_2\text{NR}^\circ_2$; $-\text{S}(\text{O})(\text{NR}^\circ)\text{R}^\circ$; $-\text{S}(\text{O})_2\text{N}=\text{C}(\text{NR}^\circ_2)_2$; $-(\text{CH}_2)_{0-4}\text{S}(\text{O})\text{R}^\circ$; $-\text{N}(\text{R}^\circ)\text{S}(\text{O})_2\text{NR}^\circ_2$; $-\text{N}(\text{R}^\circ)\text{S}(\text{O})_2\text{R}^\circ$; $-\text{N}(\text{OR}^\circ)\text{R}^\circ$; $-\text{C}(\text{NH})\text{NR}^\circ_2$; $-\text{P}(\text{O})_2\text{R}^\circ$; $-\text{P}(\text{O})\text{R}^\circ_2$; $-\text{OP}(\text{O})\text{R}^\circ_2$; $-\text{OP}(\text{O})(\text{OR}^\circ)_2$; SiR°_3 ; $-(\text{C}_{1-4}\text{ straight or branched alkylene})\text{O}-\text{N}(\text{R}^\circ)_2$; or $-(\text{C}_{1-4}\text{ straight or branched alkylene})\text{C}(\text{O})\text{O}-\text{N}(\text{R}^\circ)_2$.

[0047] Each R° is independently hydrogen, C_{1-6} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, $-\text{CH}_2-(5-6\text{ membered heteroaryl ring})$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted by a divalent substituent on a saturated carbon atom of R° selected from $=\text{O}$ and $=\text{S}$; or each R° is optionally substituted with a monovalent substituent independently selected from halogen, $-(\text{CH}_2)_{0-2}\text{R}^\bullet$, $-(\text{haloR}^\bullet)$, $-(\text{CH}_2)_{0-2}\text{OH}$, $-(\text{CH}_2)_{0-2}\text{OR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{CH}(\text{OR}^\bullet)_2$, $-\text{O}(\text{haloR}^\bullet)$, $-\text{CN}$, $-\text{N}_3$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{R}^\bullet$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{OR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SH}$, $-(\text{CH}_2)_{0-2}\text{NH}_2$, $-(\text{CH}_2)_{0-2}\text{NHR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{NR}^\bullet_2$, $-\text{NO}_2$, $-\text{SiR}^\bullet_3$, $-\text{OSiR}^\bullet_3$, $-\text{C}(\text{O})\text{SR}^\bullet$, $-(\text{C}_{1-4}\text{ straight or branched alkylene})\text{C}(\text{O})\text{OR}^\bullet$, or $-\text{SSR}^\bullet$.

[0048] Each $\text{R}^\bullet$ is independently selected from C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms

independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^\bullet$ is unsubstituted or where preceded by halo is substituted only with one or more halogens; or wherein an optional substituent on a saturated carbon is a divalent substituent independently selected from $=O$, $=S$, $=NNR^*$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*)_2)_{2-3}O-$, or $-S(C(R^*)_2)_{2-3}S-$, or a divalent substituent bound to vicinal substitutable carbons of an “optionally substituted” group is $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0049] When R^* is C_{1-6} aliphatic, R^* is optionally substituted with halogen, $-R^\bullet$, $-(haloR^\bullet)$, $-OH$, $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^\bullet$ is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0050] An optional substituent on a substitutable nitrogen is independently $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic, unsubstituted $-OPh$, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein when $R^\dagger$ is C_{1-6} aliphatic, $R^\dagger$ is optionally substituted with halogen, $-R^\bullet$, $-(haloR^\bullet)$, $-OH$, $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^\bullet$ is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0051] Spirocycle means monocyclic saturated carbon rings taken from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctanyl and optionally wherein a heteroatom, e.g., nitrogen, oxygen, or sulfur, is bonded to two carbons in the ring.

[0052] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues

of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[0053] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0054] The disclosure also includes pharmaceutical compositions comprising an effective amount of a disclosed compound and a pharmaceutically acceptable carrier. Representative "pharmaceutically acceptable salts" include, e.g., water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulinate, dihydrochloride, edetate, edisylate, estolate, esylate, fiunarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, magnesium, malate,

maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

[0055] A "subject" is a mammal, e.g., a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon or rhesus.

[0056] An "effective amount" when used in connection with a compound is an amount effective for treating or preventing a disease in a subject as described herein.

[0057] The term "carrier", as used in this disclosure, encompasses carriers, excipients, and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body of a subject.

[0058] The term "treating" with regards to a subject, refers to improving at least one symptom of the subject's disorder. Treating includes curing, improving, or at least partially ameliorating the disorder.

[0059] The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

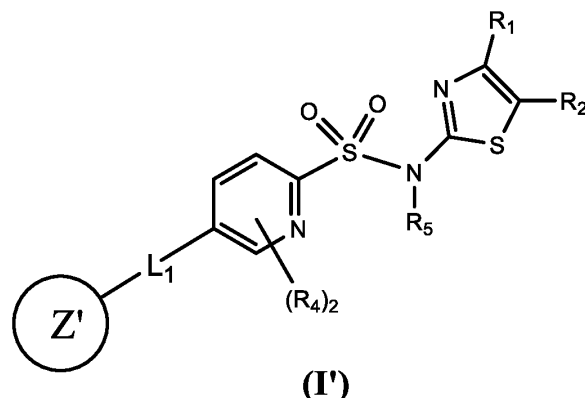
[0060] The term "administer", "administering", or "administration" as used in this disclosure refers to either directly administering a disclosed compound or pharmaceutically acceptable salt of the disclosed compound or a composition to a subject, or administering a prodrug derivative or analog of the compound or pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject's body.

[0061] The term "prodrug," as used in this disclosure, means a compound which is convertible *in vivo* by metabolic means (e.g., by hydrolysis, glucuronidation, etc.) to a disclosed compound.

Compounds

[0062] Compounds of the present disclosure include those described generally herein, and are further illustrated by the formulas and species disclosed herein.

[0063] In some embodiments, the present invention provides a compound of formula (I)

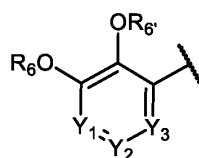


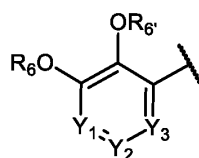
or a pharmaceutically acceptable salt thereof, wherein:

[0064] Ring Z' is an optionally substituted 5-6 membered monocyclic aromatic or heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur. One or more optional substitutions in Ring Z' include replacing one or more of the hydrogen atoms in the C-H bonds of the ring independently with one or more: halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -OR₈, or -N(R)₂, wherein R₈ is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl.

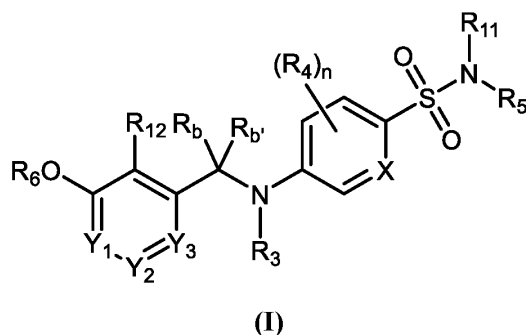
[0065] L₁ is a covalent bond or a C₁₋₆ bivalent straight or branched hydrocarbon chain wherein one or two methylene units of the chain are independently and optionally replaced by: -O-C(O)-, -C(O)O-, -OC(O)-, -N(R_a)-, -C(O)N(R_a)-, -(R_a)NC(O)-, -OC(O)N(R_a)-, -(R_a)NC(O)O-, -N(R_a)C(O)N(R_a)-, -S-, -SO-, -SO₂-, -SO₂N(R_a)-, -(R_a)NSO₂-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R_a)-, -(R_a)NC(S)-, or -(R_a)NC(S)N(R_a)-, wherein R_a is independently hydrogen or an optionally substituted group selected from C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ cycloalkyl, or C₁₋₆ halocycloalkyl or an optionally substituted group selected from C₁₋₆ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0066] In some embodiments, L_1 is $-N(R_a)CH_2-$, $-N(R_a)C(CH_3)_2-$, or $-N(R_a)C(=O)-$. In some embodiments, L_1 is $-N(R_a)CH_2-$. In some embodiments, R_a is H or Me. In some embodiments, R_a is H. In some embodiments, R_a is Me.



[0067] In some embodiments, Z' is , wherein R_6 and $R_{6'}$ are each independently hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl; and Y_1 , Y_2 , and Y_3 are each independently N or CR₁₀, wherein no more than two of Y_1 , Y_2 , and Y_3 are N. In some embodiments, R_6 and $R_{6'}$ are each independently H or C₁-C₄ alkyl. In some embodiments, R_6 is C₁-C₄ alkyl and $R_{6'}$ is H. In some embodiments, R_6 is Me and $R_{6'}$ is H.

[0068] In some embodiments, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein

X is N or CR₄;

Y_1 , Y_2 , and Y_3 are each independently N or CR₁₀, wherein no more than two of Y_1 , Y_2 , and Y_3 are N;

R_b and $R_{b'}$ are each independently H, F, or CH₃, or R_b and $R_{b'}$ taken together with the carbon atom to which they are attached form a cyclopropyl;

R_3 is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, or R_3 and Y_3 taken together with the atoms to which they are attached form a 4- to 6-membered heterocycl;

R_4 is hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R_5 is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₁₀ is hydrogen or halogen;

R₁₁ is C₆-C₁₂ aryl or 5- to 14-membered heteroaryl, each of which is substituted with one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, aryl, -(C₁-C₃ alkylene)-aryl, C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl), 3- to 14-membered heterocyclyl, and -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl);

R₁₂ is halogen, -OH, or -OR₆; and

n is 1 or 2,

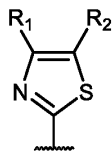
with the proviso that when X is CR₄, at least one R₄ is not H.

[0069] In embodiments of Formula (I), X, R₃, R₄, R₅, R₆, R₁₂, R_b, R_b', Y₁, Y₂, Y₃, and n are as defined herein in any combination.

[0070] In some embodiments of Formula (I), the substituents on R₁₁ is substituted or unsubstituted. In some embodiments, R₁₁ is C₆-C₁₂ aryl or 5- to 14-membered heteroaryl, each of which is substituted with one or more substituents independently selected from the group consisting of halogen, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₁-C₆ haloalkyl, substituted or unsubstituted C₁-C₃ alkoxy, substituted or unsubstituted C₁-C₃ haloalkoxy, substituted or unsubstituted aryl, substituted or unsubstituted -(C₁-C₃ alkylene)-aryl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), substituted or unsubstituted 5- to 14-membered heteroaryl, substituted or unsubstituted -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl), substituted or unsubstituted 3- to 14-membered heterocyclyl, and substituted or unsubstituted -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl);

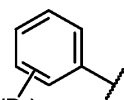
[0071] In some embodiments of Formula (I), R₁₁ is C₆-C₁₂ aryl or 5- to 14-membered heteroaryl, each of which is substituted with one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, aryl, C₃-C₆ cycloalkyl, 5- to 6-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), 3- to 14-membered heterocyclyl, and -(C₁-C₃ alkylene)-(3- to 6-membered heterocyclyl). In some embodiments, R₁₁ is phenyl or 5- to 6-membered heteroaryl, each of which is substituted with one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃

haloalkoxy, aryl, C₃-C₆ cycloalkyl, 5- to 6-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), 3- to 14-membered heterocyclyl, and -(C₁-C₃ alkylene)-(3- to 6-membered heterocyclyl). In some embodiments, R₁₁ is 5- to 6-membered heteroaryl, each of which is substituted with one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, aryl, C₃-C₆ cycloalkyl, 5- to 6-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), 3- to 14-membered heterocyclyl, and -(C₁-C₃ alkylene)-(3- to 6-membered

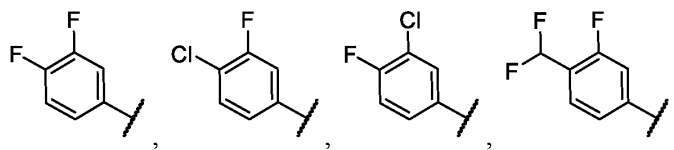


heterocyclyl). In some embodiments, R₁₁ is , wherein R₁ and R₂ are as defined herein.

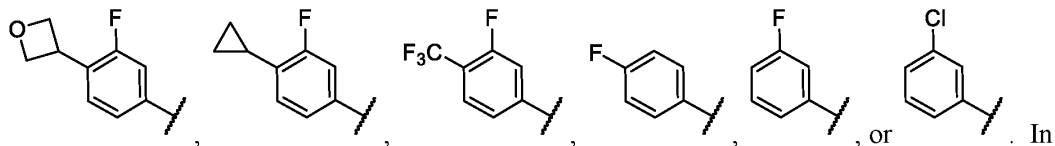
[0072] In some embodiments, R₁ is C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, or C₁-C₃-alkylene-C₆-C₁₄-aryl, each of which is substituted by one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or 3- to 14-membered heterocyclic ring. In some embodiments, R₁ is C₆-C₁₄ aryl, which is substituted by one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or 3- to 14-membered heterocyclic ring. In some embodiments, R₁ is phenyl, which is substituted by one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or 3- to 14-membered heterocyclic ring. In some embodiments, R₁ is phenyl, which is substituted by one or more halogen (e.g.,

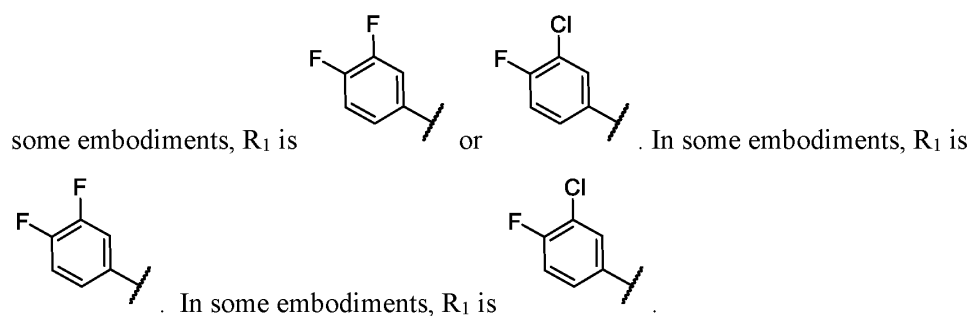


Cl or F). In some embodiments, R_1 is $(R_9)_m$, wherein R_9 and m are as defined herein.

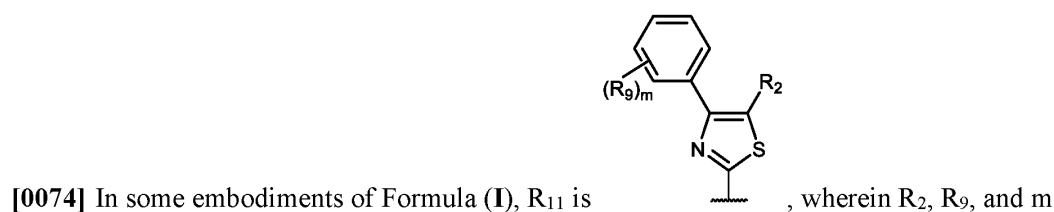


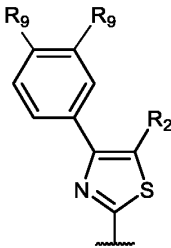
In some embodiments, R_1 is





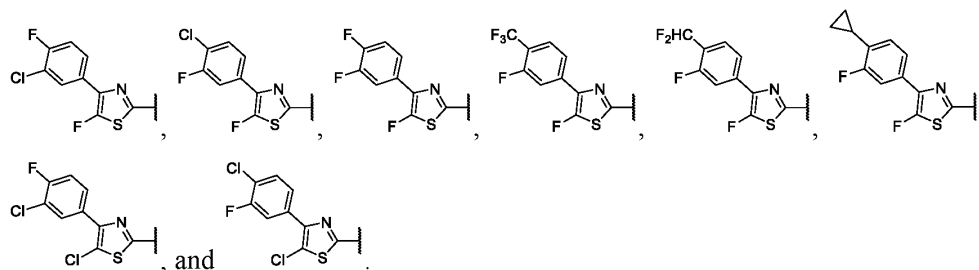
[0073] In some embodiments of Formula (I), at least one of R₁₀ is not H or at least one of Y₁, Y₂, and Y₃ is N. In some embodiments, at least one of R₁₀ is not H. In some embodiments, at least one of at least one of Y₁, Y₂, and Y₃ is N.



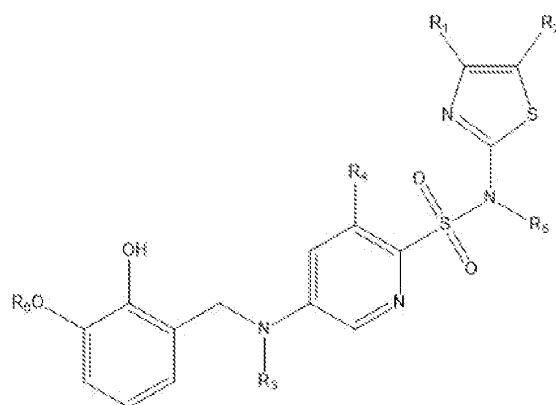
are as defined herein. In some embodiments, R₁₁ is , wherein R₂ and R₉ are as defined herein. In some embodiments, R₂ is a substituted or unsubstituted group selected from the group consisting of 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl), C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), phenyl, and -(C₁-C₃ alkylene)-phenyl. In a specific embodiment, R₂ is a 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), or -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl). In another specific embodiment, a 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, or -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl).

[0075] In some embodiments of Formula (I), R₁₂ is halogen or -OH. In some embodiments, R₁₂ is F or -OH. In some embodiments, R₁₂ is -OH or -OR₆, wherein R₆ is as defined herein. In some embodiments, R₁₂ is -OH.

[0076] In some embodiments of Formula (I), when R₃ and R₅ are H, R₄ is H or Me, R₆ is Me, R₁₂ is -OH, and n is 1, the 5- to 14-membered heteroaryl is not one or more of:



[0077] Further provided herein is a compound of Formula (Ia)



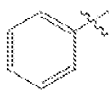
(Ia)

or a pharmaceutically acceptable salt thereof,

wherein

R₁ is H, C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, or C₁-C₃-alkylene-C₆-C₁₄-aryl, each of which is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or 3- to 14-membered heterocyclic ring;

R₂ is H, CN, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₂-C₆ alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₁-C₃-alkylene-C₃-C₈-cycloalkyl, substituted or unsubstituted C₃-C₈-cycloalkylene-C₁-C₃-alkyl, C₁-C₃-alkylene-C₆-C₁₄-aryl, substituted or unsubstituted C₆-C₁₄ aryl and aralkyl

including  and , substituted or unsubstituted 3- to 14-membered heterocyclic ring including pyrazolyl, pyridinyl, pyrimidinyl, oxetanyl, and imidazolyl, or

amide including $\text{H}_2\text{N}-\text{C}(=\text{O})-$, $\text{HN}(\text{R}_7)-\text{C}(=\text{O})-$, and $\text{R}_7-\text{N}(\text{R}_7)-\text{C}(=\text{O})-$, wherein R_7 is independently selected from C_1 - C_3 alkyl, C_3 - C_8 cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 3- to 14-membered heterocyclic ring, including pyrazolyl, pyridinyl, pyrimidinyl, oxetanyl, and imidazolyl;

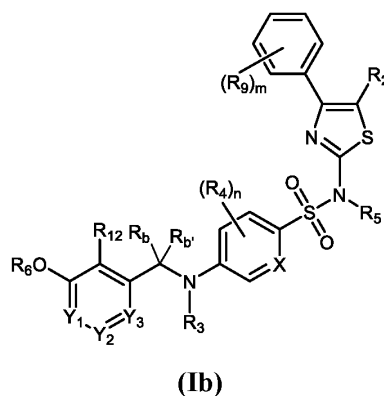
R_3 is hydrogen, C_1 - C_3 alkyl, or C_1 - C_3 haloalkyl;

R_4 is hydrogen, CD_3 , substituted or unsubstituted phenyl, C_3 - C_8 cycloalkyl, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkoxy, or halogen;

R_5 is hydrogen, C_1 - C_3 alkyl, or C_1 - C_3 haloalkyl; and

R_6 is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_8 cycloalkyl, or C_3 - C_8 halocycloalkyl.

[0078] Further provided herein is a compound of Formula (Ib):



or a pharmaceutically acceptable salt thereof,

wherein

X is N or CR_4 ;

Y_1 , Y_2 , and Y_3 are each independently N or CR_{10} , wherein no more than two of Y_1 , Y_2 , and Y_3 are N ;

R_b and $\text{R}_{b'}$ are each independently H , F , or CH_3 , or R_b and $\text{R}_{b'}$ taken together with the carbon atom to which they are attached form a cyclopropyl;

R_2 is a halogen or a substituted or substituted group selected from the group consisting of 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, $-(\text{C}_1\text{-C}_3 \text{ alkylene})-(5\text{- to } 14\text{-membered heteroaryl})$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})-(3\text{- to } 14\text{-membered heterocyclyl})$, $\text{C}_3\text{-C}_8$ cycloalkyl, $-(\text{C}_1\text{-C}_3 \text{ alkylene})-(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, phenyl, and $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{-phenyl}$;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, or R₃ and Y₃ taken together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl;

R₄ is each independently hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₉ is each independently halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy or 3- to 14-membered heterocyclic ring;

R₁₀ is hydrogen or halogen;

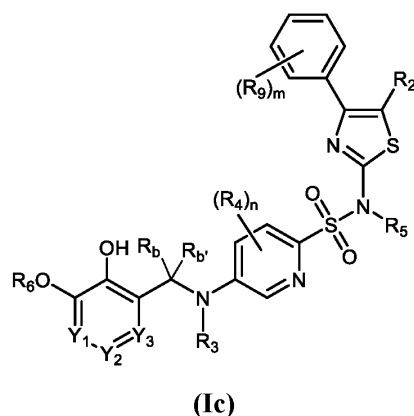
R₁₂ is halogen, -OH, or -OR₆;

m is 0, 1, 2, or 3; and

n is 1 or 2,

with the proviso that when X is CR₄, at least one R₄ is not H.

[0079] Further provided herein is a compound of Formula (Ic):



or a pharmaceutically acceptable salt thereof,

wherein

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R_b and R_{b'} are each independently H, F, or CH₃, or R_b and R_{b'} taken together with the carbon atom to which they are attached form a cyclopropyl;

R₂ is a substituted or unsubstituted group selected from the group consisting of 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 14-

membered heteroaryl), $-(C_1-C_3 \text{ alkylene})-(3- \text{ to } 14\text{-membered heterocyclyl})$, C_3-C_8 cycloalkyl, $-(C_1-C_3 \text{ alkylene})-(C_3-C_8 \text{ cycloalkyl})$, phenyl, and $-(C_1-C_3 \text{ alkylene})\text{-phenyl}$;

R_3 is hydrogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl, or R_3 and Y_3 taken together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl;

R_4 is each independently hydrogen, CD_3 , substituted or unsubstituted phenyl, C_3-C_8 cycloalkyl, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, or halogen;

R_5 is hydrogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl;

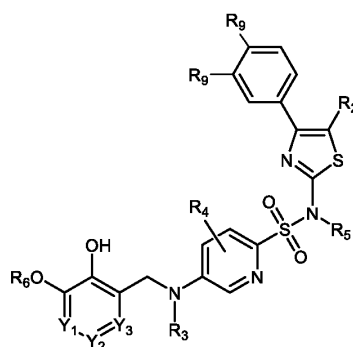
R_6 is hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, or C_3-C_8 halocycloalkyl;

R_9 is each independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy or 3- to 14-membered heterocyclic ring;

R_{10} is hydrogen or halogen; and

m is 0, 1, 2, or 3.

[0080] Further provided herein is a compound of Formula (Id):



(Id)

or a pharmaceutically acceptable salt thereof,

wherein

Y_1 , Y_2 , and Y_3 are each independently N or CR_{10} , wherein no more than two of Y_1 , Y_2 , and Y_3 are N;

R_2 is a substituted or substituted group selected from the group consisting of 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, $-(C_1-C_3 \text{ alkylene})-(5- \text{ to } 14\text{-membered heteroaryl})$, $-(C_1-C_3 \text{ alkylene})-(3- \text{ to } 14\text{-membered heterocyclyl})$, C_3-C_8 cycloalkyl, $-(C_1-C_3 \text{ alkylene})-(C_3-C_8 \text{ cycloalkyl})$, phenyl, and $-(C_1-C_3 \text{ alkylene})\text{-phenyl}$;

R_3 is hydrogen, C_1-C_3 alkyl, or C_1-C_3 haloalkyl, or R_3 and Y_3 taken together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl;

R₄ is each independently hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

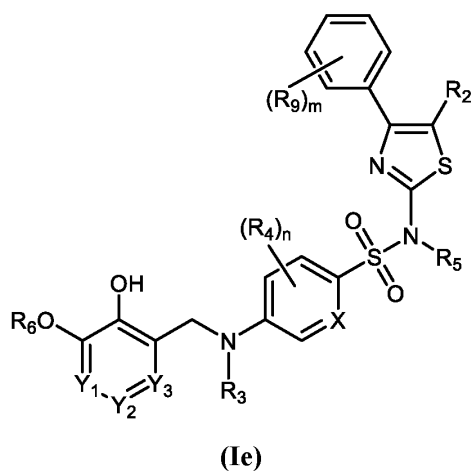
R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₉ is each independently F, Cl, CF₃, CHF₂, CH₂F, cyclopropyl, or oxetanyl; and

R₁₀ is hydrogen or halogen.

[0081] Further provided herein is a compound of Formula (Ie):



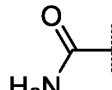
or a pharmaceutically acceptable salt thereof,

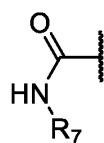
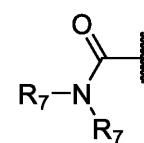
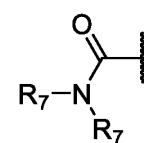
wherein

X is C-R₄ or N;

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R₂ is H, CN, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₂-C₆ alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₁-C₃-alkylene-C₃-C₈-cycloalkyl, substituted or unsubstituted C₃-C₈-cycloalkylene-C₁-C₃-alkyl, substituted or unsubstituted C₁-C₃-alkylene-C₆-C₁₄-aryl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted 3- to 14-membered heterocyclic ring, substituted or unsubstituted 5- to 14-membered heteroaryl, substituted or unsubstituted -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclic ring), substituted or unsubstituted -(C₁-C₃ alkylene)-(5- to

14-membered heteroaryl), or amide selected from the group consisting of ,



 , and 
 , wherein R₇ is independently selected from C₁-C₃ alkyl, C₃-C₈ cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted 4- to 6-membered heterocyclic ring, or 5- or 6-membered heteroaryl;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₄ is H, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₉ is each independently halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy or 3- to 14-membered heterocyclic ring;

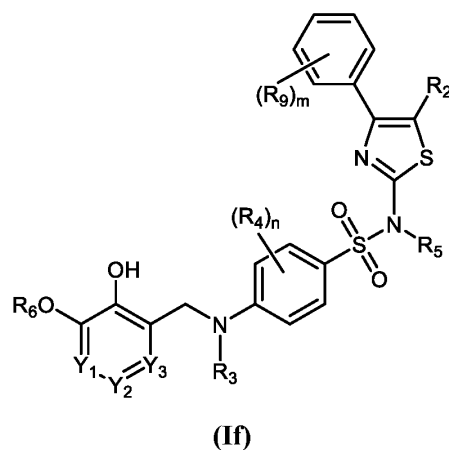
R₁₀ is hydrogen or halogen; and

m is 0, 1, 2, or 3; and

n is 1 or 2,

with the proviso that at least one of R₁₀ is not H or at least one of Y₁, Y₂, and Y₃ is N.

[0082] Further provided herein is a compound of Formula **(If)**:

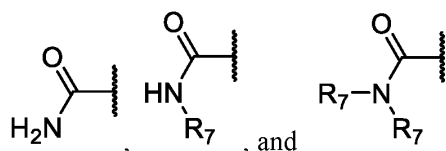


or a pharmaceutically acceptable salt thereof,

wherein

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R₂ is H, CN, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₂-C₆ alkoxyalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted C₁-C₃-alkylene-C₃-C₈-cycloalkyl, substituted or unsubstituted C₃-C₈-cycloalkylene-C₁-C₃-alkyl, C₁-C₃-alkylene-C₆-C₁₄-aryl, or substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted 3- to 14-membered heterocyclic ring, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl), or amide selected from the group consisting of



, wherein R₇ is independently C₁-C₃ alkyl, C₃-C₈ cycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted 4- to 6-membered heterocyclic ring, or 5- or 6-membered heteroaryl;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, or R₃ and Y₃ taken together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl;

R₄ is CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₉ is each independently halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy or 3- to 14-membered heterocyclic ring;

R₁₀ is hydrogen or halogen; and

m is 0, 1, 2, or 3.

[0083] In some embodiments, X is N. In some embodiments, X is CR₄.

[0084] In some embodiments, Y₁ is N, Y₂ is CR₁₀, and Y₃ is CR₁₀. In some embodiments, Y₂ is N, Y₁ is CR₁₀, and Y₃ is CR₁₀. In some embodiments, Y₃ is N, Y₁ is CR₁₀, and Y₂ is CR₁₀.

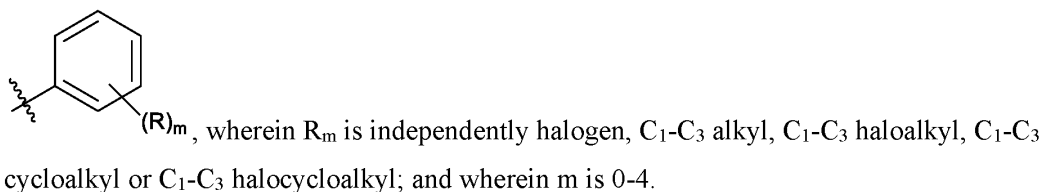
[0085] In some embodiments, when Y₁ is CR₁₀, R₃ and R₁₀ taken together with the atoms to which they are attached form a heterocyclic ring. In some embodiments, the heterocyclic ring is a 5- or 6-membered heterocyclic ring.

[0086] In some embodiments, R_b and R_{b'} are each independently H or C₁-C₅ alkyl. In some embodiments, R_b and R_{b'} are each independently H or CH₃. In some embodiments, R_b and R_{b'} are each H. In some embodiments, R_b and R_{b'} are each CH₃. In some embodiments, R_b

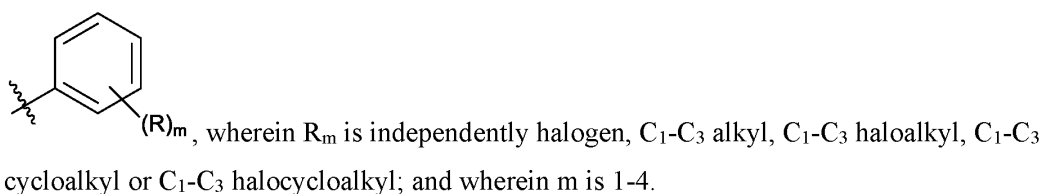
and $R_{b'}$ are each H. In some embodiments, R_b and $R_{b'}$ taken together with the carbon atom to which they are attached form a cyclopropyl.

[0087] In some embodiments, R_1 is optionally substituted aryl, e.g., as defined below.

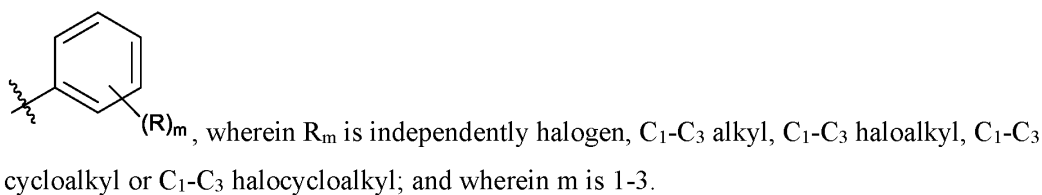
[0088] In some embodiments, R_1 is



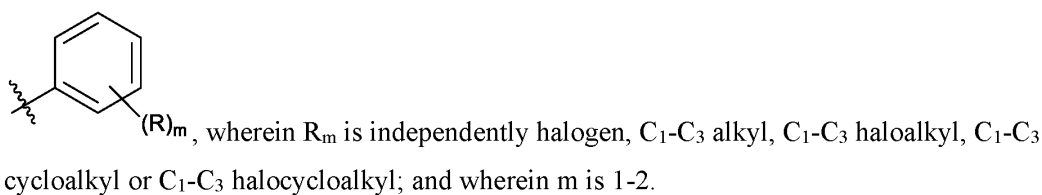
[0089] In some embodiments, R_1 is



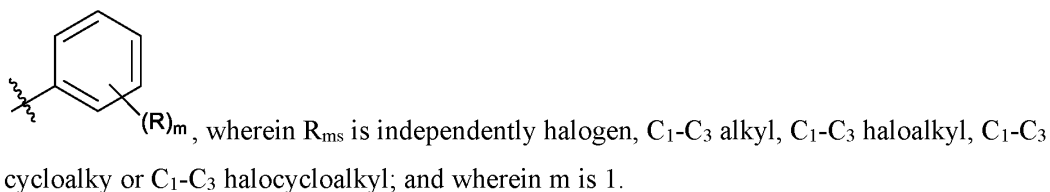
[0090] In some embodiments, R_1 is



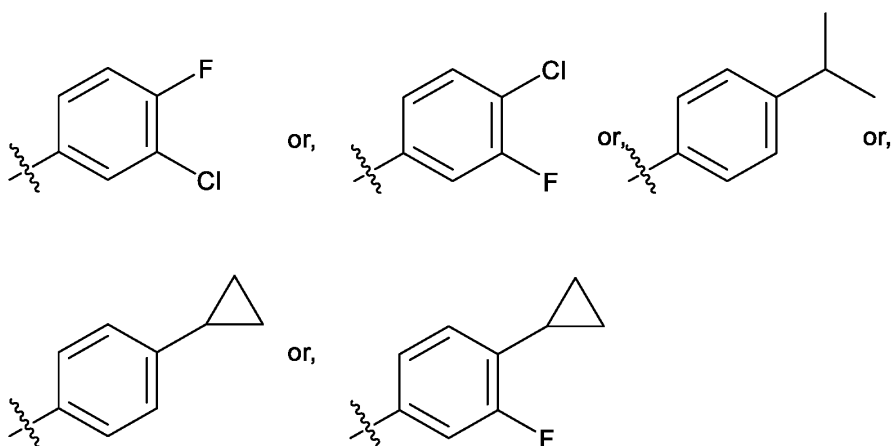
[0091] In some embodiments, R_1 is

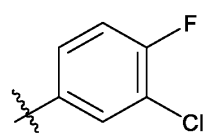


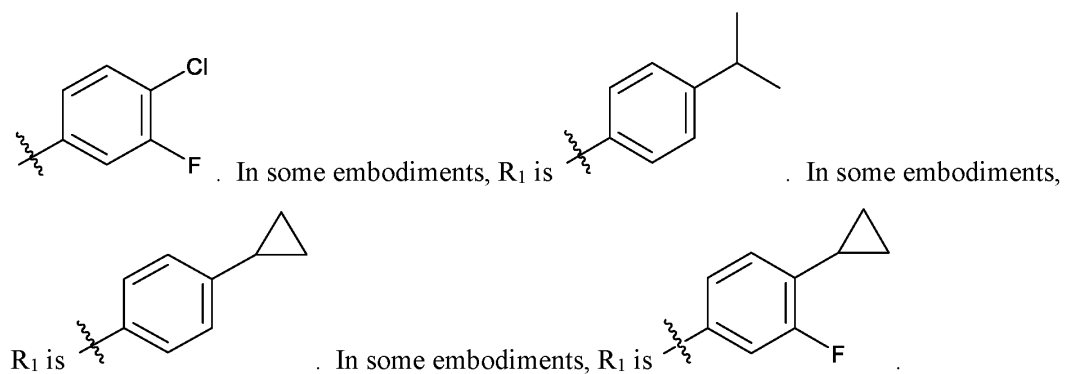
[0092] In some embodiments, R_1 is



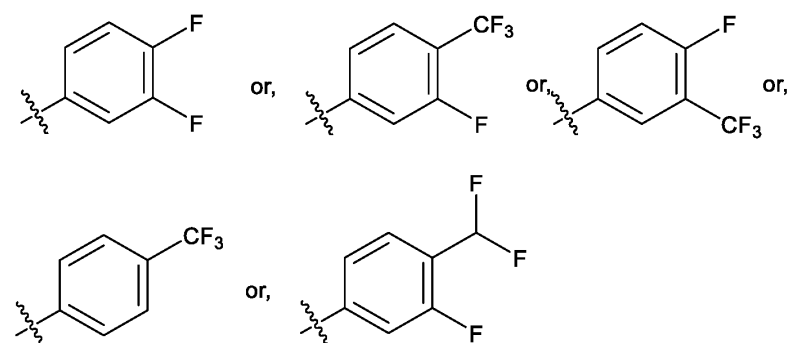
[0093] In some embodiments, R_1 is

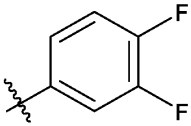
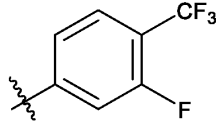
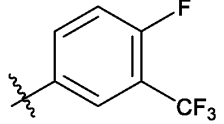
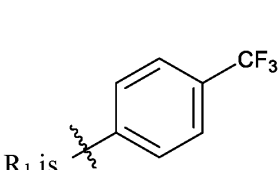
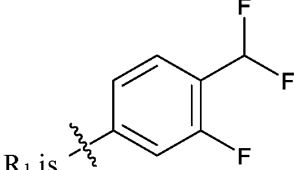


[0094] In some embodiments, R_1 is . In some embodiments, R_1 is

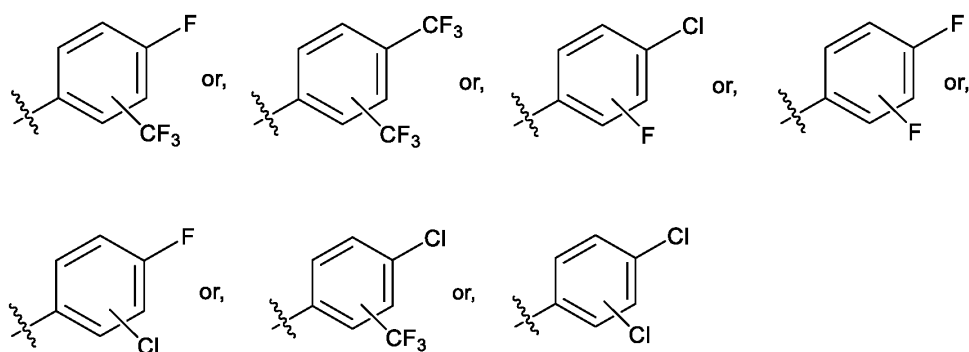


[0095] In some embodiments, R_1 is:

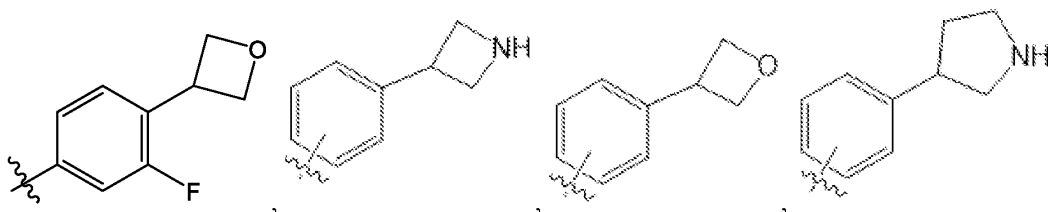


[0096] In some embodiments, R₁ is . In some embodiments, R₁ is . In some embodiments, R₁ is . In some embodiments, R₁ is . In some embodiments, R₁ is .

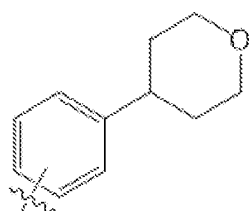
[0097] In some embodiments, R₁ is



[0098] In some embodiments, R₁ is phenyl substituted with a heterocycle, including, without limitation:



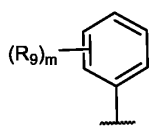
and



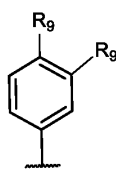
, wherein aryl may be optionally substituted with 3-halogen.

[0099] In some embodiments, R_1 is selected from the groups in the R_1 position of the compounds recited in Table 1, below.

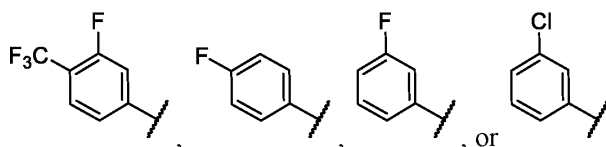
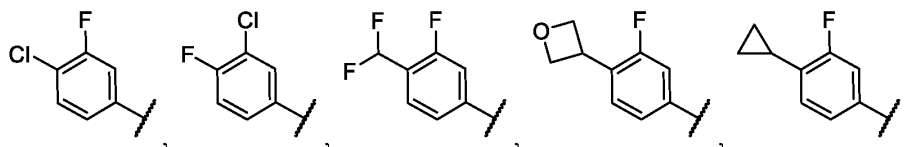
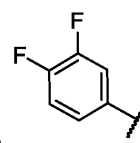
[0100] In some embodiments, R_1 is optionally substituted aryl. In some embodiments, R_1 is phenyl, which is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkoxy, or 3- to 14-membered heterocyclic ring. In some embodiments, R_1 is



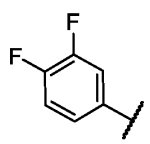
, wherein R_9 and m are as defined herein. In some embodiments, R_1 is



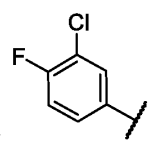
, wherein R_9 is as defined herein. In some embodiments, R_1 is



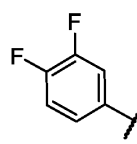
. In some embodiments, R_1 is



or

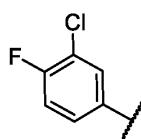


. In some embodiments, R_1 is



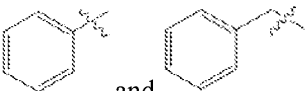
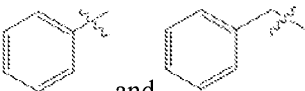
. In some

embodiments, R_1 is

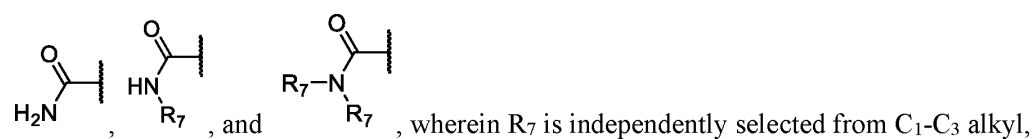


[0101] As defined generally above, R_2 is $-CN$, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_3 alkoxy and C_1 - C_3 haloalkoxy, C_2 - C_6 alkoxyalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted C_1 - C_3 -alkylene- C_3 - C_8 -cycloalkyl, substituted or unsubstituted C_3 - C_8 -cycloalkylene- C_1 - C_3 -alkyl, C_1 - C_3 -alkylene- C_6 - C_{14} -aryl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted 3- to 14-membered heterocyclic ring, or amide. In some embodiments, R_2 is hydrogen or deuterium. In some embodiments, R_2 is $-CN$. In some embodiments, R_2 is halogen. In some embodiments, R_2 is F, Cl, Br or I. In some

embodiments, R_2 is F, Cl or Br. In some embodiments, R_2 is F or Cl. In some embodiments, R_2 is F. In some embodiments, R_2 is Cl. In some embodiments, R_2 is Br. In some embodiments, R_2 is I. In some embodiments, R_2 is alkyl. In some embodiments, R_2 is methyl, ethyl, n-propyl or isopropyl. In some embodiments, R_2 is methyl. In some embodiments, R_2 is C_1 - C_3 -alkylene- C_6 - C_{14} -aryl. In some embodiments, R_2 is methylene-aryl. In some embodiments, R_2 is substituted or unsubstituted benzyl. In some embodiments, R_2 is substituted benzyl. In some embodiments, R_2 is substituted or unsubstituted C_3 - C_8 cycloalkyl, or substituted or unsubstituted C_3 - C_8 -cycloalkylene- C_1 - C_3 -alkyl, including cyclopropyl

including  and . In some embodiments, R_2 is aryl or aralkyl, including  and . In some embodiments, R_2 is substituted or unsubstituted phenyl.

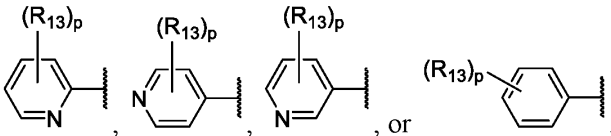
In some embodiments, R_2 is substituted phenyl. In some embodiments, R_2 is cyclopropyl. In some embodiments, R_2 is cyclobutyl. In some embodiments, R_2 is cyclopentyl. In some embodiments, R_2 is cyclohexyl. In some embodiments, R_2 is 3-pyrazolyl. In some embodiments, R_2 is 4-pyrazolyl. In some embodiments, R_2 is 2-pyridinyl. In some embodiments, R_2 is 3-pyridinyl. In some embodiments, R_2 is 4-pyridinyl. In some embodiments, R_2 is 4-pyrimidinyl. In some embodiments, R_2 is 3-oxetanyl. In some embodiments, R_2 is 4-imidazolyl. In some embodiments, R_2 is haloalkyl. In some embodiments, R_2 is fluoromethyl, fluoroethyl or fluoropropyl. In some embodiments, R_2 is fluoromethyl. In some embodiments, R_2 is trifluoromethyl. In some embodiments, R_2 is C_1 - C_3 alkoxy. In some embodiments, R_2 is an amide, selected from the group consisting of

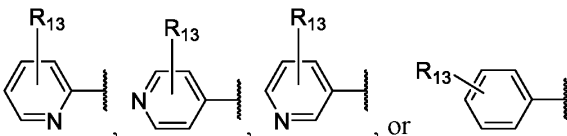


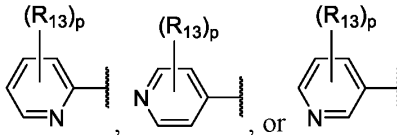
C_3 - C_8 cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 3- to 14-membered heterocyclic ring including pyrazolyl, pyridinyl, pyrimidinyl, oxetanyl, and imidazolyl. In some embodiments, R_2 is OMe or OEt or O^i Pr. In some embodiments, R_2 is OMe. In some embodiments, R_2 is OCF_3 . In some embodiments, R_2 is OCH_2F . In some embodiments, R_2 is CH_2OH or CH_2CH_2OH or $CH_2CH_2CH_2OH$ or $CH_2C(OH)(CH_3)_2$. In some embodiments, R_2 is CH_2OCH_3 or $CH_2CH_2OCH_3$ or $CH_2OCH_2CH_3$. In some embodiments, R_2 is selected from the groups in the R_2 position of the compounds recited in Table 1, below.

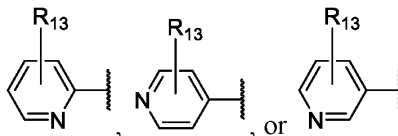
[0102] In some embodiments, R₂ is H, CN, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₂-C₆ alkoxyalkyl, C₃-C₈ cycloalkyl, C₁-C₃-alkylene-C₃-C₈-cycloalkyl, C₃-C₈-cycloalkylene-C₁-C₃-alkyl, C₁-C₃-alkylene-C₆-C₁₄-aryl, C₆-C₁₄ aryl, 3- to 14-membered heterocyclic ring, 5- to 14-membered heteroaryl, or -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl). In some embodiments, R₂ is H, CN, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₂-C₆ alkoxyalkyl, C₃-C₈ cycloalkyl, C₁-C₃-alkylene-C₃-C₈-cycloalkyl, C₃-C₈-cycloalkylene-C₁-C₃-alkyl, C₁-C₃-alkylene-C₆-C₁₄-aryl, C₆-C₁₄ aryl, 3- to 8-membered heterocyclic ring, 5- to 6-membered heteroaryl, or -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl). In some embodiments, R₂ is a halogen, 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl), C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), phenyl, or -(C₁-C₃ alkylene)-phenyl. In some embodiments, R₂ is a halogen, 3- to 8-membered heterocyclyl, 5- to 6-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 8-membered heterocyclyl), C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), phenyl, or -(C₁-C₃ alkylene)-phenyl. In some embodiments, R₂ is a 3- to 8-membered heterocyclyl, 5- to 6-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 8-membered heterocyclyl), or C₃-C₈ cycloalkyl. In some embodiments, R₂ is a 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl), or phenyl. In some embodiments, R₂ is a 3- to 8-membered heterocyclyl, 5- to 6-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), or -(C₁-C₃ alkylene)-(3- to 8-membered heterocyclyl). In some embodiments, R₂ is a 3- to 8-membered heterocyclyl, 5- to 6-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), or phenyl. In some embodiments, R₂ is a 3- to 8-membered heterocyclyl, 5- to 6-membered heteroaryl, or -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl). In some embodiments, R₂ is a 3- to 14-membered heterocyclyl or 5- to 14-membered heteroaryl. In some embodiments, R₂ is a 3- to 14-membered heterocyclyl. In some embodiments, R₂ is a 3- to 8-membered heterocyclyl. In some embodiments, R₂ is a 5- to 14-membered heteroaryl. In some embodiments, R₂ is a 3- to 6-membered heterocyclyl, 5- or 6-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 6-membered heterocyclyl), C₃-C₆ cycloalkyl, or phenyl. In some embodiments, R₂ is a 3- to 6-membered heterocyclyl, 5- or 6-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), or -(C₁-C₃ alkylene)-(3- to 6-membered heterocyclyl). In some embodiments, R₂ is a 3- to 6-membered heterocyclyl, a 5-

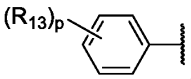
or 6-membered heteroaryl, or a phenyl. In some embodiments, R_2 is a 3- to 6-membered heterocyclyl or a 5- or 6-membered heteroaryl. In some embodiments, R_2 is a 5- or 6-membered heteroaryl. In some embodiments, R_2 is substituted phenyl.

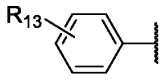
[0103] In some embodiments, R_2 is , wherein each R_{13} is independently halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, or C₃-C₆ cycloalkyl; and p is as defined herein. In some embodiments, R_2 is

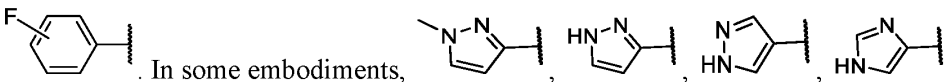
, wherein R_{13} is halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, or C₃-C₆ cycloalkyl. In some embodiments,

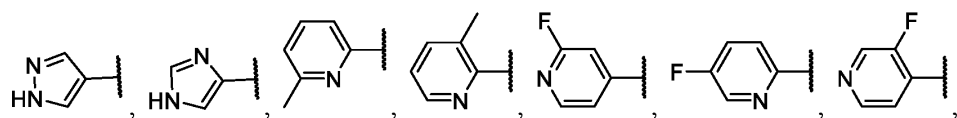
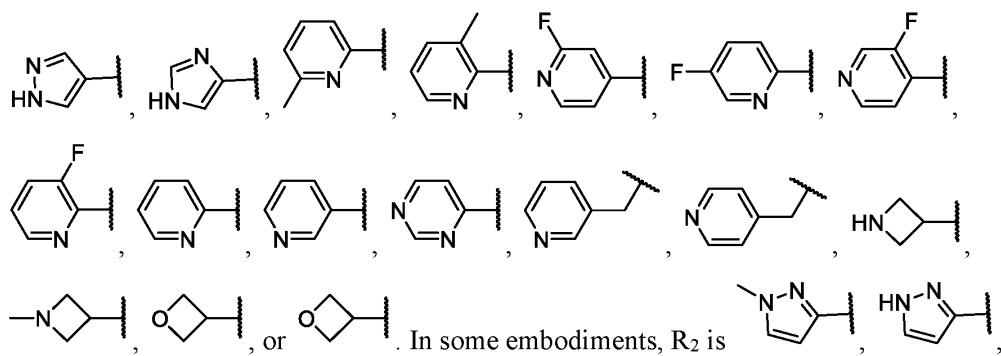
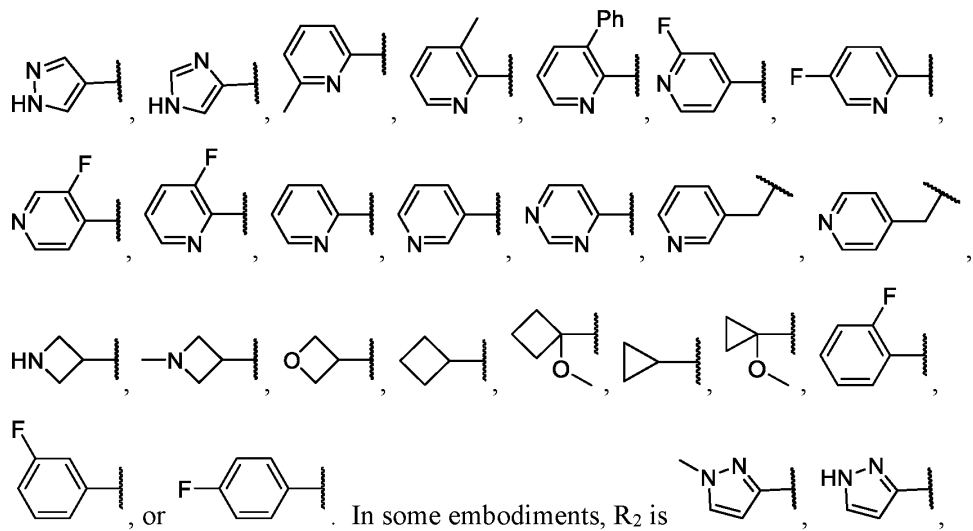
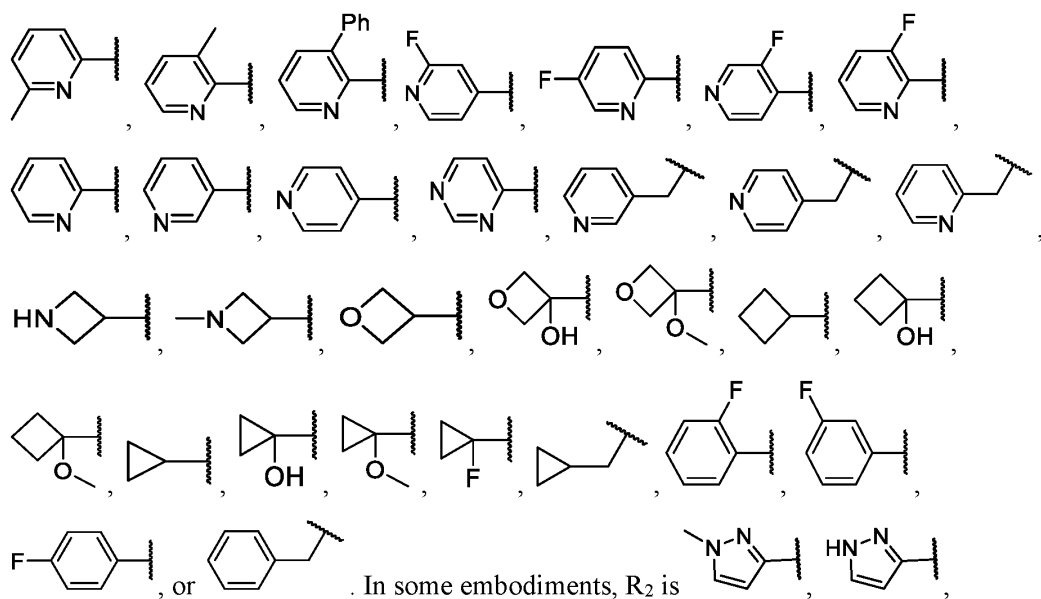
R_2 is , wherein each R_{13} is independently halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, or C₃-C₆ cycloalkyl; and p is as

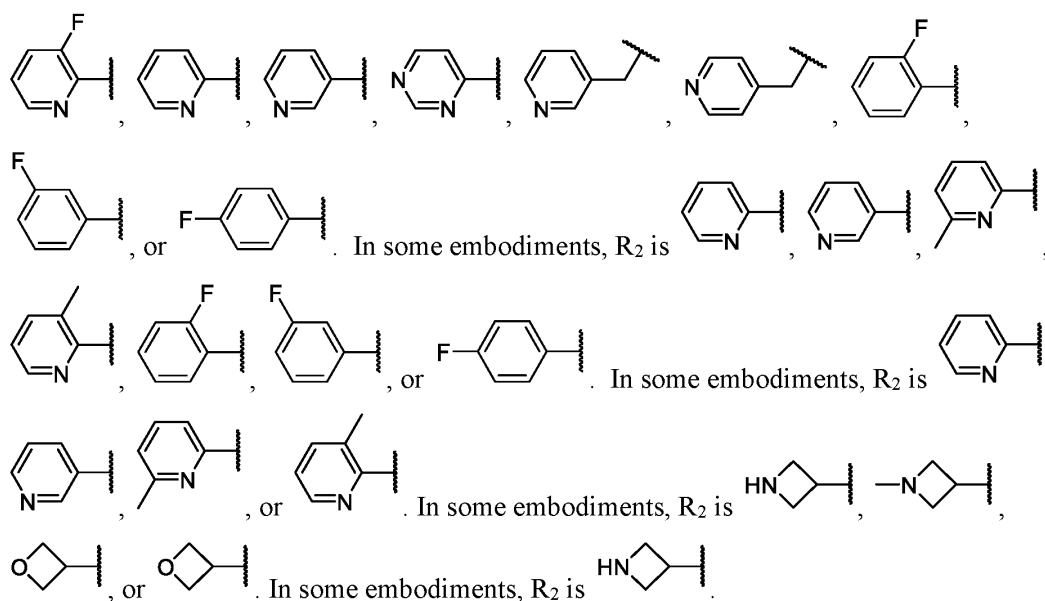
defined herein. In some embodiments, R_2 is , wherein R_{13} is halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, or C₃-C₆

cycloalkyl. In some embodiments, R_2 is , wherein each R_{13} is independently halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, or C₃-C₆ cycloalkyl;

and p is as defined herein. In some embodiments, R_2 is , wherein R_{13} is halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, or C₃-C₆ cycloalkyl. In some embodiments, each R_{13} is independently F, Cl, Me, Et, *i*Pr, cyclopropyl, -OMe, -OEt, -O*i*Pr, CF₃, CF₂H, or CFH₂. In some embodiments, each R_{13} is independently F. In some embodiments, R_2 is phenyl substituted with a halogen. In some embodiments, R_2 is

. In some embodiments,





[0104] R₂, as disclosed herein, can be substituted or unsubstituted. In some embodiments, R₂ is substituted with one or more halogens, C₁-C₅ alkyl, C₁-C₅ haloalkyl, C₁-C₅ alkoxy, C₁-C₅ haloalkoxy, -CN, -OH, C₃-C₆ cycloalkyl, phenyl, or a combination thereof. In some embodiments, R₂ is substituted with one or more F, Cl, Me, Et, *i*Pr, *t*Bu, CF₃, CF₂H, CFH₂, CH₂CF₃, CF₂CH₃, -OMe, -OEt, O-*i*Pr, O-*t*Bu, -OCF₃, -OCF₂H, -OCFH₂, -OCH₂CF₃, -OCF₂CH₃, -CN, -OH, cyclopropyl, phenyl, or a combination thereof. In some embodiments, R₂ is substituted with one or more halogens, C₁-C₅ alkyl, or a combination thereof. In some embodiments, R₂ is substituted with one or more halogens. In some embodiments, the one or more halogens is F or Cl. In some embodiments the one or more halogens is F. In some embodiments, the C₁-C₅ alkyl is methyl, ethyl, isopropyl or *tert*-butyl.

[0105] In some embodiments, each R₂, as defined herein, can be independently optionally substituted with one or more halogens (e.g., F, Cl, or Br), C₁-C₄ alkyl (e.g., Me, Et, or *i*Pr), C₁-C₃ haloalkyl (CF₃, CF₂H, CFH₂, CH₂CF₃), -OH, -CN, C₁-C₄ alkoxy (e.g., -OMe, -OEt, or -OiPr), C₁-C₃ haloalkoxy (-OCF₃, -OCF₂H, -OCFH₂, or -OCH₂CF₃), or C₃-C₆ cycloalkyl.

[0106] As generally described above, R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl. In some embodiments, R₃ is hydrogen. In some embodiments, R₃ is halogen. In some embodiments, R₃ is F, Cl, Br or I. In some embodiments, R₃ is F, Cl or Br. In some embodiments, R₃ is F or Br. In some embodiments, R₃ is F or Cl. In some embodiments, R₃ is Cl or Br. In some embodiments, R₃ is Cl. In some embodiments, R₃ is F. In some embodiments, R₃ is C₁-C₃ alkyl, or C₁-C₃ haloalkyl. In some embodiments, R₃ is C₁-C₃ alkyl.

In some embodiments, R₃ is C₁-C₃ haloalkyl. In some embodiments, R₃ is methyl or ethyl. In some embodiments, R₃ is selected from the groups in the R₃ position of the compounds recited in Table 1, below.

[0107] In some embodiments, R₃ is hydrogen, C₁-C₃ alkyl, of C₃-C₆ cycloalkyl. In some embodiments, R₃ is hydrogen or C₁-C₃ alkyl. In some embodiments, R₃ is H, Me, *i*Pr, or cyclopropyl. In some embodiments, R₃ is H, Me, or cyclopropyl. In some embodiments, R₃ is H or Me. In some embodiments, R₃ is H. In some embodiments, R₃ is Me.

[0108] In some embodiments, R₃ and Y₃ taken together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl. In some embodiments, R₃ and Y₃ taken together with the atoms to which they are attached form a 5-membered heterocyclyl. In some embodiments, R₃ and Y₃ taken together with the atoms to which they are attached form a 6-membered heterocyclyl.

[0109] As generally defined above each R₄ is hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen. In some embodiments, R₄ is H. In some embodiments, R₄ is halogen. In some embodiments, R₄ is F, Cl, Br or I. In some embodiments, R₄ is F, Cl or Br. In some embodiments, R₄ is F or Br. In some embodiments, R₄ is F or Cl. In some embodiments, R₄ is Cl or Br. In some embodiments, R₄ is Cl. In some embodiments, R₄ is F. In some embodiments, R₄ is Br. In some embodiments, R₄ is I. In some embodiments, R₄ is C₁-C₃ alkyl. In some embodiments, R₄ is methyl, ethyl, *n*-propyl or isopropyl. In some embodiments, R₄ is methyl. In some embodiments, R₄ is independently haloalkyl. In some embodiments, R₄ is independently fluoromethyl, fluoroethyl or fluoropropyl. In some embodiments, R₄ is independently fluoromethyl. In some embodiments, R₄ is independently trifluoromethyl. In some embodiments, R₄ is independently C₁-C₃ alkoxy. In some embodiments, R₄ is independently OMe or OEt or *Oi*Pr. In some embodiments, R₄ is independently OMe. In some embodiments, R₄ is independently OCF₃. In some embodiments, R₄ is independently OCH₂F. In some embodiments, R₄ is independently CH₂OH or CH₂CH₂OH or CH₂CH₂CH₂OH or CH₂C(OH)(CH₃)₂. In some embodiments, R₄ is independently CH₂OCH₃ or CH₂CH₂OCH₃ or CH₂OCH₂CH₃. In some embodiments, R₄ is independently selected from the groups in the R₄ position of the compounds recited in Table 1, below.

[0110] In some embodiments, R₄ is substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen. In some embodiments, R₄ is hydrogen, halogen, C₁-C₄ alkyl, C₁-C₃ haloalkyl, or C₃-C₆ cycloalkyl. In some embodiments, R₄ is hydrogen, halogen, C₁-C₃ alkyl or C₁-C₃ haloalkyl. In some embodiments, R₄ is hydrogen or C₁-C₃ alkyl. In some embodiments, R₄ is H, Me, Et, *i*Pr, CF₃, CHF₂, CH₂F, cyclopropyl, F or Cl. In some embodiments, R₄ is Me, Et, *i*Pr, CF₃, CHF₂, CH₂F, cyclopropyl, F or Cl. In some embodiments, R₄ is H, Me, CF₃, cyclopropyl, F or Cl. In some embodiments, R₄ is H, Me, CF₃, F or Cl. In some embodiments, R₄ is Me, CF₃, F, or Cl. In some embodiments, R₄ is H or Me. In some embodiments, R₄ is H. In some embodiments, R₄ is Me.

[0111] As generally defined above R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl. In some embodiments, R₅ is H. In some embodiments, R₅ is C₁-C₃ alkyl, or C₁-C₃ haloalkyl. In some embodiments, R₅ is C₁-C₃ alkyl. In some embodiments, R₅ is methyl, ethyl or propyl. In some embodiments, R₅ is methyl or ethyl. In some embodiments, R₅ is methyl. In some embodiments, R₅ is ethyl or propyl. In some embodiments, R₅ is ethyl. In some embodiments, R₅ is propyl. In some embodiments, R₅ is n-propyl. In some embodiments, R₅ is isopropyl. In some embodiments, R₅ is C₁-C₃ haloalkyl. In some embodiments, R₅ is fluoromethyl, fluoroethyl or fluoropropyl. In some embodiments, R₅ is fluoromethyl. In some embodiments, R₅ is trifluoromethyl. In some embodiments, R₅ is selected from the groups in the R₅ position of the compounds recited in Table 1, below.

[0112] In some embodiments, R₅ is hydrogen, C₁-C₃ alkyl, or C₃-C₆ cycloalkyl. In some embodiments, R₅ is hydrogen or C₁-C₃ alkyl. In some embodiments, R₅ is H, Me, Et, *i*Pr, or cyclopropyl. In some embodiments, R₅ is H or Me. In some embodiments, R₅ is H. In some embodiments, R₅ is Me.

[0113] As generally described above, R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl. In some embodiments, R₆ is hydrogen. In some embodiments, R₆ is C₁-C₆ alkyl, or C₁-C₆ haloalkyl. In some embodiments, R₆ is C₁-C₃ alkyl, or C₁-C₃ haloalkyl. In some embodiments, R₆ is C₁-C₃ alkyl. In some embodiments, R₆ is methyl, ethyl or propyl. In some embodiments, R₆ is methyl or ethyl. In some embodiments, R₆ is methyl. In some embodiments, R₆ is ethyl or propyl. In some embodiments, R₆ is ethyl. In some embodiments, R₆ is propyl. In some embodiments, R₆ is n-propyl. In some embodiments, R₆ is isopropyl. In some embodiments, R₆ is C₁-C₃ haloalkyl. In some embodiments, R₆ is fluoromethyl, fluoroethyl or fluoropropyl. In some embodiments, R₆ is

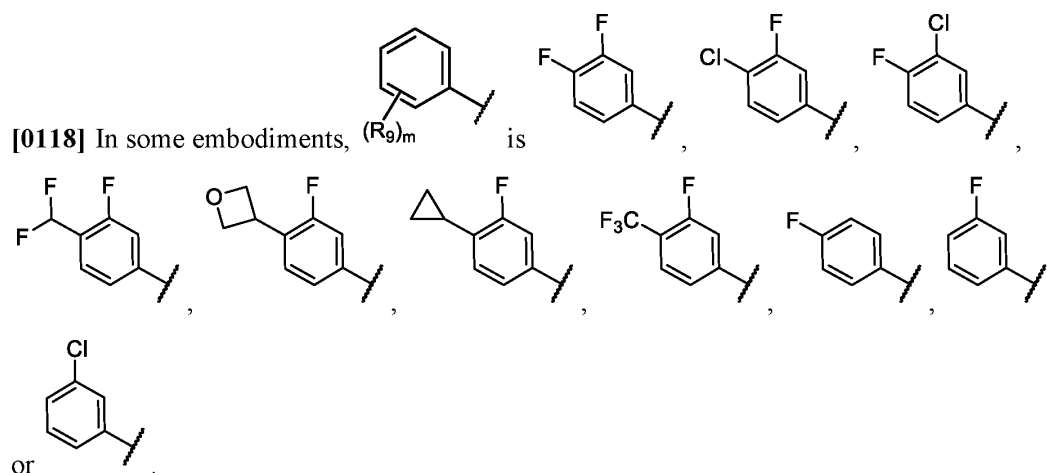
fluoromethyl. In some embodiments, R_6 is trifluoromethyl. In some embodiments, R_6 is C_3 - C_8 cycloalkyl.

[0114] In some embodiments, R_6 is H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_3 - C_6 cycloalkyl. In some embodiments, R_6 is C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_3 - C_6 cycloalkyl. In some embodiments, R_6 is C_1 - C_4 alkyl or C_1 - C_4 haloalkyl. In some embodiments, R_6 is C_1 - C_4 alkyl. In some embodiments, R_6 is H, Me, Et, CD_3 , CF_3 , CHF_2 , or cyclopropyl. In some embodiments, R_6 is H, Me, Et, CF_3 , CHF_2 , or cyclopropyl. In some embodiments, R_6 is Me or Et. In some embodiments, R_6 is Me.

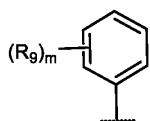
[0115] In some embodiments, each R_9 is independently a halogen, C_1 - C_4 alkyl, C_{1-4} haloalkyl, or C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl. In some embodiments, each R_9 is independently a halogen, C_{1-4} haloalkyl, or C_{3-6} cycloalkyl, or 4- to 6-membered heterocyclyl. In some embodiments, each R_9 is independently F, Cl, CF_3 , CHF_2 , CH_2F , or cyclopropyl. In some embodiments, each R_9 is independently a halogen. In some embodiments, each R_9 is independently F or Cl. In some embodiments, each R_9 is F.

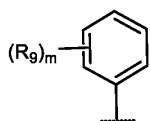
[0116] In some embodiments, m is 0, 1, or 2. In some embodiments, m is 0 or 1. In some embodiments, m is 1 or 2. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.

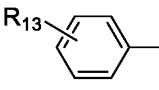
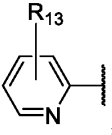
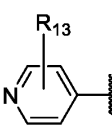
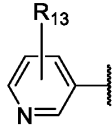
[0117] In some embodiments, n is 1. In some embodiments, n is 2.

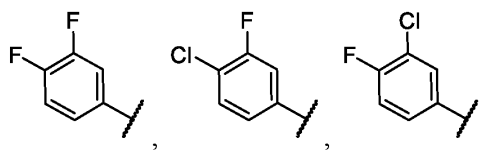


[0119] In some embodiments, each R_{10} is independently H or F. In some embodiments, each R_{10} is H.

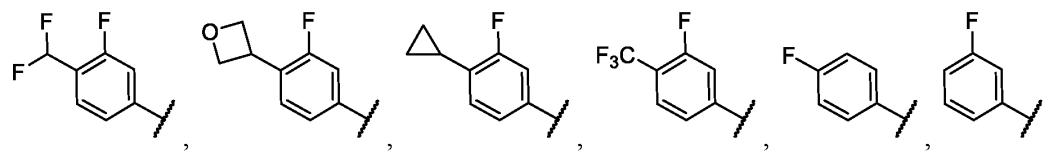


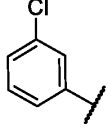
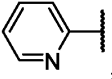
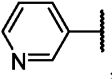
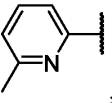
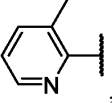
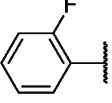
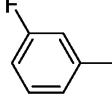
[0120] In some embodiments, R_1 is , wherein R_9 and m are as defined herein; R_2

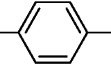
is , , , or , wherein R_{13} is as defined herein; R_3 is H; R_4 is hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_3 haloalkyl, or C_3 - C_6 cycloalkyl; R_5 is H; R_6 is C_1 - C_4 alkyl; R_{12} , when present, is H; R_b and $R_{b'}$, when present, are each H; X , when present, is N; Y_1 , Y_2 , and Y_3 are as defined herein; and n , when present, is 1 or 2.



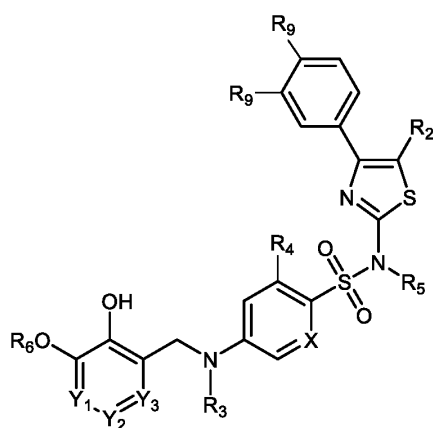
[0121] In some embodiments, R_1 is



or ; R_2 is , , , , , , or

; R_3 is H; R_4 is hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_3 haloalkyl, or C_3 - C_6 cycloalkyl; R_5 is H; R_6 is C_1 - C_4 alkyl; R_{12} , when present, is H; R_b and $R_{b'}$, when present, are each H; X , when present, is N; Y_1 , Y_2 , and Y_3 are as defined herein; and n , when present, is 1 or 2.

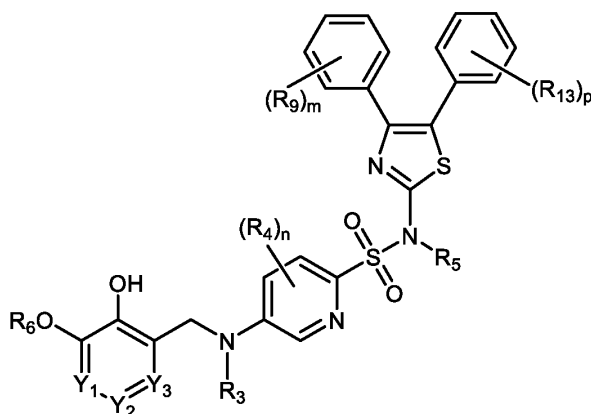
[0122] In some embodiments, the present disclosure provides a compound of Formula (Ig):



(Ig)

or a pharmaceutically acceptable salt thereof, wherein R_2 , R_3 , R_4 , R_5 , R_6 , R_9 , X , Y_1 , Y_2 , and Y_3 are as defined herein.

[0123] In some embodiments, the present disclosure provides a compound of Formula (Ih):



(Ih)

or a pharmaceutically acceptable salt thereof, wherein R_3 , R_4 , R_5 , R_6 , R_9 , R_{13} , m , n , Y_1 , Y_2 , and Y_3 are as defined herein; and p is 1, or 2, or 3.

[0124] In some embodiments, p is 1 or 2. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3.

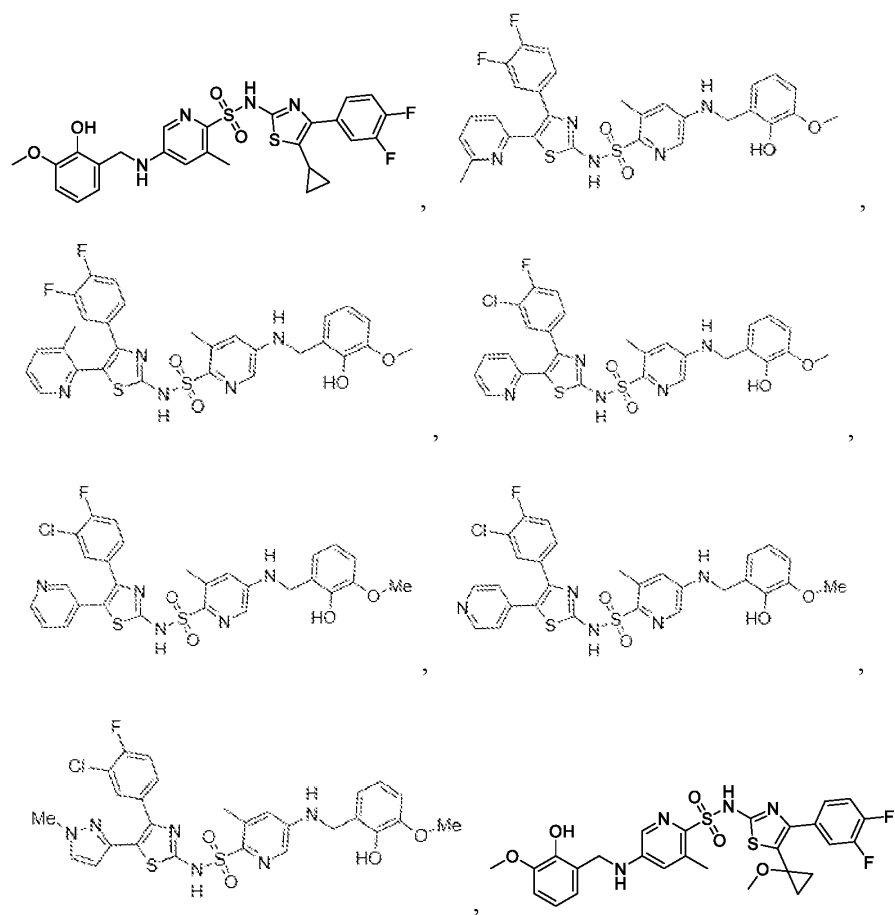
[0125] In some embodiments, each R_{13} is independently halogen, C_1 - C_5 alkyl, or C_1 - C_5 haloalkyl and p is 1 or 2. In some embodiments, each R_{13} is independently halogen or C_1 - C_5 alkyl and p is 1 or 2. In some embodiments, each R_{13} is independently a halogen and p is 1 or

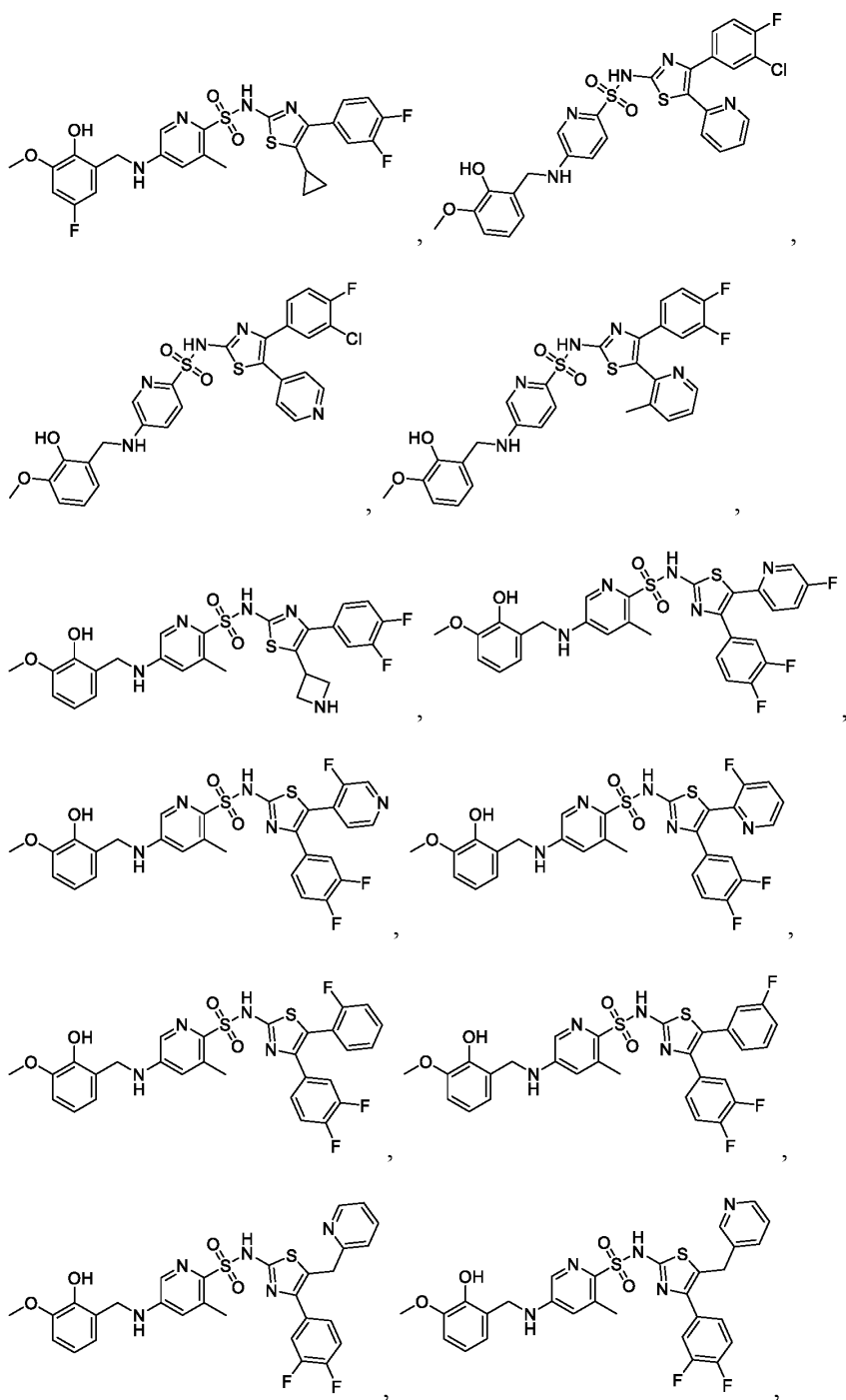
2. In some embodiments, each R_{13} is independently F or Cl and p is 1 or 2. In some embodiments, each R_{13} is F and p is 1 or 2. In some embodiments, R_{13} is F and p is 1.

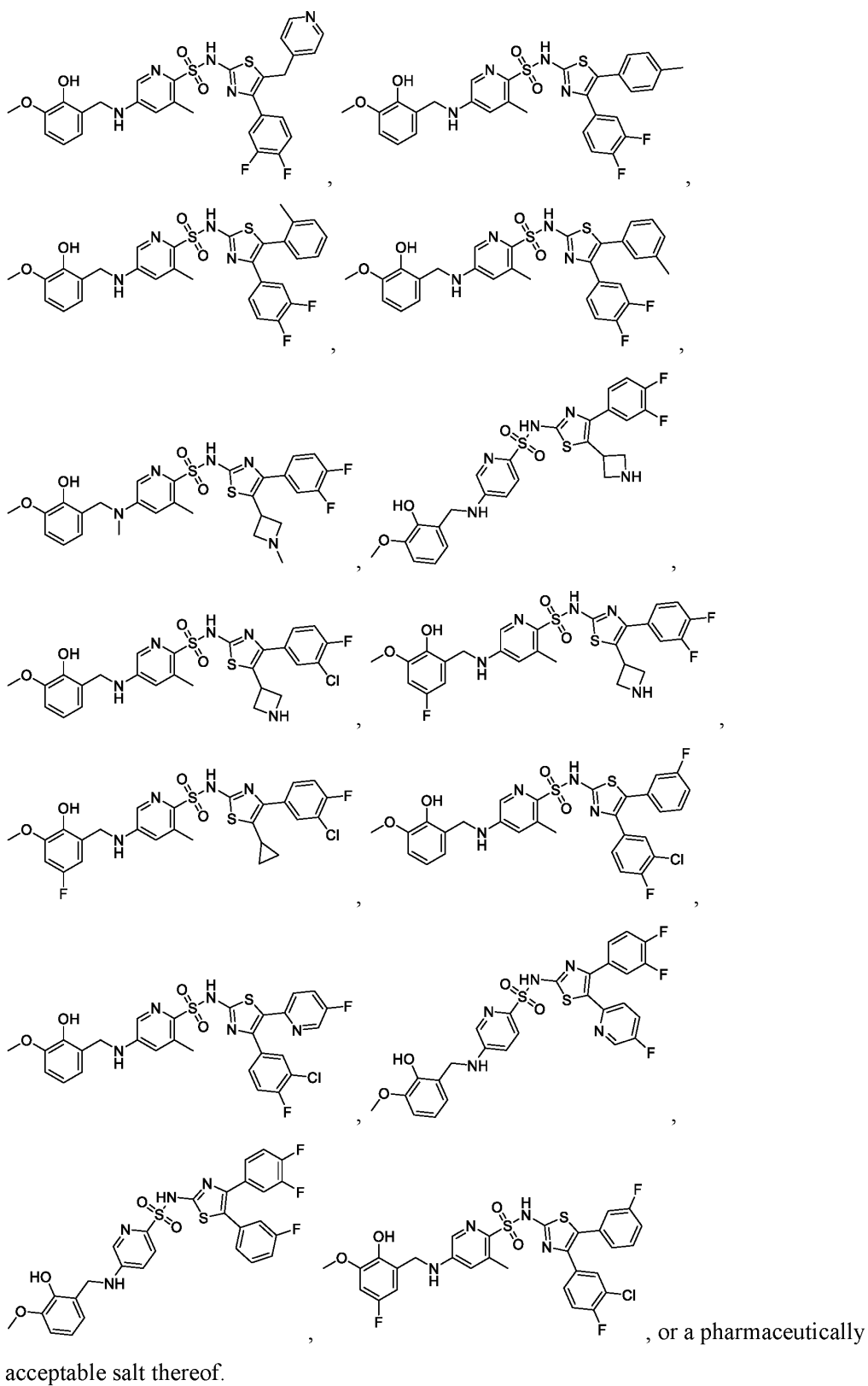
[0126] Embodiments as disclosed herein for Formula (I) are embodiments to Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), or (Ih) provided that the embodiments are within reasonable scope of each of the formula as defined herein, and vice versa. Similarly, an embodiment for one group (e.g., R_3) defined herein can apply to any formula disclosed herein that bears said group.

[0127] In some embodiments, the compound of the present disclosure is a compound of Table 1 or a pharmaceutically acceptable salt thereof.

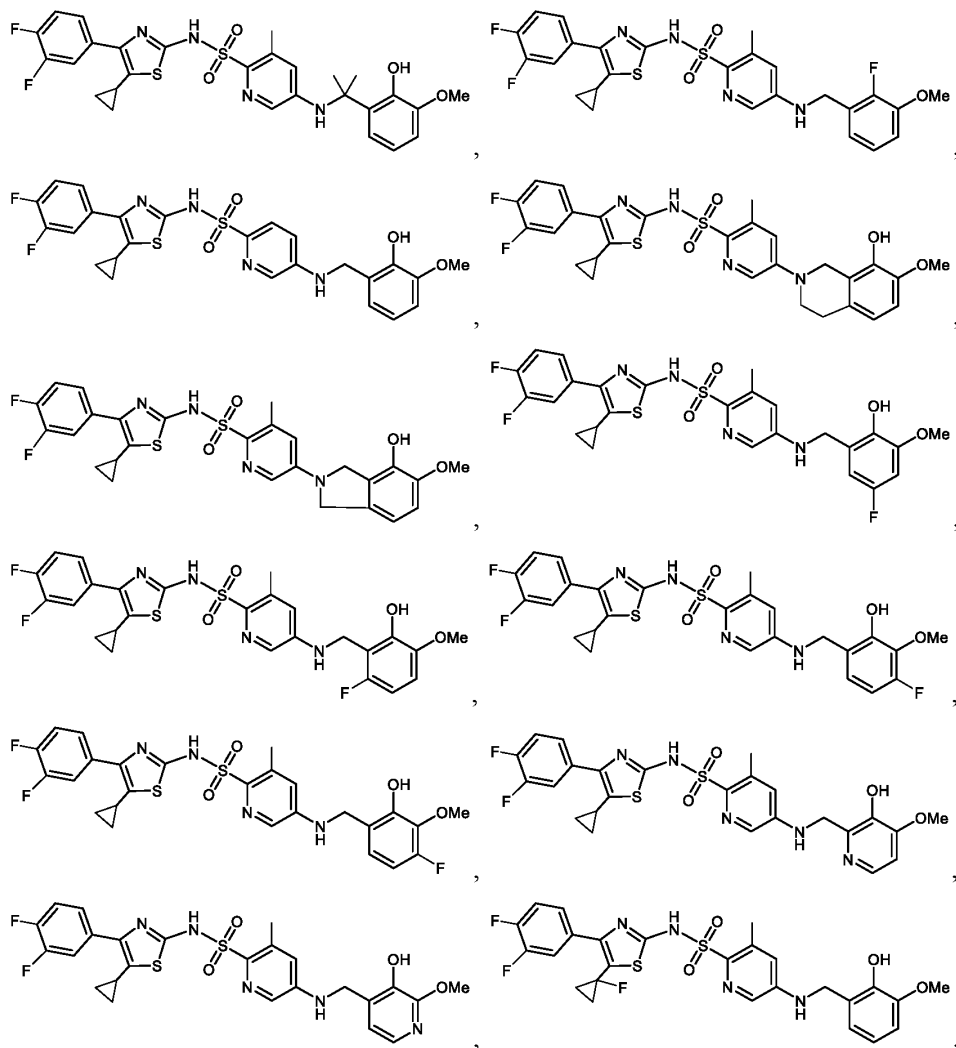
[0128] The present disclosure further provides a compound having the structure:







[0129] In some embodiments, the compound of the present disclosure is:



or pharmaceutically acceptable salt thereof.

[0130] In some embodiments, the compound of the disclosure (e.g., a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), or (Ih)) is not a compound disclosed in WO2023/122494, which is incorporated herein by reference in its entirety.

[0131] In some embodiments, the compound of the disclosure (e.g., a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), or (Ih)) is not one or more of the compounds listed in Table A:

Table A

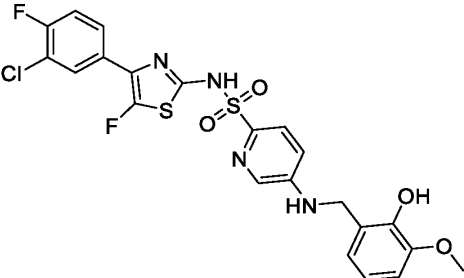
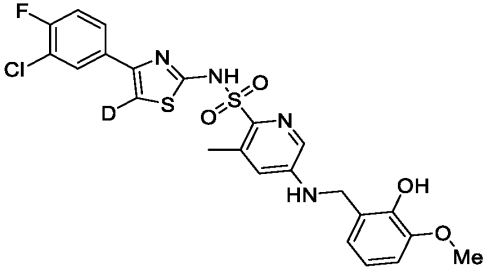
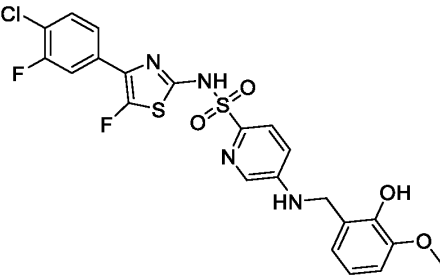
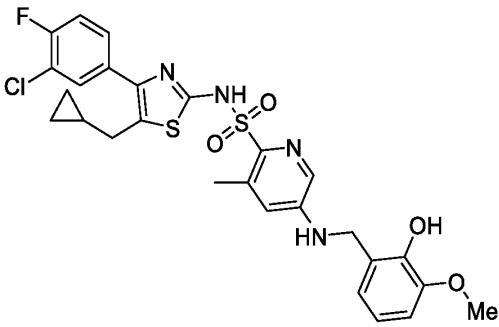
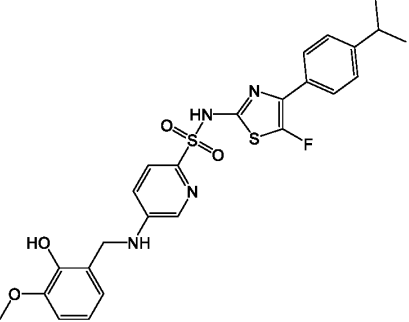
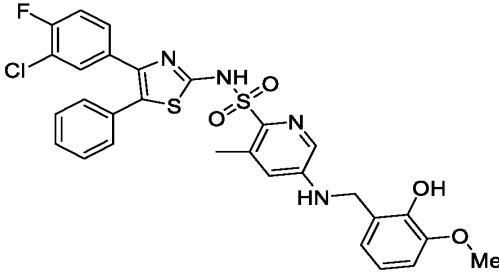
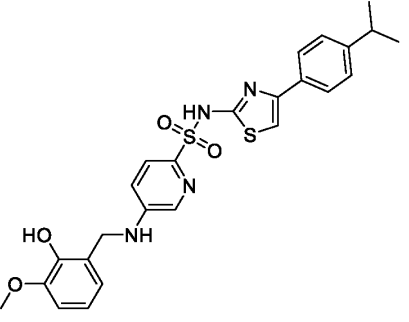
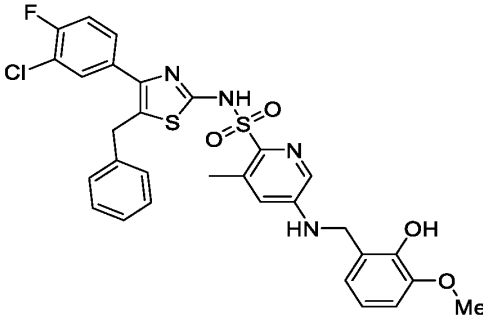
	
	
	
	

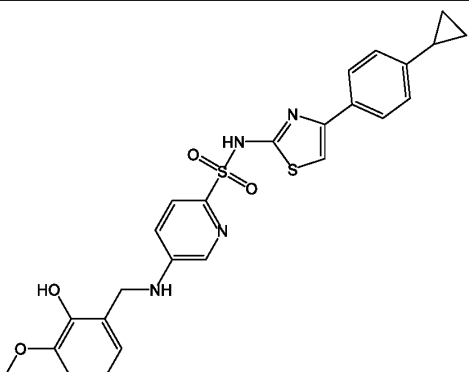
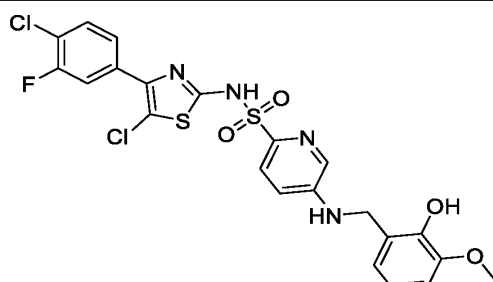
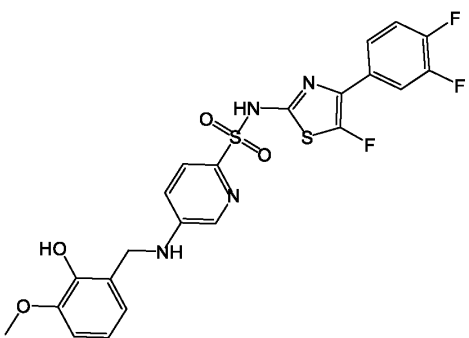
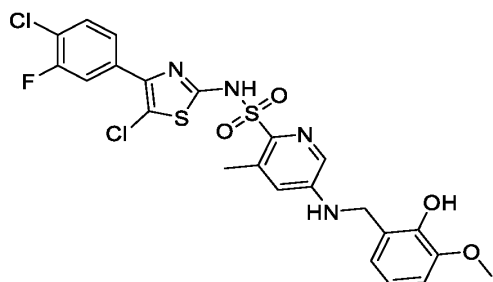
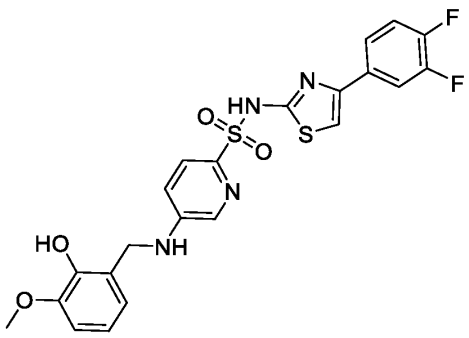
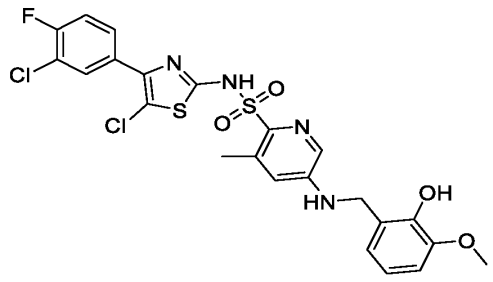
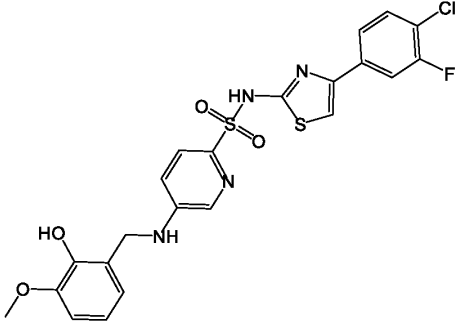
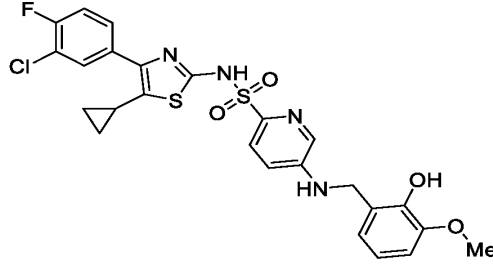
Table A	
	
	
	
	

Table A

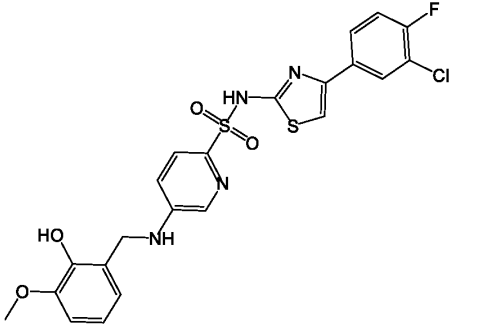
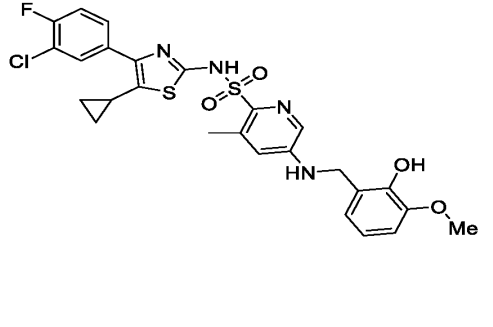
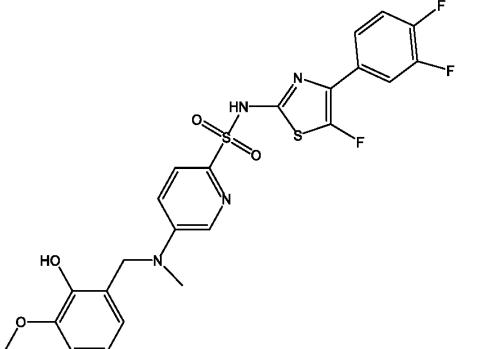
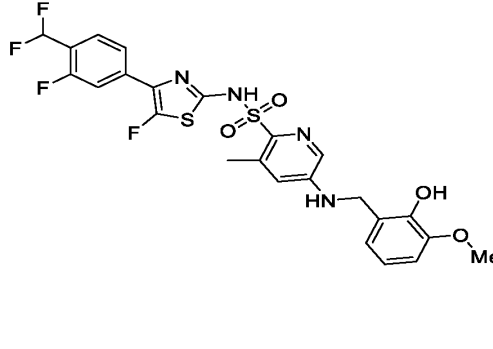
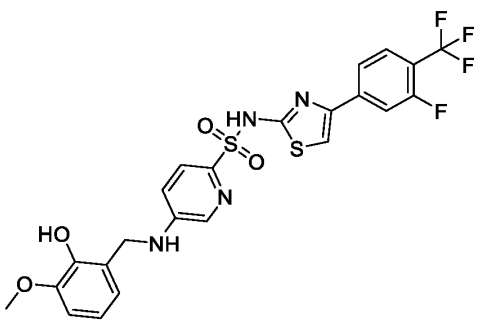
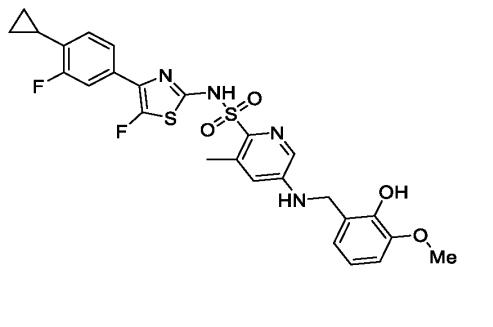
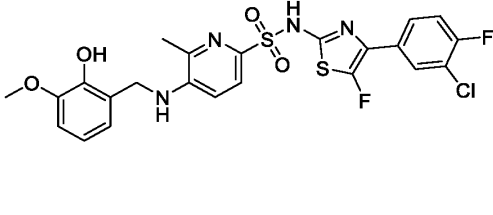
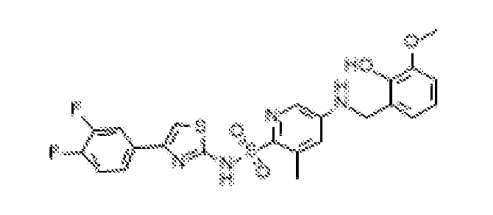
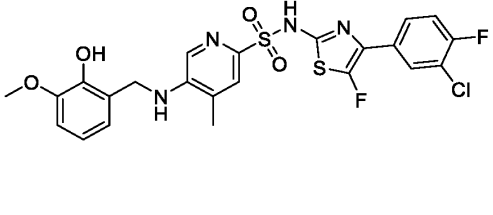
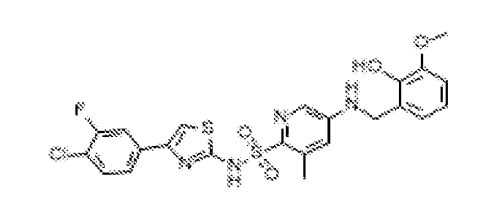
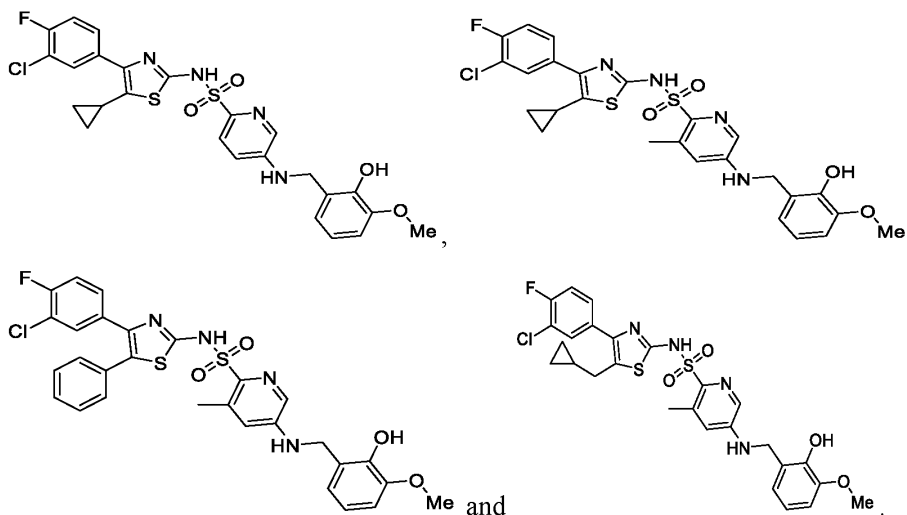
	
	
	
	
	

Table A	

Table A	

and

[0132] In some embodiments, the compound of the disclosure (e.g., a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), or (Ih)) is not one or more of:



Stereoisomers

[0133] The compounds of the present disclosure may contain, for example, double bonds, one or more asymmetric carbon atoms, and bonds with a hindered rotation, and therefore, may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers (E/Z)), enantiomers, diastereomers, and atropisomers. Accordingly, the scope of the instant disclosure is to be understood to encompass all possible stereoisomers of the illustrated compounds, including the stereoisomerically pure form (for example, geometrically pure, enantiomerically pure, diastereomerically pure, and atropisomerically pure) and stereoisomeric mixtures (for example, mixtures of geometric isomers, enantiomers, diastereomers, and atropisomers, or mixture of any of the foregoing) of any chemical structures disclosed herein (in whole or in part), unless the stereochemistry is specifically identified.

[0134] If the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. If the stereochemistry of a structure or a portion of a structure is indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing only the stereoisomer indicated. For example,

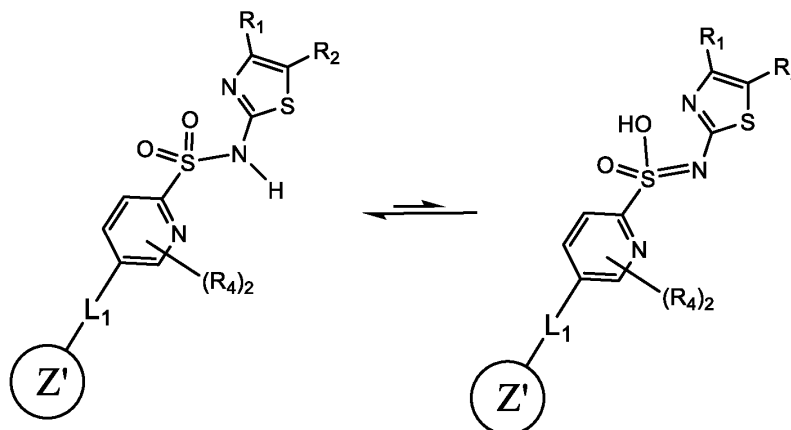
(1R)-1-methyl-2-(trifluoromethyl)cyclohexane is meant to encompass (1R,2R)-1-methyl-2-(trifluoromethyl)cyclohexane and (1R,2S)-1-methyl-2-(trifluoromethyl)cyclohexane. A bond drawn with a wavy line indicates that both stereoisomers are encompassed. This is not to be confused with a wavy line drawn perpendicular to a bond which indicates the point of attachment of a group to the rest of the molecule.

[0135] The term “stereoisomer” or “stereoisomerically pure” compound as used herein refers to one stereoisomer (for example, geometric isomer, enantiomer, diastereomer and atropisomer) of a compound that is substantially free of other stereoisomers of that compound. For example, a stereoisomerically pure compound having one chiral center will be substantially free of the mirror image enantiomer of the compound and a stereoisomerically pure compound having two chiral centers will be substantially free of the other enantiomer and diastereomers of the compound. A typical stereoisomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and equal or less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and equal or less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and equal or less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and equal or less than about 3% by weight of the other stereoisomers of the compound. This disclosure also encompasses the pharmaceutical compositions comprising stereoisomerically pure forms and the use of stereoisomerically pure forms of any compounds disclosed herein. Further, this disclosure also encompasses pharmaceutical compositions comprising mixtures of stereoisomers of any compounds disclosed herein and the use of said pharmaceutical compositions or mixtures of stereoisomers. These stereoisomers or mixtures thereof may be synthesized in accordance with methods well known in the art and methods disclosed herein. Mixtures of stereoisomers may be resolved using standard techniques, such as chiral columns or chiral resolving agents. See, for example, Jacques et al, *Enantiomers, Racemates and Resolutions* (Wiley - Interscience, New York, 1981); Wilen et al, *Tetrahedron* 33:2725; Eliel, *Stereochemistry of Carbon*

[0136] Compounds (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions*, page 268 (Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

Tautomers

[0137] As known by those skilled in the art, certain compounds disclosed herein may exist in one or more tautomeric forms. As only one specific chemical structure may only be used to represent one tautomeric form, it will be understood that for convenience, referral to a compound of a given structural formula includes all other possible tautomers of said structural formula. For example, the following is illustrative of tautomers of the compounds of Formula I' where $R_5=H$:



One skilled in the art would recognize that under standard conditions, the tautomer on the left-hand side is clearly the predominant tautomer for these two structures and this example is given for illustrative purposes only. Accordingly, the scope of the instant disclosure is to be understood to encompass all tautomeric forms of the compounds disclosed herein.

Isotopically-Labelled Compounds

[0138] Further, the scope of the present disclosure includes all pharmaceutically acceptable isotopically-labelled compounds of the compounds disclosed herein, such as the compounds of Formula I, wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds disclosed herein include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{12}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulfur, such as ^{35}S . Certain isotopically-labelled compounds of Formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium (^3H) and carbon-14 (^{14}C) are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with

isotopes such as deuterium (^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be advantageous in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies, for example, for examining target occupancy. Isotopically-labelled compounds of the compounds disclosed herein can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying General Synthetic Schemes and Examples using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

Solvates

[0139] As discussed above, the compounds disclosed herein and the stereoisomers, tautomers, and isotopically-labelled forms thereof or a pharmaceutically acceptable salt of any of the foregoing may exist in solvated or non-solvated forms.

[0140] The term “solvate” as used herein refers to a molecular complex comprising a compound or a pharmaceutically acceptable salt thereof as described herein and a stoichiometric or non-stoichiometric amount of one or more pharmaceutically acceptable solvent molecules. If the solvent is water, the solvate is referred to as a “hydrate.”

[0141] Accordingly, the scope of the instant disclosure is to be understood to encompass all solvents of the compounds disclosed herein and the stereoisomers, tautomers and isotopically-labelled forms thereof or a pharmaceutically acceptable salt of any of the foregoing.

Compositions and Formulations

[0142] The present disclosure provides pharmaceutical compositions comprising a compound disclosed herein (e.g., a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), Table 1, or Table 2) and one or more pharmaceutically acceptable carriers or excipients. The compounds of the present disclosure may be administered by any means known in the art suitable for treating the diseases and disorders described herein.

Parenteral dosage forms

[0143] In one embodiment, the novel compounds described herein can be administered in a parenteral dosage form. The term “parenteral,” as used herein, includes, but is not limited to, subcutaneous injections, intravenous, intramuscular, intraperitoneal injections, or infusion

techniques. In an embodiment, the parenteral pharmaceutical formulations described herein comprises a compound described herein and a pharmaceutically acceptable carrier. In one embodiment, the parenteral pharmaceutical formulation may contain liquid carriers, including, vegetable oils such as peanut oil, cotton seed oil, sesame oil, as well as organic solvents, PEG, propylene glycol, glycerol, and surfactants. In certain embodiments for parenteral administration, the conjugates of the invention are mixed with solubilizing agents such as Cremophor™, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[0144] In another embodiment, the parenteral pharmaceutical formulation is aqueous. In one embodiment, the aqueous parenteral pharmaceutical formulation comprises at least 50% water, preferably 70% or more of water. In another embodiment, the pharmaceutical carrier comprises a solubilizer. In a specific embodiment, the solubilizer is 2-hydroxyalkylated β -cyclodextrin such as hydroxyethyl β -CD, hydroxypropyl- β -CD, hydroxybutyl β -CD, or sulfobutylether- β -cyclodextrin.

[0145] The pharmaceutically acceptable 2-hydroxyalkylated β -cyclodextrin may be present in any suitable amount within the aqueous parenteral pharmaceutical formulations described herein. The pharmaceutically acceptable 2-hydroxyalkylated β -cyclodextrin may be present in amount of between about 5% and 50% w/v. For example, the pharmaceutically acceptable solubilizer, optionally HP- β -CD, may be in an amount of about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% w/v. In specific embodiments, the HP- β -CD may be present in amount from about 10% to about 40%, from about 20% to about 40%, from about 30% to about 40%, from about 10% to about 30%, or from about 10% to about 20% of the total formulation. In one embodiment, the 2-hydroxyalkylated β -cyclodextrin may present in amount of about 25% of the total formulation w/v.

[0146] For parenteral administration, sterile solutions and suspensions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous, administration is desired. The pharmaceutical formulations may be administered parenterally via injection of a pharmaceutical formulation comprising a compound dissolved in an inert liquid carrier, such as sterile water or other pharmaceutically acceptable diluents.

[0147] Pharmaceutical compositions or formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes that render the formulation isotonic with the blood of the

intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, e.g., water for injections, saline, dextrose in water (D5W), lactated Ringer's solution, immediately prior to use. Extemporaneous immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0148] Parenteral formulations may further comprise at least one of any suitable auxiliaries including, but not limited to, diluents, crystal inhibitors, tonicifiers, water structure forming agents or disruptors, polymers, ion pairing agents, stabilizers, buffers, salts, lipophilic solvents, preservatives, adjuvants or the like. Pharmaceutically acceptable auxiliaries are preferred. Examples and methods of preparing such sterile solutions are well known in the art and can be found in well-known texts such as, but not limited to, REMINGTON'S PHARMACEUTICAL SCIENCES (Adejare, Ed., 123rd Edition, Academic Press. (2020); Handbook of Pharmaceutical Excipients, 9th Edition, Pharmaceutical Press (2020)). Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the compound.

[0149] Pharmaceutical excipients and additives useful in the parenteral pharmaceutical formulations described herein can also include, but are not limited to, proteins, peptides, amino acids, lipids, and carbohydrates (*e.g.*, sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditols, aldonic acids, esterified sugars; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination in ranges of 1-99.99% by weight or volume. Exemplary protein excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, and casein. Representative amino acid components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, and aspartame.

[0150] Carbohydrate excipients suitable for use in the parenteral pharmaceutical formulations described herein include but are not limited to monosaccharides such as dextrose, fructose, maltose, galactose, glucose, D-mannose, and sorbose; disaccharides, such as lactose, sucrose, trehalose, and cellobiose; polysaccharides, such as raffinose, melezitose, maltodextrins,

dextrans, and starches; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol, sorbitol (glucitol), and myoinositol.

[0151] The pharmaceutical formulations comprising the compounds described herein can also a pH adjusting agent. The pH adjusting agent may be a base, optionally sodium hydroxide. The pH adjusting agent may also be an acid, optionally hydrochloric acid.

[0152] In one embodiment, the present disclosure provides stable parenteral pharmaceutical formulations as well as preserved solutions and formulations containing a preservative, as well as multi-use preserved formulations suitable for pharmaceutical or veterinary use, comprising at least one compound disclosed herein in a pharmaceutically acceptable formulation. Pharmaceutical formulations in accordance with the present disclosure may optionally comprise at least one known preservative. Preservatives include, but are not limited to, phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (e.g., hexahydrate), alkylparaben (methyl, ethyl, propyl, butyl), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used as known in the art, such as 0.001-5%, or any range or value therein. Non-limiting examples include, no preservative, 0.1-2% m-cresol, 0.1-3% benzyl alcohol, 0.001-0.5% thimerosal, 0.001-2.0% phenol, 0.0005-1.0% alkylparaben(s).

[0153] Other excipients, *e.g.*, isotonicity agents, buffers, antioxidants, preservative enhancers, can be optionally added. When used, the amount of tonicity modifier used most often ranges from 0.1 to 1% (w/v). Non-limiting examples of suitable tonicity modifiers include sodium chloride, glycerin, boric acid, calcium chloride, dextrose, and potassium chloride. The formulations can include a local anesthetic to reduce the potential of pain during injection. A physiologically tolerated buffer can be added to provide improved pH control if necessary. The pharmaceutical formulations can cover a wide range of pHs, such as from about pH 4 to about pH 10, specifically, a range from about pH 5 to about pH 9, and more specifically, a range of about 7.0 to about 9.0. In one aspect, the formulations described herein have pH between about 8.4 and about 8.7.

[0154] Methods of preparing the pharmaceutical preparations described herein are manufactured in a manner that is known, including conventional mixing, dissolving, or lyophilizing processes. Thus, aqueous pharmaceutical preparations can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting

mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary.

Oral dosage forms

[0155] Pharmaceutical formulation of the compounds described herein for oral administration may be in the form of tablets or capsules and may be immediate-release formulations or may be controlled- or extended-release formulations, which may contain pharmaceutically acceptable excipients, such as corn starch, mannitol, povidone, magnesium stearate, talc, cellulose, methylcellulose, carboxymethylcellulose and similar substances. A pharmaceutical composition comprising the compounds and/or a salt thereof may comprise one or more pharmaceutically acceptable excipients, which are known in the art. Formulations include oral films, orally disintegrating tablets, effervescent tablets and granules or beads that can be sprinkled on food or mixed with liquid as a slurry or poured directly into the mouth to be washed down.

[0156] Pharmaceutical compositions containing the compounds, salts and hydrates thereof can be prepared by any method known in the art of pharmaceuticals. In general, such preparatory methods include the steps of bringing the 12-LOX inhibitor or a pharmaceutically acceptable salt thereof into association with a carrier or excipient, and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping, and/or packaging the product into a desired single- or multi-dose unit.

[0157] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a “unit dose” is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[0158] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. The composition used in the methods of the present invention may comprise between 0.001% and 100% (w/w) active ingredient.

[0159] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[0160] In certain embodiments, the pharmaceutical composition used in the methods of the present invention may comprise a diluent. Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate, lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[0161] In certain embodiments, the pharmaceutical composition used in the methods of the present invention may comprise a granulating and/or dispersing agent. Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (VEEGUM), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[0162] In certain embodiments, the pharmaceutical composition used in the methods of the present invention may comprise a binding agent. Exemplary binding agents include starch (e.g., cornstarch and starch paste), gelatin, sugars (e.g., sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, etc.), natural and synthetic gums (e.g., acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (VEEGUM.RTM.), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[0163] In certain embodiments, the pharmaceutical composition used in the methods of the present invention may comprise a preservative. Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, antiprotozoan preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[0164] In certain embodiments, the pharmaceutical composition used in the methods of the present invention may comprise an antioxidant. Exemplary antioxidants include alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[0165] In certain embodiments, the pharmaceutical composition used in the methods of the present invention may comprise a chelating agent. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (e.g., sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (e.g., citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[0166] In certain embodiments, the pharmaceutical composition may comprise a buffering agent together with the 12-LOX inhibitor or the salt thereof. Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium

lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[0167] In certain embodiments, the pharmaceutical composition used in the methods of the present invention may comprise a lubricating agent. Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[0168] In other embodiments, the pharmaceutical composition of containing a 12-LOX inhibitor or salt thereof will be administered as a liquid oral dosage form. Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates of the invention are mixed with solubilizing agents such as Cremophor™, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[0169] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and

bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets, and pills, the dosage form may include a buffering agent.

[0170] Some oral compositions of the invention relate to extended- or controlled-release formulations. These may be, for example, diffusion-controlled products, dissolution-controlled products, erosion products, osmotic pump systems or ionic resin systems. Diffusion-controlled products comprise a water-insoluble polymer which controls the flow of water and the subsequent egress of dissolved drug from the dosage form. Dissolution-controlled products control the rate of dissolution of the drug by using a polymer that slowly solubilizes or by microencapsulation of the drug – using varying thicknesses to control release. Erosion products control release of drug by the erosion rate of a carrier matrix. Osmotic pump systems release a drug based on the constant inflow of water across a semi permeable membrane into a reservoir which contains an osmotic agent. Ion exchange resins can be used to bind drugs such that, when ingested, the release of drug is determined by the ionic environment within the gastrointestinal tract.

Administration and Dosage

[0171] One of ordinary skill in the art will appreciate that administration of pharmaceutically effective amounts of the pharmaceutical formulations described herein to a patient in need thereof, can be determined empirically, or by standards currently recognized in the medical arts. It will be understood that, when administered to a human patient, the total daily usage of the agents of the compositions described herein will be decided within the scope of sound medical judgment by the attending physician. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, gender and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts. It is well within the skill of the art to start doses of the agents at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosages until the desired effect is achieved.

[0172] Routes of administration and dosages of effective amounts of parenteral pharmaceutical formulations comprising the 12-LOX inhibitor compounds are also disclosed.

In one embodiment, the administration is intravenous. The pharmaceutical compositions and/or formulations described herein may also be administered by infusion. The pharmaceutical formulations described herein may also be administered by a bolus dosage, optionally combined with administration by infusion. The compounds described herein can be administered in combination with other pharmaceutical agents in a variety of protocols for effective treatment of disease.

[0173] The parenteral pharmaceutical formulations may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily. Doses may be administered for one week, one month, or over the course of several months, 3, 6, 9 or 12 months, or intervals known in the art and determined to be clinically relevant. In one embodiment, the parenteral pharmaceutical formulations may be administered chronically for years or for the life of the patient. For example, the pharmaceutical formulations described herein may be administered for 7 days, 14 days, 21 days, 28 days, or 35 days. The daily dosage of the formulations may be varied over a wide range from about 0.0001 to about 1,000 mg per patient, per day, more particularly from about 200 to about 700, preferably about 500 to 600 mg/day. The range may more particularly be from about 1 mg/kg to 100 mg/kg of body weight per day, about 10-50 mg/kg, 20 to 60 mg/kg, preferably 10-20 mg/kg per day for adults (at about 60 kg), or equivalent doses as determined by a practitioner, to achieve a serum concentration that is clinically relevant.

[0174] Specifically, the aqueous parenteral pharmaceutical formulations described herein may be administered at least once a day over the course of several weeks, several months, or several years. In one embodiment, the pharmaceutical formulations are administered at least once a day over several weeks to several months. In another embodiment, the pharmaceutical formulations are administered once a day over at least one year.

[0175] The aqueous parenteral pharmaceutical formulations may be administered following use of a topical anesthetic, including but not limited to, lidocaine, prilocaine, or combinations thereof. Ice or ethyl chloride spray can also be used prior to administration.

[0176] It can be sometimes desirable to deliver the compounds described herein to the subject over prolonged periods of time, for periods of one week to one year from a single administration. Certain medical devices may be employed to provide a continuous intermittent or on demand dosing of a patient. The devices may be a pump or diffusion apparatus, or other device containing a reservoir of drug and optionally diagnostic or

monitoring components to regulate the delivery of the drug. Various slow-release, depot or implant dosage forms can be utilized. These may be, for example, diffusion-controlled products, dissolution-controlled products, erosion products, osmotic pump systems or ionic resin systems. Diffusion-controlled products comprise a water-insoluble polymer which controls the flow of water and the subsequent egress of dissolved drug from the dosage form. Dissolution-controlled products control the rate of dissolution of the drug by using a polymer that slowly solubilizes or by microencapsulation of the drug – using varying thicknesses to control release. Erosion products control release of drug by the erosion rate of a carrier matrix.

[0177] In one embodiment, the aqueous parenteral pharmaceutical formulations described herein may be administered by infusion. The infusion may comprise infusing between about 1 and about 1000 mg of the novel compounds in the aqueous pharmaceutical formulation continuously. In another embodiment, the infusion is administered over 30 minutes to 23 hours.

[0178] The amount of the compound infused may be about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 mg.

[0179] In one embodiment, the infusion may be continuous or repeated over intervals. In one embodiment, the intervals are between about 1 day to 1 year, or between about 1 day to 6 months, or 1 day to 1 month. In another embodiment, the infusion may be repeated over between about 1 and 14 days, optionally between about 1 and 7 days. The infusion may be repeated over 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days. The infusion may be repeated over between about 1 and 7 days, 3 and 8 days, 5 and 14 days, 9 and 14 days, or 7 and 14 days.

[0180] For example, the pharmaceutical formulations described herein may be infused continuously or over a period of 1 to 23 hours, including all intervals in between, at a rate of about 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180, 190 mg, 200 mg, 210 mg, 220 mg,

230 mg, 240 mg, 250 mg, 260 mg, 270 mg over 1-5 hours, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 510 mg, 520 mg, 530 mg, 540 mg, 550 mg, 560 mg, 570 mg, 580 mg, 590 mg, 600 mg, 610 mg, 620 mg, 630 mg, 640 mg, 650 mg, 660 mg, 670 mg, 680 mg, 690 mg, 700 mg, 710 mg, 720 mg, 730 mg, 740 mg, 750 mg, 760 mg, 770 mg, 780 mg, 790 mg, 800 mg, 810 mg, 820 mg, 830 mg, 840 mg, 850 mg, 860 mg, 870 mg, 880 mg, 890 mg, 900 mg, 910 mg, 920 mg, 930 mg, 940 mg, 950 mg, 960 mg, 970 mg, 980 mg, 990 mg, or 1000 mg. In a specific embodiment, infusion occurs over 1 to 12 hours, 1 to 6 hours, or 1 to 4 hours.

[0181] For oral dosage forms or formulations, the pharmaceutical compositions may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily. Doses may be administered for one week, one month, or over the course of several months, 3, 6, 9 or 12 months, chronically, or intervals known in the art and determined to be clinically relevant. Doses may be continued throughout the life of the patient, or discontinued when clinical judgment warrants. The daily dosage of the compositions may be varied over a wide range from about 0.0001 to about 1,000 mg per patient, per day. The range may more particularly be from about 0.001 mg/kg to 10 mg/kg of body weight per day, about 0.1-100 mg, about 1.0-50 mg or about 1.0-0 mg per day for adults (at about 60 kg). Additionally, the dosages may be about 0.5-10 mg/kg, per day, about 1.0-5.0 mg/kg per day, 5.0-10 mg/kg per day, or equivalent doses as determined by a practitioner, to achieve a plasma/serum concentration that is clinically relevant.

[0182] The aqueous pharmaceutical formulations described herein can be administered to any animal that can experience the beneficial effects of the compounds of the invention. Preferred is administration to humans.

[0183] The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect.

Therapeutic and Prophylactic Methods

[0184] The compounds and pharmaceutically acceptable salts thereof described herein may be used as selective 12-lipoxygenase (12-LOX) inhibitors and can be used to prevent or treat 12-LOX-mediated diseases. The disclosure further provides a method for treating or preventing a 12-LOX mediated disease or disorder comprising administering to a mammal a

therapeutically or prophylactically effective amount of a novel *N*-(thiazol-2-yl)pyridine-2-sulfonamide derived compound or other compounds described herein.

[0185] Lipoxygenases are involved in the first committed step in a cascade of metabolic pathways and the products of these enzymes (eicosanoids) are precursors of hormones such as leukotrienes and lipoxins, which mediate a wide array of cellular functions. (Serhan, et al. Chem. Rev. 2011, 111, 5922-5943). Consequently, the lipoxygenase enzymes and their bioactive metabolites (*e.g.* hydroxyeicosatetraenoic acid (HETE) and leukotriene A4) have been implicated in a variety of inflammatory diseases and cancers.

[0186] 12-LOX has been demonstrated to play a role in a number of conditions and/or diseases, such as skin diseases and platelet hemostasis, transplantation/xenotransplantation, cancer (including but not limited to prostate cancer, colorectal cancer, breast cancer, lung cancer, and hematological diseases), Type 1 and Type 2 diabetes, diabetic kidney disease (diabetic nephropathy), diabetic neuropathy, diabetic retinopathy, cardiovascular disease (including but not limited to myocardial infarction, congestive heart failure, heart failure, and stroke), thrombosis, heparin induced thrombocytopenia (HIT), Alzheimer's disease, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, insulin resistance, arthritis, lupus (SLE), lupus nephritis, and inflammation.

[0187] In one embodiment, the invention provides a method for reducing U46619-induced, thrombin-induced, PAR1-AP, PAR4-AP-induced or collagen-induced platelet aggregation, comprising administering to a mammal thereof a therapeutically or prophylactically effective amount of any of compounds, salts, prodrugs, enantiomers, a mixture of enantiomers, or diastereomer thereof.

[0188] In one embodiment, the invention provides a method for reducing FcγRIIA-mediated platelet activation (*e.g.* via anti-CD9 or IV.3+GAM-induced activation) comprising administering to a mammal thereof a therapeutically or prophylactically effective amount of any of the compounds, salts, prodrugs, enantiomers, mixture of enantiomers, or diastereomer thereof.

[0189] In certain embodiments, the disorder is an immune-mediated thrombocytopenia and thrombosis disorder, including but not limited to, thrombocytopenia associated with sepsis, and heparin-induced thrombocytopenia (HIT).

[0190] In preferred embodiments, the disease or disorder to be treated by the disclosed 12-LOX inhibitor compounds is selected from thrombosis, HIT, and Type 1 and Type 2 diabetes.

[0191] In a specific embodiment, the disorder is heparin-induced thrombocytopenia (HIT).

[0192] In a specific embodiment, the disorder is Type 1 diabetes.

[0193] In a specific embodiment, the disorder is lupus (SLE) or lupus nephritis.

[0194] In one embodiment, the invention provides method of treating or preventing a 12-lipoxygenase mediated disease or disorder, comprising administering to a mammal thereof a therapeutically or prophylactically effective amount of any of compounds or a salt, prodrugs, enantiomers, a mixture of enantiomers, or diastereomer thereof.

Combination therapy

[0195] The pharmaceutical formulations described herein can also include additional therapeutic agents or combinations thereof.

[0196] An additional therapeutic agent may be other 12-LOX inhibitors. A 12-LOX inhibitor can be an organic compound, an inorganic compound, a biological compound (*e.g.*, proteins or fragments thereof, antibodies or fragments thereof, nucleic acids, nucleic acid analogs, saccharides, or peptides), or any combination thereof. A 12-LOX inhibitor can also be synthetic or naturally occurring. Selective 12-LOX inhibitors are described in U.S. Patent No. 10,266,488 and 10,752,581.

[0197] The mixing ratios of the 12-LOX inhibitors may be optimized to provide maximum therapeutic effects.

[0198] Additional agents include but not limited to anti-thrombotic agents such as argatroban, fondaparinux, lepirudin, bivalirudin, danaparoid and drotrecogin alfa; antidiabetic agents such as exenatide, albiglutide, pramlintide, semaglutide, lixisenatide, and dulaglutide. Combinations with direct-acting oral coagulants is also contemplated, including but not limited to, apixaban, dabigatran, rivaroxaban, and edoxaban.

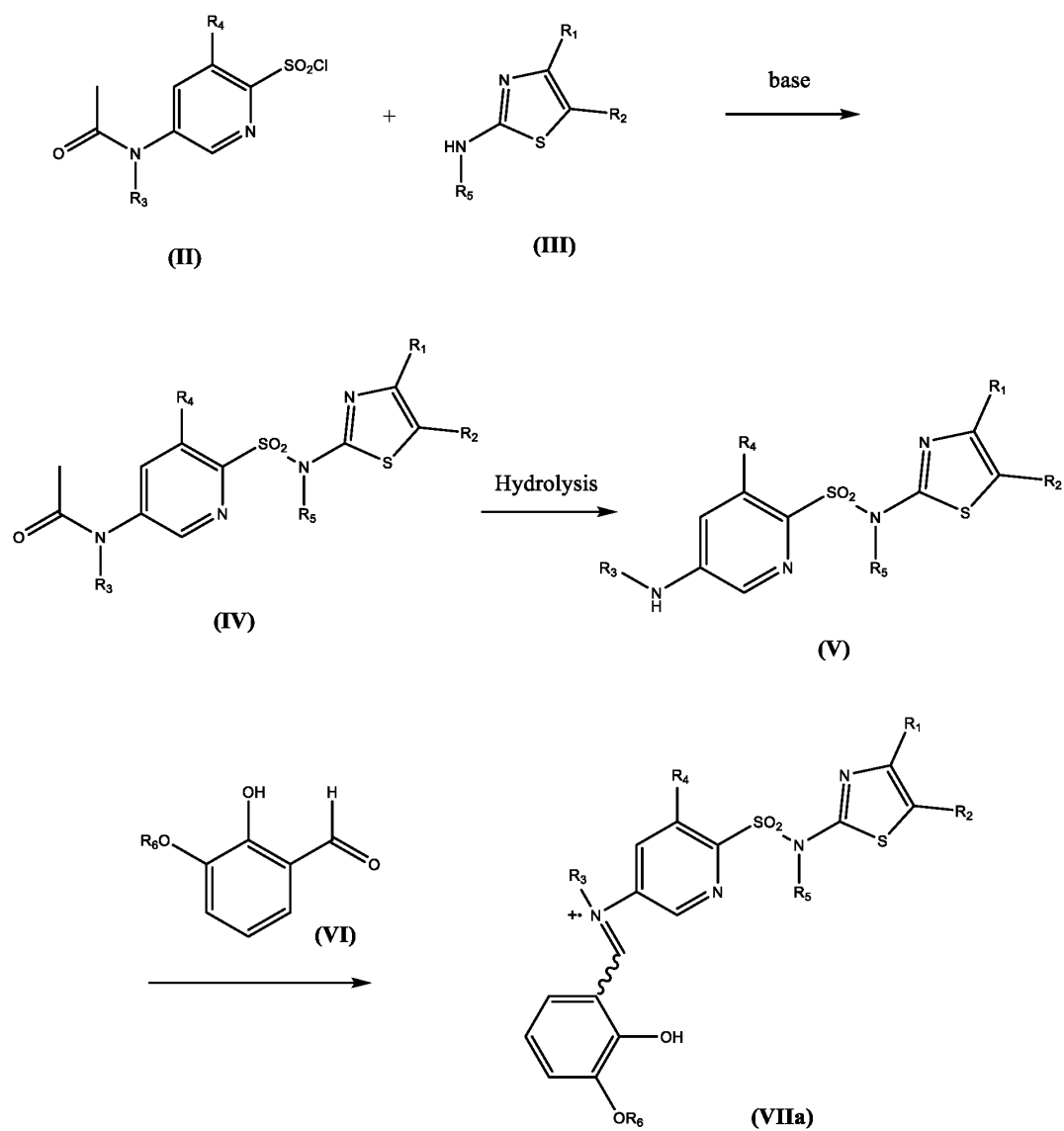
[0199] The invention also contemplates co-administration of the foregoing additional therapeutic agents in separate compositions or formulations, either at the same time, before or after administration of the 12-LOX inhibitor compounds of the disclosure.

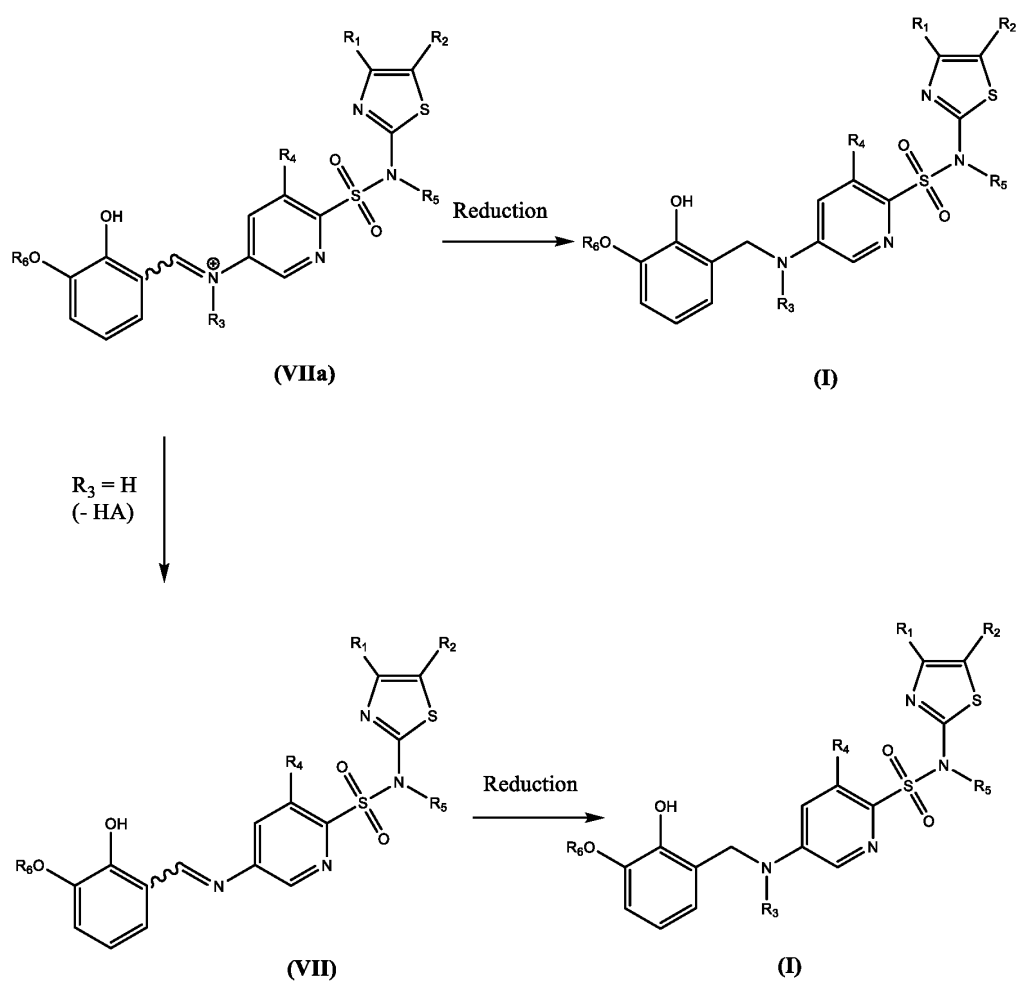
General Methods for Preparing the Disclosed Compounds

[0200] The compounds described herein may be prepared or isolated in general by synthetic and/or semi-synthetic methods known to those skilled in the art for analogous compounds and by methods described in detail in the examples, herein.

[0201] One skilled in the art would recognize that various functional groups present in compounds of the invention such as aliphatic groups, alcohols, carboxylic acids, esters, amides, aldehydes, halogens and nitriles can be interconverted by techniques well known in the art including, but not limited to reduction, oxidation, esterification, hydrolysis, partial oxidation, partial reduction, halogenation, dehydration, partial hydration, and hydration. See, for example, “March’s Advanced Organic Chemistry”, 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entirety of which is incorporated herein by reference. Such interconversions may require one or more of the aforementioned techniques, and certain methods for synthesizing compounds of the invention are described herein.

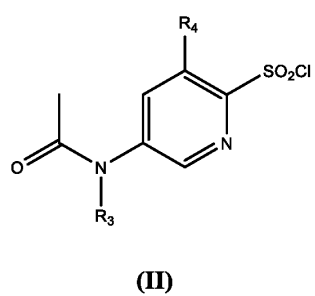
[0202] Scheme 1 illustrates a general method of preparing compounds of Formula (I). In one aspect, certain compounds of the present invention of Formula (I), or sub-formulae thereof, are generally prepared according to Scheme 1 set forth below:



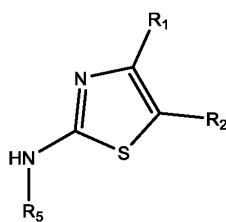


Scheme 1

[0203] In an embodiment, the compound of formula (II) is

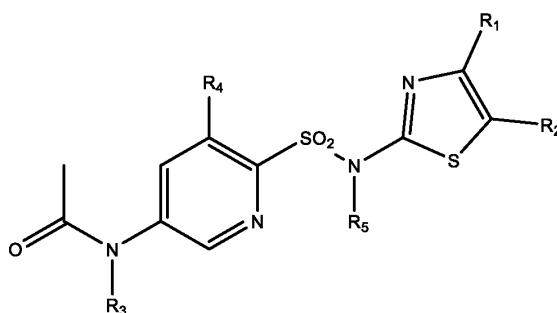


wherein R_3 and R_4 are defined above, is reacted with a compound of formula (III):



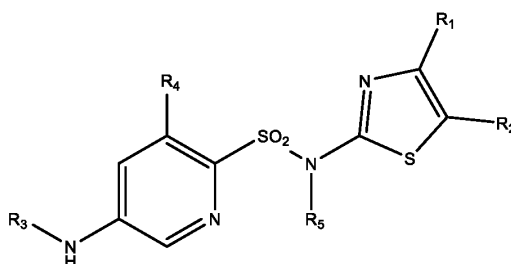
(III)

wherein R₁, R₂, and R₅, are defined above, to provide a compound of formula (IV):



(IV)

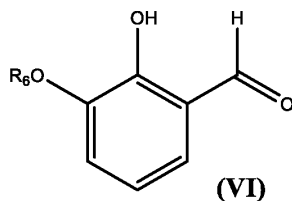
wherein R₁ to R₅ are defined above. The compound of formula (IV) is hydrolyzed according to methods known to the person of ordinary skill in the art, for example basic hydrolysis, to provide a compound of formula (V):



(V)

wherein R₁ to R₅ are defined above; or a salt thereof.

[0204] The compound of formula (V), or a salt thereof, is then reacted with a compound of formula (VI),

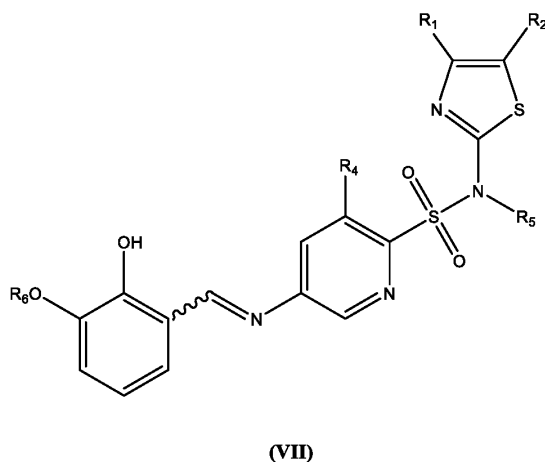
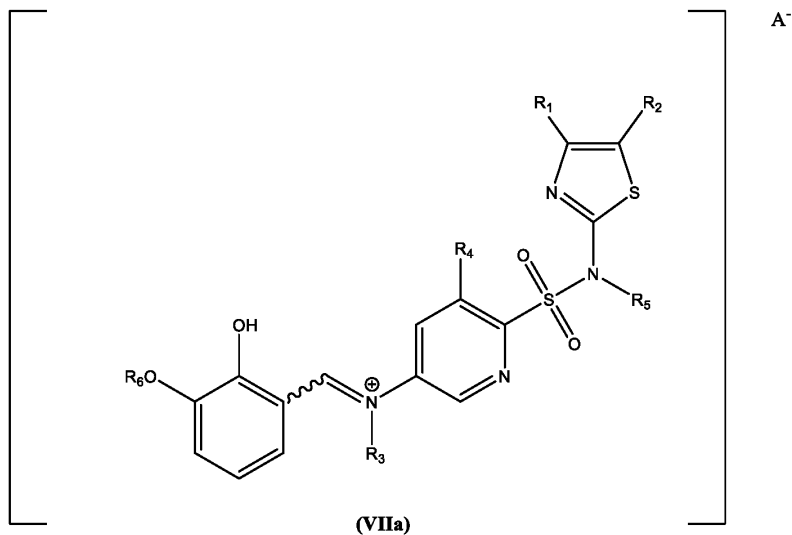


(VI)

wherein

R₆ is defined above;

optionally in the presence of a strong acid, to provide a salt of formula (VIIa) or a compound of formula (VII) or a salt thereof:



wherein R₁ to R₆ are defined above, and wherein A is a counterion known to a person of ordinary skill in the art.

[0205] The salt of formula (VIIa) and/or compound of formula (VII), or a salt thereof, may be reacted with a reducing agent, e.g., a borohydride such as triacetoxyborohydride, to provide the compound of formula (I).

Scheme 2.

[0206] As generally shown in Scheme 1, a starting material compound comprising structure (II) is coupled with a compound of general structure (III) to provide a compound of general structure (IV). Compounds of general structure (IV) may then be deprotected via a hydrolysis reaction affording a compound of general structure (V). Reaction of (V) with aldehyde (VI) affords (VIIa) which may be reduced by a variety of well-known methods to afford compound (I). One skilled in the art would recognize that compound (V) may be converted to compound (I) via well-known reductive amination or other similar methods.

[0207] In some embodiments, before performing the hydrolysis reaction, compounds of formula (IV) may undergo further reactions such that the R² substituent is replaced by another substituent R^{2'}.

[0208] In some embodiments, compounds of formula (I) may undergo further reactions such that the R² substituent is replaced by another substituent R^{2''}. In some embodiments, the 2'-hydroxyl group of compounds of formula (I) is protected by a *tert*-butyldimethylsilyl (TBS) protecting group before undergoing further reactions to replace the R² substituent with substituent R^{2''}.

[0209] In cases where R₃ is hydrogen in compounds of structure (V), a Schiff base of formula (VII) may be formed and concomitantly or subsequently reduced to afford compound (I'') where R₃ is hydrogen.

Synthesis of Specific Intermediates

[0210] Abbreviations

[0211] The following abbreviations are used herein.

equiv or eq: molar equivalents
o/n: overnight
rt: room temperature
UV: ultra violet
h: hour or hours
HPLC: high pressure liquid chromatography
Rt: retention time
LC-MS: liquid chromatography-mass spectrometry
NMR: nuclear magnetic resonance
CC: column chromatography
TLC: thin layer chromatography
sat: saturated
aq: aqueous
Ac: acetyl

DCM: dichloromethane
DCE: dichloroethane
DEA: diethylamine
DMF: dimethylformamide
DMSO: dimethylsulfoxide
ACN or MeCN: acetonitrile
DIPEA: diisopropylethylamine
EA or EtOAc: ethyl acetate
TEA: triethylamine
THF: tetrahydrofuran
NCS: N-chlorosuccinimide
PE: petroleum ether
Prep.: preparative
TFA: trifluoroacetic acid
FA: formic acid
h: hour(s)
min: minutes
s or sec: second(s)
STAB: sodium triacetoxymethylborohydride
Cy: cyclohexyl
Tol: toluene

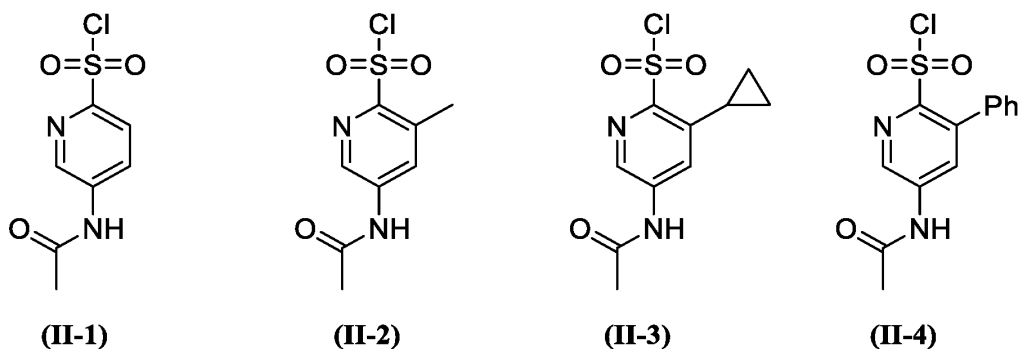
General Information

[0212] All air or moisture sensitive reactions were performed under positive pressure of nitrogen with oven-dried glassware. Chemical reagents and anhydrous solvents were obtained from commercial sources and used as-is. Preparative purification was performed on a Waters semipreparative HPLC. The column used was a Phenomenex Luna C18 (10 μ m, 250 $\times$ 75 mm) at a flow rate of 45 mL/min. The mobile phase consisted of acetonitrile and water (each containing 0.1% hydrochloric acid). A gradient of 50–80% acetonitrile over 23 min was used during the purification. Fraction collection was triggered by UV detection (220 nm).

Analytical analysis for purity was determined by one method denoted as final QC. Method: Analysis was performed on an Agilent 1260 Infinity series LCMS: LCMS Long Gradient Equivalent 5–100% acetonitrile (0.018% trifluoroacetic acid) in water (0.037% trifluoroacetic acid) over 3 min run time of 4 min with a flow rate of 1 mL/min. A Shim-pack Velox SP-C18 2.7 μ m column (3.0 $\times$ 30 mm) was used at a temperature of 50 °C. Purity determination was performed using an Agilent diode array detector for method. Mass determination was performed using an Agilent 1260 mass spectrometer with electrospray ionization in the

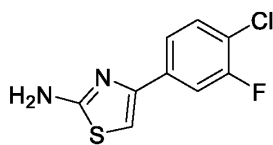
positive mode. ¹H and ¹⁹F NMR spectra were recorded on Bruker 400 (400) MHz or 600 (376) MHz spectrometers.

[0213] Intermediate compounds of formula **II**, **II-1**, **II-2**, **II-3**, and **II-4**:

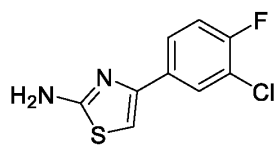


[0214] Intermediates **II** may be reacted with intermediates **III** to produce compounds of formula **(IV)**.

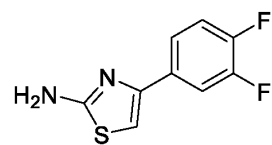
[0215] In another embodiment, compounds of formula **II-1**, **II-2**, **II-3**, and/or **II-4** may be reacted with specific intermediate compounds of formula **III**, below, to produce the compounds of formula **(IV)**:



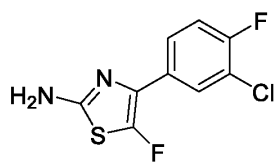
(III-1)



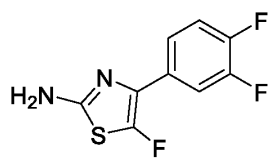
(III-2)



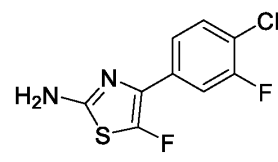
(III-3)



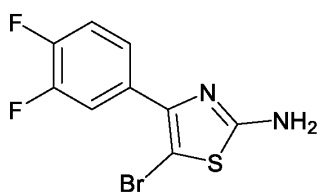
(III-4)



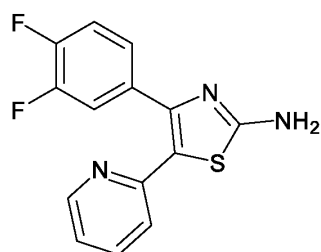
(III-5)



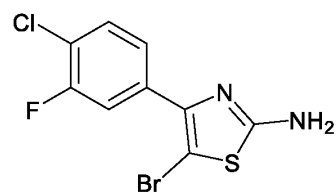
(III-6)



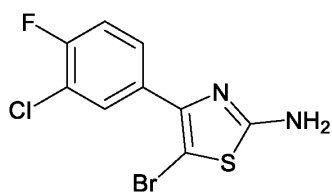
(III-7)



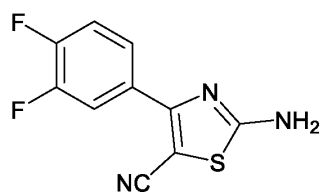
(III-8)



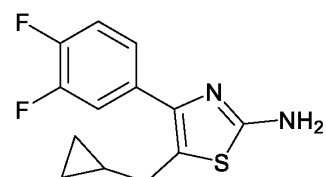
(III-9)



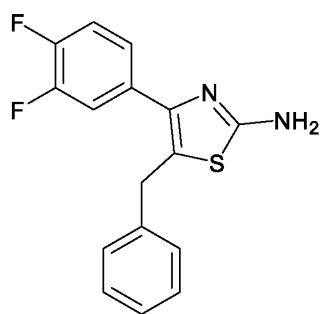
(III-10)



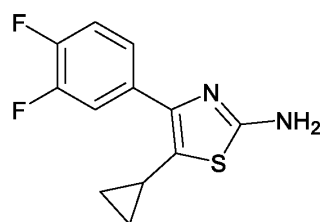
(III-11)



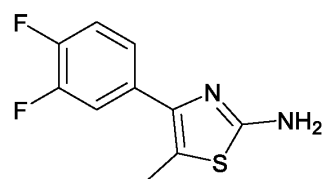
(III-12)



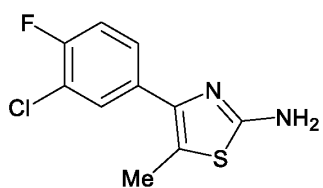
(III-13)



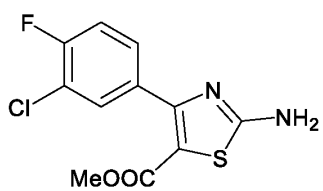
(III-14)



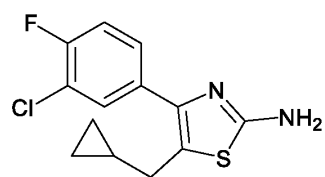
(III-15)



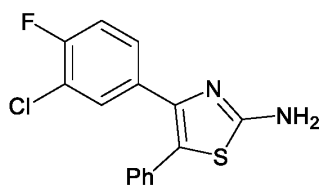
(III-16)



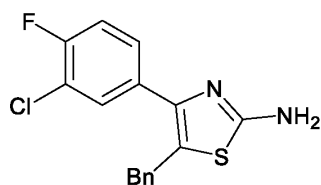
(III-17)



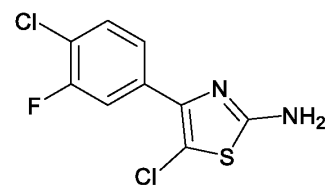
(III-18)



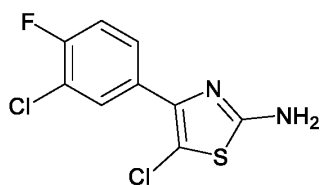
(III-19)



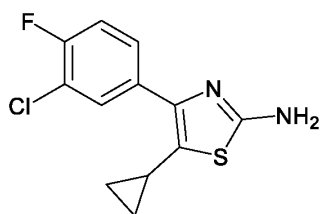
(III-20)



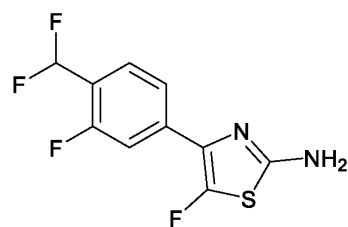
(III-21)



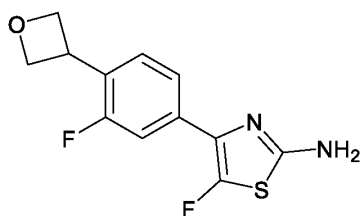
(III-22)



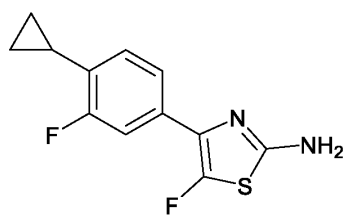
(III-23)



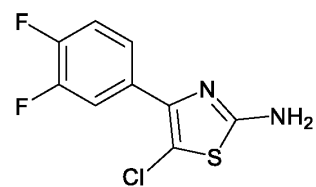
(III-24)



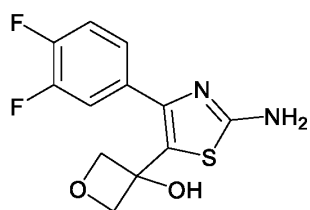
(III-25)



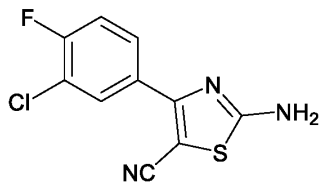
(III-26)



(III-27)

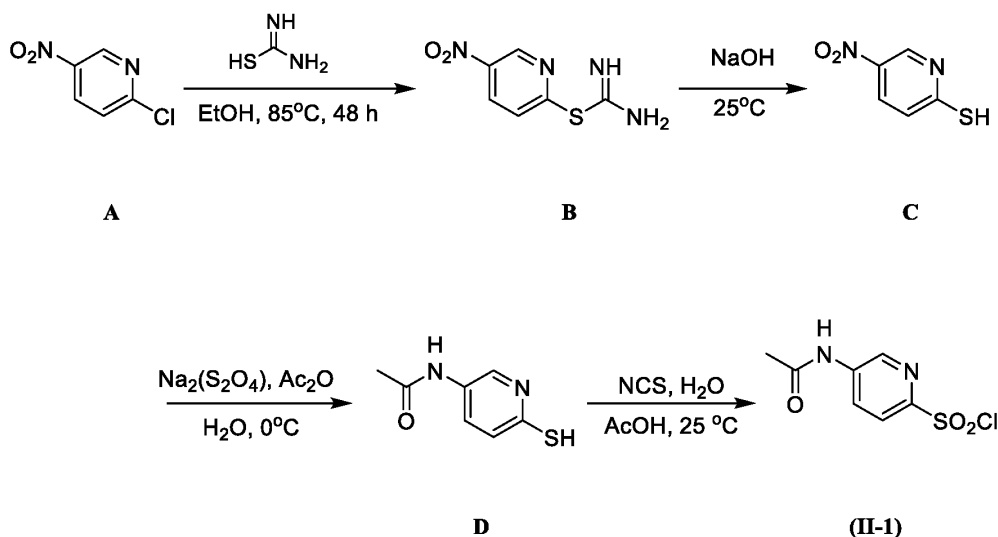


(III-28)



(III-29)

Examples

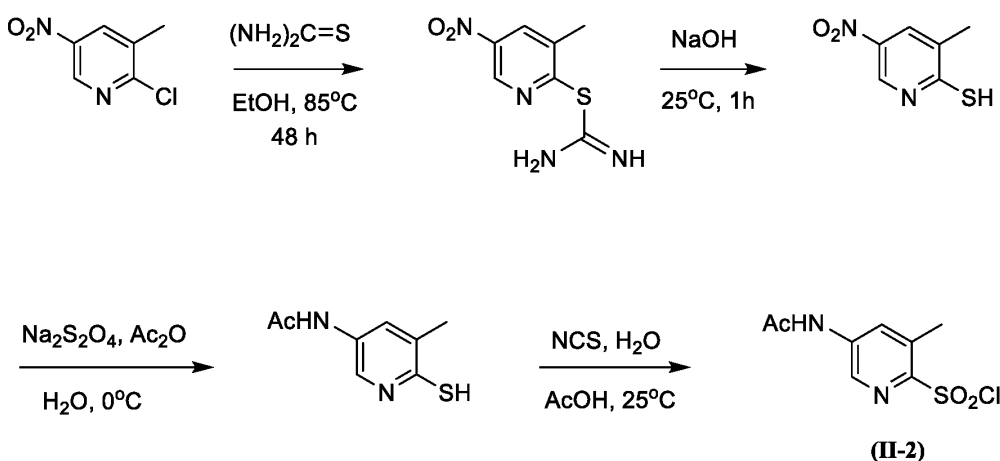
[0216] Synthesis of Intermediates**[0217] Example 1:** Synthesis of 5-acetamidopyridine-2-sulfonyl chloride (**II-1**, Scheme 3).**Scheme 3**

[0218] Synthesis of 4-nitro-2-thiopyridine (C). To a mixture of 2-chloro-4-nitropyridine ((A) 8 g, 50.46 mmol, 1 eq) in EtOH (120 mL) was added thiourea (3.99 g, 52.48 mmol, 1.04 eq) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 10 min, then heated to 85 °C and stirred for 48 hours. LC-MS showed the starting material was consumed completely. The mixture was cooled to 25 °C and filtered to get crude Compound **B**. The residue was poured into water (20 mL) treated with 20% NaOH (100 mL). The mixture was stirred for 30 min and filtered. The pH of solution was adjusted to 7 with HCl (2 M), and the precipitated solid collected by filtration, to provide Compound **C**. (3.5 g, 42% yield, 95% purity) was obtained as a red solid. ¹H NMR (400 MHz, CDCl₃) δ 8.48 (d, J = 2.5 Hz, 1H), 7.92 (dd, J = 9.6, 2.6 Hz, 1H), 7.39 (d, J = 9.6 Hz, 1H).

[0219] N-(6-mercapto-3-pyridyl)acetamide (D). To a mixture of Compound **C** (1.58 g, 9.61 mmol, 1 eq) in H₂O (15 mL) was added Na₂(S₂O₄) (5.85 g, 33.62 mmol, 7.32 mL, 3.5 eq) in one portion at 0°C under N₂. Acetic anhydride (1.37 g, 13.45 mmol, 1.26 mL, 1.4 eq) was then added. The mixture was stirred at 0 °C for 2 hours. LC-MS showed the starting material was consumed completely. A yellow precipitate was filtered, washed with water, and dried to give a yellow solid. (940 mg, 58% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO) δ 13.35 (s, 1H), 10.07 (s, 1H), 8.22 (d, J = 3.8 Hz, 1H), 7.37 – 7.22 (m, 2H), 2.03 (s, 3H).

[0220] 5-acetamidopyridine-2-sulfonyl chloride (**II-1**). To a mixture of Compound **D** (700 mg, 4.16 mmol, 1 eq) in acetic acid (18 mL) and H₂O (2 mL) was added N-chlorosuccinimide (2.2 g, 16.65 mmol, 4 eq) in one portion at 0°C under N₂. The mixture was stirred at 25 °C for 4 hours. Thin Layer Chromatography showed the starting material was consumed completely. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine (15 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuum to provide 5-acetamidopyridine-2-sulfonyl chloride (**II-1**) (800 mg, 78% yield, 95% purity) as an orange solid. ¹H NMR (400 MHz, DMSO) δ 11.30 (s, 1H), 9.07 (s, 1H), 8.52 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H), 2.18 (d, J = 11.4 Hz, 3H).

[0221] **Example 2: Synthesis of 5-acetamido-3-methylpyridine-2-sulfonyl chloride (**II-2**, Scheme 4).**



Scheme 4

[0222] A mixture of thiourea (2.21 g, 28.97 mmol) and 2-chloro-3-methyl-5-nitropyridine (5 g, 28.97 mmol) in EtOH (50 mL) was degassed and purged with dry N₂ 3 times. The mixture was stirred at 85°C for 4h under a N₂ atmosphere affording a yellow precipitate. The precipitate was filtered, washed with water (200 mL), and dried to give a yellow solid. Removal of the excess water from the residue under vacuum gave 3-methyl-5-nitropyridin-2-yl carbamimidothioate (4.64 g, 21.9 mmol, 75.5% yield) as a yellow solid.

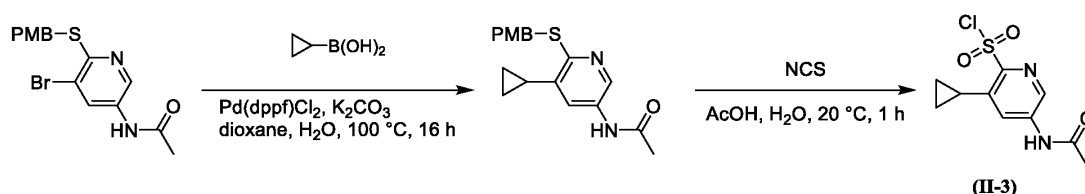
[0223] To a solution of 3-methyl-5-nitropyridin-2-yl carbamimidothioate (4.64 g, 21.86 mmol) in H₂O (9 mL) was added NaOH (54 mL, 20% in H₂O). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was filtered undissolved substance and adjust pH to 7 with HCl (aq., 3M in H₂O), and filtered get to get crude product. Remove the excess water

from the filter residue under pressure reduction to give 3-methyl-5-nitropyridine-2-thiol (3 g, 17.6 mmol, 81% yield) as a red solid. LCMS: (M+H)⁺ = 171.2.

[0224] A mixture of 3-methyl-5-nitropyridine-2-thiol (3 g, 17.63 mmol) in H₂O (60 mL) was added Na₂S₂O₄ (10.74 g, 61.7 mmol, 13.4 mL) under N₂, and then added acetyl acetate (2.52 g, 24.7 mmol, 2.31 mL), then the mixture was stirred at 0 °C for 0.5 hour under N₂ atmosphere. The yellow precipitate was filtered, washed with water (100 mL), and dried to give a yellow solid. Removal of the excess water from the filter residue under pressure reduction to give N-(6-mercapto-5-methylpyridin-3-yl)acetamide (1.3 g, 7.13 mmol, 40.5% yield) as a yellow solid.

[0225] A solution of N-(6-mercapto-5-methylpyridin-3-yl)acetamide (1.3 g, 7.13 mmol) in AcOH (10 mL) and H₂O (2 mL) was degassed and purged with N₂ 3 times, and NCS (3.33 g, 24.97 mmol) was then added. The mixture was stirred at 0°C for 0.5h under N₂ atmosphere. The reaction mixture was diluted with ethyl acetate (10 mL x 3), washed with brine (15 mL x 2), dried over Na₂SO₄ and concentrated to dryness. The residue was purified by column chromatography (silica gel, 100-200 mesh, 70% ethyl acetate in petroleum ether). 5-acetamido-3-methylpyridine-2-sulfonyl chloride (**II-2**, 1.1 g, 2.48 mmol, 35% yield) was obtained as a brown solid. LCMS:(M+H)⁺ = 249.1.

[0226] **Example 3: Synthesis of 5-acetamido-3-cyclopropylpyridine-2-sulfonyl chloride (II-3, Scheme 5).**

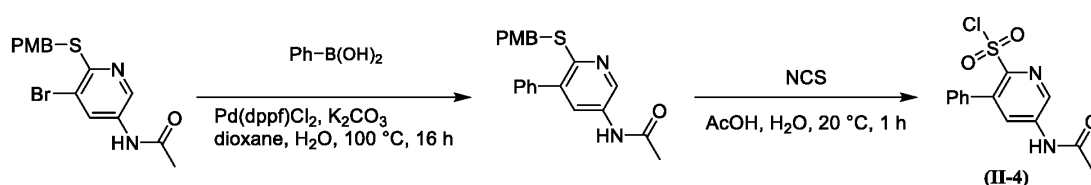


Scheme 5

[0227] A mixture of *N*-(5-bromo-6-((4-methoxybenzyl)thio)pyridin-3-yl)acetamide (5 g, 13.6 mmol, 1 *eq*), cyclopropylboronic acid (1.40 g, 16.3 mmol, 1.2 *eq*), Pd(dppf)Cl₂ (996 mg, 1.36 mmol, 0.1 *eq*) and K₂CO₃ (3.76 g, 27.2 mmol, 2.0 *eq*) in dioxane (50 mL)/H₂O (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 100 °C for 16 hr under N₂ atmosphere. The reaction mixture was then cooled to 20 °C, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 20/80) to give *N*-(5-cyclopropyl-6-((4-methoxybenzyl)thio)pyridin-3-yl)acetamide (2.62 g, 7.98 mmol, 59% yield) was obtained as a gray solid.

[0228] To a solution of *N*-(5-cyclopropyl-6-((4-methoxybenzyl)thio)pyridin-3-yl)acetamide (500 mg, 1.52 mmol, 1 *eq*) in AcOH (5 mL)/H₂O (1 mL) was added NCS (813 mg, 6.1 mmol, 4 *eq*) with a water bath. The mixture was stirred at 25 °C under N₂ for 1 hr. After this time, the reaction mixture was poured into ice-water (30 mL) and extracted with DCM 60 mL (30 mL × 2). The combined organic layers were washed with brine (50 mL × 2) and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 40/60) to give 5-acetamido-3-cyclopropylpyridine-2-sulfonyl chloride (**II-3**, 361 mg, 1.31 mmol, 86% yield) as a white solid.

[0229] **Example 4: Synthesis of 5-acetamido-3-phenylpyridine-2-sulfonyl chloride (II-4, Scheme 6).**

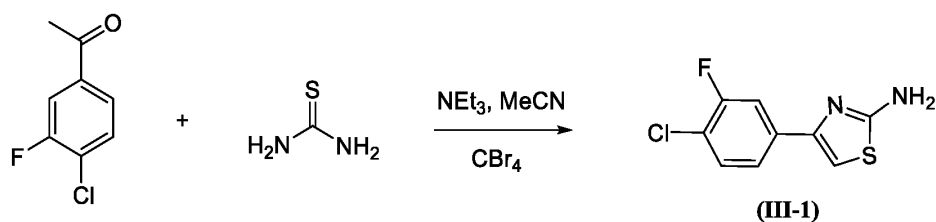


Scheme 6

[0230] A mixture of *N*-(5-bromo-6-((4-methoxybenzyl)thio)pyridin-3-yl)acetamide (5 g, 13.61 mmol, 1 *eq*), phenylboronic acid (1.99 g, 16.34 mmol, 1.2 *eq*), Pd(dppf)Cl₂ (996 mg, 1.36 mmol, 0.1 *eq*) and K₂CO₃ (3.76 g, 27.2 mmol, 2.0 *eq*) in dioxane (50 mL)/H₂O (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 100 °C for 16 hr under N₂ atmosphere. The reaction mixture was then cooled to 20 °C and filtered. The filtrate was concentrated to give a residue which was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 20/80) to give *N*-(6-((4-methoxybenzyl)thio)-5-phenylpyridin-3-yl)acetamide (3.61 g, 9.91 mmol, 73% yield) as a gray solid.

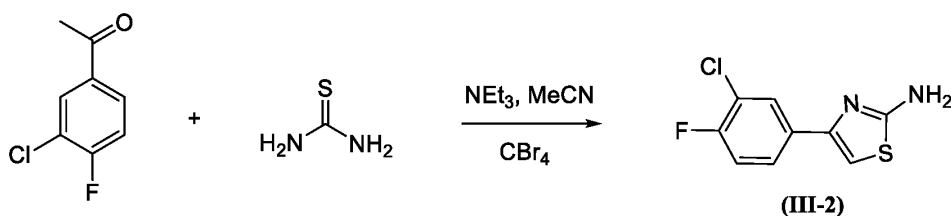
[0231] To a solution of *N*-(6-((4-methoxybenzyl)thio)-5-phenylpyridin-3-yl)acetamide (500 mg, 1.37 mmol, 1 *eq*) in AcOH (5 mL)/H₂O (1 mL) was added NCS (733 mg, 5.49 mmol, 4 *eq*) with a water bath. The mixture was stirred at 25 °C under N₂ for 1 hr then the reaction mixture was poured into ice-water (30 mL) and extracted with DCM 60 mL (30 mL × 2). The combined organic layers were washed with brine (50 mL × 2) and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 40/60) to give 5-acetamido-3-phenylpyridine-2-sulfonyl chloride (**II-4**, 260 mg, 834 μmol, 61% yield) as a white solid.

[0232] **Example 5: Synthesis of 4-(4-chloro-3-fluorophenyl)thiazol-2-amine (III-1, Scheme 7).**

**Scheme 7**

To a mixture of 1-(4-chloro-3-fluorophenyl)ethan-1-one (2.27 g, 13.15 mmol, 1 eq), triethylamine (2.00 g, 19.73 mmol, 2.75 mL, 1.5 eq) and thiourea (2.50 g, 32.88 mmol, 2.5 eq) in MeCN (20 mL) was added carbon tetrabromide (6.54 g, 19.73 mmol, 1.5 eq) in one portion at 25°C under N₂. The mixture was stirred at 25°C for 16 hours. LC-MS showed the acetophenone was consumed completely and one new main peak with desired mass was detected. The mixture was concentrated under reduced pressure and the resulting residue poured into water (50 mL) and stirred for 10 min. The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1/0, 1/1) to provide 4-(4-chloro-3-fluorophenyl)thiazol-2-amine (**III-1**) as a yellow solid (2.88 g, 96% yield).

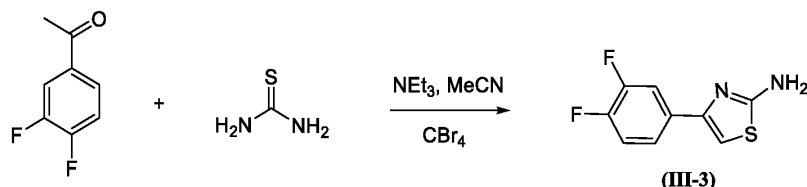
[0233] Example 6: Synthesis of 4-(3-chloro-4-fluorophenyl)-1,3-thiazol-2-ylamine (**III-2**, Scheme 8).

**Scheme 8**

[0234] To a mixture of 1-(3-chloro-4-fluorophenyl)ethan-1-one (15 g, 86.91 mmol, 1 eq) and thiourea (9.92 g, 130.37 mmol, 1.5 eq) in MeCN (100 mL) was added CBr₄ (43.23 g, 130.37 mmol, 1.5 eq) and Et₃N (13.19 g, 130.37 mmol, 1.5 eq) degassed and purged with N₂ three times. The mixture was stirred at 25 °C for 16 hr. under N₂ atmosphere. LC-MS showed the starting material was consumed completely. The reaction mixture was diluted with 1N HCl (50 mL) and extracted with ethyl acetate (200 mL) and water (200 mL), then was added NH₄Cl and solids were precipitated, and filtered. The filter cake was dried under reduced pressure to provide 4-(3-chloro-4-fluorophenyl)-1,3-thiazol-2-ylamine (**III-2**) (3.5 g,

14% yield, 80% purity) as a red solid. ^1H NMR (400MHz, DMSO- d_6) δ 7.96 (dd, $J=2.1$, 7.3 Hz, 1H), 7.79 (ddd, $J=2.2$, 4.8, 8.7 Hz, 1H), 7.40 (t, $J=9.0$ Hz, 1H), 7.14 (s, 3H).

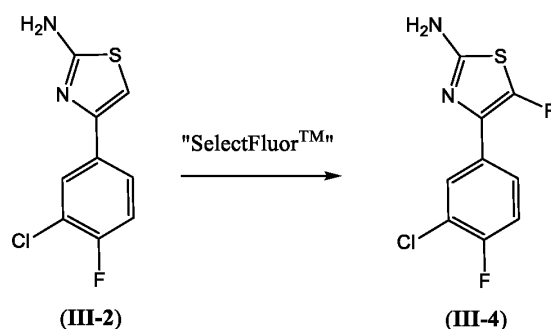
[0235] **Example 7:** Synthesis of 4-(3,4-difluorophenyl)-1,3-thiazol-2-amine (**III-3**, Scheme 9).



Scheme 9

[0236] To a mixture of 1-(3,4-difluorophenyl)ethan-1-one (20 g, 128.10 mmol, 16.00 mL) and thiourea (14.63 g, 192.15 mmol) in acetonitrile (300 mL) was added triethylamine (19.44 g, 192.15 mmol, 26.74 mL) and carbon tetrabromide (63.72 g, 192.15 mmol). The mixture was stirred at 25 °C for 16 hours. LC-MS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure to remove the solvent. The resulting residue was triturated with water (200 mL) and extracted with EtOAc (150 mL x 3). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 22~30% Ethyl acetate/Petroleum ether gradient at 120 mL/min), Petroleum ether/Ethyl acetate=3:1, $R_f=0.3$) to yield 4-(3,4-difluorophenyl)-1,3-thiazol-2-amine (**III-3**, 12.7 g, 58.65 mmol, 6% yield, 98% purity) as a brown solid. LC-MS: $(\text{M}+\text{H})^+ = 212.7$; ^1H NMR (400 MHz, DMSO- d_6): δ 7.78 (ddd, $J = 1.9$, 8.0, 12.4 Hz, 1H), 7.66 - 7.61 (m, 1H), 7.46 - 7.36 (m, 1H), 7.11 (br d, $J = 5.5$ Hz, 3H).

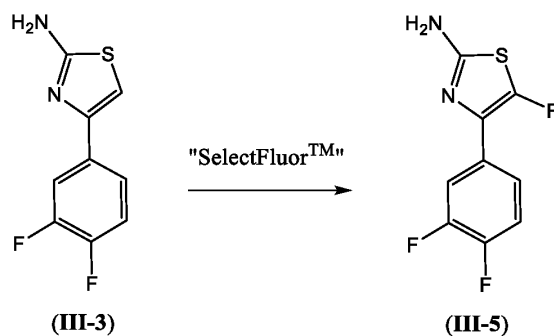
[0237] **Example 8:** Synthesis of 4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-amine (**III-4**, Scheme 10).



Scheme 10

To a solution of 4-(3-chloro-4-fluorophenyl)-1,3-thiazol-2-ylamine (**III-2**, 1 g, 4.37 mmol, 1.0 *eq*) in MeCN (20 mL) was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane; ditetrafluoroborate (SelectfluorTM) (1.55 g, 4.37 mmol, 1.0 *eq*) in one portion at 0°C under N₂. The mixture was warmed to 25°C and stirred for 6 hours. After this time, LC-MS indicated that approximately 12% of the starting material remained. Several new peaks were shown by LC-MS and about 22% of the desired compound (**III-4**) was detected. Water (30 mL) was added; and the reaction mixture was diluted with EtOAc (30 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with water (2 x 15 mL) and brine (2 x 15 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by silica gel chromatography (SiO₂, PE / EtOAc = 0 to 100% EA). 4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-amine (**III-4**) was isolated (230 mg, 21% yield) as a brown solid and used into the next step without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ 7.79 (dd, J = 7.3, 2.1 Hz, 1H), 7.68 (ddd, J = 8.6, 4.7, 2.2 Hz, 1H), 7.48 (t, J = 9.0 Hz, 1H), 7.08 (s, 2H).

[0238] Example 9: Synthesis of 4-(3,4-difluorophenyl)-5-fluorothiazol-2-amine (III-5**, Scheme 11).**

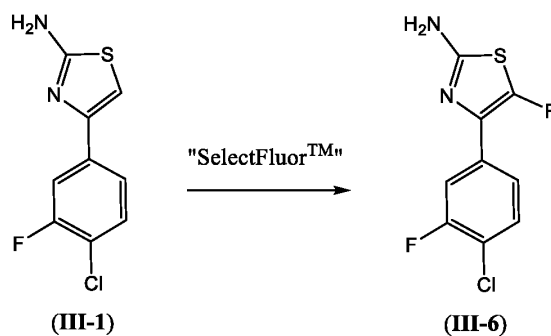


Scheme 11

[0239] To a solution of 4-(3,4-difluorophenyl)-1,3-thiazol-2-amine (**III-3**, 12.7 g, 59.84 mmol, 1 *eq*) in DMF (150 mL) was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane; ditetrafluoroborate (SelectfluorTM) (21.20 g, 59.84 mmol, 1 *eq*) and 2,6-dimethylpyridine (6.41 g, 59.84 mmol, 6.97 mL, 1 *eq*). The mixture was stirred at 25°C for 10 hours after this time, LC-MS showed that the reaction was complete. The mixture was extracted with ethyl acetate (400 mL x 3). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was evaporated to dryness to give the crude product, which was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 22~25% Ethyl acetate/Petroleum ether gradient at 80 mL/min), Petroleum

ether/Ethyl acetate=3: 1, R_f=0.4) to afford the product 4-(3,4-difluorophenyl)-5-fluorothiazol-2-amine, **III-5** (8.9 g, 36.6 mmol, 61% yield) as a gray solid. LC-MS: (M+H)⁺ = 230.7; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.58 (br d, J = 2.0 Hz, 1H), 7.55 - 7.51 (m, 1H), 7.45 (s, 1H), 7.06 (s, 2H).

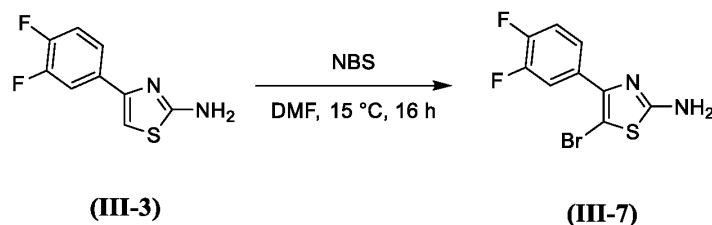
[0240] Example 10: Synthesis of 4-(4-chloro-3-fluorophenyl)-5-fluoro-1,3-thiazol-2-ylamine (III-6, Scheme 12).



Scheme 12

[0241] To a solution of 4-(4-chloro-3-fluorophenyl)thiazol-2-amine (**III-1**, 1 g, 4.37 mmol, 1.0 *eq*) in MeCN (15 mL) was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane; ditetrafluoroborate (SelectfluorTM) (1.55 g, 4.37 mmol, 1.0 *eq*) at 25 °C under N₂. The mixture was stirred at 25°C for 16 hours. LC-MS showed ~11% of the starting material remained. Several new peaks were shown on LC-MS and ~21% of desired compound was detected. The reaction mixture was diluted with EtOAc (30 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with water (2 x 15 mL) and brine (2 x 15 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (SiO₂, petroleum ether / EtOAc = 0 to 100% EtOAc). The title compound (350 mg, 32% yield) was obtained as a brown solid.

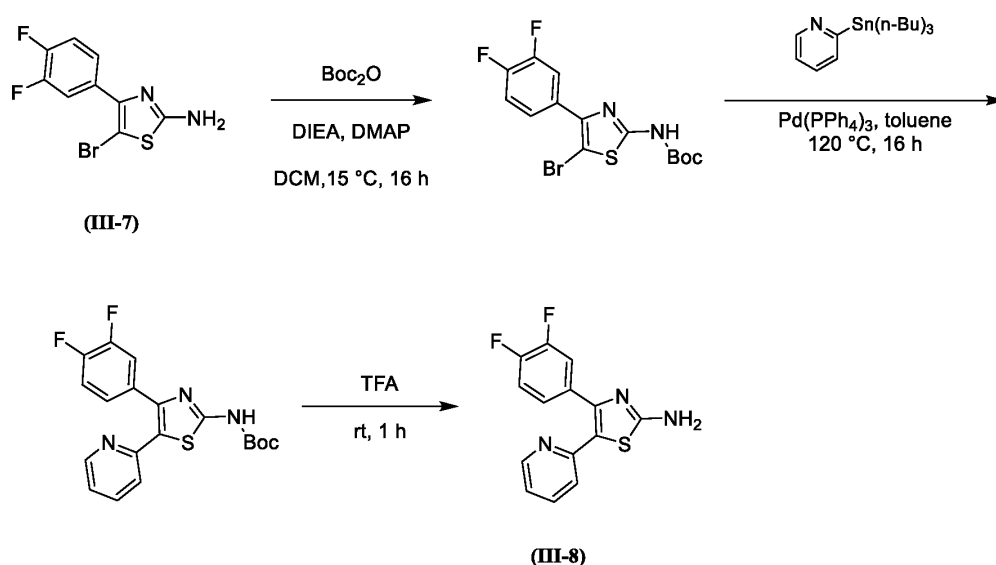
[0242] Example 11: Synthesis of 5-bromo-4-(3,4-difluorophenyl)thiazol-2-amine (III-7, Scheme 13).



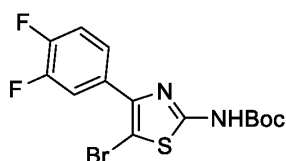
Scheme 13

[0243] To a solution of **III-3** (25 g, 117.80 mmol, 1 *eq*; prepared via Scheme 9) in DMF (25 mL) was added NBS (23.06 g, 129.6 mmol, 1.1 *eq*). The mixture was stirred at 25 °C for 16hr then the reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient at 50 mL/min) to give 5-bromo-4-(3,4-difluorophenyl)thiazol-2-amine (**III-7**, 25 g, 85.9 mmol, 73% yield) as a black solid.

[0244] **Example 12: Synthesis of 4-(3,4-difluorophenyl)-5-(pyridin-2-yl)thiazol-2-amine (III-8, Scheme 14).**

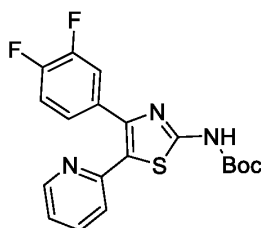


Scheme 14



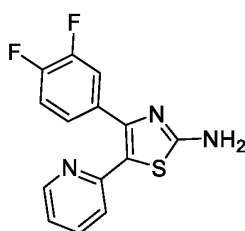
[0245] A mixture of Boc₂O (5.62 g, 25.8 mmol, 5.9 mL, 1.5 *eq*), **III-7** (5 g, 17.2 mmol, 1 *eq*), DIEA (3.33 g, 25.8 mmol, 4.49 mL, 1.5 *eq*), DMAP (210 mg, 1.72 mmol, 0.1 *eq*) in DCM (50 mL) was degassed and purged with N₂ 3 times, then the mixture was stirred at 25 °C for 16 hr under N₂ atmosphere. After this time, the reaction mixture was concentrated under reduced pressure to remove DCM (50 mL). The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~4% Ethyl

acetate/Petroleum ether gradient at 50 mL/min) to give *tert*-butyl (5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (4.8 g, 12.3 mmol, 71% yield) as a yellow solid.



***tert*-butyl (4-(3,4-difluorophenyl)-5-(pyridin-2-yl)thiazol-2-yl)carbamate**

[0246] A mixture of 2-(Tri-*n*-butylstannyl)pyridine (470 mg, 1.28 mmol, 1 *eq*), *tert*-butyl (5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (500 mg, 1.28 mmol, 1 *eq*) and Pd(PPh₃)₄ (74 mg, 63.9 μmol, 0.05 *eq*) in toluene (1 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 120 °C for 16 hr under N₂ atmosphere. LCMS showed that most of the starting material was consumed, and ~25% of desired product was observed. The reaction mixture was cooled to 20 °C and concentrated to give the crude product. The crude product *tert*-butyl (4-(3,4-difluorophenyl)-5-(pyridin-2-yl)thiazol-2-yl)carbamate (497 mg, crude) was obtained as a brown oil and used in the next step without further purification.

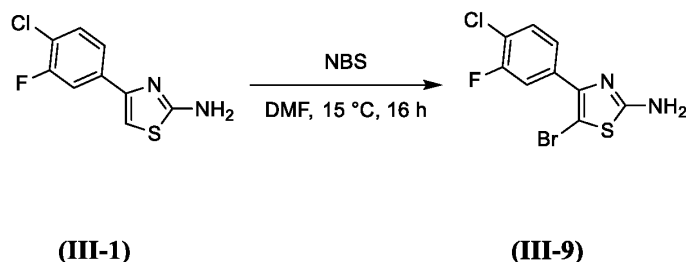


(III-8)

4-(3,4-difluorophenyl)-5-(pyridin-2-yl)thiazol-2-amine

[0247] A mixture of *tert*-butyl (4-(3,4-difluorophenyl)-5-(pyridin-2-yl)thiazol-2-yl)carbamate (497 mg, 1.28 mmol, 1 *eq*) in TFA (2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 20 °C for 1 hr under N₂ atmosphere. LCMS showed most of *tert*-butyl (4-(3,4-difluorophenyl)-5-(pyridin-2-yl)thiazol-2-yl)carbamate was consumed, and ~49% of desired product was observed. The reaction mixture was adjusted to pH 11 by a 2M NaOH solution, and then extracted with EA (30 mL × 2). The combined organic layers were concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 75/25). 4-(3,4-difluorophenyl)-5-(pyridin-2-yl)thiazol-2-amine (**III-8**, 92 mg, 318 μmol, 25% yield) was obtained as a yellow solid.

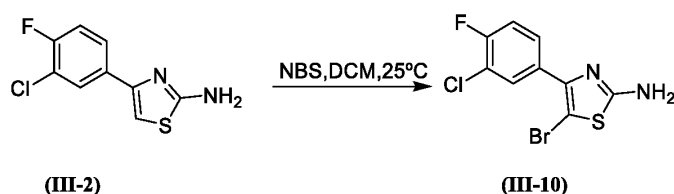
[0248] **Example 13:** Synthesis of 5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-amine (**III-9**, Scheme 15).



Scheme 15

[0249] To a solution of **III-1** (4.80 g, 21 mmol, 1 *eq*; prepared via Scheme 7) in DMF (25 mL) was added NBS (4.11 g, 23.1 mmol, 1.1 *eq*). The mixture was stirred at 25 °C for 16 hr. The reaction mixture was then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with aqueous NaCl (50 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient at 25 mL/min) to give 5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-amine (**III-9**, 6.4 g, 20.8 mmol, 99% yield) as a black solid.

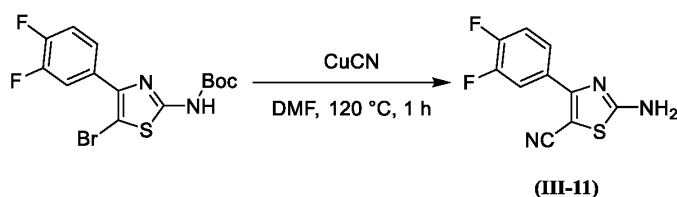
[0250] **Example 14:** Synthesis of 5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-amine (**III-10**, Scheme 16).



Scheme 16

[0251] To a solution of 4-(3-chloro-4-fluorophenyl)thiazol-2-amine (**III-2**, 5 g, 21.87 mmol, 1 *eq*) in DCM (50 mL) was added NBS (4.28 g, 24.05 mmol, 1.1 *eq*). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was diluted with ethyl acetate (100 mL × 3), washed with brine (150 mL × 2), dried over Na₂SO₄ and concentrated to dryness. The residue was purified by column chromatography (silica gel, 100-200 mesh, 15% ethyl acetate in petroleum ether). 5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-amine (**III-10**, 5.2 g, 16.91 mmol, 77% yield) was obtained as a red solid.

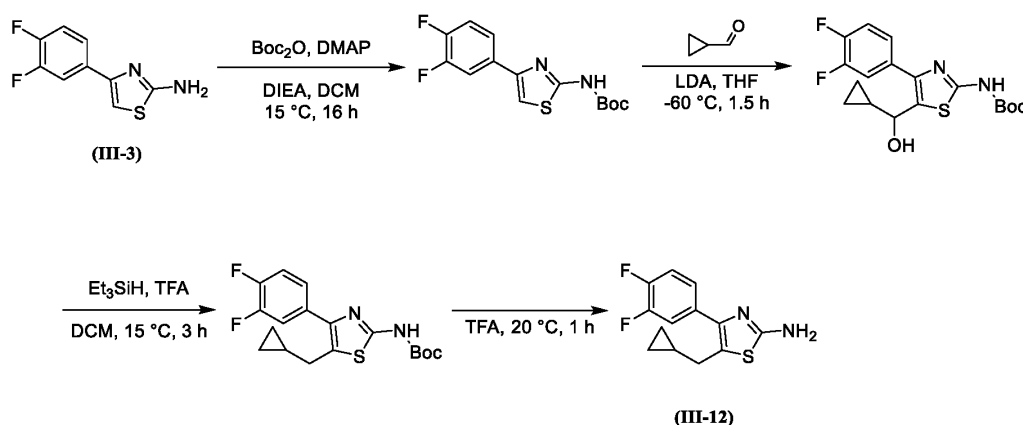
[0252] **Example 15:** Synthesis of 2-amino-4-(3,4-difluorophenyl)thiazole-5-carbonitrile (**III-11**, Scheme 17).



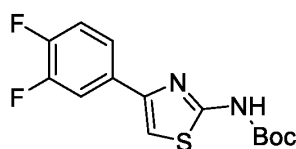
Scheme 17

[0253] To a solution of *tert*-butyl (5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (1 g, 2.56 mmol, 1 *eq*; prepared via Scheme 14) in DMF (5 mL) was added CuCN (1.14 g, 12.78 mmol, 2.79 mL, 5.0 *eq*). The mixture was stirred at 120 °C for 1 hr. LCMS showed that most of *tert*-butyl (5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate was consumed. The reaction mixture was cooled to 20 °C and filtered. The filter cake was washed with EtOAc (100 mL). Then the filtrate was concentrated to give crude products. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 60/40). 2-amino-4-(3,4-difluorophenyl)thiazole-5-carbonitrile (**III-11**, 100 mg, 422 μmol, 17% yield) was obtained as yellow solid.

[0254] Example 16: Synthesis of 5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-amine (III-12, Scheme 18).



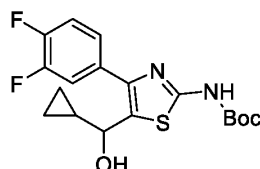
Scheme 18



***tert*-butyl (4-(3,4-difluorophenyl)thiazol-2-yl)carbamate**

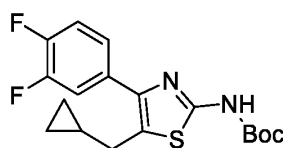
[0255] To a solution of **III-3** (6 g, 28.3 mmol, 1 *eq*; prepared via Scheme 9) in DCM (60 mL) was added Boc₂O (7.40 g, 33.9 mmol, 7.8 mL, 1.2 *eq*), DMAP (345 mg, 2.83 mmol, 0.1 *eq*)

and DIEA (5.48 g, 42.4 mmol, 7.39 mL, 1.5 *eq*). The mixture was stirred at 20 °C for 16 hr. LC-MS showed the starting material was consumed and one peak with desired mass was detected. The reaction mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 90/10). *tert*-butyl (4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (8.38 g, 26.8 mmol, 95% yield) was obtained as a yellow oil.



***tert*-butyl (5-(cyclopropyl(hydroxy)methyl)-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate**

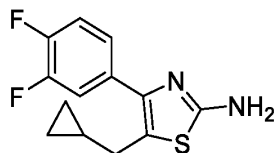
[0256] To a solution of *tert*-butyl (4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (1 g, 3.20 mmol, 1 *eq*) in THF (10 mL) was cooled to -60 °C and LDA (2 M, 3.36 mL, 2.1 *eq*) was added under N₂. The mixture was stirred at -60 °C under N₂ for 0.5 h, followed by cyclopropanecarbaldehyde (269 mg, 3.84 mmol, 287 µL, 1.2 *eq*). The resulting mixture was stirred at -60 °C for 1 hr. LC-MS showed that the starting material was consumed and one main peak with desired mass was detected. The reaction mixture was warmed to 0 °C and H₂O (40 mL) was added slowly, and then extracted with EA (30 mL × 2). The combined organic layers were concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 60/40). *tert*-butyl (5-(cyclopropyl(hydroxy)methyl)-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (517 mg, 1.35 mmol, 42% yield) was obtained as a yellow oil.



***tert*-butyl (5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate**

[0257] To a solution of *tert*-butyl (5-(cyclopropyl(hydroxy)methyl)-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (480 mg, 1.26 mmol, 1 *eq*) in DCM (5 mL) was added TFA (300 mg, 2.64 mmol, 196 µL, 2.1 *eq*) and Et₃SiH (438 mg, 3.77 mmol, 601 µL, 3 *eq*). LCMS showed the desired product was formed. The pH of the reaction mixture was adjusted

to 9 by addition of 2M NaOH solution and then extracted with DCM (40 mL $\times$ 2). The combined organic layers were concentrated to give the crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 80/20) to give *tert*-butyl (5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (412 mg, 1.12 mmol, 89% yield) as a colorless oil.

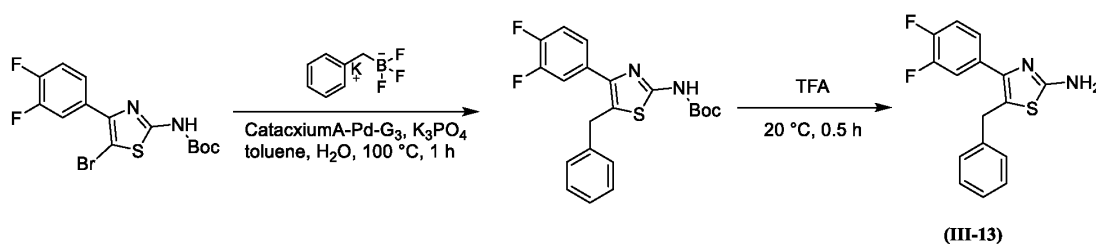


(III-12)

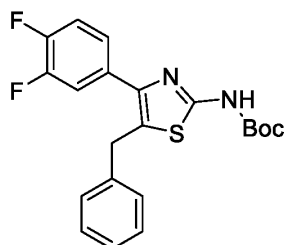
5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-amine

[0258] To a solution of *tert*-butyl (5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (412 mg, 1.12 mmol, 1 *eq*) in TFA (2 mL) was stirred at 20 °C for 1 hr. LC-MS showed that the starting material had been consumed and one peak with desired mass was detected. The pH of the reaction mixture was adjusted to 9 by addition of 2M NaOH solution and then extracted with EA (20 mL $\times$ 2). The combined organic layers were concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 60/40). 5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-amine (III-12, 209 mg, 785 μ mol, 70% yield) was obtained as a yellow solid.

[0259] **Example 17: Synthesis of 5-benzyl-4-(3,4-difluorophenyl)thiazol-2-amine (III-13, Scheme 19).**

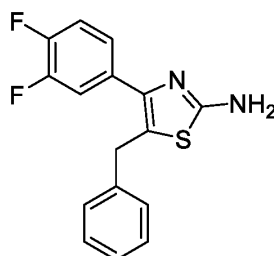


Scheme 19



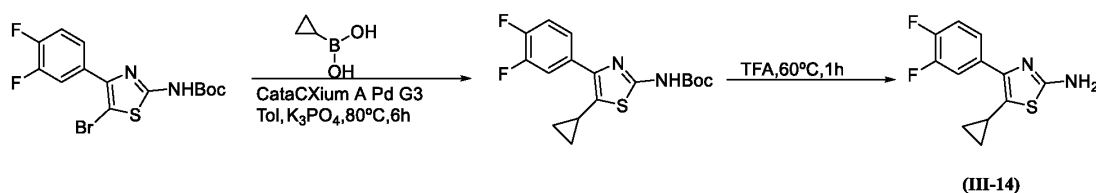
***tert*-butyl (5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate**

[0260] A mixture of *tert*-butyl (5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (500 mg, 1.28 mmol, 1 *eq*; prepared via Scheme 14), benzyltrifluoroborate (305 mg, 1.92 mmol, 1.5 *eq*), K₃PO₄ (1.5 M, 2.56 mL, 3 *eq*), Pd(dppf)Cl₂ (187 mg, 256 μmol, 0.2 *eq*) in toluene (5 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 100 °C for 3 hr under an N₂ atmosphere. LC-MS showed that the starting material was consumed and one peak with desired mass was detected. The reaction mixture was diluted with H₂O (50 mL) and extracted with EA (50 mL × 3). The combined organic layers were washed with aqueous NaCl (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=99/1 to 20/1). *tert*-butyl (5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (360 mg, 895 μmol, 70% yield) was obtained as a black solid.

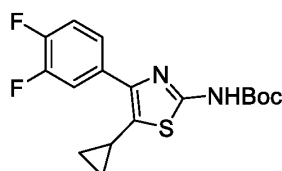
**(III-13)****5-benzyl-4-(3,4-difluorophenyl)thiazol-2-amine**

[0261] To a solution of *tert*-butyl (5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (360 mg, 895 μmol, 1 *eq*) in TFA (3 mL). The mixture was stirred at 25 °C for 0.5 hr. LC-MS showed that the starting material was consumed and one main peak with desired mass was detected. To the reaction mixture was added H₂O (20 mL) and the pH was adjusted to 10 by addition of solid K₂CO₃. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~17% Ethyl acetate/Petroleum ether gradient at 25 mL/min). 5-benzyl-4-(3,4-difluorophenyl)thiazol-2-amine (**III-13**, 120 mg, 397 μmol, 44% yield) was obtained as a yellow solid.

[0262] **Example 18: Synthesis of 5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-amine (III-14, Scheme 20).**

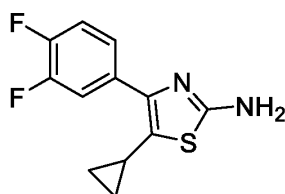


Scheme 20



***tert*-butyl (5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate**

[0263] To a solution of *tert*-butyl (5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (1 g, 2.56 mmol, 1 *eq*; prepared via Scheme 14), cyclopropylboronic acid (659 mg, 7.67 mmol, 3 *eq*), [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butylphosphane;methanesulfonate (372 mg, 511 μ mol, 0.2 *eq*), K_3PO_4 (1.63 g, 7.67 mmol, 3 *eq*) in toluene (10 mL) was degassed and purged with N_2 3 times, then the mixture was stirred at 80 °C for 16 hr under N_2 atmosphere. LC-MS showed the starting material had been consumed. The reaction mixture was then diluted with H_2O (50 mL) and extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with aqueous NaCl (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The combined organic layers were concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=99/1 to 20/1). To give *tert*-butyl (5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (870 mg, 2.47 mmol, 97% yield) as a black solid.

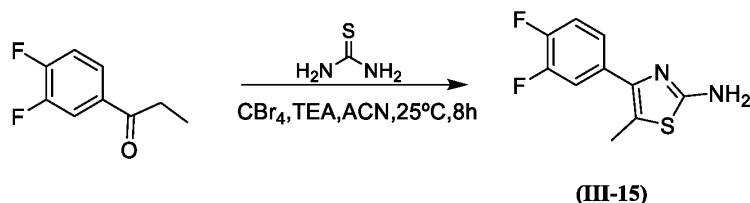
**(III-14)**

5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-amine

[0264] A solution of *tert*-butyl (5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (870 mg, 2.47 mmol, 1 *eq*) in TFA (3 mL) was stirred at 25 °C for 0.5 hr. LCMS showed that the starting material had been consumed. The reaction mixture was adjusted to pH 9 by 2M

NaOH solution and extracted with DCM (40 mL $\times$ 2). The combined organic layers were concentrated to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient at 25 mL/min) to give 5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-amine (**III-14**, 580 mg, 2.30 mmol, 93% yield) as a yellow solid.

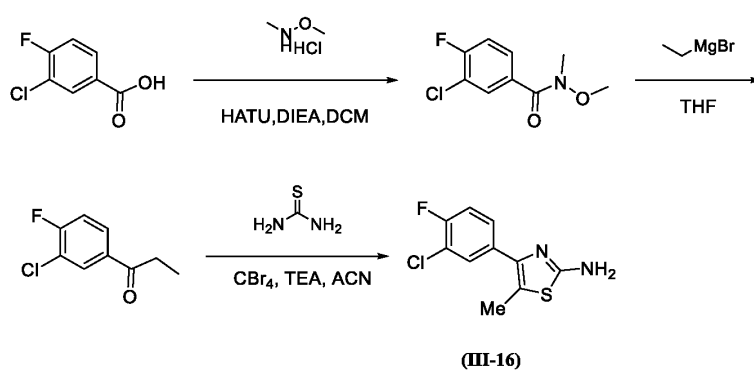
[0265] **Example 19: Synthesis of 4-(3,4-difluorophenyl)-5-methylthiazol-2-amine (III-15, Scheme 21).**



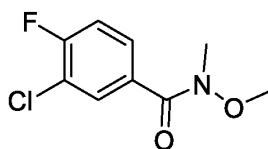
Scheme 21

[0266] To a solution of thiourea (671 mg, 8.82 mmol, 1.5 eq) and 1-(3,4-difluorophenyl)propan-1-one (1 g, 5.88 mmol, 1 eq) in ACN (10 mL) was added TEA (892 mg, 8.82 mmol, 1.23 mL, 1.50 eq) and carbon tetrabromide (2.92 g, 8.82 mmol, 1.5 eq). The mixture was stirred at 25 °C for 8 hr then the reaction mixture was concentrated under reduced pressure to give a residue. The resulting residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient at 30 mL/min) to give 4-(3,4-difluorophenyl)-5-methylthiazol-2-amine (**III-15**, 850 mg, 3.76 mmol, 64% yield) as a white solid.

[0267] **Example 20: Synthesis of 4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-amine (III-16, Scheme 22).**

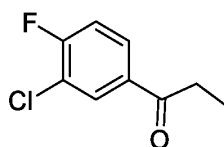


Scheme 22



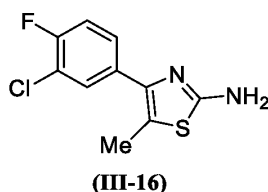
3-chloro-4-fluoro-*N*-methoxy-*N*-methylbenzamide

[0268] To a solution of 3-chloro-4-fluorobenzoic acid (1.12 g, 11.46 mmol, 1 *eq*) in DCM (20 mL) was added DIEA (4.44 g, 34.37 mmol, 5.99 mL, 3 *eq*) and HATU (6.53 g, 17.19 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 1hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 1/1) to give 3-chloro-4-fluoro-*N*-methoxy-*N*-methylbenzamide (2.49 g, 11.44 mmol, 100.00% yield) as a white solid.



1-(3-chloro-4-fluorophenyl)propan-1-one

[0269] A mixture of 3-chloro-4-fluoro-*N*-methoxy-*N*-methylbenzamide (500 mg, 2.30 mmol, 1 *eq*) in THF (5 mL) was degassed and purged with N₂ 3 times, and then EtMgBr (3 M, 1.53 mL, 2 *eq*) was added. The reaction mixture was then stirred at 25 °C for 1 hr under N₂ atmosphere. The reaction mixture was quenched by addition sat. NH₄Cl (10mL), and then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient at 30 mL/min) to give 1-(3-chloro-4-fluorophenyl)propan-1-one (350 mg, 1.88 mmol, 82% yield) as a white solid.

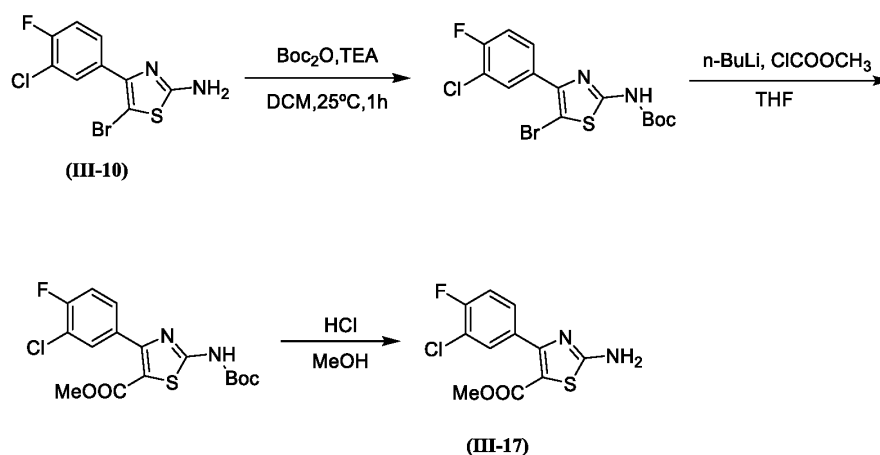


4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-amine

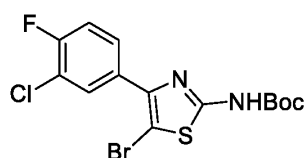
[0270] To a solution of 1-(3-chloro-4-fluorophenyl)propan-1-one (350 mg, 1.88 mmol, 1 *eq*) and thiourea (214 mg, 2.81 mmol, 1.5 *eq*) in ACN (4 mL) was added TEA (285 mg, 2.81 mmol, 391.58 μL, 1.5 *eq*) and CBr₄ (933 mg, 2.81 mmol, 1.5 *eq*). The mixture was stirred at

25 °C for 6 hr then the reaction mixture was concentrated under reduced pressure to give a residue. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient at 30 mL/min) to give 4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-amine (**III-16**, 350 mg, 1.44 mmol, 77% yield) as a white solid.

[0271] Example 21: Synthesis of methyl 2-amino-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylate (III-17**, Scheme 23).**

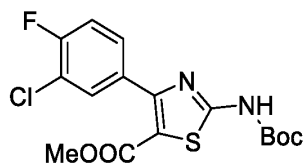


Scheme 23



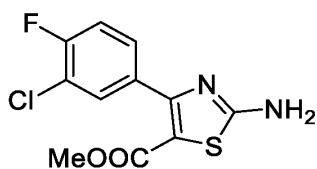
***tert*-butyl (5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate**

[0272] A mixture of **III-10** (2 g, 6.50 mmol, 1 *eq*; prepared via Scheme 16, Example 12), di-*tert*-butyl dicarbonate (2.84 g, 13.01 mmol, 3.0 mL, 2 *eq*) and TEA (1.97 g, 19.51 mmol, 2.7 mL, 3 *eq*) was added into DCM (10 mL), and then the mixture was stirred at 25 °C for 1 hr. The reaction mixture was diluted with H₂O (50 mL) and extracted with EA (30 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient at 18 mL/min) to give a product. *tert*-butyl (5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate (0.828 g, 2.03 mmol, 31% yield) was obtained as a yellow solid.



Methyl 2-((tert-butoxycarbonyl)amino)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylate

[0273] To a solution of *tert*-butyl (5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate (7.5 g, 18.40 mmol, 1 *eq*) in THF (60 mL) was cooled to -60 °C and *n*-BuLi (2.5 M, 15.45 mL, 2.1 *eq*) was added. The mixture was stirred at -60 °C under N₂ for 0.5 h, followed by addition of methyl carbonochloridate (2.4 g, 25.4 mmol, 1.96 mL, 1.38 *eq*). The resulting mixture was stirred at -60 °C for 2 hr. TLC indicated the starting material was consumed completely. The reaction was clean according to TLC. The reaction mixture was warmed to 0 °C and added NaHCO₃ (100 mL), and then extracted with EA (50 mL × 2). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~4% Ethyl acetate/Petroleum ether gradient at 50 mL/min). Methyl 2-((tert-butoxycarbonyl)amino)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylate (4.0 g, 10.34 mmol, 56% yield) was obtained as a yellow solid.

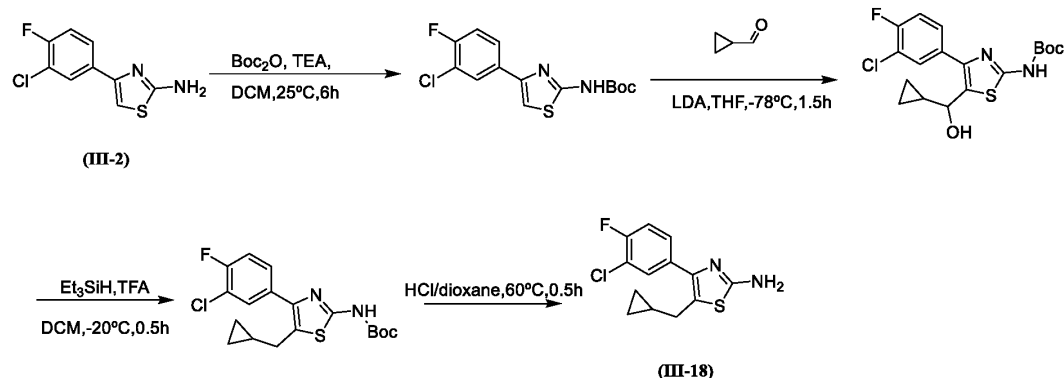


(III-17)

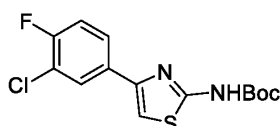
Methyl 2-amino-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylate

[0274] To a solution of Methyl 2-((tert-butoxycarbonyl)amino)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylate (4 g, 10.34 mmol, 1 *eq*) in TFA (8 mL). The mixture was stirred at 25 °C for 1 hr. LC-MS showed that the starting material was completely consumed and one peak with desired mass was detected. To the reaction mixture was added H₂O (50 mL) and the pH was adjusted to pH 10 by addition of K₂CO₃ solid. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient at 25 mL/min). Methyl 2-amino-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylate (**III-17**, 2.29 g, 7.99 mmol, 77% yield) was obtained as a red solid.

[0275] **Example 22:** Synthesis of 4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-amine (**III-18**, Scheme 24).

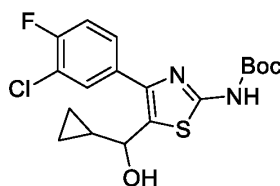


Scheme 24



***tert*-butyl (4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate**

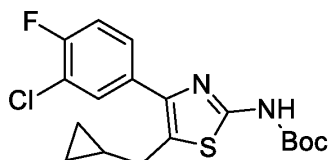
[0276] To a solution of **III-2** (5 g, 21.87 mmol, 1 *eq*) in ACN (30 mL) was added Boc_2O (14.32 g, 65.60 mmol, 15.07 mL, 3 *eq*) and TEA (6.64 g, 65.60 mmol, 9.13 mL, 3 *eq*). The mixture was stirred at 25 °C for 6 hr then the reaction mixture was concentrated under reduced pressure to give a residue. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient at 40 mL/min) to give *tert*-butyl (4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate (2 g, 6.08 mmol, 28% yield) as a yellow solid.



***tert*-butyl (4-(3-chloro-4-fluorophenyl)-5-(cyclopropyl(hydroxy)methyl)thiazol-2-yl)carbamate**

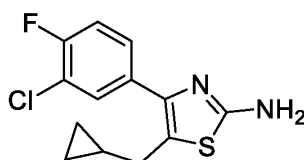
[0277] Cyclopropanecarbaldehyde (499 mg, 7.12 mmol, 532 μL , 3 *eq*) was added into the mixture of *tert*-butyl (4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate (780 mg, 2.37 mmol, 1 *eq*), LDA (2 M, 3.56 mL, 3 *eq*) in THF (0.5 mL) at -78°C under N_2 , and then the mixture was stirred at -78 °C for 1.5 hr under a N_2 atmosphere. The reaction mixture was quenched by addition H_2O (20 mL) at 25 °C, and then diluted with H_2O (20 mL) and

extracted with EA (50 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient at 30 mL/min) to give *tert*-butyl (4-(3-chloro-4-fluorophenyl)-5-(cyclopropyl(hydroxy)methyl)thiazol-2-yl)carbamate (450 mg, 1.13 mmol, 48% yield) as a white solid.



***tert*-butyl (4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)carbamate**

[0278] To a solution of *tert*-butyl (4-(3-chloro-4-fluorophenyl)-5-(cyclopropyl(hydroxy)methyl)thiazol-2-yl)carbamate (450 mg, 1.13 mmol, 1 *eq*) in DCM (1 mL) was added TFA (643 mg, 5.64 mmol, 419 μ L, 5 *eq*) and Et₃SiH (328 mg, 2.82 mmol, 451 μ L, 2.5 *eq*). The mixture was stirred at -20 °C for 0.5 hr then the reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. *tert*-butyl (4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)carbamate (430 mg, 1.12 mmol, 99% yield) was obtained as a white solid.

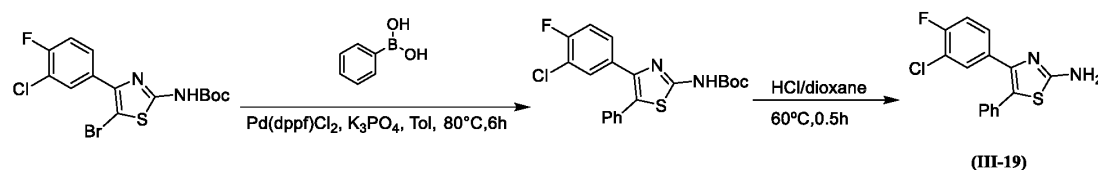


(III-18)

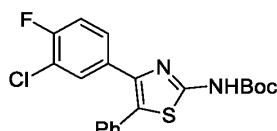
4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-amine

[0279] A mixture of *tert*-butyl (4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)carbamate (430 mg, 1.12 mmol, 1 *eq*) in HCl/dioxane (4M, 10 mL) was stirred at 60 °C for 0.5 hr. The reaction mixture was then quenched by addition NaOH (20%) to a pH of 7, and then diluted with H₂O (20 mL) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient at 30 mL/min) to give 4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-amine (**III-18**, 300 mg, 1.06 mmol, 95% yield) as a white solid.

[0280] **Example 23:** Synthesis of 4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-amine (**III-19**, Scheme 25).

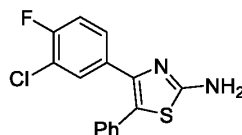


Scheme 25



***tert*-butyl (4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)carbamate**

[0281] A mixture of *tert*-butyl (5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate (1 g, 2.45 mmol, 1 *eq*; prepared via Scheme 23), phenylboronic acid (598.15 mg, 4.91 mmol, 2 *eq*), K₃PO₄ (1.5 M, 4.91 mL, 3 *eq*), Pd(dppf)Cl₂ (359 mg, 490.6 μmol, 0.2 *eq*) in Tol. (5 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 80 °C for 6 hr under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient at 15 mL/min). *tert*-butyl (4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)carbamate (220 mg, 543 μmol, 22% yield) was obtained as a white solid.

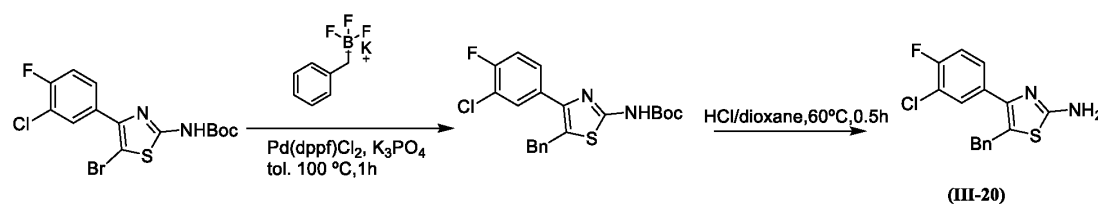


(**III-19**)

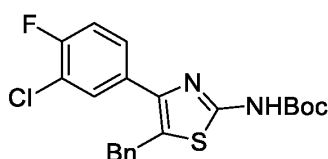
4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-amine

[0282] The mixture was of *tert*-butyl (4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)carbamate (220 mg, 543 μmol, 1 *eq*) in HCl/dioxane (4 mL) at 60 °C for 0.5 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient at 30 mL/min). 4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-amine (**III-19**, 120 mg, 394 μmol, 72% yield) was obtained as a white solid.

[0283] **Example 24:** Synthesis of 5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-amine (**III-20**, Scheme 26).

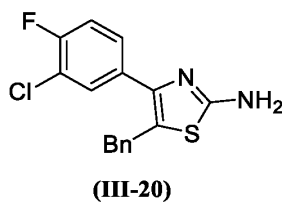


Scheme 26



***tert*-butyl (5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate**

[0284] A mixture of *tert*-butyl (5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate (0.470 g, 1.15 mmol, 1 *eq*; prepared via Scheme 23), potassium trifluoro(phenyl)borate (221 mg, 1.12 mmol, 1 *eq*), [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butylphosphane;methanesulfonate (168 mg, 231 μ mol, 0.2 *eq*), tripotassium phosphate (1.5 M, 2.31 mL, 3 *eq*) was added into Tol. (4 mL), then the mixture was degassed and purged with N₂ 3 times, then the mixture was stirred at 100 °C for 1 hr under a N₂ atmosphere. The reaction mixture was diluted with EA (30 mL) and washed with H₂O (30 mL $\times$ 3) and brine (30 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient at 18 mL/min) to give a product. *tert*-butyl (5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate (0.188 g, 449 μ mol, 39% yield) was obtained as a yellow solid.

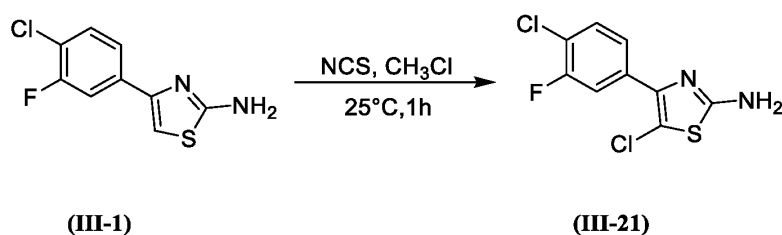


5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-amine

[0285] A mixture of *tert*-butyl (5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate (0.180 g, 429.7 μ mol, 1 *eq*) in HCl/dioxane (5 mL) was degassed, and then the mixture was stirred at 60 °C for 0.5 hr. The reaction mixture was quenched by addition NaOH to pH = 7-8

at 25°C. The reaction mixture was diluted with H₂O (20 mL) and extracted with EA (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethylacetate/Petroleum ether gradient at 18 mL/min) to give a product. 5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-amine (**III-20**, 0.108 g, 338.8 μmol, 79% yield) was obtained as a white solid.

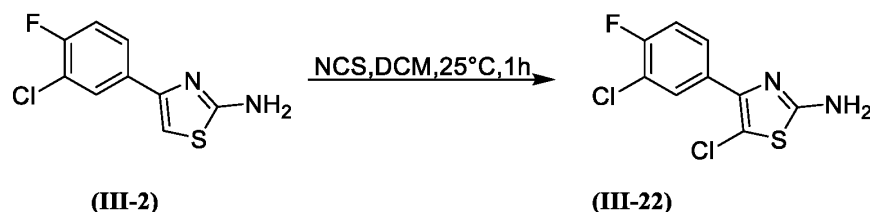
[0286] **Example 25: Synthesis of 5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-amine (III-21, Scheme 27).**



Scheme 27

[0287] To a mixture of **III-1** (5 g, 21.87 mmol, 1 *eq*; prepared via Scheme 7) in DCM (50 mL) was added NCS (3.21 g, 24.1 mmol, 1.1 *eq*) in one portion at 0 °C under N₂. The mixture was stirred at 25 °C for 1 hour then diluted with ethyl acetate (80 mL × 3), washed with brine (100 mL × 2), dried over Na₂SO₄ and concentrated to dryness. The residue was purified by column chromatography (silica gel, 100-200 mesh, 12% ethyl acetate in petroleum ether) to give 5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-amine (**III-21**, 4.9 g, 18.6 mmol, 85% yield) as a brown solid.

[0288] **Example 26: Synthesis of 5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-amine (III-22, Scheme 28).**

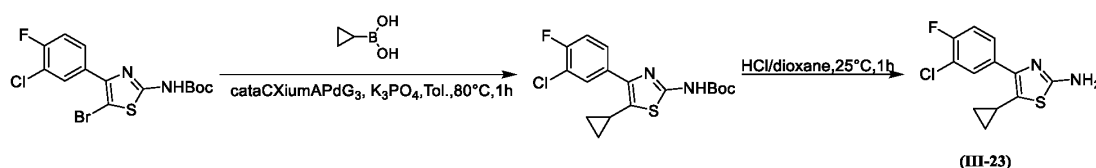


Scheme 28

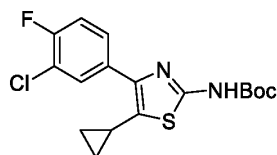
[0289] A mixture of 4-(3-chloro-4-fluorophenyl)-1,3-thiazol-2-ylamine (**III-2**, 3 g, 13.12 mmol, 1 *eq*), NCS (2.10 g, 15.74 mmol, 1.2 *eq*) in DCM (50 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 25 °C for 1 hr under N₂ atmosphere. The reaction mixture was quenched by addition H₂O (100 mL) at 25 °C and extracted with DCM

(100 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient at 40 mL/min). 5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-amine (**III-22**, 2.7 g, 10.3 mmol, 78% yield) was obtained as a yellow solid.

[0290] **Example 27: Synthesis of 4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-amine (III-23, Scheme 29).**

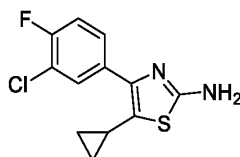


Scheme 29



***tert*-butyl (4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)carbamate**

[0291] To a solution of *tert*-butyl (5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate (800 mg, 1.96 mmol, 1 *eq*; prepared via Scheme 23) and potassium cyclopropyl(trifluoro)borohydride (581 mg, 3.92 mmol, 2 *eq*) in Tol. (1 mL) was added [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butyl-phosphane methanesulfonate (286 mg, 392 μ mol, 0.2 *eq*) and K₃PO₄ (1.5 M, 3.92 mL, 3 *eq*). The mixture was stirred at 80 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient at 30 mL/min). *tert*-butyl (4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)carbamate (650 mg, 1.76 mmol, 90% yield) was obtained as a white solid.

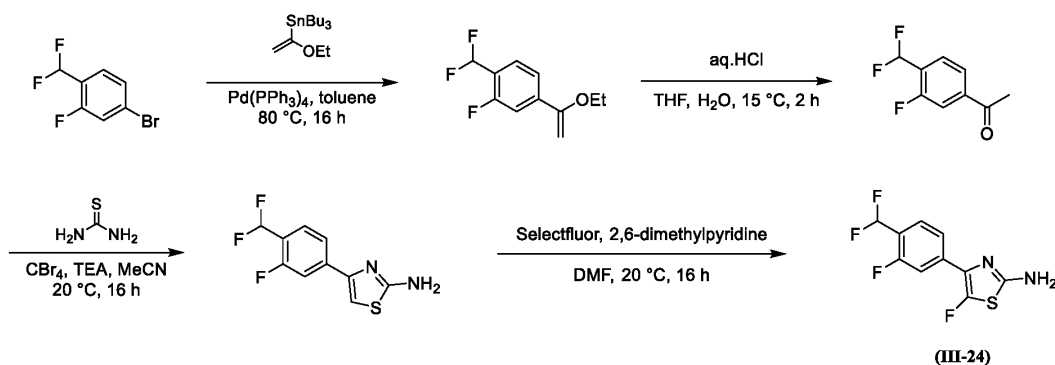


(III-23)

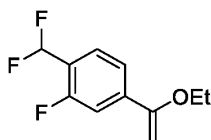
4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-amine

[0292] The mixture of *tert*-butyl 4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)carbamate (600 mg, 1.63 mmol, 1 *eq*) in HCl/dioxane (0.5 mL) was stirred at 25 °C for 1 hr. The reaction mixture was quenched by addition aq. NaOH to pH 6, and then diluted with H₂O (20 mL) and extracted with EA (20 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient at 30 mL/min). 4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-amine (**III-23**, 300 mg, 1.12 mmol, 69% yield) was obtained as a white solid.

[0293] **Example 28:** Synthesis of 4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-amine (**III-24**, Scheme 30).



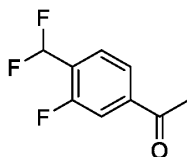
Scheme 30



1-(difluoromethyl)-4-(1-ethoxyvinyl)-2-fluorobenzene

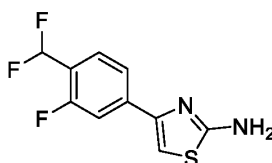
[0294] To a mixture of 4-bromo-1-(difluoromethyl)-2-fluorobenzene (5 g, 22.22 mmol, 1 *eq*), tributyl(1-ethoxyvinyl)stannane (8.99 g, 24.89 mmol, 8.40 mL, 1.12 *eq*) and Pd(PPh₃)₄ (2.57 g, 2.22 mmol, 0.1 *eq*) in toluene (50 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 80 °C for 16 hr under N₂ atmosphere. TLC showed **HDB-0320-A1** was almost consumed. The reaction mixture was cooled to 20 °C and added KF solution (100 mL). The mixture was stirred at 25 °C for a further 1 hr and filtered. The filtrate was extracted with EtOAc (80 mL × 2). The combined organic layers were dried over Na₂SO₄ and filtered again. The filtrate was concentrated to give the crude product 1-(difluoromethyl)-4-

(1-ethoxyvinyl)-2-fluorobenzene (4.80 g, crude) as a yellow solid and used into the next step without further purification.



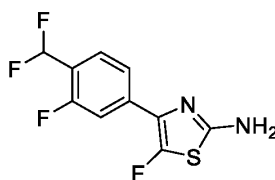
1-(4-(difluoromethyl)-3-fluorophenyl)ethan-1-one

[0295] To a solution of 1-(difluoromethyl)-4-(1-ethoxyvinyl)-2-fluorobenzene (4.8 g, 22.20 mmol, 1 *eq*) in THF (48 mL)/H₂O (8 mL) was added HCl (3 M, 7.40 mL, 1 *eq*). The mixture was stirred at 15 °C for 2 hr. TLC showed most of 1-(difluoromethyl)-4-(1-ethoxyvinyl)-2-fluorobenzene was consumed. The reaction mixture was concentrated to give the crude product which was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 70/30) to give 1-(4-(difluoromethyl)-3-fluorophenyl)ethan-1-one (2.33 g, 12.38 mmol, 56% yield) as a yellow solid.



4-(4-(difluoromethyl)-3-fluorophenyl)thiazol-2-amine

[0296] A mixture of 1-(4-(difluoromethyl)-3-fluorophenyl)ethan-1-one (2.33 g, 12.38 mmol, 1 *eq*), thiourea (1.89 g, 24.77 mmol, 2.0 *eq*), CBr₄ (8.21 g, 24.77 mmol, 2.0 *eq*) and TEA (2.76 g, 27.24 mmol, 3.79 mL, 2.2 *eq*) in MeCN (25 mL) was degassed and purged with N₂ 3 times, then the mixture was stirred at 20 °C for 16 hr under N₂ atmosphere. LCMS showed evidence of the desired product. The reaction mixture was then concentrated to remove MeCN, and then re-dissolved in H₂O (100 mL) and extracted with EtOAc (80 mL × 2). The combined organic layers were washed with aqueous NaCl (80 mL × 2) and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 60/40) to give 4-(4-(difluoromethyl)-3-fluorophenyl)thiazol-2-amine (1.24 g, 5.08 mmol, 41% yield) as a yellow solid.

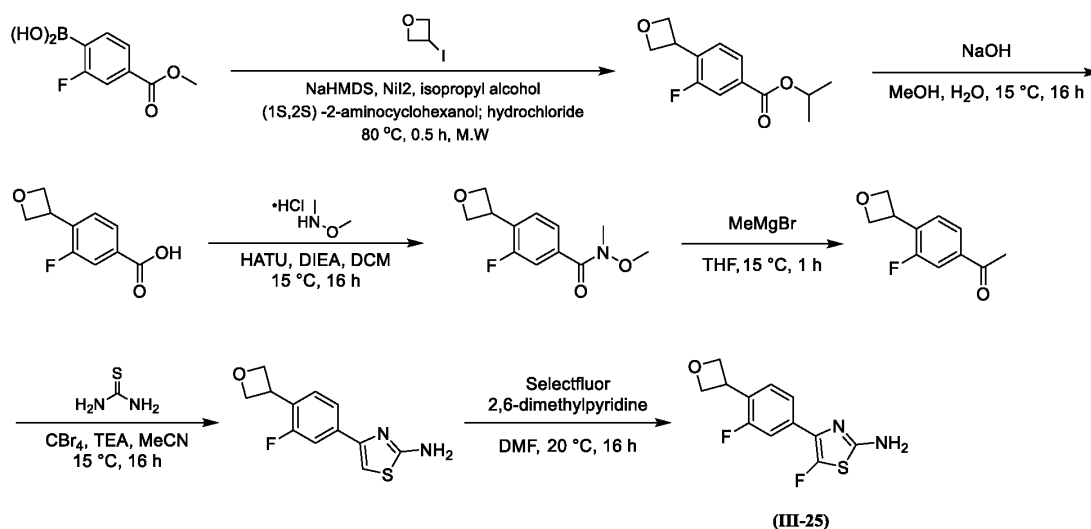


(III-24)

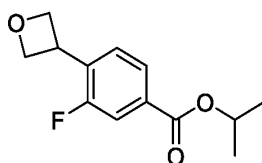
4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-amine

[0297] To a solution of 4-(4-(difluoromethyl)-3-fluorophenyl)thiazol-2-amine (1.24 g, 5.08 mmol, 1 *eq*) in DMF (20 mL) was added 2,6-dimethylpyridine (653 mg, 6.09 mmol, 710 μ L, 1.2 *eq*) and Selectfluor (2.16 g, 6.09 mmol, 1.2 *eq*). The mixture was stirred at 20 °C for 16 hr under N₂. LCMS showed most of 4-(4-(difluoromethyl)-3-fluorophenyl)thiazol-2-amine was consumed. To the reaction mixture was added H₂O (100 mL) and then extracted with EtOAc (70 mL $\times$ 2). The combined organic layers concentrated to give a residue which was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 60/40) to give 4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-amine (**III-24**, 337 mg, 1.29 mmol, 25% yield) as a yellow solid.

[0298] **Example 29: Synthesis of 5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-amine (**III-25**, Scheme 31).**



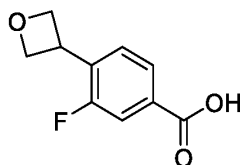
Scheme 31



Isopropyl 3-fluoro-4-(oxetan-3-yl)benzoate

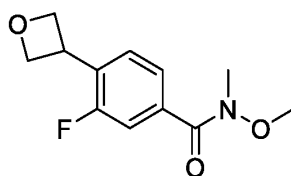
[0299] Compound 3-iodooxetane (465 mg, 2.53 mmol, 1 *eq*), NiI₂ (118 mg, 379 μ mol, 20.3 μ L, 0.15 *eq*), (1S,2S)-2-aminocyclohexanol;hydrochloride (57 mg, 379 μ mol, 0.15 *eq*) and NaHMDS (2 M, 2.53 mL, 2 *eq*) were taken up into a microwave tube in isopropyl alcohol (8 mL). The mixture was stirred at 25 °C for 10 min under N₂, then was added (2-fluoro-4-(methoxycarbonyl)phenyl)boronic acid (1 g, 5.05 mmol, 2 *eq*). The sealed tube was heated at

80 °C for 30 min under microwave. TLC indicated (2-fluoro-4-(methoxycarbonyl)phenyl)boronic acid was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was added EtOH (50 mL) and filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient at 12 mL/min). Isopropyl 3-fluoro-4-(oxetan-3-yl)benzoate (300 mg, 1.26 mmol, 50% yield) was obtained as a white oil.



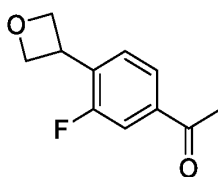
3-fluoro-4-(oxetan-3-yl)benzoic acid

[0300] To a solution of isopropyl 3-fluoro-4-(oxetan-3-yl)benzoate (880 mg, 3.69 mmol, 1 *eq*) in MeOH (10 mL)/H₂O (2 mL) was added NaOH (443 mg, 11.1 mmol, 3.0 *eq*). The mixture was stirred at 15 °C for 16 hr. LCMS showed isopropyl 3-fluoro-4-(oxetan-3-yl)benzoate was almost consumed, and ~82% of desired product was observed. The reaction mixture was adjusted to pH 5-6 with 3M HCl, and then extracted with EA (20 mL × 3). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude product. The crude product 3-fluoro-4-(oxetan-3-yl)benzoic acid (616 mg, 3.14 mmol, 85% yield) was obtained as a white solid and used in the next step without further purification.



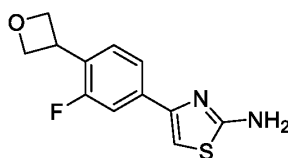
3-fluoro-N-methoxy-N-methyl-4-(oxetan-3-yl)benzamide

[0301] To a solution of *N,O*-dimethylhydroxylamine hydrochloride (337 mg, 3.45 mmol, 1.1 *eq*) in DCM (8 mL) was added 3-fluoro-4-(oxetan-3-yl)benzoic acid (616 mg, 3.14 mmol, 1.0 *eq*), HATU (1.43 g, 3.77 mmol, 1.2 *eq*) and DIEA (1.01 g, 7.85 mmol, 1.37 mL, 2.5 *eq*). The mixture was stirred at 15 °C for 16 hr. LCMS showed most of 3-fluoro-4-(oxetan-3-yl)benzoic acid was consumed. The reaction mixture was concentrated to give a residue and was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 65/35). 3-fluoro-*N*-methoxy-*N*-methyl-4-(oxetan-3-yl)benzamide (751 mg, 3.14 mmol, 100% yield) was obtained as a white oil.



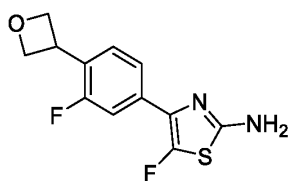
1-(3-fluoro-4-(oxetan-3-yl)phenyl)ethan-1-one

[0302] To a solution of 3-fluoro-*N*-methoxy-*N*-methyl-4-(oxetan-3-yl)benzamide (750 mg, 3.13 mmol, 1 *eq*) in THF (10 mL) was cooled to 0 °C and added MeMgBr (3 M, 1.25 mL, 1.2 *eq*). The mixture was stirred at 15 °C for 1 hr. LCMS showed most of 3-fluoro-*N*-methoxy-*N*-methyl-4-(oxetan-3-yl)benzamide was consumed. The reaction mixture was added MeOH (50 mL) slowly. The resulting mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 80/20). 1-(3-fluoro-4-(oxetan-3-yl)phenyl)ethan-1-one (600 mg, 3.09 mmol, 99% yield) was obtained as a yellow oil.



4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-amine

[0303] A mixture of thiourea (470 mg, 6.18 mmol, 2.0 *eq*), 1-(3-fluoro-4-(oxetan-3-yl)phenyl)ethan-1-one (600 mg, 3.09 mmol, 1.0 *eq*), CBr₄ (2.05 g, 6.18 mmol, 2.0 *eq*) and TEA (688 mg, 6.80 mmol, 946 μL, 2.2 *eq*) in MeCN (30 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 15 °C for 16 hr under N₂ atmosphere. LCMS showed most of 1-(3-fluoro-4-(oxetan-3-yl)phenyl)ethan-1-one was consumed, and ~39% of desired product was observed. The reaction mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 65/35). 4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-amine (388 mg, 1.55 mmol, 50% yield) was obtained as a yellow solid.

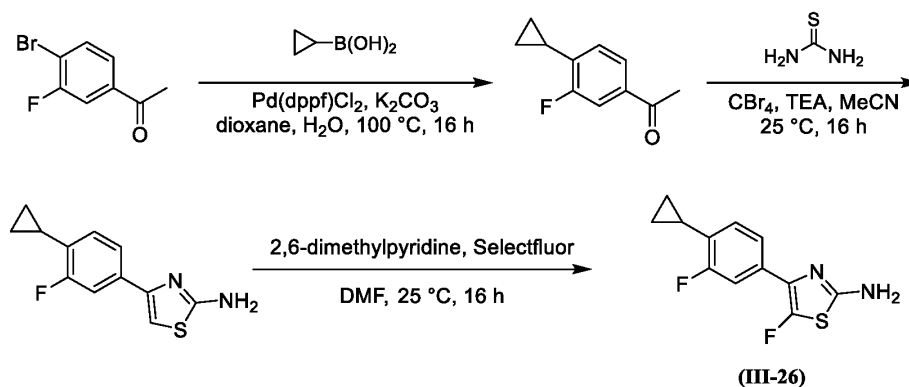


(III-25)

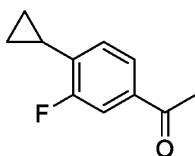
5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-amine

[0304] To a solution of 4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-amine (388 mg, 1.55 mmol, 1 *eq*) in DMF (3 mL) was added 2,6-dimethylpyridine (199 mg, 1.86 mmol, 217 μ L, 1.2 *eq*) and cooled to 0 °C, followed by Selectfluor (659 mg, 1.86 mmol, 1.2 *eq*). The mixture was stirred at 20 °C for 16 hr under N₂. LCMS showed most of 4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-amine was consumed, and ~31% of desired product was observed. To the reaction mixture was added H₂O (30 mL) and extracted with EA (30 mL $\times$ 2). The combined organic layers were washed with brine (50 mL $\times$ 2) and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 60/40). 5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-amine (**III-25**, 112 mg, 417 μ mol, 27% yield) was obtained as a yellow solid.

[0305] **Example 30: Synthesis of 4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-amine (III-26, Scheme 32).**



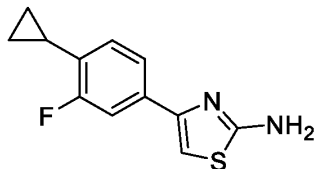
Scheme 32



1-(4-cyclopropyl-3-fluorophenyl)ethan-1-one

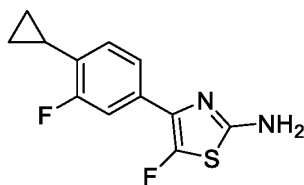
[0306] A mixture of 1-(4-bromo-3-fluorophenyl)ethan-1-one (5 g, 23.04 mmol, 1 *eq*), cyclopropylboronic acid (2.18 g, 25.34 mmol, 1.1 *eq*), K₂CO₃ (9.55 g, 69.11 mmol, 3 *eq*), Pd(dppf)Cl₂ (843 mg, 1.15 mmol, 0.05 *eq*) in dioxane (25 mL) and H₂O (5 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 100 °C for 16 hr under N₂ atmosphere. The reaction mixture was then diluted with H₂O (30 mL) and extracted with EtOAc (50 mL $\times$ 3). The combined organic layers were washed with aqueous NaCl (60 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g

SepaFlash® Silica Flash Column, Eluent of 0~7% Ethyl acetate/Petroleum ether gradient at 50 mL/min) to give 1-(4-cyclopropyl-3-fluorophenyl)ethan-1-one (3.44 g, 19.30 mmol, 84% yield) as a white oil.



4-(4-cyclopropyl-3-fluorophenyl)thiazol-2-amine

[0307] To a mixture of 1-(4-cyclopropyl-3-fluorophenyl)ethan-1-one (3.44 g, 19.30 mmol, 1 *eq*), thiourea (2.20 g, 28.96 mmol, 1.5 *eq*) in MeCN (30 mL) was added CBr₄ (9.60 g, 28.96 mmol, 1.5 *eq*), TEA (2.93 g, 28.96 mmol, 4.03 mL, 1.5 *eq*). The mixture was degassed and purged with N₂ 3 times, and then the mixture was stirred at 25 °C for 16 hr under N₂ atmosphere. The reaction mixture was then concentrated under reduced pressure to remove MeCN (30 mL). The residue was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL). The combined organic layers were washed with aqueous NaCl (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient at 50 mL/min) to give 4-(4-cyclopropyl-3-fluorophenyl)thiazol-2-amine (2.24 g, 9.56 mmol, 50% yield) as a yellow solid.



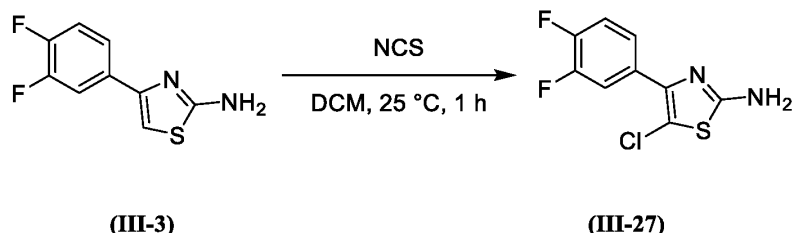
(III-26)

4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-amine

[0308] A mixture of 4-(4-cyclopropyl-3-fluorophenyl)thiazol-2-amine (2.24 g, 9.60 mmol, 1 *eq*) in DMF (25 mL) was added 2,6-dimethylpyridine (1.23 g, 11.52 mmol, 1.34 mL, 1.2 *eq*) and selectfluor (4.08 g, 11.52 mmol, 1.2 *eq*) at 0 °C, and then the mixture was stirred at 25 °C for 16 hr under N₂ atmosphere. The reaction mixture was then diluted with H₂O (50 mL) and extracted with EtOAc (60 mL). The combined organic layers were washed with aqueous NaCl (60 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography

(ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient at 25 mL/min) to give 4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-amine (**III-26**, 920 mg, 3.65 mmol, 38% yield) was obtained as a black solid.

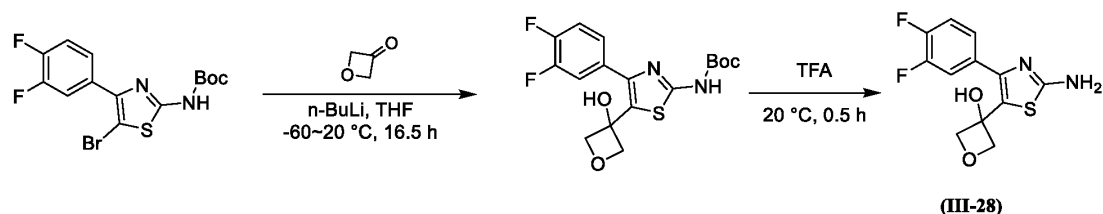
[0309] **Example 31:** Synthesis of 5-chloro-4-(3,4-difluorophenyl)thiazol-2-amine (**III-27**, Scheme 33).



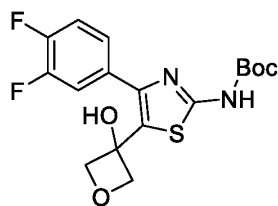
Scheme 33

[0310] To a solution of **III-3** (1 g, 4.71 mmol, 1 *eq*; prepared via Scheme 9) in DCM (10 mL) was added NCS (944 mg, 7.07 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 1 hr then concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give 5-chloro-4-(3,4-difluorophenyl)thiazol-2-amine (**III-27**, 800 mg, 3.24 mmol, 69% yield) as a white solid.

[0311] **Example 32:** Synthesis of 3-(2-amino-4-(3,4-difluorophenyl)thiazol-5-yl)oxetan-3-ol (**III-28**, Scheme 34).



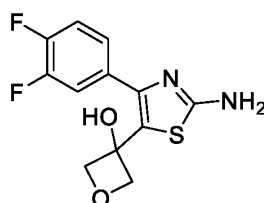
Scheme 34



tert-butyl (4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)carbamate

[0312] To a solution of *tert*-butyl (5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)carbamate (1 g, 2.56 mmol, 1 *eq*; prepared via Scheme 14) in THF (10 mL) was cooled to -60 °C and added *n*-BuLi (2.5 M, 1.64 mL, 1.6 *eq*) slowly under N₂. The mixture was stirred at -60 °C

under N₂ for 0.5 h, followed by addition of oxetan-3-one (276 mg, 3.83 mmol, 1.5 *eq*). The resulting mixture was warmed to RT and stirred at 20 °C for a further 16 hr. LCMS showed evidence of the desired product. The reaction mixture was then cooled to 0 °C and added H₂O (40 mL) slowly, then the mixture was extracted with EA (30 mL × 3). The combined organic layers were concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 70/30) to give *tert*-butyl (4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)carbamate (247 mg, 643 μmol, 25% yield) as a yellow oil.

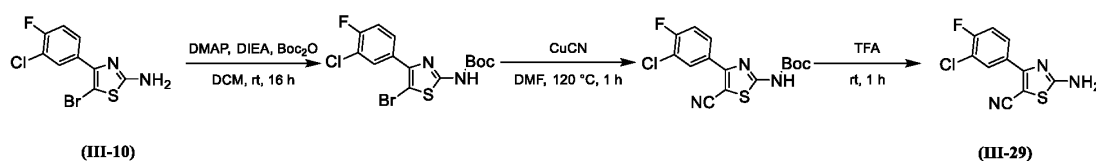


(III-28)

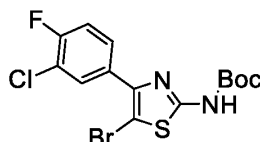
3-(2-amino-4-(3,4-difluorophenyl)thiazol-5-yl)oxetan-3-ol

[0313] To a mixture of *tert*-butyl (4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)carbamate (240 mg, 624 μmol, 1 *eq*) in TFA (1 mL) was stirred at 20 °C for 0.5 hr. TLC showed most of the starting material had been consumed. The reaction mixture was then adjusted to pH 5 by NaHCO₃ solution. Then the mixture was extracted with EtOAc (20 mL × 2). The combined organic layers were concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 20/80) to give 3-(2-amino-4-(3,4-difluorophenyl)thiazol-5-yl)oxetan-3-ol (147 mg, 517 μmol, 83% yield) as a yellow oil

[0314] **Example 33:** Synthesis of 2-amino-4-(3-chloro-4-fluorophenyl)thiazole-5-carbonitrile (III-29, Scheme 35).

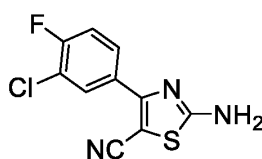


Scheme 35



tert-butyl (5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate

[0315] A mixture of Boc2O (8.51 g, 39.02 mmol, 8.96 mL, 1.5 *eq*), **III-10** (8 g, 26.0 mmol, 1 *eq*; prepared via Scheme 16), DIEA (5.04 g, 39.0 mmol, 6.80 mL, 1.5 *eq*), DMAP (318 mg, 2.60 mmol, 0.1 *eq*) in DCM (50 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 25 °C for 16 hr under an N₂ atmosphere. The reaction mixture was then concentrated under reduced pressure to remove DCM (50 mL). The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~4% Ethyl acetate/Petroleum ether gradient at 50 mL/min) to give *tert*-butyl (5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate (4.8 g, 11.8 mmol, 45% yield) as a black solid.



(**III-29**)

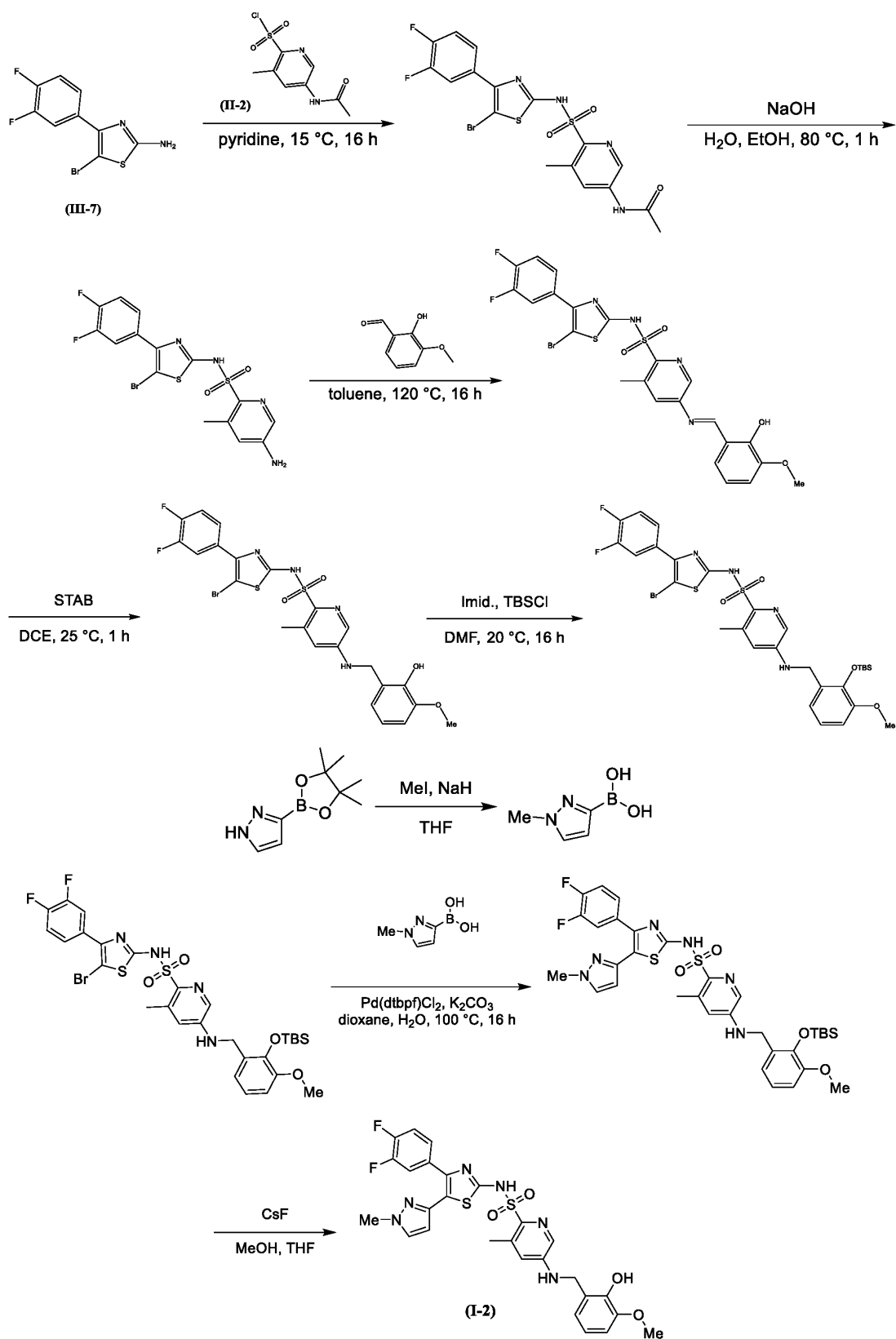
2-amino-4-(3-chloro-4-fluorophenyl)thiazole-5-carbonitrile

[0316] To a solution of *tert*-butyl (5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)carbamate (4.8 g, 11.8 mmol, 45% yield) (1.8 g, 4.42 mmol, 1 *eq*), CuCN (1.98 g, 22.1 mmol, 4.82 mL, 5 *eq*) in DMF (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 120 °C for 1hr under an N₂ atmosphere. The reaction mixture was then cooled to 20 °C and filtered. The filter cake was washed with EA (100 mL). Then the filtrate was concentrated to give crude products. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ether gradient at 25 mL/min) to give 2-amino-4-(3-chloro-4-fluorophenyl)thiazole-5-carbonitrile (**III-29**, 400 mg, 1.58 mmol, 36% yield) as a yellow solid.

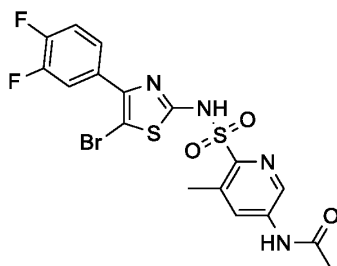
[0317] Preparation of Compounds of Formula (I)

[0318] **Example 34:** Synthesis of *N*-(4-(3,4-difluorophenyl)-5-(1-methyl-1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-2**, Scheme 36).

[0319] Compound **I-2** may be prepared according to Scheme 36:

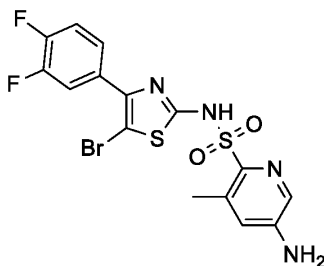


Scheme 36



N-(6-(N-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide

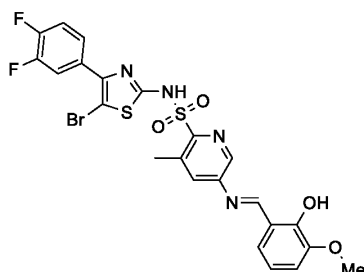
[0320] To a solution of **III-7** (5.09 g, 17.5 mmol, 1 *eq*; prepared via Scheme 13) in pyridine (20 mL) was added 5-acetamido-3-methylpyridine-2-sulfonyl chloride (**II-2**, 5 g, 20.1 mmol, 1.2 *eq*; prepared via Scheme 4). LC-MS showed **II-2** was consumed completely and one main peak with desired *m/z* was detected. The reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with aqueous NaCl (100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~65% Ethyl acetate/Petroleum ether gradient at 25 mL/min). N-(6-(N-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (7.12 g, 14.2 mmol, 81% yield) was obtained as a yellow solid.



5-amino-N-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

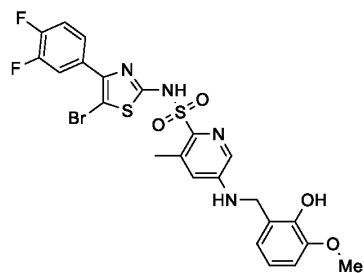
[0321] To a solution of N-(6-(N-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (6.1 g, 12.12 mmol, 1 *eq*) in EtOH (40 mL) and H₂O (10 mL) was added NaOH (4.85 g, 121.2 mmol, 10 *eq*). The mixture was stirred at 80 °C for 2 hr. The reaction mixture was then concentrated under reduced pressure to remove EtOH (40 mL) and diluted with H₂O (100 mL) and extracted with EtOAc (100 mL × 2). The combined organic layers were washed with aqueous NaCl (100 mL), dried over Na₂SO₄, filtered, and

concentrated under reduced pressure to give a residue. The crude product 5-amino-N-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide was obtained as a yellow solid and used directly in the next step without further purification (5.3 g, 11.5 mmol, 95% yield) was obtained as a yellow solid.



I-N-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

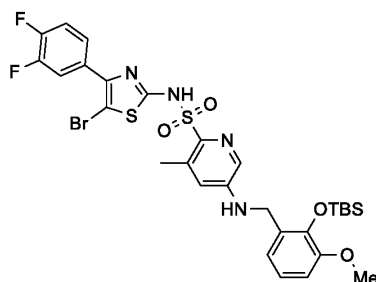
[0322] To a solution of 5-amino-N-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (5.3 g, 11.49 mmol, 1 *eq*) in toluene (50 mL) was added 2-hydroxy-3-methoxybenzaldehyde (1.92 g, 12.64 mmol, 1.1 *eq*). The mixture was then stirred at 25 °C for 16 hr under N₂ atmosphere. The reaction mixture was then concentrated under reduced pressure to remove toluene (50 mL). Crude product I-N-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (6.84 g, 11.49 mmol, 100% yield) was isolated as a black solid and used directly in the next step.



N-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide

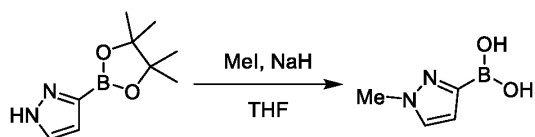
[0323] To a solution of I-N-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (6.84 g, 11.49 mmol, 1 *eq*), NaBH(OAc)₃ (12.17 g, 57.44 mmol, 5 *eq*) in DCE (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 25 °C for 2 hr under N₂ atmosphere. LC-MS showed evidence of the desired product. The reaction mixture was then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with

aqueous NaCl (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient at 50 mL/min). *N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (4.3 g, 7.20 mmol, 63% yield) was obtained as a yellow solid.



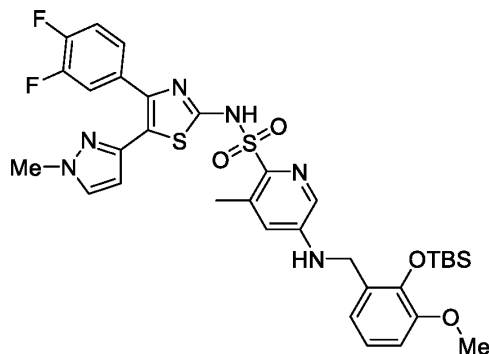
***N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0324] To a solution of *N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (4.1 g, 6.86 mmol, 1 *eq*) in DMF (20 mL) was added TBSCl (2.59 g, 17.16 mmol, 2.11 mL, 2.5 *eq*) and imidazole (1.64 g, 24.0 mmol, 3.5 *eq*). The mixture was stirred at 25 °C for 16 hr. LC-MS showed evidence of the desired product. The reaction mixture was then diluted with H₂O (20 mL) and extracted with EtOAc (25 mL × 3). The combined organic layers were washed with aqueous NaCl (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/DCM at 25 mL/min to give **HDB-Int-D** (4.2 g, 5.90 mmol, 86% yield) was obtained as a white solid.



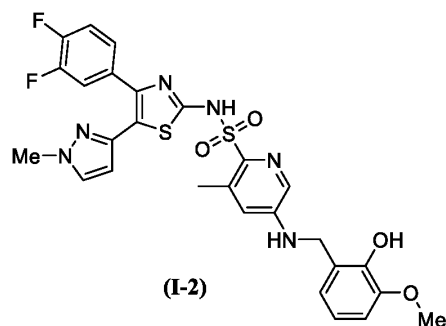
[0325] To a solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (500 mg, 2.58 mmol, 1 *eq*) in THF (3 mL) was cooled to 0 °C and added NaH (134 mg, 3.35 mmol, 60% purity, 1.3 *eq*) slowly under N₂. The mixture was stirred at 0 °C for 0.5 hr, followed by addition of MeI (549 mg, 3.87 mmol, 241 µL, 1.5 *eq*). The mixture was stirred at 20 °C for a further 0.5 hr. LC-MS showed most of the starting material had been consumed, and the main peak matched the mass of the desired product. The reaction mixture was cooled

to 0 °C and H₂O (0.5 mL) was added slowly, then concentrated to give a residue. The crude product was purified by reversed-phase HPLC to give (1-methyl-1*H*-pyrazol-3-yl)boronic acid (300 mg, 2.38 mmol, 93% yield) as a white solid.



5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1-methyl-1*H*-pyrazol-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0326] A mixture of *N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (170 mg, 238 μmol, 1 *eq*), (1-methyl-1*H*-pyrazol-3-yl)boronic acid (150 mg, 1.19 mmol, 5 *eq*), [2-(2-aminophenyl)phenyl]palladium(1+);dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate (20 mg, 24 μmol, 0.1 *eq*), Cs₂CO₃ (233 mg, 715 μmol, 3 *eq*) in dioxane (2 mL) and H₂O (0.2 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 90 °C for 16 hr under a N₂ atmosphere. LC-MS showed most of the starting material had been consumed and a peak corresponding to the desired product. The reaction mixture was then concentrated under reduced pressure to remove dioxane (2 mL). The residue was purified by prep-HPLC to give 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1-methyl-1*H*-pyrazol-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (50 mg, 70 μmol, 29% yield) as a white solid.

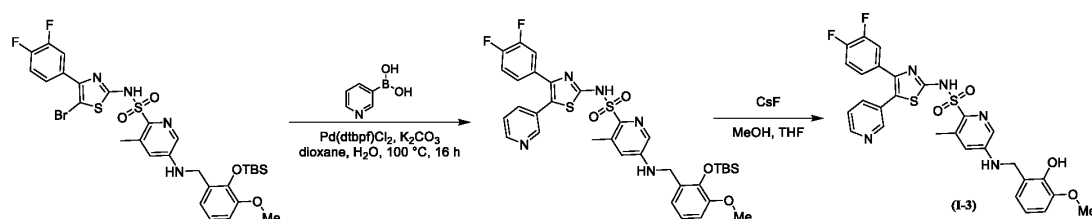


***N*-(4-(3,4-difluorophenyl)-5-(1-methyl-1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

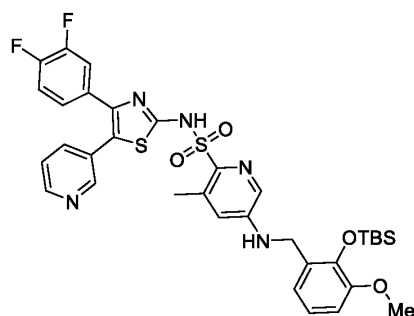
[0327] To a solution of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1-methyl-1*H*-pyrazol-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (50 mg, 70 μ mol, 1 *eq*) in THF (4 mL) and MeOH (2 mL) was added CsF (107 mg, 701 μ mol, 26 μ L, 10 *eq*). The mixture was stirred at 25 °C for 2 hr. LC-MS showed desired mass was detected. The reaction mixture was then concentrated under reduced pressure to remove THF (4 mL) and MeOH (2 mL). The residue was purified by prep-HPLC to give *N*-(4-(3,4-difluorophenyl)-5-(1-methyl-1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-2**, 14 mg, 23 μ mol, 33% yield) as a white solid.

[0328] **Example 35: Synthesis of *N*-(4-(3,4-difluorophenyl)-5-(pyridine-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-3**, Scheme 37).**

[0329] Compound **I-3** may be prepared according to Scheme 37:



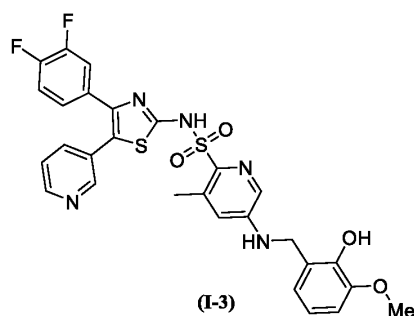
Scheme 37



5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(pyridine-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0330] A mixture of *N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (200 mg, 281.01 μ mol, 1 *eq*; prepared via Scheme 36), 3-pyridylboronic acid (103.62 mg, 843 μ mol, 3 *eq*), K₂CO₃ (117 mg, 843 μ mol, 3 *eq*), ditert-butyl(cyclopentyl)phosphane;dichloropalladium,iron (37 mg, 56.20 μ mol, 0.2 *eq*) in dioxane

(2 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 100 °C for 16 hr under N₂ atmosphere. LC-MS showed starting material was consumed completely and desired mass was detected. The reaction mixture was diluted with H₂O (20 mL) and extracted with EA (20 mL × 3). The combined organic layers were washed with aqueous NaCl (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC. 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(pyridine-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (100 mg, 140.9 μmol, 55% yield) was obtained as a white solid.

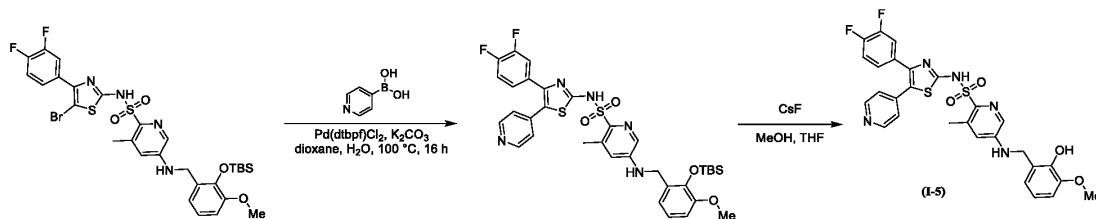


***N*-(4-(3,4-difluorophenyl)-5-(pyridine-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

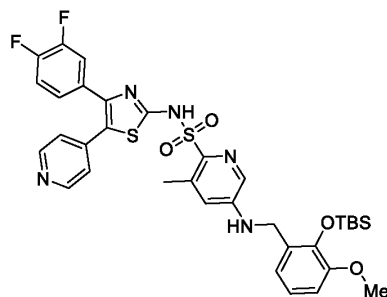
[0331] To a solution of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(pyridine-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (100 mg, 140.9 μmol, 1 *eq*) in THF (4 mL) and MeOH (2 mL) was added CsF (107 mg, 704 μmol, 26 μL, 5 *eq*). The mixture was stirred at 25 °C for 2 hr. LC-MS showed the desired mass. The reaction mixture was concentrated under reduced pressure to remove THF (4 mL) and MeOH (2 mL). The residue was purified by prep-HPLC and *N*-(4-(3,4-difluorophenyl)-5-(pyridine-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-3**, 53 mg, 89 μmol, 63% yield) was obtained as a yellow solid.

[0332] Example 36: Synthesis of *N*-(4-(3,4-difluorophenyl)-5-(pyridine-4-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (I-5**, Scheme 38).**

[0333] Compound **I-5** may be prepared according to Scheme 38:

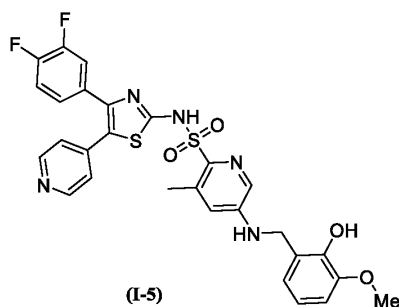


Scheme 38



5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(pyridine-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0334] A mixture of *N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (200 mg, 280.5 μ mol, 1 *eq*; prepared via Scheme 36), 4-pyridylboronic acid (52 mg, 422 μ mol, 3 *eq*), K_2CO_3 (58 mg, 421.5 μ mol, 3 *eq*), ditert butyl(cyclopentyl)phosphane-dichloropalladium-iron (18 mg, 28.1 μ mol, 0.2 *eq*) in dioxane (2 mL) and H_2O (0.2 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 100 $^{\circ}C$ for 16 hr under N_2 atmosphere. LC-MS showed that the starting material was consumed completely, and the desired mass was detected. The reaction mixture was diluted with H_2O (20 mL) and extracted with EA (20 mL $\times$ 3). The combined organic layers were washed with aqueous NaCl (20 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition). 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(pyridine-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (76 mg, 107 μ mol, 76% yield) was obtained as a white solid.



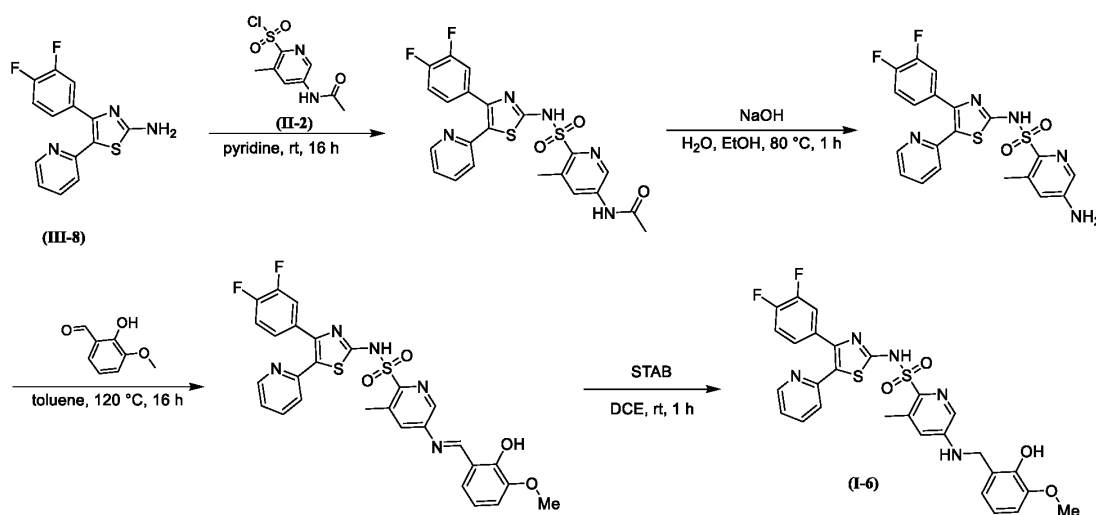
***N*-(4-(3,4-difluorophenyl)-5-(pyridine-4-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0335] To a solution of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(pyridine-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (140 mg,

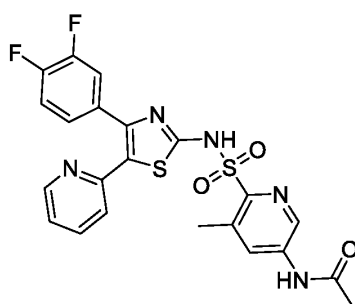
197 μmol , 1 *eq*) in THF (4 mL) and MeOH (2 mL) was added CsF (150 mg, 986 μmol , 36 μL , 5 *eq*). The mixture was stirred at 25 °C for 2 hr. LC-MS showed the desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove THF (4 mL) and MeOH (2 mL). The residue was purified by prep-HPLC. Compound *N*-(4-(3,4-difluorophenyl)-5-(pyridine-4-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-5**, 53 mg, 89 μmol , 45% yield) was obtained as a yellow solid.

[0336] Example 37: Synthesis of *N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (I-6**, Scheme 39).**

[0337] Compound **I-6** may be prepared according to Scheme 39:



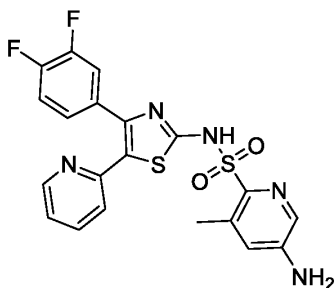
Scheme 39



N-(6-(*N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide

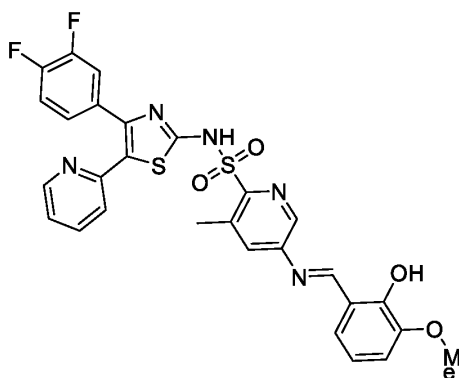
[0338] To a mixture of 4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-amine (**III-8**, 75 mg, 259 μmol , 1.0 *eq*; prepared via Scheme 14) and **II-2** (65 mg, 259 μmol , 1.0 *eq*; prepared

via Scheme 4) in pyridine (1 mL) was stirred at 20°C for 16 hr. LCMS showed the desired product. The reaction mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 0/100). *N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (47 mg, 94 μmol, 36% yield) was obtained as a yellow solid.



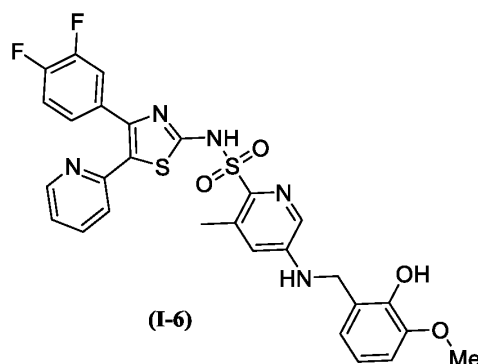
5-amino-*N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0339] To a solution of *N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (47 mg, 93.7 μmol, 1 *eq*) in EtOH (2 mL)/H₂O (0.4 mL) was added NaOH (400 mg, 10.0 mmol, 106 *eq*). The mixture was stirred at 80 °C for 1 hr. LCMS showed *N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide was almost consumed. The reaction mixture was concentrated to give a residue. To the residue was added H₂O (15 mL) and extracted with EA (20 mL × 3). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude product. The crude product 5-amino-*N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (43 mg, crude) was obtained as a yellow solid and used into the next step without further purification.



1-*N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0340] To a mixture of 2-hydroxy-3-methoxybenzaldehyde (14 mg, 94 μ mol, 1 *eq*) and 5-amino-*N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (43 mg, 94 μ mol, 1 *eq*) in toluene (5 mL) was heated to 120 °C and stirred for 16 hr. The reaction mixture was cooled to 20 °C and concentrated to remove the solvent. *I-N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (55 mg, crude) was obtained as a yellow solid and used in the next step without further purification.

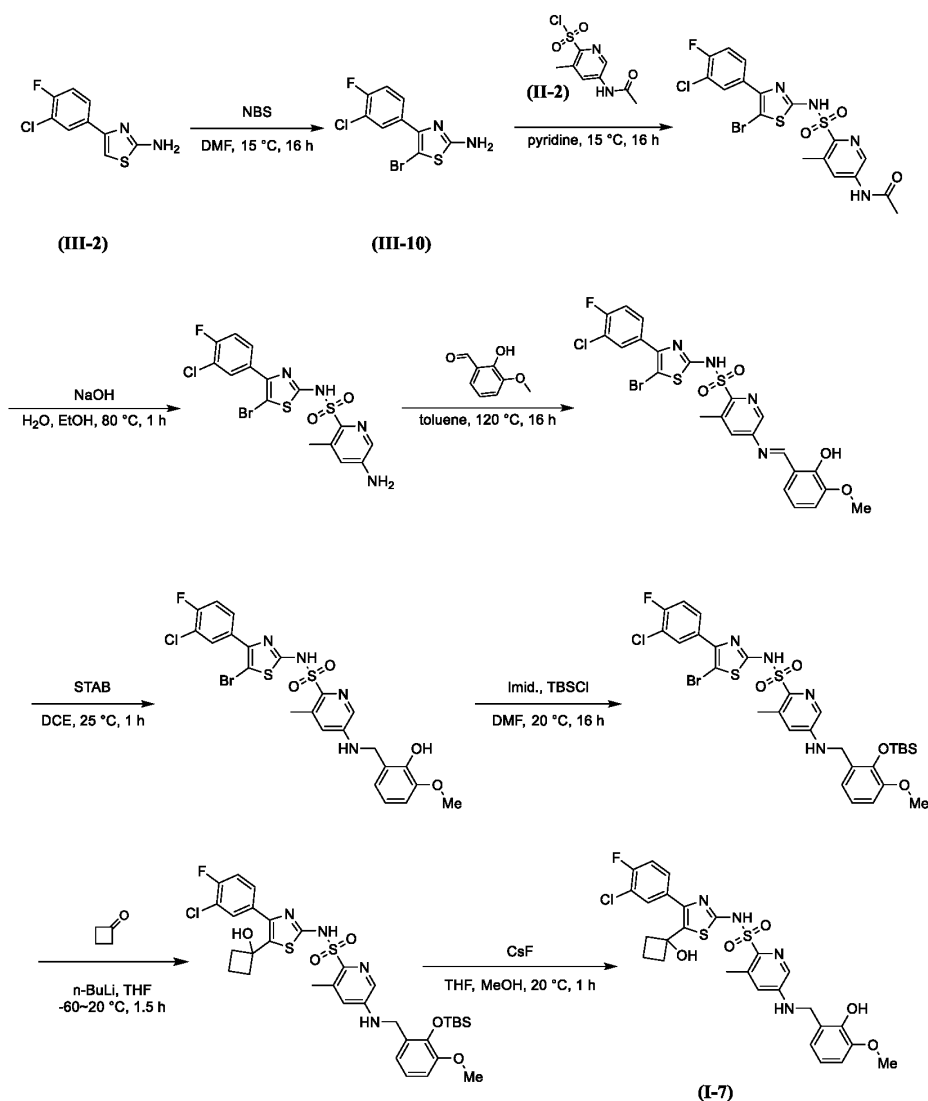


***N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

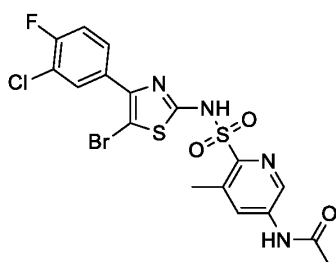
[0341] To a solution of *I-N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (55 mg, 93 μ mol, 1 *eq*) in DCE (2 mL) was added NaBH(OAc)₃ (98 mg, 463 μ mol, 5.0 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed that most of *I-N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide was consumed. The reaction mixture was added H₂O (15 mL) and extracted with EA (20 mL $\times$ 2). The combined organic layers were concentrated to give a crude product. The residue was purified by prep-HPLC. *N*-(4-(3,4-difluorophenyl)-5-(pyridine-2-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-6**, 28 mg, 46 μ mol, 50% yield) was obtained as a yellow solid.

[0342] **Example 38:** Synthesis of *N*-(4-(3-chloro-4-fluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-7**, Scheme 40).

[0343] Compound **I-7** may be prepared according to Scheme 40:

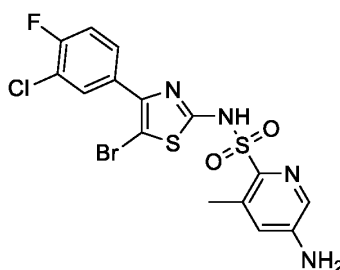


Scheme 40



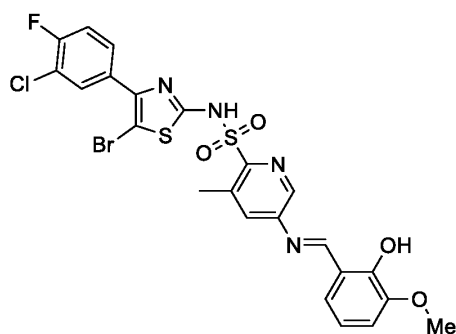
N-(6-(*N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide

[0344] To a solution of **III-10** (4.09 g, 13.3 mmol, 1 *eq*; prepared via Scheme 16) in pyridine (20 mL) was added 5-acetamido-3-methylpyridine-2-sulfonyl chloride (**II-2**, 3.8 g, 15.3 mmol, 1.15 *eq*; prepared via Scheme 4). The mixture was stirred at 25 °C for 16h. The reaction was clean according to TLC. The reaction mixture was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with aqueous NaCl (50 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~65% Ethyl acetate/Petroleum ether gradient at 25 mL/min) to give *N*-(6-(*N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (5.2 g, 10.0 mmol, 75% yield) as a yellow solid.



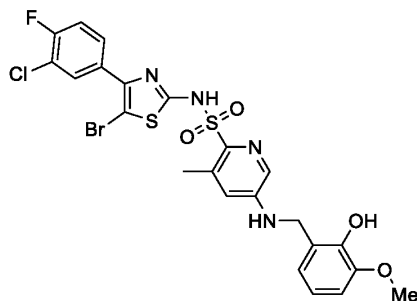
5-amino-*N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0345] To a solution of *N*-(6-(*N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide in EtOH (30 mL) and H₂O (10 mL) was added NaOH (4.00 g, 100 mmol, 10 *eq*). The mixture was stirred at 80 °C for 2hr then the reaction mixture was concentrated under reduced pressure to remove EtOH (30 mL). The reaction mixture was then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with aqueous NaCl (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. Crude product 5-amino-*N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (4.2 g, 8.79 mmol, 88% yield) was obtained as a red solid and used directly in the next step.



(E)-N-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

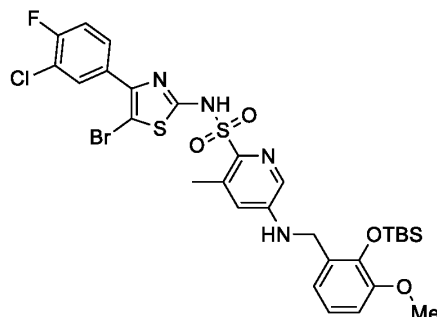
[0346] To a solution of 5-amino-*N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (4.2 g, 8.79 mmol, 1 *eq*) in toluene (40 mL) was added 2-hydroxy-3-methoxybenzaldehyde (1.47 g, 9.67 mmol, 1.1 *eq*). The mixture was stirred at 120 °C for 16 hr under an N₂ atmosphere. After this time, the reaction mixture was concentrated under reduced pressure to remove toluene (40 mL). Crude product (*E*)-*N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (5.38 g, 8.79 mmol, 100% yield) was obtained as a red solid and used directly in the next step.



***N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide**

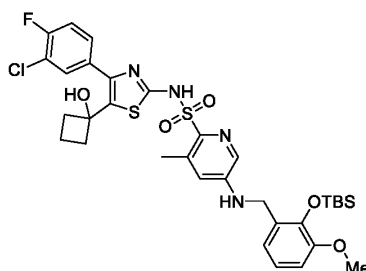
[0347] A mixture of (*E*)-*N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (5.38 g, 8.79 mmol, 1 *eq*), NaBH(OAc)₃ (9.32 g, 44 mmol, 5 *eq*) in DCE (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 25 °C for 2 hr under a N₂ atmosphere. The reaction mixture was then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with aqueous NaCl (50 mL), dried over Na₂SO₄,

filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient at 50 mL/min). to give *N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (2.2 g, 3.58 mmol, 41% yield) as a yellow solid.



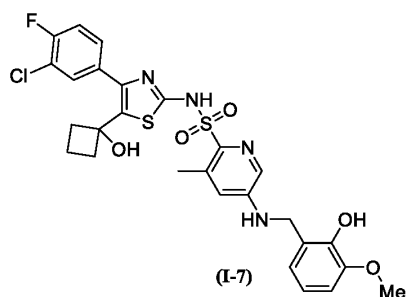
***N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0348] To a solution of *N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (2.2 g, 3.58 mmol, 1 *eq*) in DMF (10 mL) was added TBSCl (2.97 g, 19.7 mmol, 2.43 mL, 5.5 *eq*) and imidazole (854 mg, 12.54 mmol, 3.5 *eq*). The mixture was stirred at 25 °C for 16 hr then the reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (30mL × 2). The combined organic layers were washed with aqueous NaCl (50 mL) (50 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/DCM at 25 mL/min) to give *N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (2.3 g, 3.16 mmol, 88% yield) as a white solid.



5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3-chloro-4-fluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0349] To a solution of *N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (200 mg, 275 μ mol, 1.0 *eq*) in THF (5 mL) was cooled to -60 °C and added *n*-BuLi (2.5 M, 341 μ L, 3.1 *eq*) slowly under N₂. The mixture was stirred at -60 °C under N₂ for 0.5 h, followed by addition of cyclobutanone (193mg, 2.75 mmol, 205 μ L, 10 *eq*) in THF (2 mL). The resulting mixture was stirred at -20 °C for a further 1 hr. LCMS showed consumption of the starting material. The reaction mixture was then cooled to 0 °C and a NH₄Cl solution was added slowly, then the mixture was adjusted to pH 5. The resulting mixture was extracted with EtOAc (30 mL $\times$ 2). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give a residue. The residue was purified by prep-HPLC to give 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3-chloro-4-fluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (50 mg, crude) as a yellow oil.

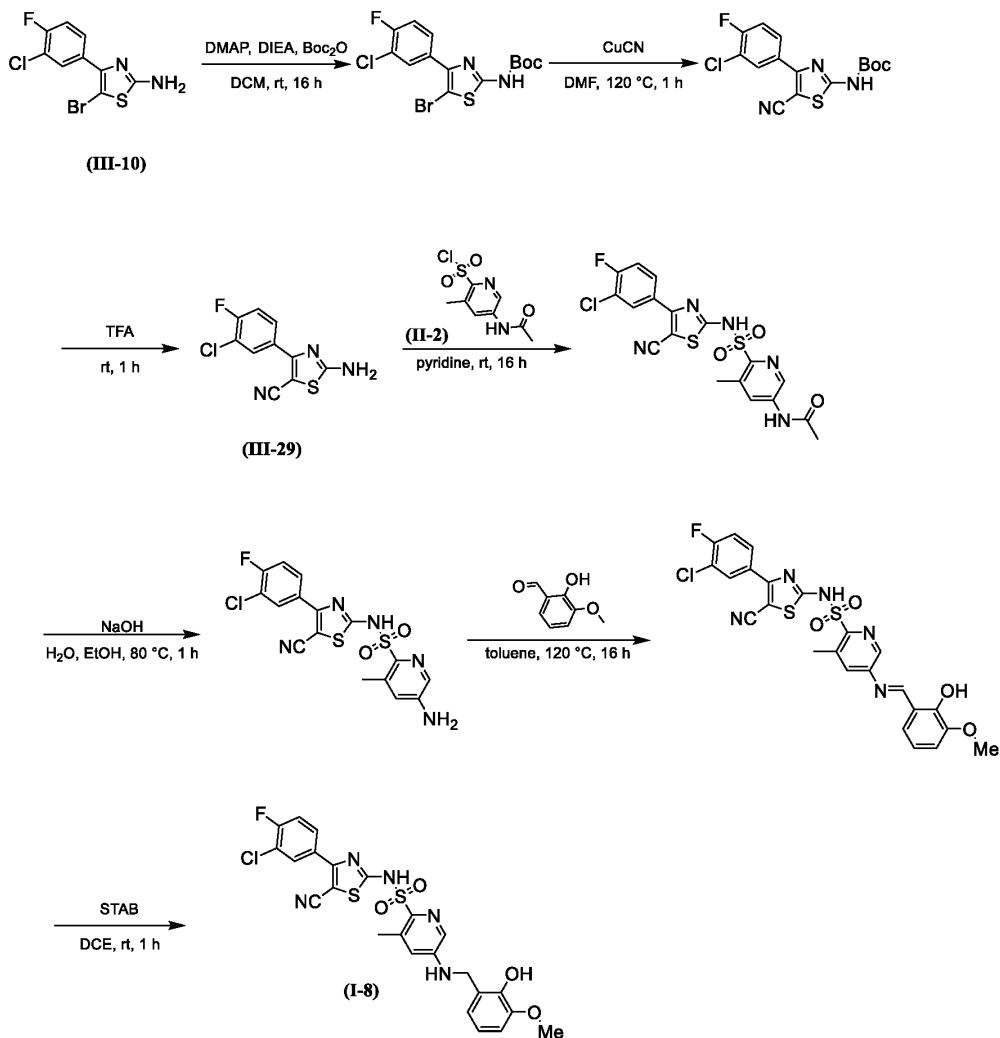


***N*-(4-(3-chloro-4-fluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

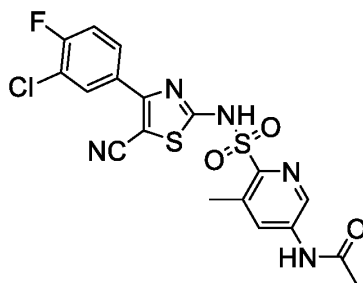
[0350] To a solution of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3-chloro-4-fluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (80 mg, 111.2 μ mol, 1 *eq*) in THF (2 mL)/MeOH (0.5 mL) was added CsF (85 mg, 556 μ mol, 20.5 μ L, 5 *eq*). The mixture was stirred at 20 °C for 1 hr. LCMS showed most of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3-chloro-4-fluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide was consumed. The reaction mixture was then concentrated to give a residue. The residue was purified by SFC (DAICEL CHIRALPAK AS (250 mm $\times$ 30 mm, 10 μ m): CO₂-EtOH, 0.1% NH₃·H₂O) to give *N*-(4-(3-chloro-4-fluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (I-7, 20 mg, 33.1 μ mol, 30% yield) as a yellow solid.

[0351] **Example 39:** Synthesis of *N*-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-8**, Scheme 41).

[0352] Compound **I-8** may be prepared according to Scheme 41:

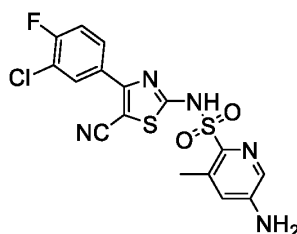


Scheme 41



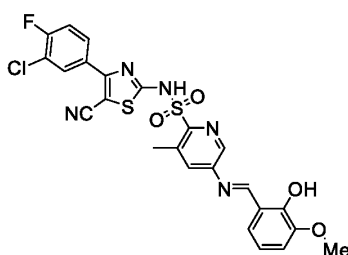
N-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide

[0353] To a mixture of **III-29** (200 mg, 789 μ mol, 1 *eq*; prepared via Scheme 35), 5-acetamido-3-methylpyridine-2-sulfonyl chloride (**II-2**, 392 mg, 1.58 mmol, 2.0 *eq*; prepared via Scheme 4) in pyridine (20 mL) was degassed and purged with N₂ 3 times, then the mixture was stirred at 25 °C for 16hr under an N₂ atmosphere. The reaction mixture was then diluted with H₂O (60 mL) and extracted with EtOAc (60 mL $\times$ 3). The combined organic layers were washed with aqueous NaCl (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12g SepaFlash® Silica Flash Column, Eluent of 0~85% Ethyl acetate/Petroleum ether gradient at 12 mL/min) to give *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (49 mg, 105.2 μ mol, 13% yield) as a red oil.



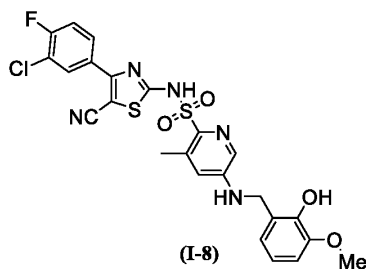
5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0354] To a solution of *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (49 mg, 105 μ mol, 1 *eq*) in H₂O (1 mL) and EtOH (5 mL) was added NaOH (42 mg, 1.05 mmol, 10 *eq*). The mixture was stirred at 80 °C for 16 hr. After this time, LCMS revealed that most of the starting material had been consumed. The reaction mixture was then concentrated under reduced pressure to remove EtOH (5 mL) and was diluted with H₂O (20 mL) and extracted with EtOAc (20 mL $\times$ 2). The combined organic layers were washed with aqueous NaCl (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The filtrate was concentrated to give the crude product 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)-3-methylpyridine-2-sulfonamide (38 mg, 89.65 μ mol, 85% yield) as a yellow solid.



I-N-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0355] To a mixture of 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)-3-methylpyridine-2-sulfonamide (38 mg, 90 μ mol, 1 *eq*) in toluene (3 mL) was added 2-hydroxy-3-methoxybenzaldehyde (15 mg, 99 μ mol, 1.1 *eq*). The mixture was stirred at 120 °C for 16 hr then cooled to 20 °C and concentrated to remove the solvent. The crude product *I*-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (50 mg, 89.6 μ mol, 100% yield) was obtained as a yellow solid and used in the next step without further purification.

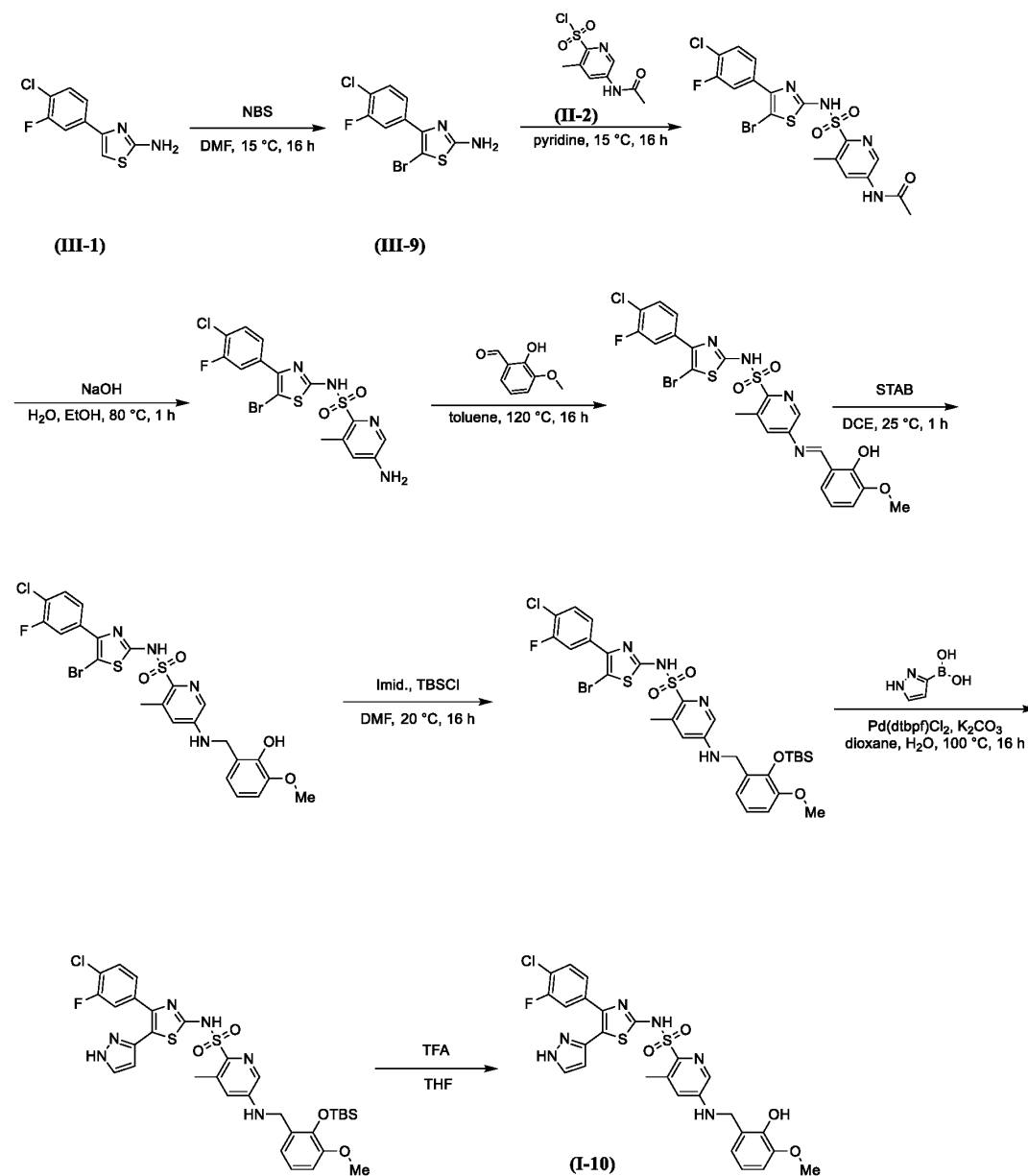


***N*-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

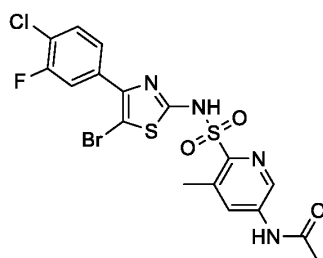
[0356] A solution of *I*-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (50 mg, 90 μ mol, 1 *eq*), NaBH(OAc)₃ (95 mg, 448 μ mol, 5 *eq*) in DCE (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 25 °C for 2 hr under N₂ atmosphere. The reaction mixture was then diluted with H₂O (30 mL) and extracted with EtOAc (30 mL $\times$ 3). The combined organic layers were washed with aqueous NaCl (30 mL $\times$ 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give *N*-(4-(3-chloro-4-fluorophenyl)-5-cyanothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-8**, 2.7 mg, 4.82 μ mol, 5% yield) as a yellow solid.

[0357] **Example 40:** Synthesis of *N*-(4-(4-chloro-3-fluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-10**, Scheme 42).

[0358] Compound **I-10** may be prepared according to Scheme 42:

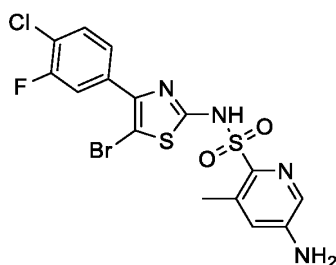


Scheme 42



***N*-(6-(*N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

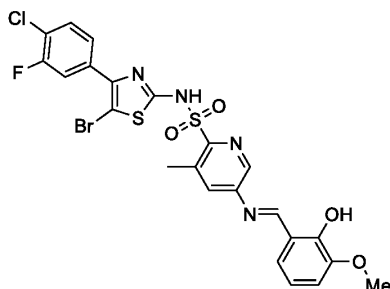
[0359] To a solution of **III-9** (1.61 g, 5.23 mmol, 1.0 *eq*; prepared via Scheme 15) and 5-acetamido-3-methyl-pyridine-2-sulfonyl chloride (**II-2**, 1.3 g, 5.23 mmol, 1.0 *eq*; prepared via Scheme 4) in pyridine (10 mL) was stirred at 15 °C for 16 hr. The reaction mixture was then diluted with H₂O (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with aqueous NaCl (50 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 30/70) to give *N*-(6-(*N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (1 g, 1.92 mmol, 37% yield) as a yellow solid.



5-amino-*N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

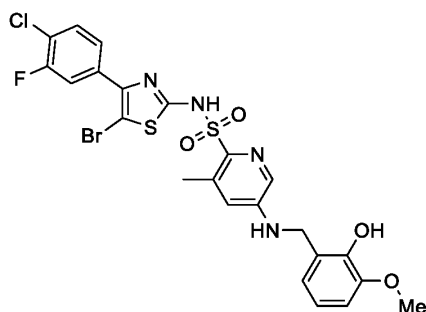
[0360] To a solution of *N*-(6-(*N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (1 g, 1.92 mmol, 1 *eq*) in EtOH (15 mL) and H₂O (5 mL) was added NaOH (770 mg, 19.2 mmol, 10 *eq*). The reaction mixture was stirred at 80 °C for 2hr. The reaction mixture was concentrated under reduced pressure to remove EtOH (15 mL) then it was diluted with H₂O (15 mL) and extracted with EtOAc (20 mL × 2). The combined organic layers were washed with aqueous NaCl (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. 5-amino-*N*-(5-bromo-4-

(4-chloro-3-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (910 mg, 1.90 mmol, 99.01% yield) was obtained as a red solid and used directly in the next step.



(E)-N-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

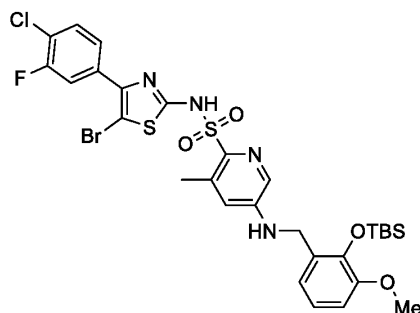
[0361] To a solution of 5-amino-*N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (910 mg, 1.90 mmol, 1 *eq*) in toluene (10 mL) was added 2-hydroxy-3-methoxybenzaldehyde (319 mg, 2.10 mmol, 1.1 *eq*). The mixture was stirred at 120 °C for 16 hr under an N₂ atmosphere. The reaction mixture was then concentrated under reduced pressure to remove toluene (10 mL) and (*E*)-*N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (1.17 g, 1.91 mmol, 100% yield) was obtained as a red solid and used directly in the next step.



***N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide**

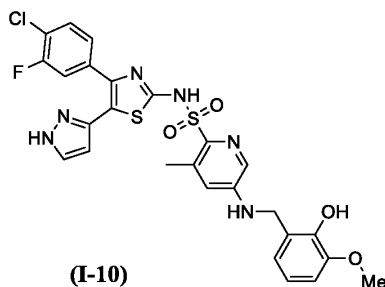
[0362] A mixture of (*E*)-*N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (1.17 g, 1.91 mmol, 1 *eq*), NaBH(OAc)₃ (2.03 g, 9.56 mmol, 5 *eq*) in DCE (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 25 °C for 2hr under an N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to remove EtOH (15 mL) then diluted with H₂O (15 mL) and extracted with EA (20 mL × 2). The combined organic layers were washed

with aqueous NaCl (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient at 50 mL/min) to give *N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (400 mg, 651.6 μmol, 34% yield) as a yellow solid.



***N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-(((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0363] To a solution of *N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (370 mg, 603 μmol, 1 *eq*) in DMF (6 mL) was added TBSCl (500 mg, 3.31 mmol, 408 μL, 5.5 *eq*) and imidazole (144 mg, 2.11 mmol, 3.5 *eq*). The mixture was then stirred at 25 °C for 16hr then diluted with H₂O (20 mL) and extracted with EtOAc (30mL × 2). The combined organic layers were washed with aqueous NaCl (50 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/DCM at 25 mL/min) to give *N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-(((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (370 mg, 508 μmol, 84% yield) as a white solid.

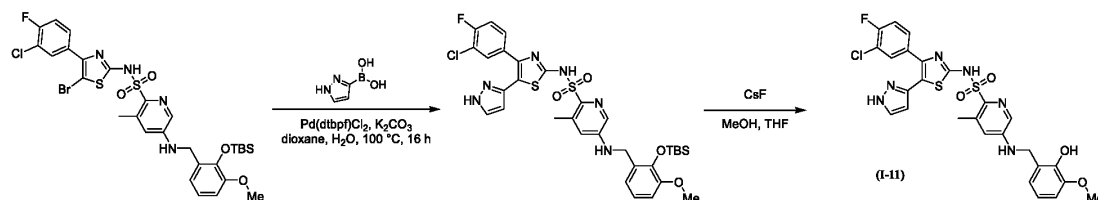


***N*-(4-(4-chloro-3-fluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

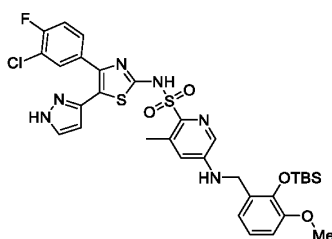
[0364] A mixture of 1*H*-pyrazol-3-ylboronic acid (23.1 mg, 206.0 μ mol, 3 *eq*), *N*-(5-bromo-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (50 mg, 69 μ mol, 1 *eq*) and [2-(2-aminophenyl)phenyl]palladium(1+);dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate (6 mg, 6.9 μ mol, 0.1 *eq*), Cs₂CO₃ (67 mg, 206 μ mol, 3 *eq*) in dioxane (2 mL) and H₂O (0.2 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 90 °C for 16 hr under N₂ atmosphere. LC-MS showed the desired mass. The reaction mixture was diluted with H₂O (10 mL) and extracted with EA (15 mL $\times$ 3). The combined organic layers were washed with aqueous NaCl (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue which was then dissolved in THF and TFA was added (2 *eq.*) and allowed to stir at RT for 2 hr. The resulting residue was purified by prep-HPLC to give *N*-(4-(4-chloro-3-fluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-10**, 2 mg, 3.74 μ mol, 5% yield) as a white solid.

[0365] **Example 41:** Synthesis of *N*-(4-(3-chloro-4-fluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-11**, Scheme 43).

[0366] Compound **I-11** may be prepared according to Scheme 43:

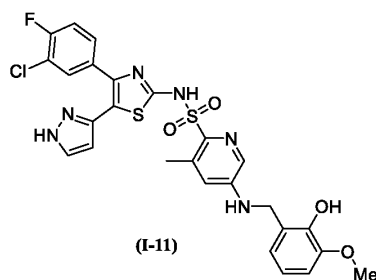


Scheme 43



5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3-chloro-4-fluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0367] A mixture of *N*-(5-bromo-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (100 mg, 137.3 μ mol, 1 *eq*; prepared via Scheme 40), 1*H*-pyrazol-3-ylboronic acid (46 mg, 412 μ mol, 3 *eq*), [2-(2-aminophenyl)phenyl]palladium(1+);dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate (11.6 mg, 13.7 μ mol, 0.1 *eq*), Cs₂CO₃ (134 mg, 412 μ mol, 3 *eq*) in dioxane (2 mL) and H₂O (0.2 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 90 °C for 16 hr under N₂ atmosphere. LC-MS showed the starting material was consumed completely and desired mass was detected. The reaction mixture was diluted with H₂O 20 mL and extracted with EA (20 mL $\times$ 3). The combined organic layers were washed with aqueous NaCl (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3-chloro-4-fluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (21 mg, 29.3 μ mol, 21% yield) as a white solid.

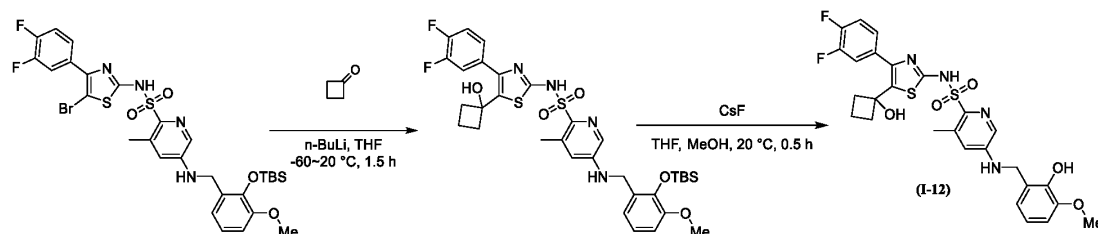


***N*-(4-(3-chloro-4-fluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

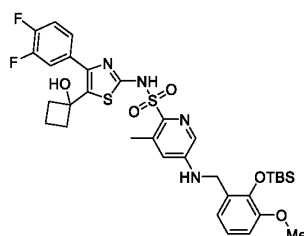
[0368] To a solution of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3-chloro-4-fluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (21 mg, 29.4 μ mol, 1 *eq*) in THF (2 mL) and MeOH (1 mL) was added CsF (22 mg, 147 μ mol, 5.4 μ L, 5 *eq*). The mixture was stirred at 25 °C for 2 hr. LC-MS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove THF (2 mL) and MeOH (1 mL). The residue was purified by prep-HPLC and *N*-(4-(3-chloro-4-fluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-11**, 6 mg, 9.9 μ mol, 33% yield) was obtained as a yellow solid.

[0369] **Example 42:** Synthesis of *N*-(4-(3,4-difluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-12**, Scheme 44).

[0370] Compound **I-12** may be prepared according to Scheme 44:

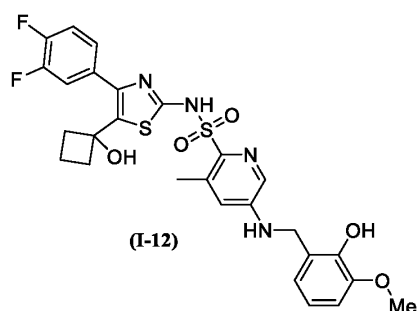


Scheme 44



5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0371] To a solution of *N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (500 mg, 702.53 μ mol, 1.0 *eq*; prepared via Scheme 36) in THF (5 mL) was cooled to -60 °C and added *n*-BuLi (2.5 M, 871 μ L, 3.1 *eq*) slowly under N₂. The mixture was stirred at -60 °C under N₂ for 0.5 h, followed by addition of cyclobutanone (492 mg, 7.03 mmol, 525 μ L, 10 *eq*). The resulting mixture was stirred at 20 °C for an additional 1 hr. LCMS showed evidence of the desired product. The reaction mixture was cooled to 0 °C and a NH₄Cl solution was added slowly, then the mixture was adjusted to pH 5. The resulting mixture was extracted with EtOAc (30 mL $\times$ 2). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give a residue. The resulting residue was purified by prep-HPLC twice to give 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (56 mg, 79.7 μ mol, 11% yield) as a yellow oil.

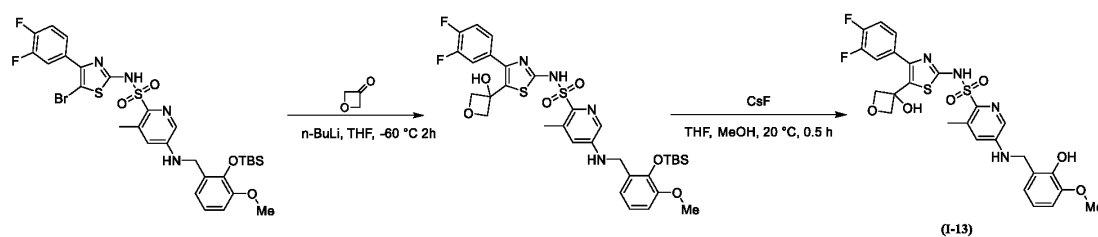


***N*-(4-(3,4-difluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

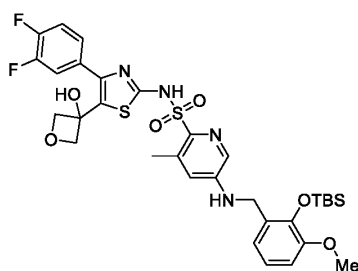
[0372] To a solution of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (56 mg, 79.7 μ mol, 1 *eq*) in THF (0.8 mL)/MeOH (0.2 mL) was added CsF (61 mg, 398 μ mol, 15 μ L, 5 *eq*). The mixture was stirred at 20 °C for 1 hr. LCMS showed that most of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide was consumed, and a main peak with desired product was observed. The reaction mixture was concentrated to give a residue. The residue was purified by prep-HPLC to give *N*-(4-(3,4-difluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-12**, 33 mg, 56.3 μ mol, 71% yield) as a white solid.

[0373] Example 43: Synthesis of *N*-(4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (I-13**, Scheme 45).**

[0374] Compound **I-13** may be prepared according to Scheme 45:

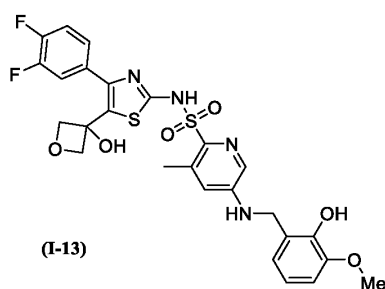


Scheme 45



5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0375] A mixture of *N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (500 mg, 703 μ mol, 1 *eq*; prepared via Scheme 36) in THF (10 mL) was added dropwise *n*-BuLi (2.5 M, 871 μ L, 3.1 *eq*) at -60 °C over 15 min. After addition, the mixture was stirred at this temperature for 30 min, and then oxetan-3-one (506 mg, 7.0 mmol, 10 *eq*) was added dropwise at -60 °C. The resulting mixture was stirred at 20 °C for 30 min. LC-MS showed the starting material was consumed. The reaction mixture was quenched by addition NH₄Cl 50 mL at 25 °C, and then diluted with H₂O (20 mL) and extracted with EA (20 mL $\times$ 3). The combined organic layers were washed with aqueous NaCl (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used directly in the next step. 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (480 mg, 681 μ mol, 97% yield crude) was obtained as a green oil.



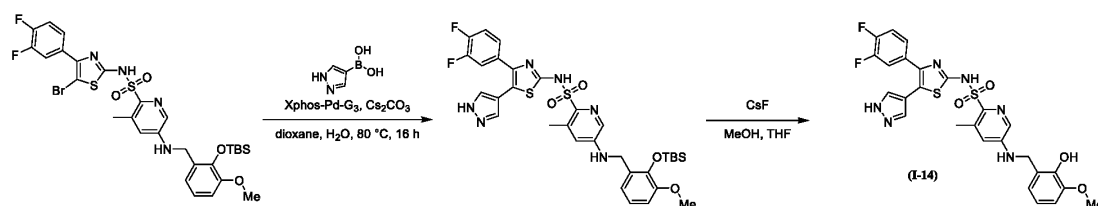
***N*-(4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0376] To a solution of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (450 mg, 638.41 μ mol, 1 *eq*) in THF (6 mL) and MeOH (3 mL) was added cesium fluoride (485 mg, 3.19 mmol, 118 μ L, 5 *eq*). The mixture was stirred at 0.5 °C for 24 hr. LC-MS showed the desired mass was detected. The reaction mixture was concentrated under reduced

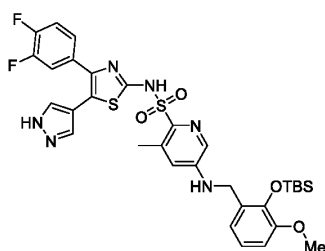
pressure to remove THF (6 mL) and MeOH (3 mL). The residue was purified by prep-HPLC. *N*-(4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-13**, 10 mg, 16.3 μ mol, 3% yield) was obtained as a white solid.

[0377] **Example 44:** Synthesis of *N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-4-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-14**, Scheme 46).

[0378] Compound **I-14** may be prepared according to Scheme 46:

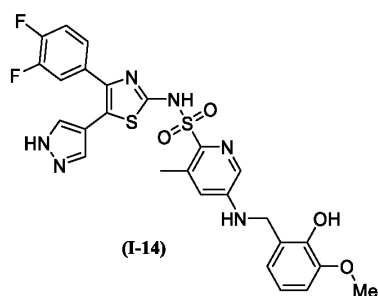


Scheme 46



5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0379] A mixture of 1*H*-pyrazol-4-ylboronic acid (94.33 mg, 843.04 μ mol, 3 *eq*), *N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (200 mg, 281 μ mol, 1 *eq*; prepared via Scheme 36), [2-(2-aminophenyl)phenyl]palladium(1+);dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate (24 mg, 28.1 μ mol, 0.1 *eq*), Cs_2CO_3 (275 mg, 843 μ mol, 3 *eq*) in dioxane (2 mL) and H_2O (0.2 mL) was degassed and purged with N_2 3 times. LC-MS (EH213-734-P1A) showed evidence of the desired product. The reaction mixture was concentrated under reduced pressure to remove dioxane (1 mL). The residue was purified by prep-HPLC to provide 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (25 mg, 35.8 μ mol, 13% yield) as a white solid.

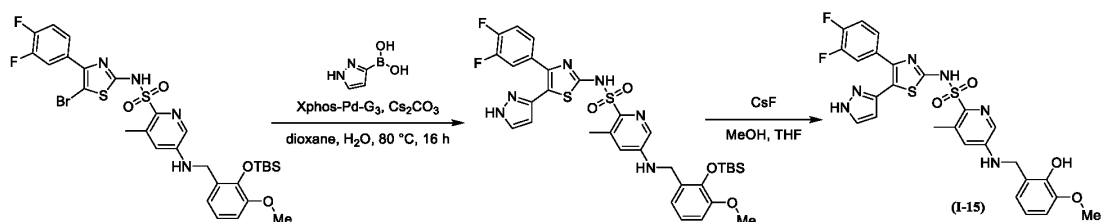


***N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-4-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

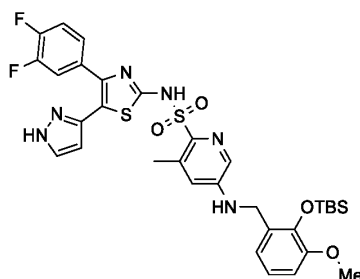
[0380] To a solution of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (25 mg, 36 μ mol, 1 *eq*) in THF (1 mL) and MeOH (0.5 mL) was added cesium fluoride (27 mg, 179 μ mol, 6.6 μ L, 5 *eq*). The reaction mixture was stirred at 0.5 °C for 25 hr at which times the LC-MS showed evidence of the desired mass. The reaction mixture was concentrated under reduced pressure to remove THF (1 mL) and MeOH (0.5 mL). The residue was purified by prep-HPLC to give *N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-4-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-14**, 2.4 mg, 4.1 μ mol, 12% yield) as a white solid.

[0381] Example 45: Synthesis of *N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-15**, Scheme 47).

[0382] Compound **I-15** may be prepared according to Scheme 47:

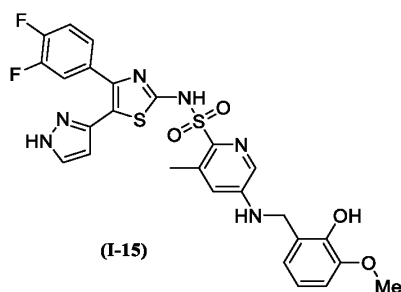


Scheme 47



5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0383] A mixture of 1*H*-pyrazol-3-ylboronic acid (94 mg, 843 μ mol, 3 *eq*), *N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (24 mg, 28.10 μ mol, 0.1 *eq*; prepared via Scheme 36), Cs₂CO₃ (275 mg, 843 μ mol, 3 *eq*) in dioxane (2 mL) and H₂O (0.2 mL) was degassed and purged with N₂ 3 times. LC-MS showed evidence of the desired product. The reaction mixture was concentrated under reduced pressure to remove dioxane (2 mL). The residue was purified by prep-HPLC and 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (120 mg, 172 μ mol, 61% yield) was obtained as a white solid.

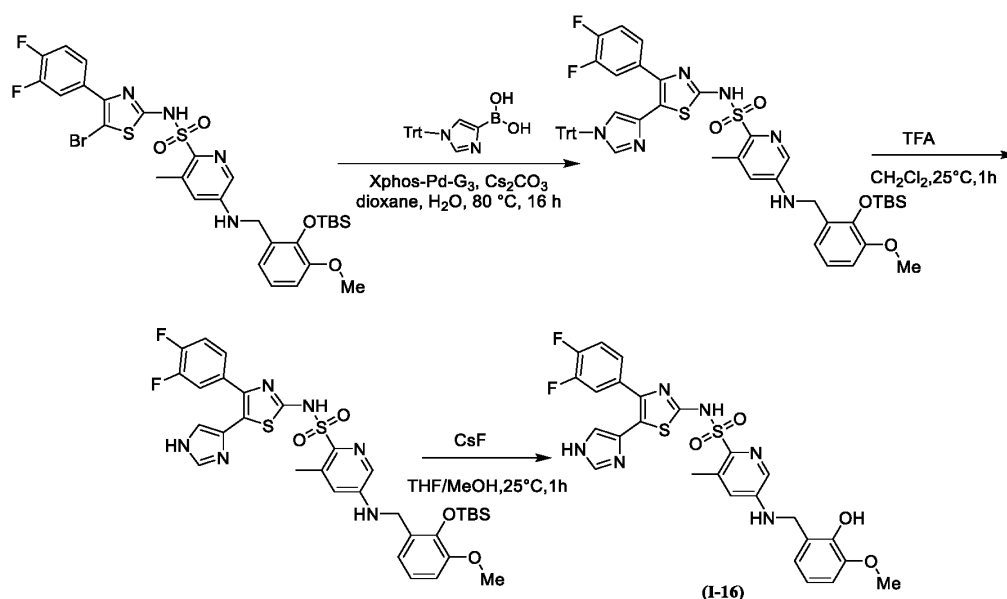


***N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

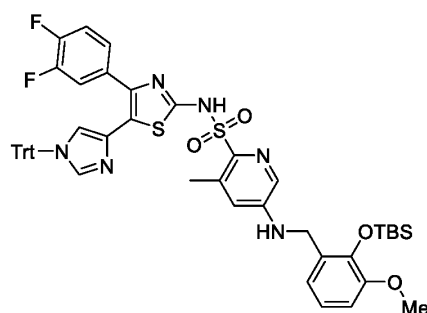
[0384] To a solution of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (120 mg, 172 μ mol, 1 *eq*) in THF (6 mL) and MeOH (3 mL) was added cesium fluoride (130 mg, 859 μ mol, 32 μ L, 5 *eq*). The mixture was stirred at 0.5 °C for 25hr. LC-MS showed the desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove THF (6 mL) and MeOH (3 mL). The residue was purified by prep-HPLC. *N*-(4-(3,4-difluorophenyl)-5-(1*H*-pyrazol-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-15**, 56 mg, 96 μ mol, 56% yield) was obtained as a white solid.

[0385] **Example 46:** Synthesis of *N*-(4-(3,4-difluorophenyl)-5-(1*H*-imidazol-4-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-16**, Scheme 48).

[0386] Compound **I-16** may be prepared according to Scheme 48:



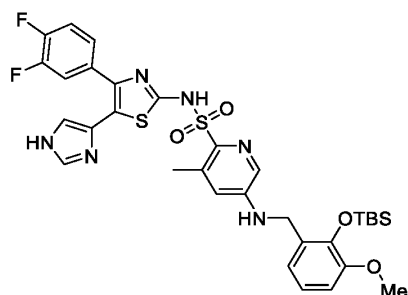
Scheme 48



5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1-*tert*-butyl-1*H*-imidazol-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

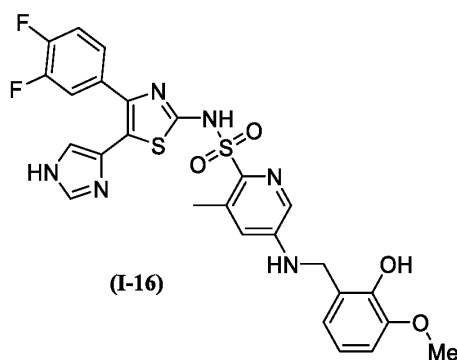
[0387] A mixture of *N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (50 mg, 70.25 μmol , 1 *eq*; prepared via Scheme 36), (1-*tert*-butyl-1*H*-imidazol-4-yl)boronic acid (74.6 mg, 210.8 μmol , 3 *eq*), [2-(2-aminophenyl)phenyl]palladium(1+);dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;methanesulfonate (11.9 mg, 14.05 μmol , 0.2 *eq*), Cs_2CO_3 (68.7 mg, 210.8 μmol , 3 *eq*) in dioxane (1 mL) and H_2O (0.1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 16hr under N_2 atmosphere. LC-MS showed that the starting material was consumed and desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove dioxane (1 mL) and H_2O (0.1 mL). The residue was purified by prep-HPLC. Compound 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1-*tert*-butyl-1*H*-

imidazol-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (28 mg, 29.8 μ mol, 42% yield) was obtained as a white solid.



5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1*H*-imidazol-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0388] A mixture of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1-trityl-1*H*-imidazol-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (28 mg, 29.8 μ mol, 1 *eq*) in CH₂Cl₂ (2 mL) was added TFA (33.9 mg, 297.5 μ mol, 22.1 μ L, 10 *eq*). The mixture was stirred at 25 °C for 2 hr. LC- showed partial consumption of the starting material and desired mass was detected. The reaction mixture was quenched by the addition aqueous NH₄Cl (20 mL) at 25 °C, and then diluted with H₂O 10 mL and extracted with EA 20 mL (20 mL $\times$ 3). The combined organic layers were washed with aqueous NaCl 20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used directly in the next step. 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1*H*-imidazol-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (20 mg, 28.6 μ mol, 96% yield) was obtained as a yellow solid.

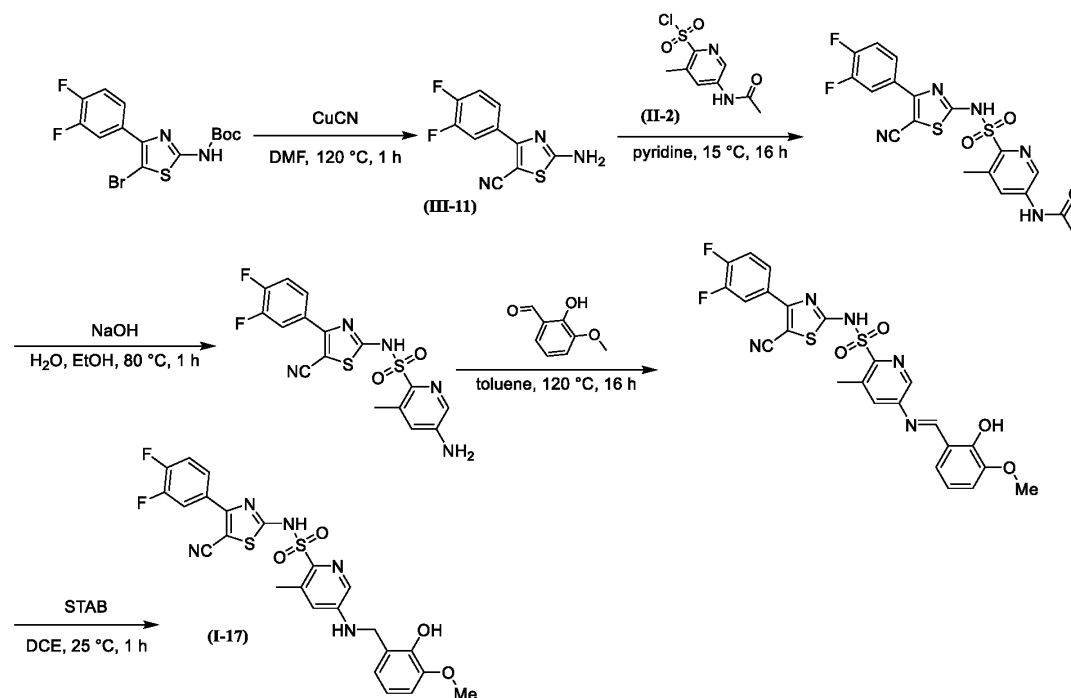


***N*-(4-(3,4-difluorophenyl)-5-(1*H*-imidazol-4-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

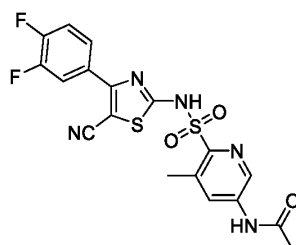
[0389] To a solution of 5-((2-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzyl)amino)-*N*-(4-(3,4-difluorophenyl)-5-(1*H*-imidazol-4-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (20 mg, 28.6 μ mol, 1 *eq*) in THF (2 mL) and MeOH (1 mL) was added cesium fluoride (21.7 mg, 143.1 μ mol, 5.3 μ L, 5 *eq*). The mixture was stirred at 25 °C for 2hr. LC-MS showed the desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove THF (2 mL) and MeOH (1 mL). The residue was purified by prep-HPLC. *N*-(4-(3,4-difluorophenyl)-5-(1*H*-imidazol-4-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-16**, 5 mg, 8.55 μ mol, 30% yield) was obtained as a white solid.

[0390] **Example 47:** Synthesis of *N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-17**, Scheme 49).

[0391] Compound **I-17** may be prepared according to Scheme 49:

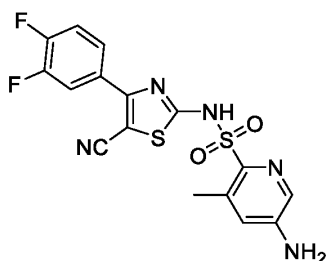


Scheme 49



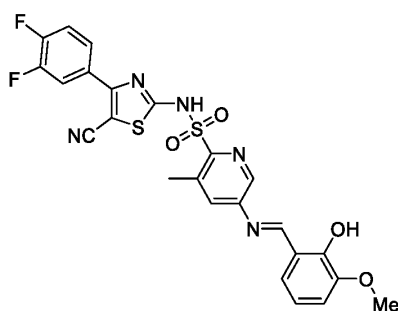
***N*-(6-(*N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

[0392] To a mixture of 2-amino-4-(3,4-difluorophenyl)thiazole-5-carbonitrile (**III-11**, 100 mg, 421.53 μ mol, 1 *eq*; prepared via Scheme 17) and 5-acetamido-3-methylpyridine-2-sulfonyl chloride (**II-2**, 104.83 mg, 421.53 μ mol, 1 *eq*; prepared via Scheme 4) in pyridine (2 mL) was stirred at 15 °C for 16 hr. LCMS showed evidence of the desired product. The reaction mixture was adjusted to pH 4 by addition of 2M HCl and extracted with EtOAc (30 mL $\times$ 2). The combined organic layers were concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 0/100). *N*-(6-(*N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (55 mg, 122.37 μ mol, 29.03% yield) was obtained as a brown solid.



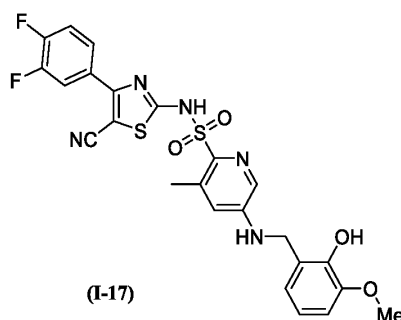
5-amino-*N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0393] To a solution of *N*-(6-(*N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (55 mg, 122 μ mol, 1 *eq*) in EtOH (2 mL)/H₂O (0.4 mL) was added NaOH (200 mg, 5.00 mmol, 41 *eq*). The mixture was stirred at 80 °C for 1 hr. LCMS showed that *N*-(6-(*N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide was mostly consumed. The reaction mixture was concentrated to give a residue. The residue was added H₂O (25 mL) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude product. 5-amino-*N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (38 mg, crude) was obtained as a yellow solid and used in the next step without further purification.



(E)-N-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0394] To a mixture of 2-hydroxy-3-methoxybenzaldehyde (14 mg, 93.27 μmol , 1 *eq*) and 5-amino-*N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (38 mg, 93.27 μmol , 1.0 *eq*) in toluene (4 mL) was heated to 120 °C and stirred for 16 hr. The reaction mixture was cooled to 20 °C and concentrated to remove the solvent. The crude product (*E*)-*N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (45 mg, crude) was obtained as a yellow solid and used directly in the next step without further purification.



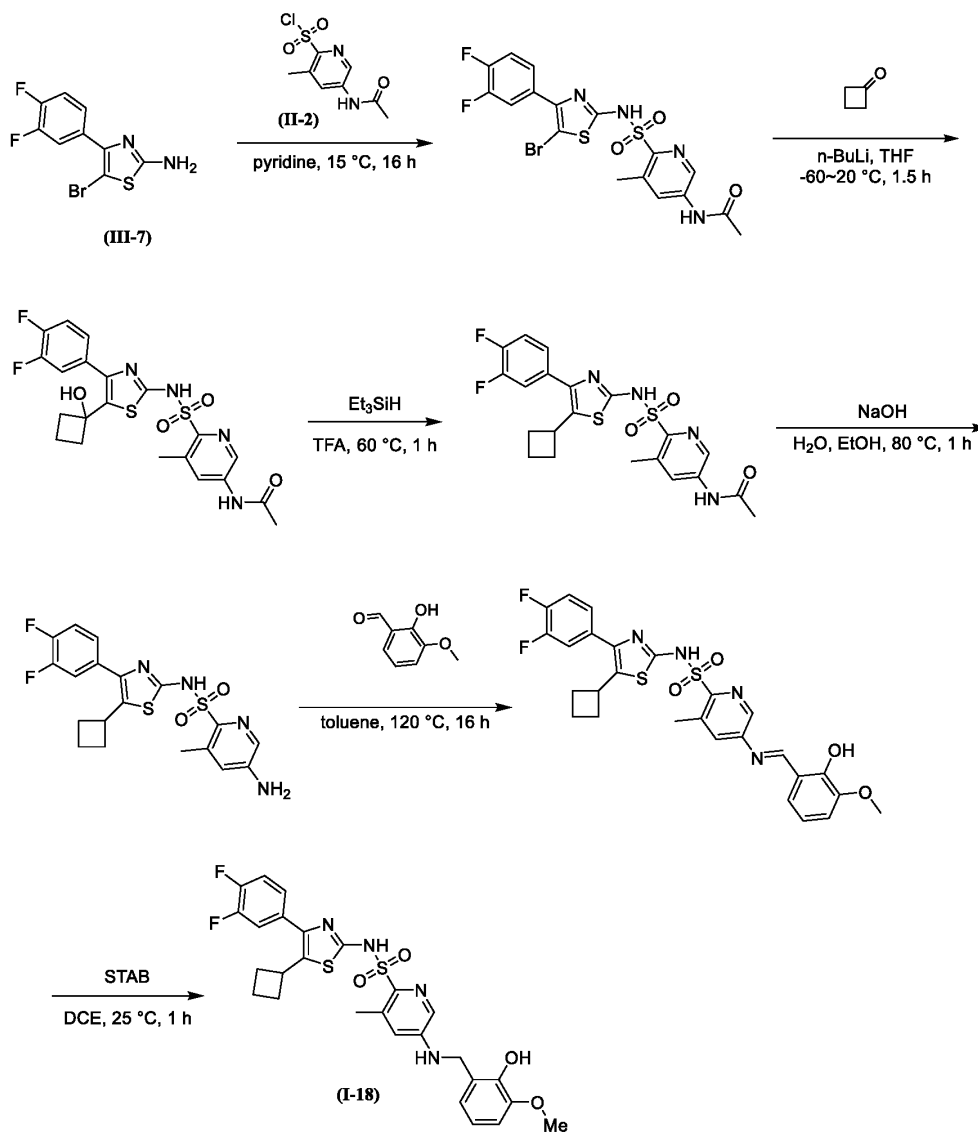
***N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0395] To a solution of (*E*)-*N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (45 mg, 83.09 μmol , 1 *eq*) in DCE (2 mL) was added $\text{NaBH}(\text{OAc})_3$ (88 mg, 416 μmol , 5.0 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed that most of (*E*)-*N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide was consumed. To the reaction mixture was added H_2O (15 mL) and then extracted with EtOAc (20 mL $\times$ 2). The combined organic layers were concentrated to give a crude product. The residue was purified by prep-HPLC. *N*-(5-cyano-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-

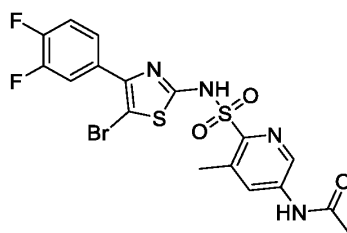
hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-17**, 6 mg, 10.4 μ mol, 13% yield) was obtained as a white solid.

[0396] **Example 48:** Synthesis of *N*-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-18**, Scheme 50).

[0397] Compound **I-18** may be prepared according to Scheme 50:

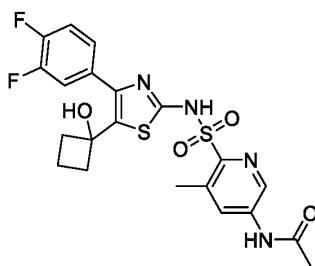


Scheme 50



***N*-(6-(*N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

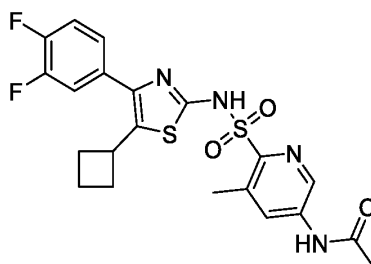
[0398] To a mixture of **III-7** (6.26 g, 21.5 mmol, 1 *eq*; prepared via Scheme 13) and **II-2** (5.35 g, 21.5 mmol, 1.0 *eq*; prepared via Scheme 4) in pyridine (50 mL) was stirred at 15 °C for 16 hr. LCMS showed evidence of the product. To the reaction mixture was added H₂O (200 mL) and it was extracted with EtOAc (120 mL × 2). The combined organic layers were concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 30/70). *N*-(6-(*N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (5.38 g, 10.69 mmol, 50% yield) was obtained as a yellow solid.



***N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

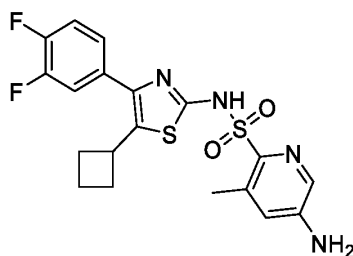
[0399] To a solution of *N*-(6-(*N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (1 g, 1.99 mmol, 1.0 *eq*) in THF (10 mL) was cooled to -60 °C and added *n*-BuLi (2.5 M, 2.46 mL, 3.1 *eq*) slowly under N₂. The mixture was stirred at -60 °C under N₂ for 0.5 h, followed by cyclobutanone (1.39 g, 19.9 mmol, 1.48 mL, 10 *eq*). The resulting mixture was stirred at 20 °C for a further 1 hr. LCMS showed evidence of the desired product. The reaction mixture was cooled to 0 °C and a NH₄Cl solution was added slowly, then the mixture was adjusted to pH 5. The resulting mixture was extracted with EtOAc (30 mL × 2). The combined organic layers were concentrated to give a residue. The residue was purified by column chromatography (SiO₂, DCM/MeOH=100/0 to 90/10). The crude product *N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-

yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (493 mg, crude) was obtained as a yellow solid and used into the next step without further purification.



***N*-(6-(*N*-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

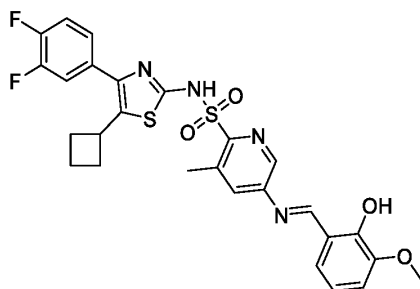
[0400] To a solution of *N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(1-hydroxycyclobutyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (493 mg, 997 μ mol, 1 *eq*) in TFA (5 mL) was added Et₃SiH (348 mg, 3 mmol, 478 μ L, 3 *eq*). The mixture was stirred at 60 °C for 1 hr. LCMS showed evidence of the desired product. The reaction mixture was adjusted to pH 9 by addition of a 2M NaOH solution and extracted with DCM (40 mL $\times$ 2). The combined organic layers were concentrated to give the crude product. The crude product was purified by reversed-phase HPLC. *N*-(6-(*N*-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (430 mg, 899 μ mol, 90% yield) was obtained as a yellow solid.



5-amino-*N*-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

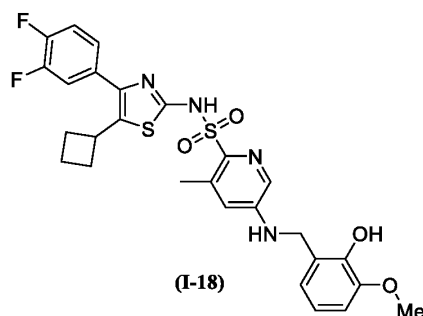
[0401] To a solution of *N*-(6-(*N*-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (50 mg, 105 μ mol, 1 *eq*) in EtOH (2 mL)/H₂O (0.4 mL) was added NaOH (400 mg, 10 mmol, 96 *eq*). The mixture was stirred at 80 °C for 1 hr. LCMS showed that the starting material was nearly completely consumed. The reaction mixture was concentrated to give a residue. The residue was added H₂O (15 mL) and extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude product. The crude product 5-amino-*N*-(5-

cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (41 mg, crude) was obtained as a yellow solid and used in the next step without further purification.



(E)-N-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0402] To a mixture of 2-hydroxy-3-methoxybenzaldehyde (14 mg, 94 μmol , 1 *eq*) and 5-amino-*N*-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (41 mg, 94 μmol , 1.0 *eq*) in toluene (5 mL) was heated to 120 °C and stirred for 16 hr. The reaction mixture was cooled to 20 °C and concentrated to remove the solvent. The crude product (*E*)-*N*-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (53 mg, crude) was obtained as a yellow solid and used in the next step without further purification.



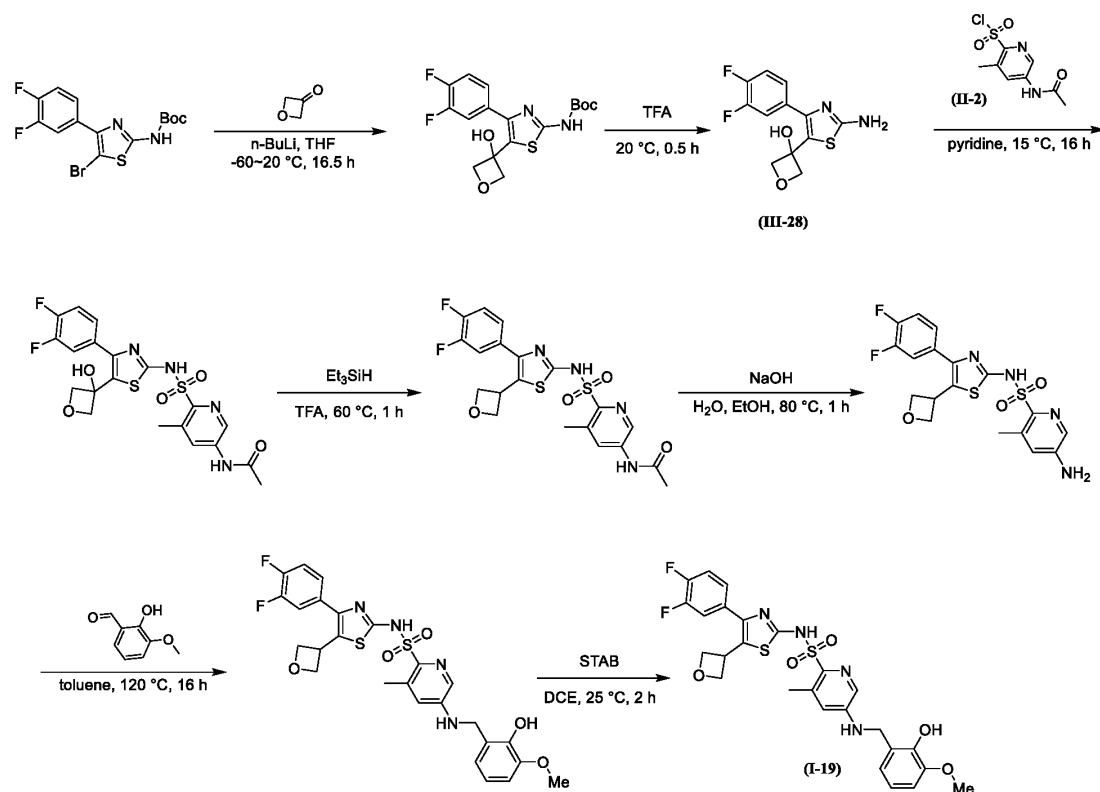
***N*-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0403] To a solution of (*E*)-*N*-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (53 mg, 93 μmol , 1 *eq*) in DCE (2 mL) was added NaBH(OAc)₃ (98 mg, 464 μmol , 5.0 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed most of (*E*)-*N*-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide. To the reaction mixture was added H₂O (15 mL) and it was then extracted with EtOAc (20 mL $\times$ 2). The combined organic layers were concentrated to give a crude

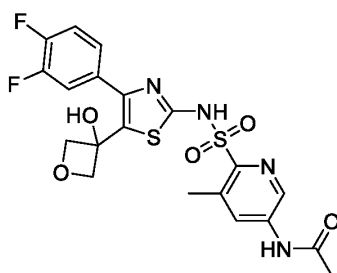
product. The residue was purified by prep-HPLC. *N*-(5-cyclobutyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-18**, 13 mg, 22 μ mol, 24% yield) was obtained as a white solid.

[0404] Example 49: Synthesis of *N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (I-19**, Scheme 51).**

[0405] Compound **I-19** may be prepared according to Scheme 51:



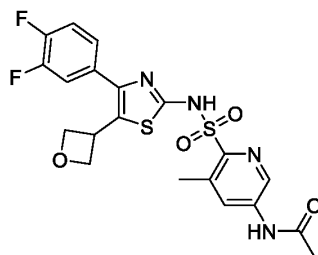
Scheme 51



***N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

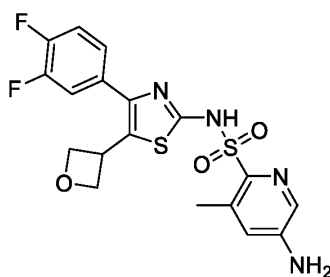
[0406] To a mixture of **III-28** (143 mg, 503.02 μ mol, 1 *eq*; prepared by Scheme 34) and **II-2** (125 mg, 503 μ mol, 1 *eq*; prepared via Scheme 4) in pyridine (2 mL) was stirred at 15 °C for

16 hr. LC-MS showed that most of the starting material had been consumed. The reaction mixture was then adjusted to pH 4 by 2M HCl and extracted with EtOAc (30 mL $\times$ 2). The combined organic layers were concentrated to give a residue. The residue was purified by column chromatography (SiO₂, DCM/MeOH = 100/0 to 90/10) to give *N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (330 mg, crude) as a yellow oil.



***N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

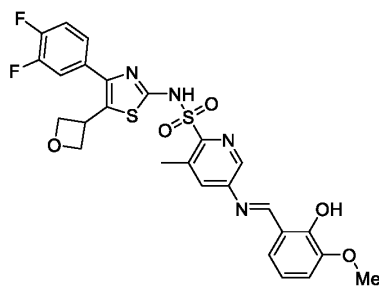
[0407] To a solution of *N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(3-hydroxyoxetan-3-yl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (270 mg, 544 μ mol, 1 *eq*) in TFA (3 mL) was added Et₃SiH (190 mg, 1.63 mmol, 261 μ L, 3 *eq*). The mixture was stirred at 60 °C for 1 hr. LCMS showed evidence of the desired product. The reaction mixture was then diluted with H₂O (30 mL) and extracted with EtOAc (30 mL $\times$ 2). The combined organic layers were concentrated to give the crude product. The residue was purified by column chromatography (SiO₂, DCM/MeOH = 100/0 to 90/10) to give *N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (59 mg, 123 μ mol, 23% yield) as a yellow oil.



5-amino-*N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

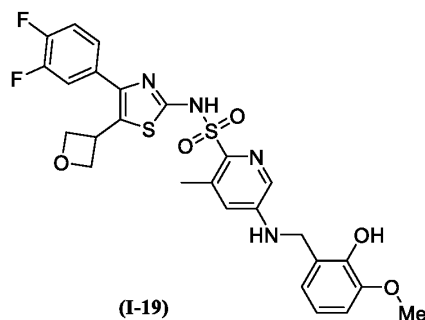
[0408] To a solution of *N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (59 mg, 122.79 μ mol, 1 *eq*) in EtOH (2 mL)/H₂O (0.4 mL) was added NaOH (200 mg, 5.00 mmol, 40.72 *eq*). The mixture was

stirred at 80 °C for 1 hr. LCMS showed evidence of the desired product. The reaction mixture was then concentrated to give a residue. The residue was diluted with H₂O (15 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude product. The crude product 5-amino-*N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (10 mg, 23 μmol, 19% yield) was obtained as a yellow solid and used in the next step without further purification.



(*E*)-*N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0409] To a mixture of 2-hydroxy-3-methoxybenzaldehyde (3.5 mg, 23 μmol, 1 *eq*) and 5-amino-*N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (10 mg, 23 μmol, 1.0 *eq*) in toluene (4 mL) was heated to 120 °C and stirred for 16 hr. The reaction mixture was cooled to 20 °C and concentrated to remove the solvent. The crude product (*E*)-*N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (13 mg, 22.70 μmol, 100% yield) was obtained as a yellow solid and used in the next step without further purification.



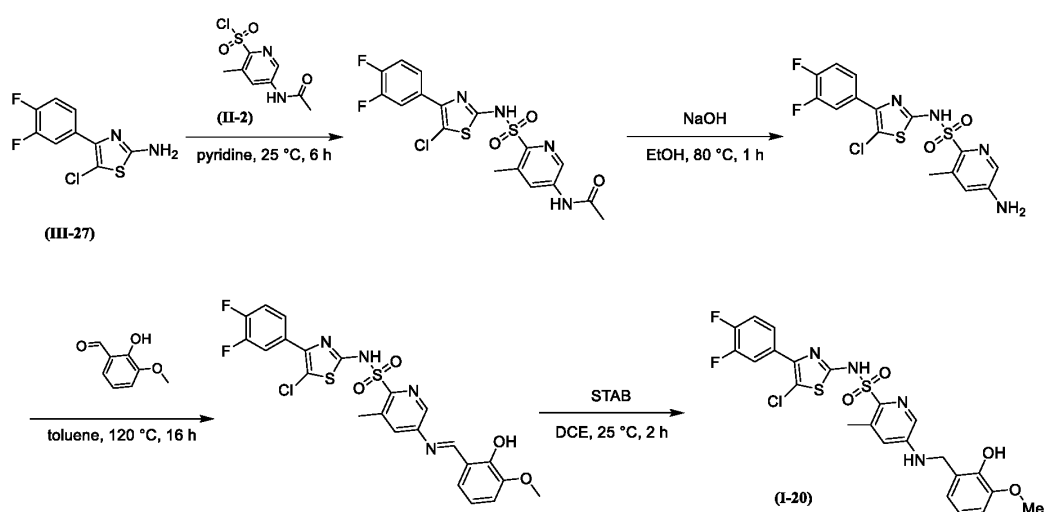
***N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0410] To a solution of (*E*)-*N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (13 mg, 22.7 μmol,

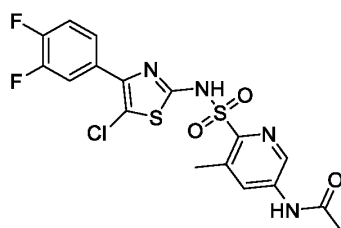
1 *eq*) in DCE (2 mL) was added NaBH(OAc)₃ (24 mg, 114 μmol, 5.0 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS evidence of the desired product. The reaction mixture was diluted with H₂O (15 mL) and extracted with EtOAc (20 mL × 2). The combined organic layers were concentrated to give a crude product. The residue was then purified by prep-HPLC to give *N*-(4-(3,4-difluorophenyl)-5-(oxetan-3-yl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-19**, 3 mg, 5.34 μmol, 24% yield) was obtained as a white solid.

[0411] **Example 50: Synthesis of *N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-20**, Scheme 52).**

[0412] Compound **I-20** may be prepared according to Scheme 52:



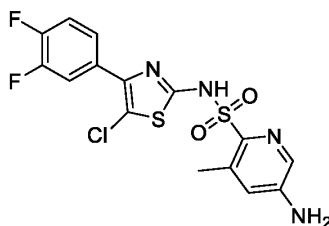
Scheme 52



N-(6-(*N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide

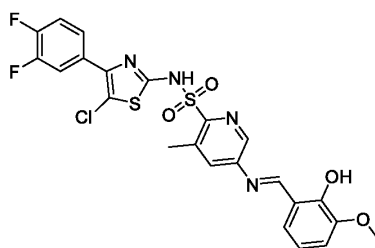
[0413] To a solution of **III-27** (800 mg, 3.24 mmol, 1 *eq*; prepared via Scheme 33) in pyridine (8 mL) was added **II-2** (1.21 g, 4.86 mmol, 1.5 *eq*; prepared via Scheme 4). The mixture was stirred at 25 °C for 6 hr then concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient

at 30 mL/min) to give *N*-(6-(*N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (1.49 g, 3.25 mmol, 100% yield) as a white solid.



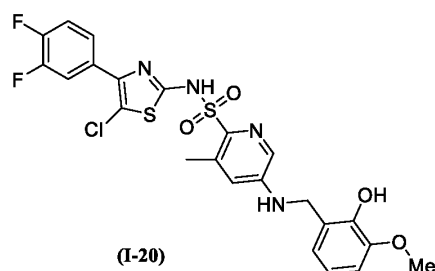
5-amino-*N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0414] To a solution of *N*-(6-(*N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (500 mg, 1.09 mmol, 1 *eq*) in EtOH (5 mL)/H₂O (1 mL) was added NaOH (1 g, 25.0 mmol, 22.94 *eq*). The mixture was stirred at 80 °C for 1 hr then the reaction mixture was concentrated to give a residue. The residue was diluted with H₂O (25 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude product 5-amino-*N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (454 mg, crude) as a red solid and was used in the next step without further purification.



(*E*)-*N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0415] To a mixture of 2-hydroxy-3-methoxybenzaldehyde (55 mg, 360 μmol, 1 *eq*) and 5-amino-*N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (150 mg, 360 μmol, 1 *eq*) in toluene (20 mL) was heated to 120 °C and stirred for 16 hr. The reaction mixture was cooled to 20 °C and concentrated to remove the solvent. The crude product (*E*)-*N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (198 mg, crude) was obtained as a yellow solid and used in the next step without further purification.

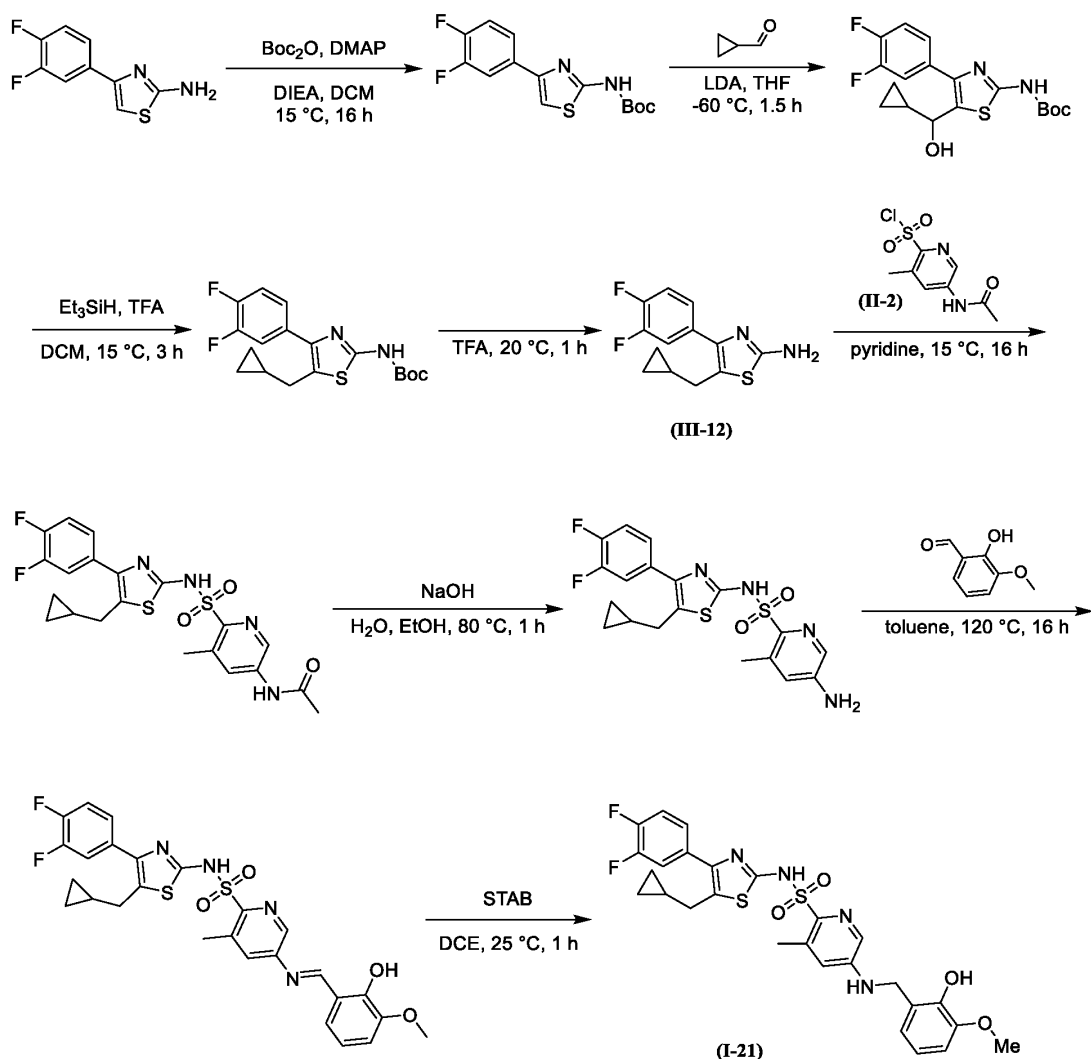


***N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

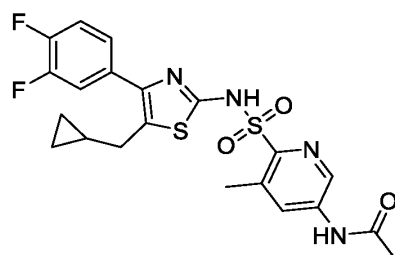
[0416] To a solution of (*E*)-*N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (198 mg, 359 μmol , 1 *eq*) in DCE (2 mL) was added $\text{NaBH}(\text{OAc})_3$ (381 mg, 1.80 mmol, 5.0 *eq*). The mixture was stirred at 25 °C for 2 hr. After this time, the reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (20 mL $\times$ 2). The combined organic layers were concentrated to give a crude product. The residue was purified by prep-HPLC to provide *N*-(5-chloro-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-20**, 62 mg, 112 μmol , 31% yield) as a white solid.

[0417] **Example 51:** Synthesis of *N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-21**, Scheme 53).

[0418] Compound **I-21** may be prepared according to Scheme 53:



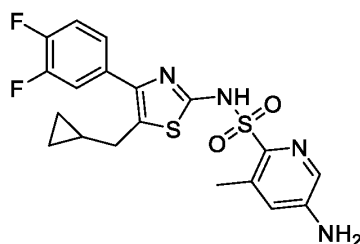
Scheme 53



***N*-(6-(*N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

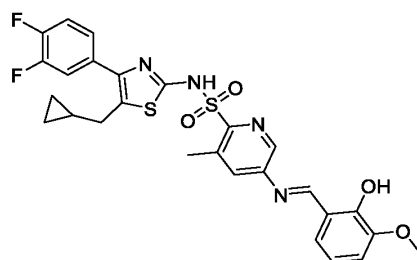
[0419] To a solution of **III-12** (209 mg, 785 μmol , 1 *eq*; prepared via Scheme 18) in pyridine (5 mL) was added 5-acetamido-3-methylpyridine-2-sulfonyl chloride (**II-2**, 253 mg, 1.02 mmol, 1.3 *eq*; prepared via Scheme 4). The mixture was stirred at 25 °C for 16 hr under N_2 .

LC-MS (EH213-668-P1A) showed that the starting material had been consumed and one peak with desired mass was detected. The reaction mixture was diluted with H₂O (50 mL) and extracted with EA (50 mL × 2). The combined organic layers were washed with aqueous NaCl 50 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, prep-TLC (SiO₂, DCM: MeOH = 10:1). *N*-(6-(*N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (370 mg, 773 μmol, 98% yield) was obtained as a yellow solid.



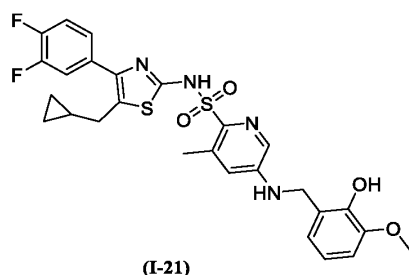
5-amino-*N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0420] To a solution of *N*-(6-(*N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (370 mg, 773 μmol, 1 *eq*) in EtOH (5 mL) and H₂O (1 mL) was added NaOH (309 mg, 7.73 mmol, 10 *eq*). The mixture was stirred at 80 °C for 2 hr. LC-MS showed that product was detected. The reaction mixture was concentrated under reduced pressure to remove EtOH (5 mL). The reaction mixture was diluted with H₂O (10 mL) and extracted with EA (20 mL × 2). The combined organic layers were washed with aqueous NaCl 20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used without further purification in the next step. 5-amino-*N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (300 mg, 687 μmol, 89% yield) was obtained as a yellow solid.



(*E*)-*N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0421] To a solution of 5-amino-*N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (200 mg, 458 μ mol, 1 *eq*) in toluene (5 mL) was added 2-hydroxy-3-methoxybenzaldehyde (77 mg, 504 μ mol, 1.1 *eq*). The mixture was stirred at 120 °C for 16 hr. The mixture was stirred at 25 °C for 16 hr under N₂. The reaction mixture was concentrated under reduced pressure to remove toluene (5 mL). The crude product was then used directly in the next step. (*E*)-*N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (260 mg, 455 μ mol, 99% yield) was obtained as a black solid.

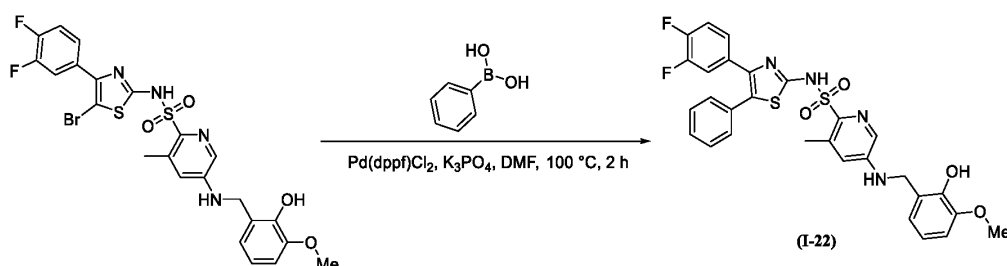


***N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0422] To a solution of (*E*)-*N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (260 mg, 455.64 μ mol, 1 *eq*), NaBH(OAc)₃ (483 mg, 2.28 mmol, 5 *eq*) in DCE (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 25 °C for 2 hr under N₂ atmosphere. LC-MS that the starting material had been consumed and the desired mass was detected. The reaction mixture and then diluted with H₂O (30 mL) and extracted with EA (45 mL $\times$ 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC. *N*-(5-(cyclopropylmethyl)-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-21**, 86 mg, 150 μ mol, 33% yield) was obtained as a yellow solid.

[0423] **Example 52:** Synthesis of *N*-(4-(3,4-difluorophenyl)-5-phenylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-22**, Scheme 54).

[0424] Compound **I-22** may be prepared according to Scheme 54:

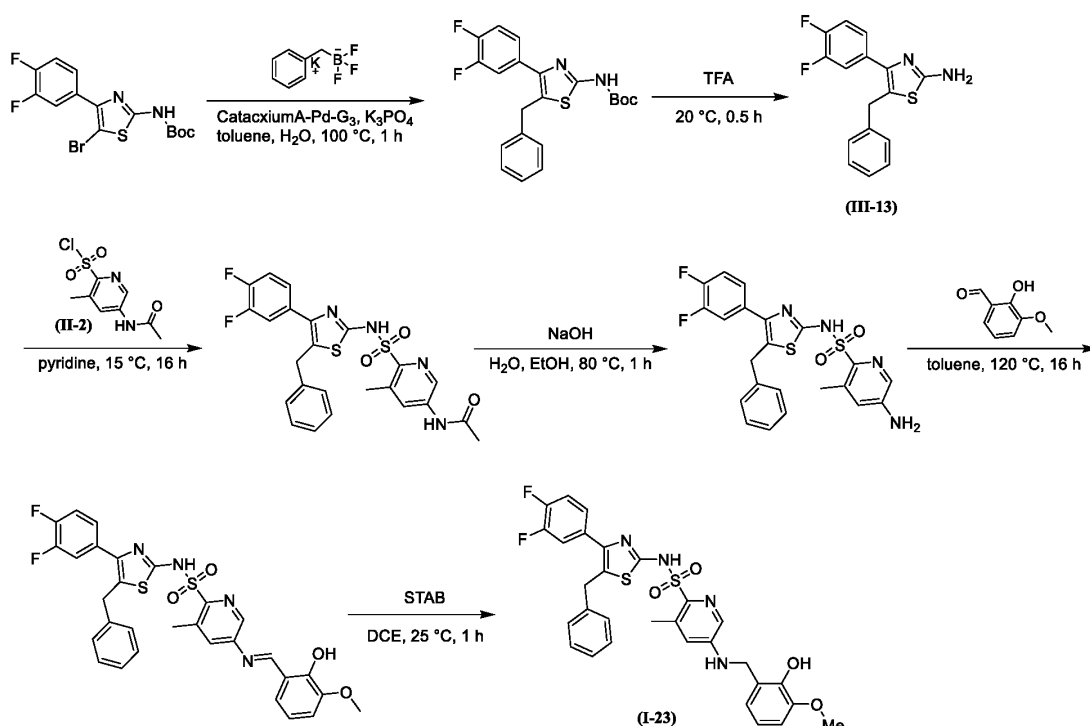


Scheme 54

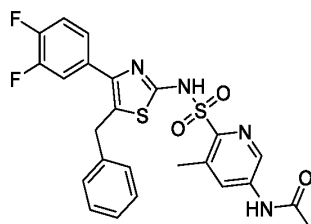
[0425] To a solution of *N*-(5-bromo-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (300 mg, 502 μmol , 1 *eq*; prepared via Scheme 36) and phenylboronic acid (123 mg, 1.00 mmol, 2 *eq*) in DMF (0.5 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (75 mg, 100 μmol , 0.2 *eq*) and K_3PO_4 (1.5 M, 1.00 mL, 3 *eq*). The mixture was stirred at $100\text{ }^\circ\text{C}$ for 2 hr then the reaction mixture was concentrated under reduced pressure to give a residue. The product was further purified by pre HPLC. The resulting residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give the product. *N*-(4-(3,4-difluorophenyl)-5-phenylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (I-22, 29 mg, 46 μmol , 9% yield) was obtained as a white solid.

[0426] **Example 53:** Synthesis of *N*-(5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (I-23, Scheme 55).

[0427] Compound I-23 may be prepared according to Scheme 55:



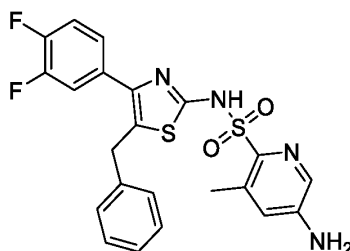
Scheme 55



***N*-(6-(*N*-(5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

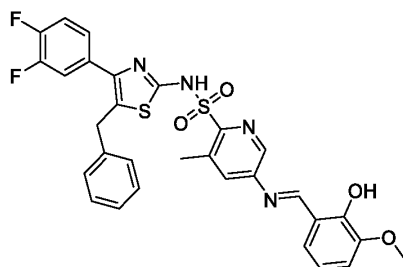
[0428] To a solution of **II-2** (123 mg, 496 μ mol, 1.25 *eq*, prepared via Scheme 4) in pyridine (3 mL) was added **III-13** (120 mg, 397 μ mol, 1 *eq*, prepared via Scheme 19). The mixture was stirred at 25 °C for 16 hr under N₂. LC-MS showed that the starting material was mostly consumed and one peak with desired mass was detected. The reaction mixture was diluted with H₂O (30 mL) and extracted with EA (30 mL $\times$ 2). The combined organic layers were washed with aqueous NaCl (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, prep-TLC (SiO₂, DCM: MeOH = 8:1). *N*-(6-(*N*-(5-benzyl-4-(3,4-

difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (120 mg, 233 μ mol, 59% yield) was obtained as a yellow solid.



5-amino-N-(5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

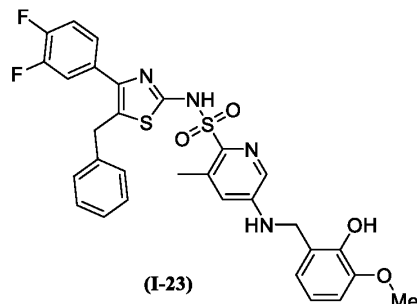
[0429] To a solution of *N*-(6-(*N*-(5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (120 mg, 233 μ mol, 1 *eq*) in EtOH (5 mL) and H₂O (1 mL) was added NaOH (93 mg, 2.33 mmol, 10 *eq*). The mixture was stirred at 80 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove EtOH (5 mL). The reaction mixture was diluted with H₂O (10 mL) and extracted with EA (20 mL $\times$ 2). The combined organic layers were washed with aqueous NaCl (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used in the next step without further purification. 5-amino-*N*-(5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (100 mg, 212 μ mol, 91% yield) was obtained as a yellow solid.



(*E*)-N-(5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0430] To a solution of 5-amino-*N*-(5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (100 mg, 212 μ mol, 1 *eq*) in toluene (5 mL) was added 2-hydroxy-3-methoxybenzaldehyde (39 mg, 254 μ mol, 1.2 *eq*). The mixture was stirred at 25 °C for 16 hr under N₂. The reaction mixture was concentrated under reduced pressure to remove toluene (5 mL). The crude product was used in the next step without further

purification. (*E*)-*N*-(5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (128 mg, 211 μ mol, 99 % yield) was obtained as a black solid.

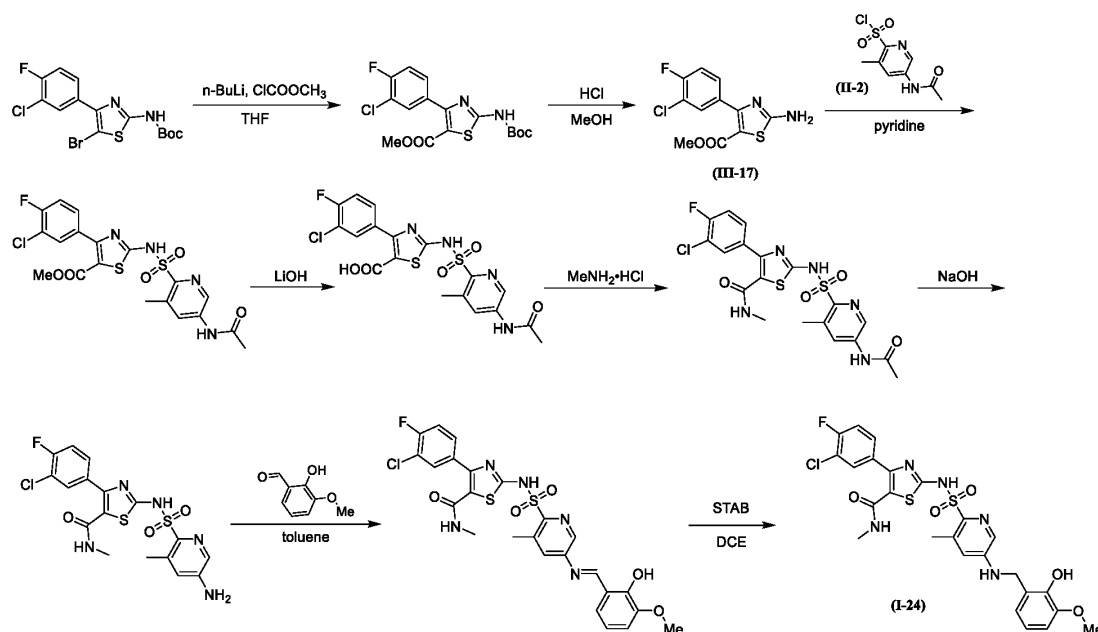


***N*-(5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

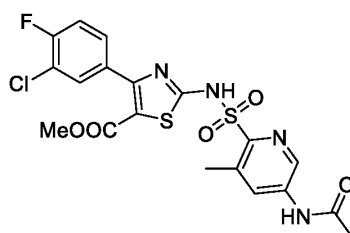
[0431] To a solution of (*E*)-*N*-(5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (128 mg, 211 μ mol, 1 *eq*), NaBH(OAc)₃ (224 mg, 1.05 mmol, 5 *eq*) in DCE (3 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 25 °C for 2 hr under N₂ atmosphere. LC-MS showed desired mass was detected. The reaction mixture was then diluted with H₂O (20 mL) and extracted with EA (25 mL $\times$ 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC. *N*-(5-benzyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-23**, 21 mg, 34.5 μ mol, 16% yield) was obtained as a white solid.

[0432] Example 54: Synthesis of 4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamido)-*N*-methylthiazole-5-carboxamide (**I-24**, Scheme 56).

[0433] Compound **I-24** may be prepared according to Scheme 56:

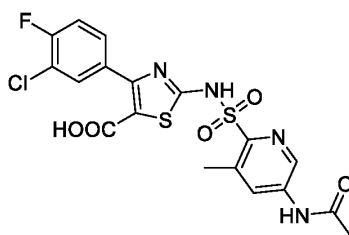


Scheme 56



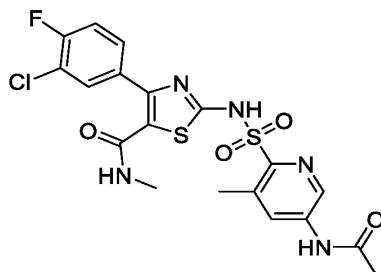
Methyl 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylate

[0434] To a solution of **III-17** (2.29 g, 7.99 mmol, 1 *eq*; prepared via Scheme 23) in pyridine (20 mL) was added 5-acetamido-3-methylpyridine-2-sulfonyl chloride (2.48 g, 9.98 mmol, 1.25 *eq*). The mixture was stirred at 25 °C for 16 hr under N_2 . LC-MS showed the starting material was consumed and one peak with desired mass was detected. The reaction mixture was diluted with H_2O 100 mL and extracted with EA (100 mL $\times$ 2). The combined organic layers were washed with aqueous NaCl 80 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , prep-TLC (SiO_2 , DCM: MeOH = 10:1). Methyl 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylate (2.0 g, 4.01 mmol, 50% yield) was obtained as a yellow solid.



2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylic acid

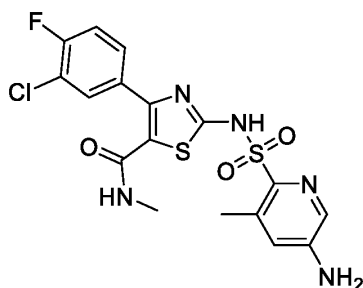
[0435] To a solution of methyl 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylate (500 mg, 1.0 mmol, 1 *eq*) in MeOH (5 mL) and H₂O (1 mL) was added LiOH (120 mg, 5.01 mmol, 5 *eq*). The mixture was stirred at 25 °C for 16 hr. LC-MS the starting material was completely consumed and one peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove MeOH (5 mL). The residue was added 3N HCl and the pH was adjusted to 6 and extracted with EA (10 mL). The combined organic layers were washed with aqueous NaCl (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used directly in the next step. 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylic acid (485 mg, 1.00 mmol, 99.8% yield) was obtained as a yellow solid.



2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-N-methylthiazole-5-carboxamide

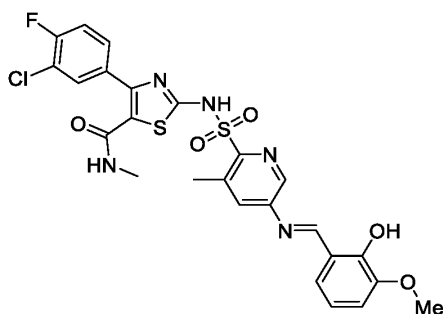
[0436] To a solution of 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylic acid (160 mg, 323 μmol, 1 *eq*) in DMF (1 mL) was added DIEA (213 mg, 1.65 mmol, 287 μL, 5 *eq*) and then HATU (188 mg, 494.9 μmol, 1.5 *eq*) and was added methanamine-hydrochloride (55.7 mg, 824.9 μmol, 2.5 *eq*) at 0°C. The mixture was stirred at 25 °C for 16 hr under N₂. LC-MS showed the starting material was consumed and one peak with desired mass was detected. The reaction mixture was extracted with EA 20 mL. The combined organic layers were washed with aqueous NaCl 20 mL (20 mL × 3), dried

over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC. 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-*N*-methylthiazole-5-carboxamide (32 mg, 64.3 μmol, 19% yield) was obtained as a white solid.



2-((5-amino-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-*N*-methylthiazole-5-carboxamide

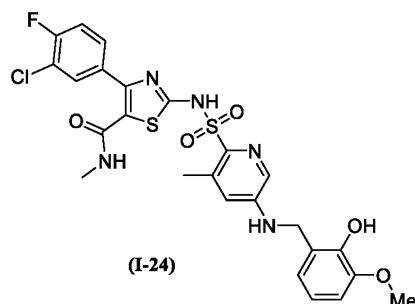
[0437] To a solution of 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-*N*-methylthiazole-5-carboxamide (32 mg, 64.3 μmol, 1 *eq*) in EtOH (3 mL) and H₂O (0.6 mL) was added NaOH (165 mg, 4.11 mmol, 64 *eq*). The mixture was stirred at 80 °C for 2 hr. LC-MS showed the starting material was completely consumed and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove EtOH (3 mL). The residue was diluted with H₂O (10 mL) and extracted with EA (10 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used directly in the next step without further purification. 2-((5-amino-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-*N*-methylthiazole-5-carboxamide (22 mg, 48.3 μmol, 75% yield) was obtained as a red solid.



(*E*)-4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine)-2-sulfonamido)-*N*-methylthiazole-5-carboxamide

[0438] A mixture of 2-((5-amino-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-*N*-methylthiazole-5-carboxamide (22 mg, 48.3 μmol, 1 *eq*) and 2-hydroxy-3-

methoxybenzaldehyde (8.8 mg, 57.91 μmol , 1.2 *eq*) in toluene (2 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 $^\circ\text{C}$ for 16 hr under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove toluene (2 mL). The crude product was used directly in the next step. (*E*)-4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine)-2-sulfonamido)-*N*-methylthiazole-5-carboxamide (28 mg, 47 μmol , 98% yield) was obtained as a red solid.

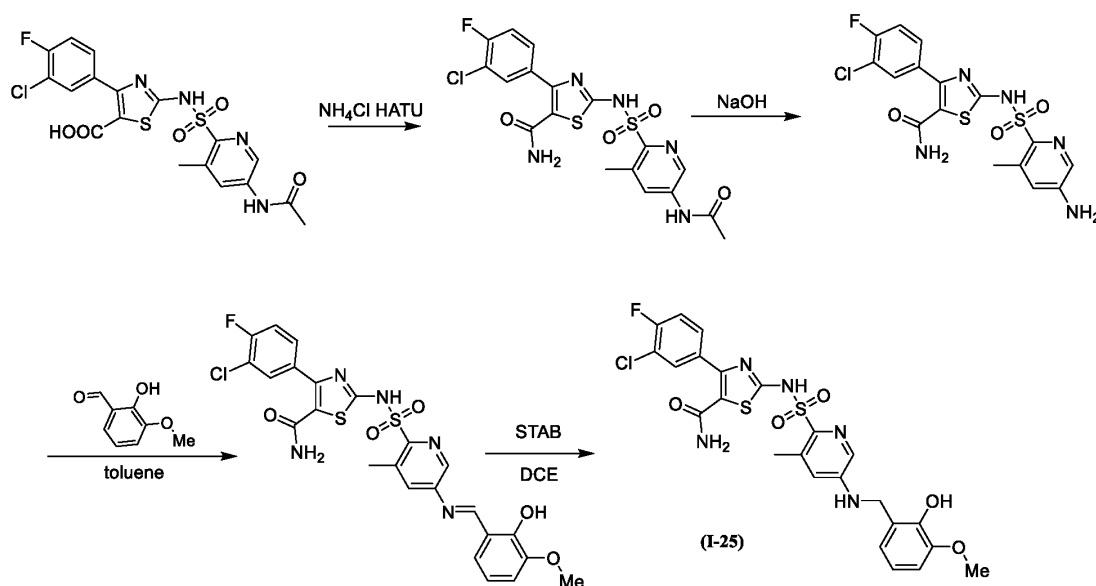


4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine)-2-sulfonamido)-*N*-methylthiazole-5-carboxamide

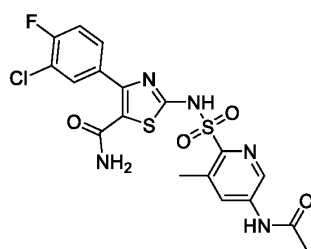
[0439] To a solution of (*E*)-4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine)-2-sulfonamido)-*N*-methylthiazole-5-carboxamide (28 mg, 47 μmol , 1 *eq*) in DCE (5 mL) was added $\text{NaBH}(\text{OAc})_3$ (30 mg, 142 μmol , 3 *eq*). The mixture was stirred at 25 $^\circ\text{C}$ for 2 hr under N_2 atmosphere. LC-MS showed desired mass was detected. The reaction mixture was diluted with H_2O 10 mL and extracted with EA (10 mL $\times$ 2). The combined organic layers were washed with aqueous NaCl 20 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition). 4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine)-2-sulfonamido)-*N*-methylthiazole-5-carboxamide (**I-24**, 3.1 mg, 5.20 μmol , 11% yield) was obtained as a white solid.

[0440] **Example 55:** Synthesis of 4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine)-2-sulfonamido)thiazole-5-carboxamide (**I-25**, Scheme 57).

[0441] Compound **I-25** may be prepared according to Scheme 57:

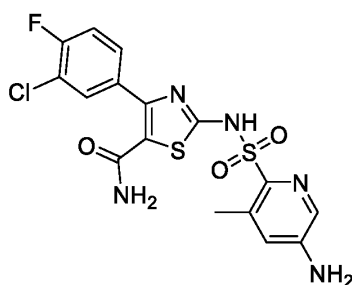


Scheme 57



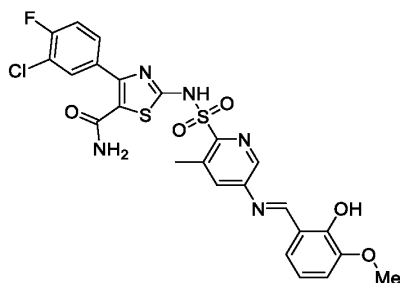
2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxamide

[0442] To a solution of 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylic acid (130 mg, 268 μmol , 1 *eq*; prepared via Scheme 56) in DMF (2 mL) was added DIEA (173 mg, 1.34 mmol, 233 μL , 5 *eq*) and NH_4Cl (36 mg, 670 μmol , 2.5 *eq*) and then HATU (153 mg, 402 μmol , 1.5 *eq*) was added at 0°C. The mixture was stirred at 25 °C for 16 hr under N_2 . LC-MS showed that the starting material was consumed and one peak with desired mass was detected. The reaction mixture was extracted with EA 20 mL. The combined organic layers were washed with aqueous NaCl 50 mL (50 mL $\times$ 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , DCM/MeOH $v/v = 99/1$ to 5/1). 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxamide (95 mg, 196. μmol , 73% yield) was obtained as a white solid.



2-((5-amino-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxamide

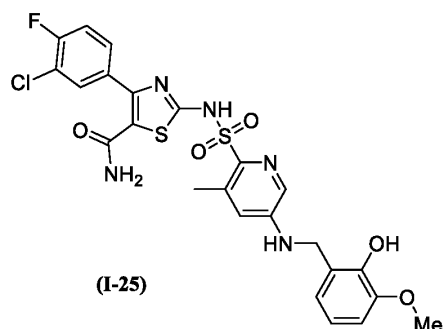
[0443] To a solution of 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxamide (95 mg, 196 μmol , 1 *eq*) in EtOH (3 mL) and H₂O (1 mL) was added NaOH (39 mg, 982 μmol , 5 *eq*). The mixture was stirred at 80 °C for 2 hr. TLC indicated starting material was consumed and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove EtOH (3 mL). The residue was diluted with H₂O (10 mL) and extracted with EA (10 mL $\times$ 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used directly in the next step. 2-((5-amino-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxamide (80 mg, 181 μmol , 92% yield) was obtained as a red solid.



(E)-4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine)-2-sulfonamido)thiazole-5-carboxamide

[0444] A mixture of 2-((5-amino-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxamide (80 mg, 181. μmol , 1 *eq*) and 2-hydroxy-3-methoxybenzaldehyde (33 mg, 217 μmol , 1.2 *eq*) in toluene (2 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 120 °C for 16 hr under N₂ atmosphere. The reaction mixture was then concentrated under reduced pressure to remove toluene (2 mL) and the crude product was used directly in the next step. (E)-4-(3-chloro-4-fluorophenyl)-2-

((5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine)-2-sulfonamido)thiazole-5-carboxamide (104 mg, 181 μ mol, 99% yield) was obtained as a red solid.

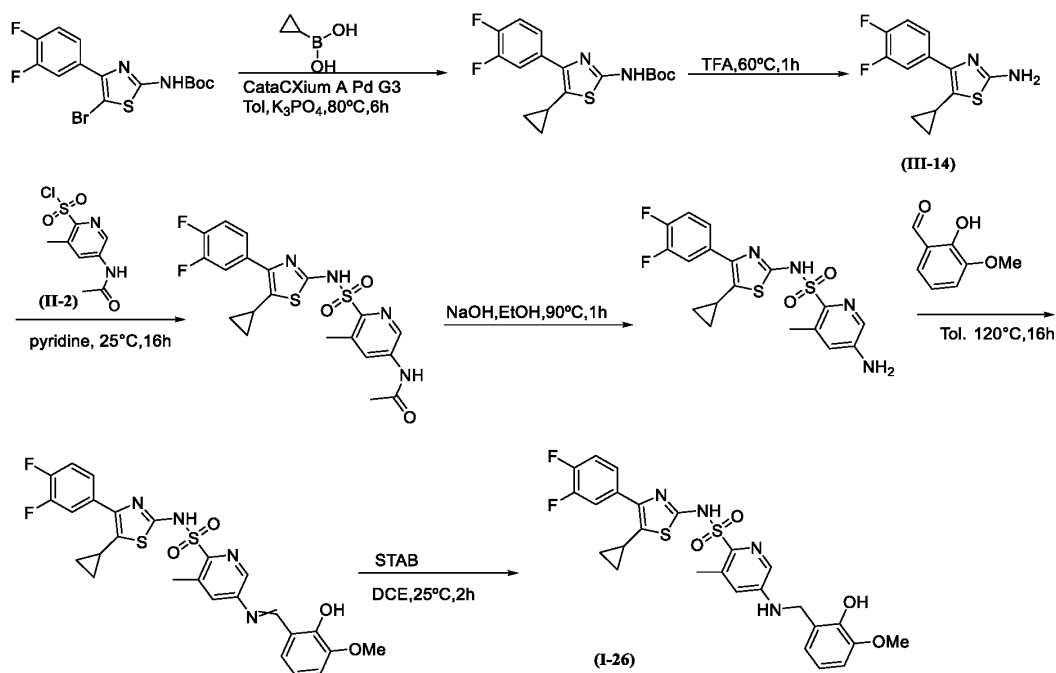


4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine)-2-sulfonamido)thiazole-5-carboxamide

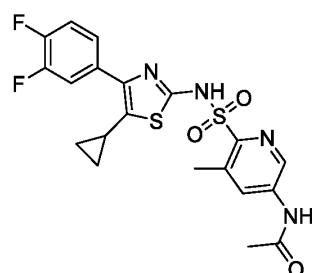
[0445] To a solution of (*E*)-4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine)-2-sulfonamido)thiazole-5-carboxamide (104 mg, 181 μ mol, 1 *eq*) in DCE (5 mL) was added NaBH(OAc)₃ (115 mg, 541.7 μ mol, 3 *eq*). The mixture was stirred at 25 °C for 2 hr under N₂ atmosphere. LC-MS showed desired mass was detected. The reaction mixture was then diluted with H₂O (20 mL) and extracted with EA (20 mL $\times$ 2). The combined organic layers were washed with aqueous NaCl 20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition). 4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine)-2-sulfonamido)thiazole-5-carboxamide (**I-25**, 3 mg, 4.26 μ mol, 2% yield) was obtained as a white solid.

[0446] Example 56: Synthesis of *N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-26**, Scheme 58).

[0447] Compound **I-26** may be prepared according to Scheme 58:

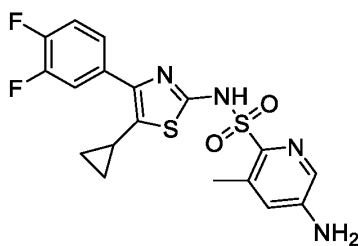


Scheme 58



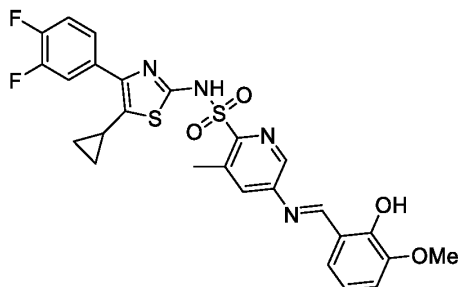
***N*-(6-(*N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

[0448] To a solution of **II-2** (686 mg, 2.76 mmol, 1.2 *eq*; prepared via Scheme 4) in pyridine (10 mL) was added **III-14** (580 mg, 2.30 mmol, 1 *eq*; prepared via Scheme 20). The mixture was stirred at 25 °C for 16 hr under N₂. LC-MS showed evidence of the desired product. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers were washed with aqueous NaCl (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~15% MeOH/DCM at 25 mL/min) to give *N*-(6-(*N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (760 mg, 1.64 mmol, 71% yield) as a yellow solid.



5-amino-*N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

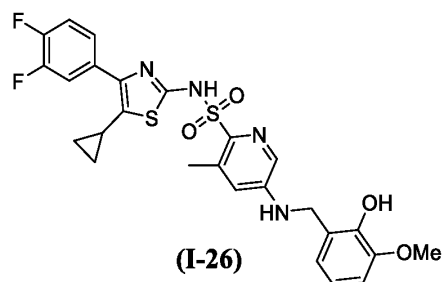
[0449] To a solution of *N*-(6-(*N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (760 mg, 1.64 mmol, 1 *eq*) in EtOH (5 mL) and H₂O (1 mL) was added NaOH (654.46 mg, 16.36 mmol, 10 *eq*). The mixture was stirred at 80 °C for 2 hr. LC-MS showed near complete consumption of the starting material. The reaction mixture was then concentrated under reduced pressure to remove EtOH (5 mL). The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (20 mL × 2). The combined organic layers were washed with aqueous NaCl (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The crude product was used directly in the next step. 5-amino-*N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (510 mg, 1.21 mmol, 74% yield) was obtained as a yellow solid.



(*E*)-*N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0450] To a solution of 5-amino-*N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (510 mg, 1.21 mmol, 1 *eq*) in toluene (5 mL) was added 2-hydroxy-3-methoxybenzaldehyde (202 mg, 1.33 mmol, 1.1 *eq*). The mixture was stirred at 25 °C for 16 hr under N₂. The reaction mixture was then concentrated under reduced pressure to remove toluene (5 mL). The crude product (*E*)-*N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-

2-sulfonamide (670 mg, 1.20 mmol, 100% yield) was obtained as a black solid and used directly in the next reaction without further purification.

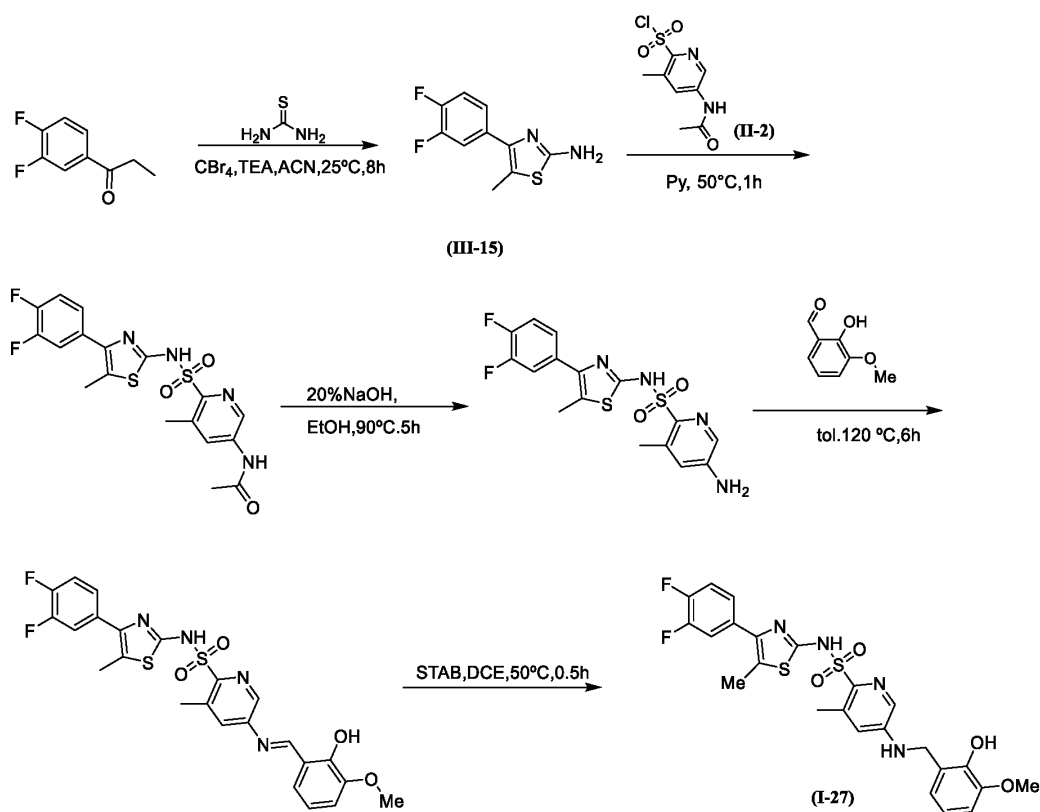


***N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

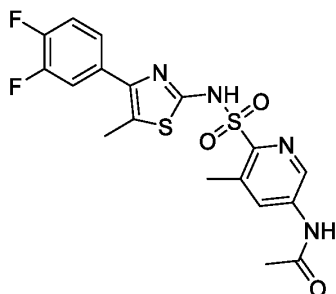
[0451] A solution of (*E*)-*N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (670 mg, 1.20 mmol, 1 *eq*), NaBH(OAc)₃ (1.28 g, 6.02 mmol, 5 *eq*) in DCE (10 mL) was degassed and purged with N₂ 3 times, then the mixture was stirred at 25 °C for 2 hr under N₂ atmosphere. LC-MS showed evidence of the desired product. The reaction mixture was then diluted with H₂O (30 mL) and extracted with EtOAc (45 mL × 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give *N*-(5-cyclopropyl-4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-26**, 301 mg, 504 μmol, 42% yield) as a yellow solid.

[0452] Example 57: Synthesis of *N*-(4-(3,4-difluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-27**, Scheme 59).

[0453] Compound **I-27** may be prepared according to Scheme 59:



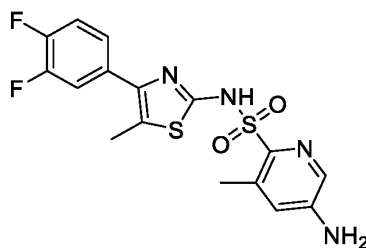
Scheme 59



***N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-methylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

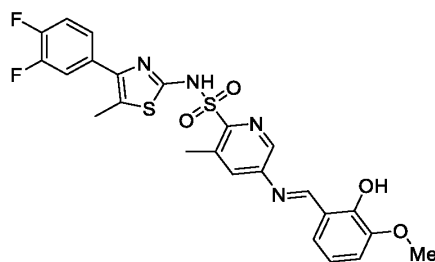
[0454] To a solution of **III-15** (850 mg, 3.76 mmol, 1 *eq*; prepared via Scheme 21) in pyridine (10 mL) was added **II-2** (1.40 g, 5.64 mmol, 1.5 *eq*; prepared via Scheme 4). The mixture was stirred at 50 °C for 1hr then the reaction mixture was concentrated under reduced pressure to give a residue. The resulting residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient at 30 mL/min) to give *N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-

methylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (1.65 g, 3.76 mmol, 100% yield) as a white solid.



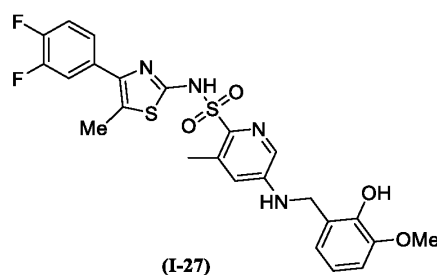
5-amino-*N*-(4-(3,4-difluorophenyl)-5-methylthiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0455] To a solution of *N*-(6-(*N*-(4-(3,4-difluorophenyl)-5-methylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (1.65 g, 3.76 mmol, 1 *eq*) in EtOH (6 mL) was added NaOH (753 mg, 3.76 mmol, 6 mL, 20% solution, 1 *eq*). The mixture was stirred at 90 °C for 0.5 hr. The reaction mixture was then concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. 5-amino-*N*-(4-(3,4-difluorophenyl)-5-methylthiazol-2-yl)-3-methylpyridine-2-sulfonamide (1.49 g, 3.76 mmol, 100% yield) was obtained as a white solid.



(*E*)-*N*-(4-(3,4-difluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0456] To a solution of 5-amino-*N*-(4-(3,4-difluorophenyl)-5-methylthiazol-2-yl)-3-methylpyridine-2-sulfonamide (300 mg, 757 μ mol, 1 *eq*) in toluene (3 mL) was added 2-hydroxy-3-methoxybenzaldehyde (173 mg, 1.14 mmol, 1.5 *eq*). The mixture was stirred at 120 °C for 6 hr then the reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. (*E*)-*N*-(4-(3,4-difluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (401 mg, 755.80 μ mol, 100% yield) was obtained as a white solid.

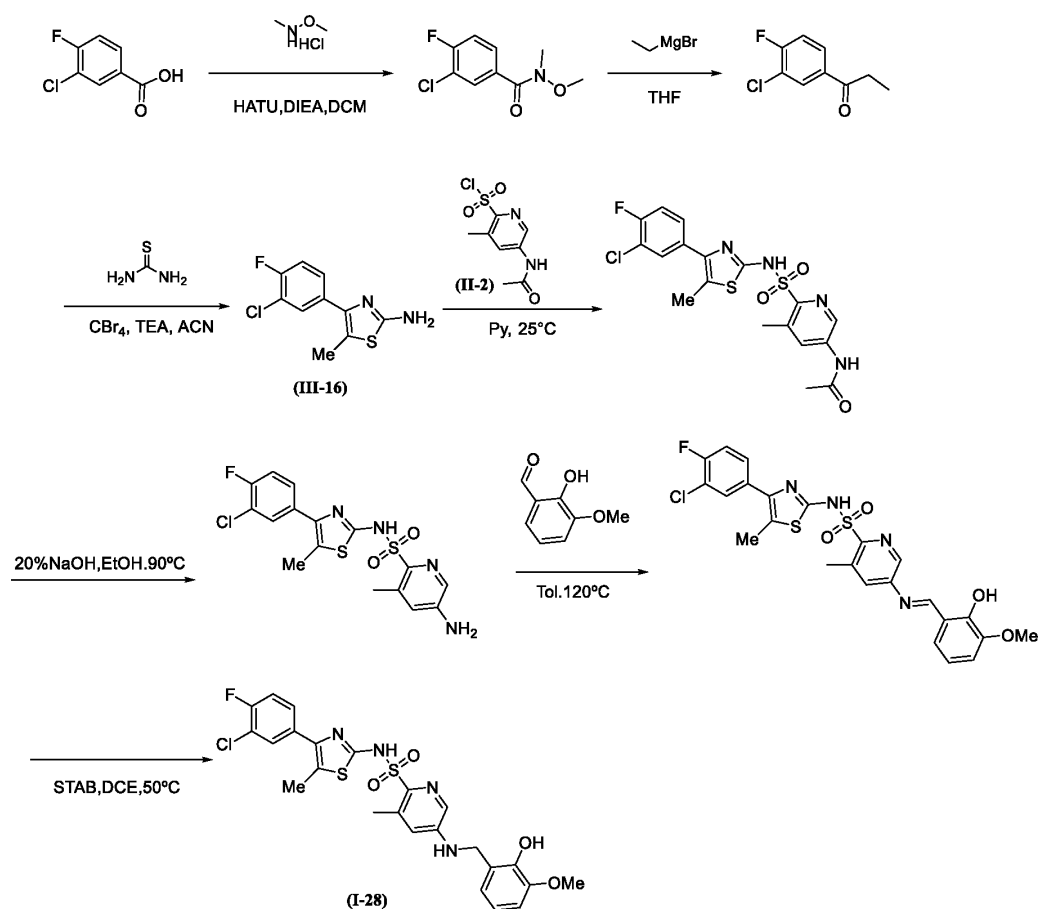


***N*-(4-(3,4-difluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

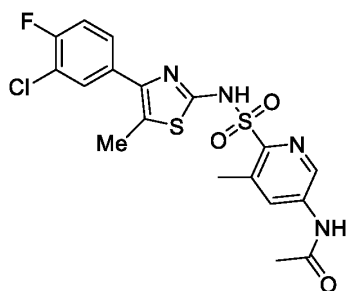
[0457] To a solution of (*E*)-*N*-(4-(3,4-difluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (401 mg, 756 μ mol, 1 *eq*) in DCE (4 mL) was added sodium triacetoxyborohydride (481 mg, 2.27 mmol, 3 *eq*). The mixture was stirred at 50 °C for 0.5 hr then the reaction mixture was concentrated under reduced pressure to give a residue. The product was further purified by prep HPLC. The resulting residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give *N*-(4-(3,4-difluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-27**, 108 mg, 199 μ mol, 26% yield) as a white solid.

[0458] Example 58: Synthesis of *N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-28**, Scheme 60).

[0459] Compound **I-28** may be prepared according to Scheme 60:



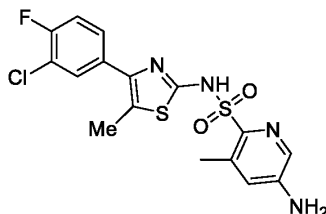
Scheme 60



***N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

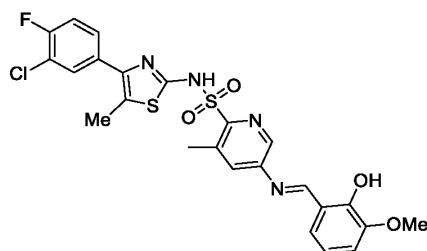
[0460] To a solution of **III-16** (350 mg, 1.44 mmol, 1 *eq*; prepared via Scheme 22) in pyridine (4 mL) was added **II-2** (359 mg, 1.44 mmol, 1 *eq*; prepared via Scheme 4). The mixture was stirred at 50 °C for 1 hr then the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl

acetate/Petroleum ether gradient at 30 mL/min) to give *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (650 mg, 1.43 mmol, 99.% yield) as a white solid.



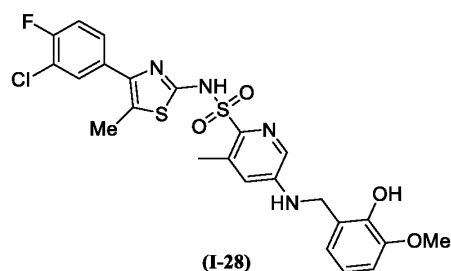
5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0461] To a solution of *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (650 mg, 1.43 mmol, 1 *eq*) in EtOH (4 mL) was added NaOH (285 mg, 1.43 mmol, 4 mL, 20% solution, 1 *eq*). The mixture was stirred at 90 °C for 0.5hr then the reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)-3-methylpyridine-2-sulfonamide (589 mg, 1.43 mmol, 99% yield) was obtained as a white solid.



(*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0462] To a solution of 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)-3-methylpyridine-2-sulfonamide (300 mg, 727 μmol, 1 *eq*) in Toluene (4 mL) was added 2-hydroxy-3-methoxybenzaldehyde (166 mg, 1.09 mmol, 1.5 *eq*). The mixture was stirred at 120 °C for 6 hr then the reaction mixture was concentrated under reduced pressure to give a residue. The resulting crude product was used in the next step without further purification. (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (397 mg, 723 μmol, 100% yield) was obtained as a white solid.

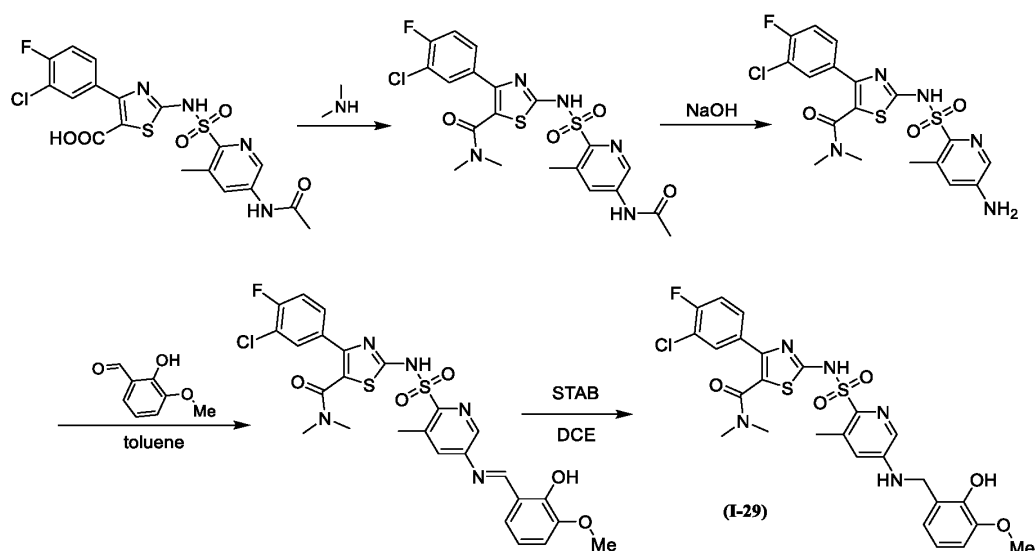


***N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

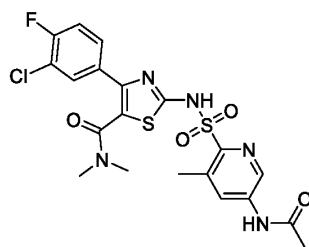
[0463] To a solution of (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (390 mg, 712.95 μ mol, 1 *eq*) in DCE (4 mL) was added sodium triacetoxyborohydride (453 mg, 2.14 mmol, 3 *eq*). The mixture was stirred at 60 °C for 0.5 hr. The reaction mixture was then concentrated under reduced pressure to give a residue. The product was further purified by prep and the residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give *N*-(4-(3-chloro-4-fluorophenyl)-5-methylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-28**, 108 mg, 194.6 μ mol, 27% yield) as a white solid.

[0464] Example 59: Synthesis of 4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine)-2-sulfonamido)-*N,N*-dimethylthiazole-5-carboxamide (**I-29**, Scheme 61).

[0465] Compound **I-29** may be prepared according to Scheme 61:

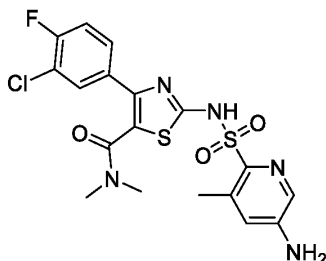


Scheme 61



2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-*N,N*-dimethylthiazole-5-carboxamide

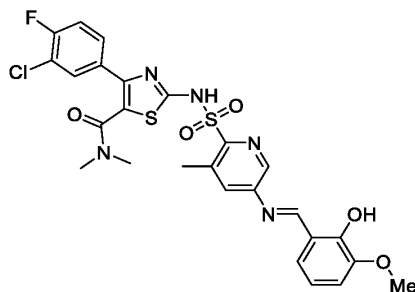
[0466] To a solution of 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)thiazole-5-carboxylic acid (160 mg, 330 μ mol, 1 *eq*; prepared via Scheme 56) in DMF (2 mL) was added DIEA 128 mg, 990 μ mol, 172 μ L, 3 *eq*) and then HATU (188 mg, 495 μ mol, 1.5 *eq*) and was added dimethylamine (37 mg, 825 μ mol, 42 μ L, 2.5 *eq*) at 0°C. The mixture was stirred at 25 °C for 16 hr under N₂. LC-MS showed the starting material was consumed and one peak with desired mass was detected. The reaction mixture was extracted with EA (20 mL). The combined organic layers were washed with aqueous NaCl 20 mL (20 mL $\times$ 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC. 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-*N,N*-dimethylthiazole-5-carboxamide (44 mg, 85.9 μ mol, 26% yield) was obtained as a white solid.



2-((5-amino-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-*N,N*-dimethylthiazole-5-carboxamide

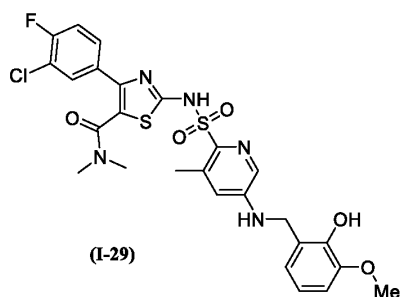
[0467] To a solution of 2-((5-acetamido-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-*N,N*-dimethylthiazole-5-carboxamide (48 mg, 93.75 μ mol, 1 *eq*) in EtOH (3 mL) and H₂O (0.6 mL) was added NaOH (240 mg, 6.0 mmol, 64 *eq*). The reaction mixture was stirred at 80 °C for 2 hr. LC-MS the starting material was consumed, and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove EtOH (3 mL). The residue was diluted with H₂O (10 mL) and extracted with EA (10 mL $\times$ 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue.

The crude product was used directly in the next step. 2-((5-amino-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-*N,N*-dimethylthiazole-5-carboxamide (43 mg, 85.1 μ mol, 91% yield) was obtained as a red solid.



(*E*)-4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine)-2-sulfonamido)-*N,N*-dimethylthiazole-5-carboxamide

[0468] A mixture of 2-((5-amino-3-methylpyridine)-2-sulfonamido)-4-(3-chloro-4-fluorophenyl)-*N,N*-dimethylthiazole-5-carboxamide (43 mg, 91.5 μ mol, 1 *eq*) and 2-hydroxy-3-methoxybenzaldehyde (16.7 mg, 109.8 μ mol, 1.2 *eq*) in toluene (2 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 120 °C for 16 hr under N₂ atmosphere. The reaction mixture was then concentrated under reduced pressure to remove toluene (2 mL) and the crude product was used directly in the next step. (*E*)-4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine)-2-sulfonamido)-*N,N*-dimethylthiazole-5-carboxamide (55 mg, 91 μ mol, 99.5% yield) was obtained as a red solid.



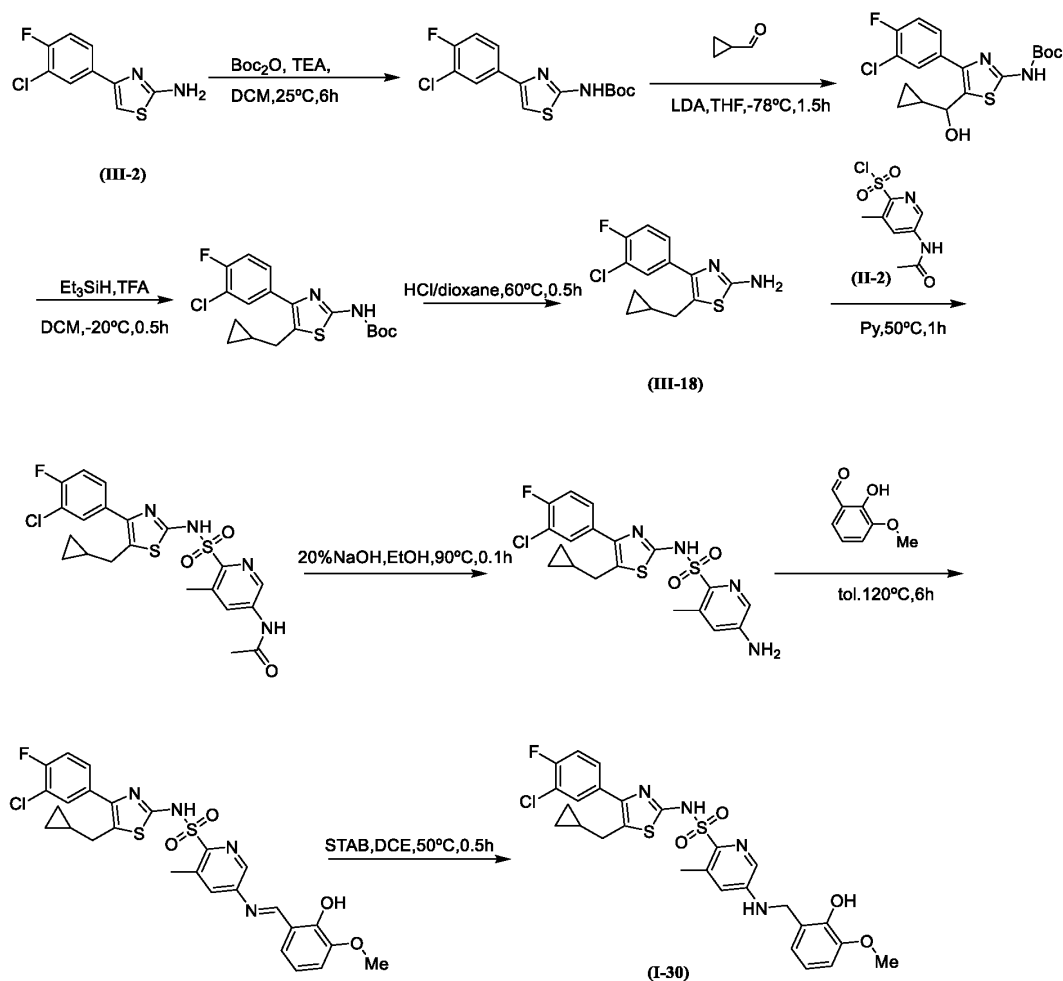
4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine)-2-sulfonamido)-*N,N*-dimethylthiazole-5-carboxamide

[0469] To a solution of (*E*)-4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine)-2-sulfonamido)-*N,N*-dimethylthiazole-5-carboxamide (55.27 mg, 91.50 μ mol, 1 *eq*) in DCE (5 mL) was added NaBH(OAc)₃ (58 mg, 275 μ mol, 3 *eq*). The mixture was stirred at 25 °C for 2 hr under an N₂ atmosphere. LC-MS showed desired mass was detected. The reaction mixture was diluted with H₂O (10 mL) and

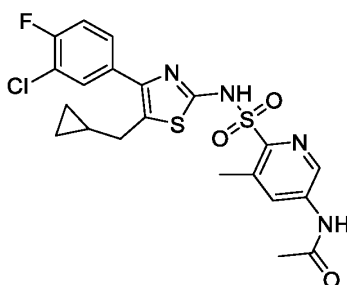
extracted with EA (10 mL $\times$ 2). The combined organic layers were washed with aqueous NaCl (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC. 4-(3-chloro-4-fluorophenyl)-2-((5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine)-2-sulfonamido)-*N,N*-dimethylthiazole-5-carboxamide (**I-29**, 7 mg, 11.9 μ mol, 13% yield) was obtained as a white solid.

[0470] **Example 60:** Synthesis of *N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-30**, Scheme 62).

[0471] Compound **I-30** may be prepared according to Scheme 62:

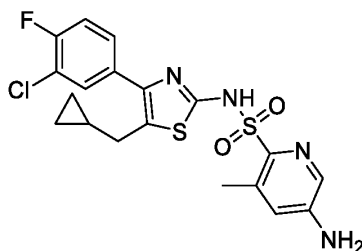


Scheme 62



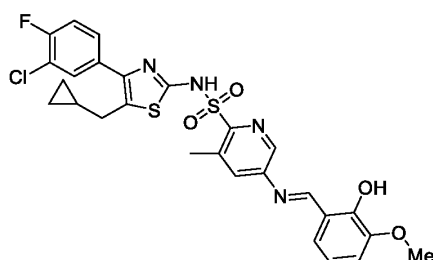
***N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

[0472] To a solution of **III-18** (300 mg, 1.06 mmol, 1 *eq*; prepared via Scheme 24) in pyridine (3 mL) was added 5-acetamido-3-methylpyridine-2-sulfonyl chloride (**II-2**, 396 mg, 1.59 mmol, 1.5 *eq*; prepared via Scheme 4). The mixture was then stirred at 50 °C for 1 hr and then concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient at 30 mL/min) to give *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (400 mg, 808 μmol, 76% yield) as a white solid.



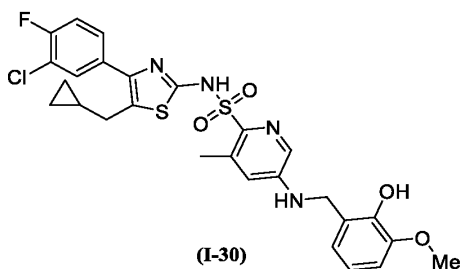
5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0473] To a solution of *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (400 mg, 808.10 μmol, 1 *eq*) in EtOH (2 mL) was added NaOH (162 mg, 80 μmol, 2 mL, 20% solution, 1 *eq*). The mixture was stirred at 90 °C for 0.1 hr, then the reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The crude product was used in the next step without further purification. 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (280 mg, 618 μmol, 77% yield) was obtained as a white solid.



(*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0474] To a solution of 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (280 mg, 618 μmol , 1 *eq*) in Tol. (5 mL) was added 2-hydroxy-3-methoxybenzaldehyde (14 mg, 927 μmol , 1.5 *eq*) and the mixture was stirred at 120 °C for 6 hr. The reaction mixture was then concentrated under reduced pressure to give a residue. The resulting crude product was used in the next step without further purification. (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (362 mg, 616 μmol , 100% yield) was obtained as a white solid.



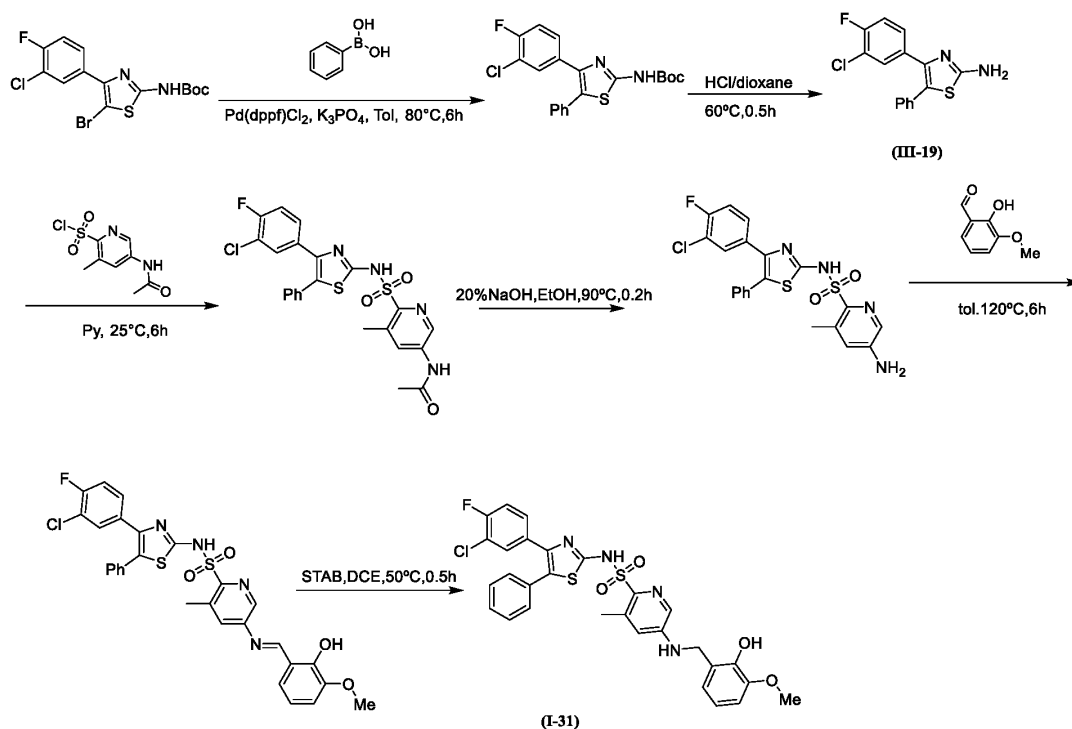
***N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0475] To a solution of (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (362 mg, 617 μmol , 1 *eq*) in DCE (4 mL) was added sodium triacetoxyborohydride (392 mg, 1.85 mmol, 3 *eq*). The resulting mixture was stirred at 50 °C for 0.5 hr then the reaction mixture was concentrated under reduced pressure to give a residue. The product was further purified by prep HPLC and the pure fractions were collected and the volatiles were removed under vacuum. The residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give *N*-(4-(3-chloro-4-fluorophenyl)-5-(cyclopropylmethyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-

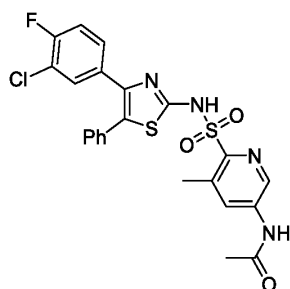
2-sulfonamide (**I-30**, 28 mg, 47.0 μ mol, 8% yield, 98.78% purity) was obtained as a white solid.

[0476] **Example 61:** Synthesis of *N*-(4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-31**, Scheme 63).

[0477] Compound **I-31** may be prepared according to Scheme 63:



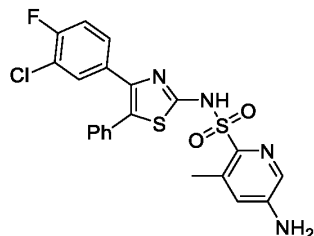
Scheme 63



***N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

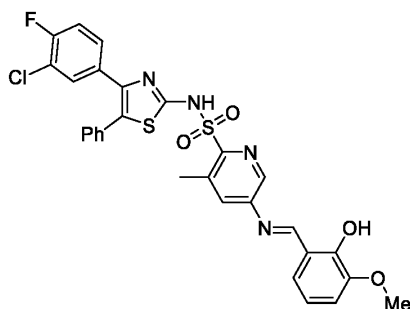
[0478] To a solution of **III-19** (120 mg, 394 μ mol, 1 *eq*; prepared via Scheme 25) in Py. (1 mL) was added **II-2** (147 mg, 591 μ mol, 1.5 *eq*; prepared via Scheme 4). The mixture was stirred at 25 °C for 6 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g

SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient at 18 mL/min). *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (150 mg, 290 μ mol, 74% yield) was obtained as a white solid.



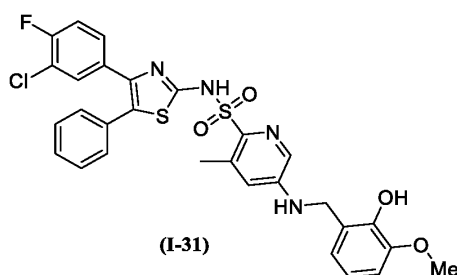
5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0479] To a solution of *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (140 mg, 270.8 μ mol, 1 *eq*) in EtOH (2 mL) was added NaOH (54 mg, 271 μ mol, 1 mL, 20% purity, 1 *eq*). The mixture was stirred at 90 °C for 0.2 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)-3-methylpyridine-2-sulfonamide (120 mg, 253 μ mol, 93% yield) was obtained as a white solid.



(*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0480] To a solution of **HDB-0328-A4** (120 mg, 252.65 μ mol, 1 *eq*) in Tol. (2 mL) was added 2-hydroxy-3-methoxybenzaldehyde (58 mg, 379 μ mol, 1.5 *eq*). The mixture was stirred at 120 °C for 6 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (150 mg, 246 μ mol, 97% yield) was obtained as a white solid.

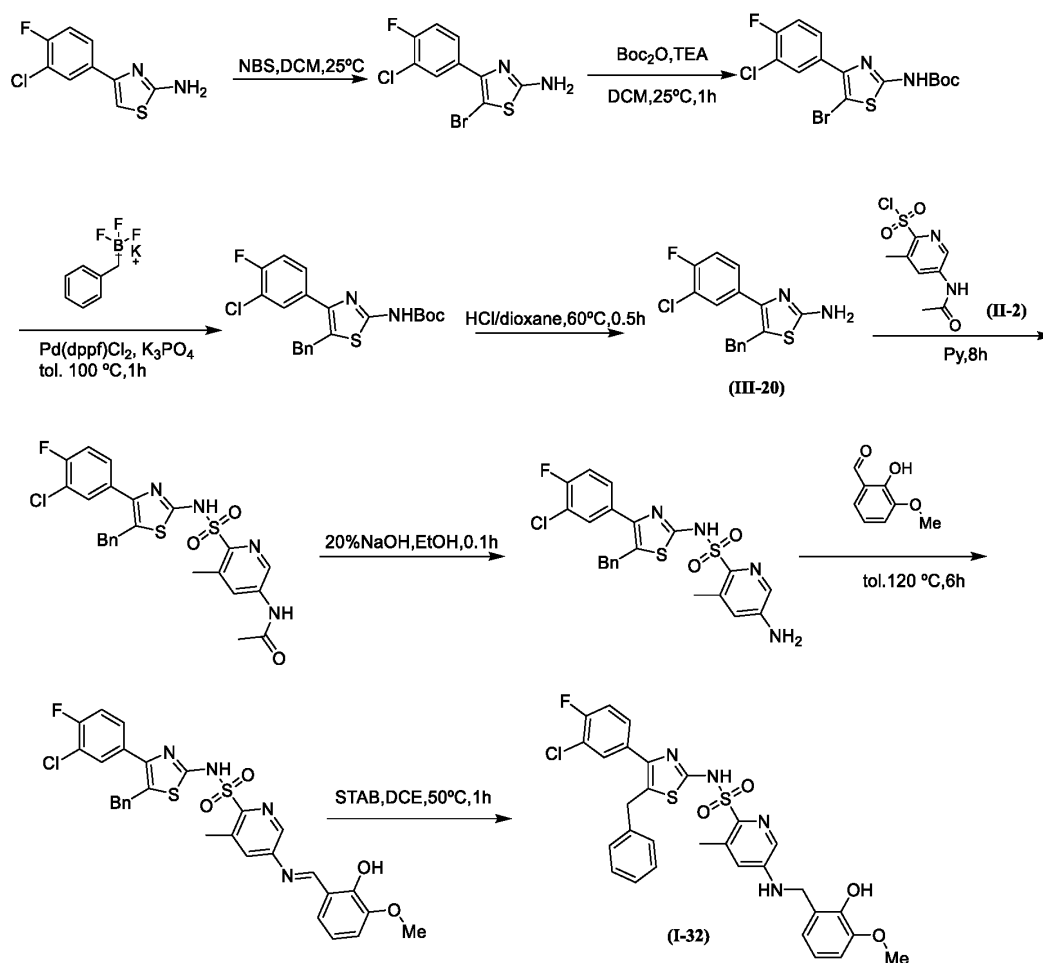


***N*-(4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

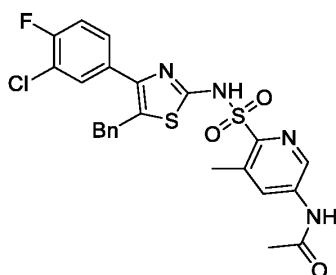
[0481] To a solution of (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (150 mg, 246 μ mol, 1 *eq*) in DCE (2 mL) was added sodium triacetoxyborohydride (157 mg, 739 μ mol, 3 *eq*). The mixture was stirred at 50 °C for 0.5 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The product was then further purified by prep. HPLC (Column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μ m, Mobile Phase A: water(0.225%FA), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 50% B to 80%). The pure fractions were collected, and the volatiles were removed under vacuum. The residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give the product. *N*-(4-(3-chloro-4-fluorophenyl)-5-phenylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-31**, 36 mg, 56 μ mol, 23% yield) was obtained as a white solid.

[0482] Example 62: Synthesis of *N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (I-32**, Scheme 64).**

[0483] Compound **I-32** may be prepared according to Scheme 64:



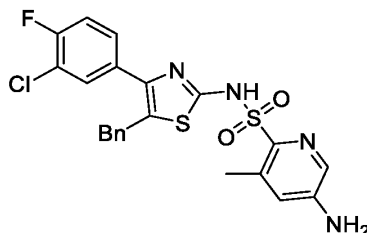
Scheme 64



***N*-(6-(*N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

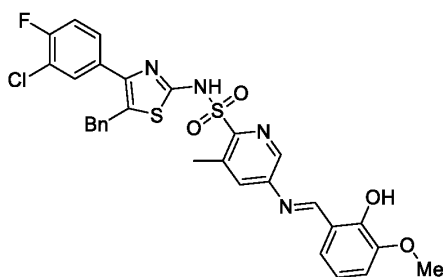
[0484] A mixture of **III-20** (0.108 g, 338.8 μmol , 1 *eq*; prepared via Scheme 26) and **II-2** (118 mg, 474 μmol , 1.4 *eq*; prepared via Scheme 4) was added to pyridine (5 mL), and then the mixture was stirred at 25 °C for 8 hr. The reaction mixture was diluted with EA (10 mL) and washed with H_2O (5 mL $\times$ 3) and brine (5 mL). The organic layer was dried over

Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4g SepaFlash® Silica Flash Column, Eluent of 0~60% Ethylacetate/Petroleum ether gradient at 60mL/min) to give a product. *N*-(6-(*N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (0.165 g, 311 μmol, 92% yield) was obtained as a brown solid.



5-amino-*N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

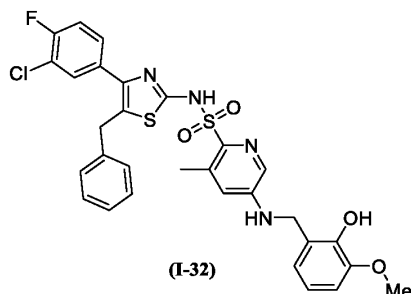
[0485] To a solution of *N*-(6-(*N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (165 mg, 337 μmol, 1 *eq*) in EtOH (1 mL) was added NaOH (67 mg, 337 μmol, 1 *eq*). The mixture was stirred at 90 °C for 0.1 hr. The reaction mixture was quenched by addition H₂O 10 mL at 25 °C, and then diluted with H₂O (10 mL) and extracted with EA 20 mL (20 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. 5-amino-*N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (110 mg, 225 μmol, 67% yield) was obtained as a white solid.



(*E*)-*N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0486] To a solution of 5-amino-*N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (110 mg, 225 μmol, 1 *eq*) in Tol. (2 mL) was added 2-hydroxy-3-methoxybenzaldehyde (51 mg, 337 μmol, 1.5 *eq*). The mixture was stirred at 120 °C for 6 hr. The reaction mixture was concentrated under reduced pressure to give a residue.

The crude product was used into the next step without further purification. (*E*)-*N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (140 mg, 225 μ mol, 99% yield) was obtained as a white solid.

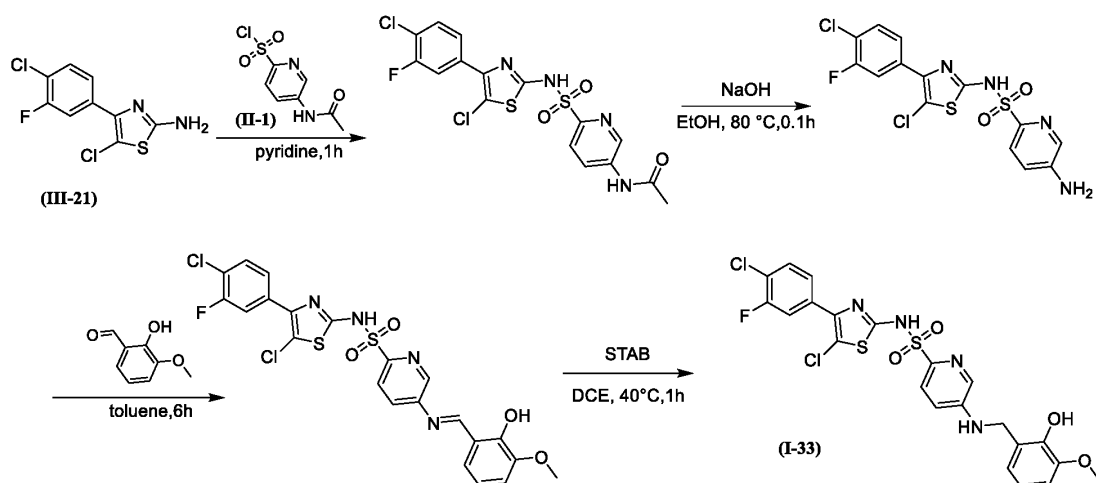


***N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

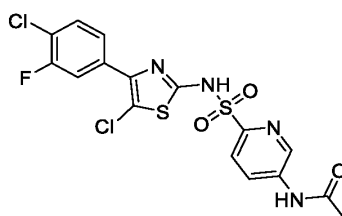
[0487] To a solution of (*E*)-*N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (140 mg, 224.68 μ mol, 1 *eq*) in DCE (1 mL) was added sodium triacetoxyborohydride (143mg, 674 μ mol, 3 *eq*). The mixture was stirred at 50 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. Then the product was further purified by prep. HPLC (Column: Phenomenex luna C18 100 $\times$ 40mm $\times$ 3 μ m, Mobile Phase A: water (0.225%FA), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 48% B to 78%). The pure fractions were collected, and the volatiles were removed under vacuum. The residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give the product *N*-(5-benzyl-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-32**, 38 mg, 58 μ mol, 26% yield) as a white solid.

[0488] **Example 63:** Synthesis of *N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)pyridine-2-sulfonamide (**I-33**, Scheme 65).

[0489] Compound **I-33** may be prepared according to Scheme 65:

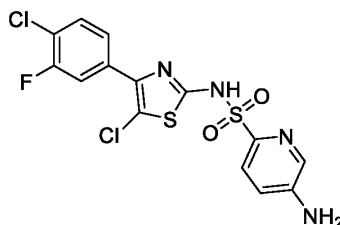


Scheme 65



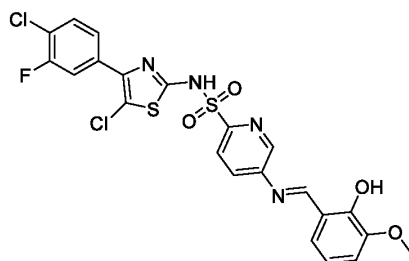
***N*-(6-(*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)pyridin-3-yl)acetamide**

[0490] To a solution of **III-21** (1 g, 3.80 mmol, 1 *eq*; prepared via Scheme 27) in pyridine (10 mL) was added 5-acetamidopyridine-2-sulfonyl chloride (**II-1**, 1.07 g, 4.56 mmol, 1.2 *eq*; prepared via Scheme 3). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient at 30 mL/min). *N*-(6-(*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)pyridin-3-yl)acetamide (1.2 g, 2.60 mmol, 68% yield) was obtained as a white solid.



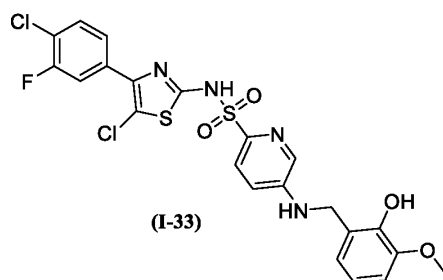
5-amino-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)pyridine-2-sulfonamide

[0491] To a solution of *N*-(6-(*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)pyridin-3-yl)acetamide (1.2 g, 2.60 mmol, 1 *eq*) in EtOH (6 mL) was added NaOH (520 mg, 2.60 mmol, 6 mL, 20% solution, 1 *eq*). The mixture was stirred at 80 °C for 0.1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. 5-amino-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)pyridine-2-sulfonamide (1 g, 2.39 mmol, 92% yield) was obtained as a white solid.



(*E*)-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)pyridine-2-sulfonamide

[0492] To a solution of 5-amino-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)pyridine-2-sulfonamide (300 mg, 715.5 μmol, 1 *eq*) in Tol. (5 mL) was added 2-hydroxy-3-methoxybenzaldehyde (152 mg, 1.00 mmol, 1.4 *eq*). The mixture was stirred at 120 °C for 6 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. (*E*)-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)pyridine-2-sulfonamide (390 mg, 704.7 μmol, 98% yield) was obtained as a white solid.



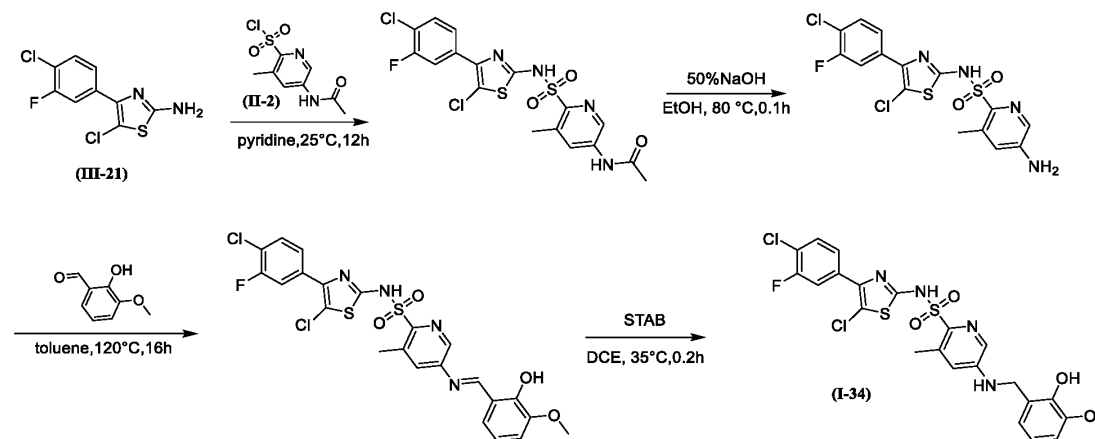
***N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)pyridine-2-sulfonamide**

[0493] To a solution of (*E*)-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)pyridine-2-sulfonamide (390 mg, 704.72 μmol, 1 *eq*) in DCE (4 mL) was added STAB (448 mg, 2.11 mmol, 3 *eq*). The mixture was stirred at 40 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue.

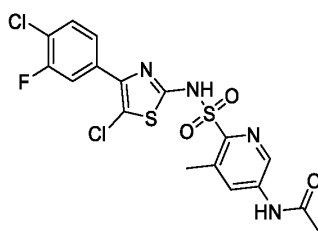
Then the product was further purified by prep. HPLC (Column: Phenomenex luna C18 150 × 25mm × 10μm, Mobile Phase A: water (0.225%FA), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 49% B to 79%). The pure fractions were collected, and the volatiles were removed under vacuum. The residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give the product *N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)pyridine-2-sulfonamide (**I-33**, 119 mg, 208 μmol, 30% yield) as a white solid.

[0494] Example 64: Synthesis of *N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-34**, Scheme 66).

[0495] Compound **I-34** may be prepared according to Scheme 66:



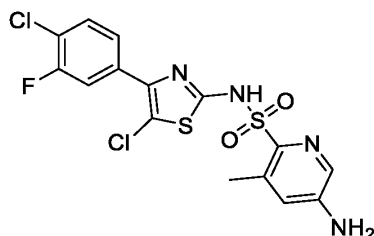
Scheme 66



N-(6-(*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide

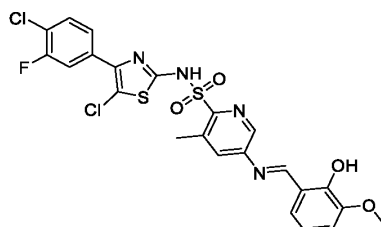
[0496] A mixture of **III-21** (882 mg, 3.35 mmol; prepared via Scheme 27) in pyridine (15 mL) was degassed and purged with N₂ at 0 °C, and then added 5-acetamido-3-methylpyridine-2-sulfonyl chloride (**II-2**, 1 g, 4.02 mmol; prepared via Scheme 4), the mixture was stirred at 25 °C for 1.5 hours under N₂ atmosphere. The reaction mixture was extracted with ethyl acetate (60 mL × 3), washed with brine (40 mL × 2), dried over Na₂SO₄

and concentrated to dryness. The residue was purified by column chromatography (silica gel, 100-200 mesh, 60% ethyl acetate in petroleum ether) to afford *N*-(6-(*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (1.35 g, 85% yield) as a brown solid.



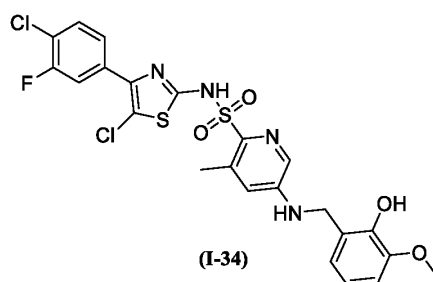
5-amino-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0497] To a solution of *N*-(6-(*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (1.35 g, 2.84 mmol) in EtOH (2 mL) and H₂O (4.5 mL) was added NaOH (909 mg, 22.72 mmol). The mixture was stirred at 80 °C for 0.1 hour. The reaction mixture was extracted with ethyl acetate (30 mL × 3), washed with brine (50 mL × 2), dried over Na₂SO₄ and concentrated to give the crude product 5-amino-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (1.12 g, crude) as a red solid, which was used directly in the next step without further purification.



(*E*)-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0498] To a solution of 2-hydroxy-3-methoxybenzaldehyde (147 mg, 969 μmol) in Toluene (5 mL) was added 5-amino-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (300 mg, crude). The mixture was stirred at 120 °C for 16 hours. The solvent was removed under pressure reduction to afford (*E*)-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (390 mg, crude) as a brown solid, which was used into the next step without further purification.

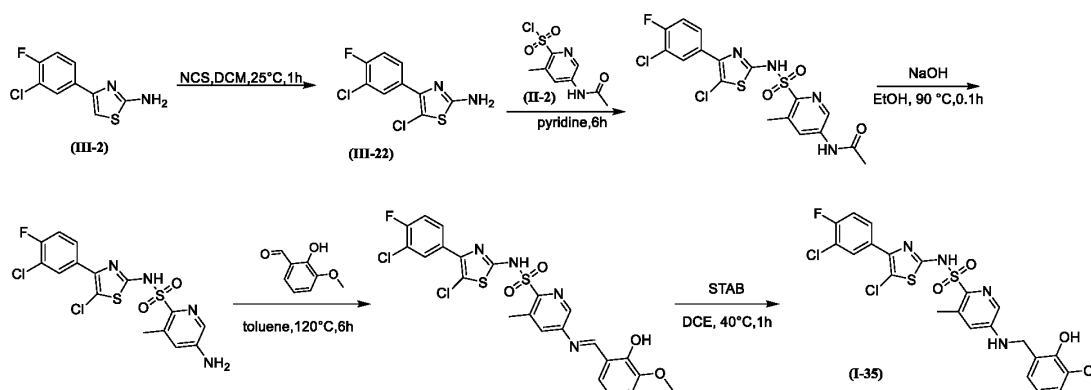


***N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

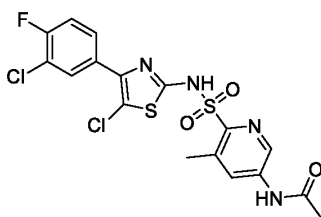
[0499] A mixture of (*E*)-*N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (390 mg, crude) was added into DCE (6 mL) and then added sodium triacetoxyborohydride (437 mg, 2.06 mmol), the mixture was stirred at 35 °C for 0.2 hour. The mixture was extracted with ethyl acetate (30 mL × 3), washed with brine (40 mL × 2), dried over Na₂SO₄ and concentrated to dryness. The crude was purified by prep HPLC (column: Phenomenex luna C18 150 × 25mm × 10um; mobile phase: [water(FA)-ACN];gradient:50%-80% B over 8 min). The pure fractions were collected, and the volatiles were removed under vacuum. The residue was partitioned between acetonitrile (20 mL) and water (100 mL). The solution was lyophilized to dryness to give the product *N*-(5-chloro-4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-34**, 82 mg, 21% yield) as a white solid.

[0500] Example 65: Synthesis of *N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (I-35**, Scheme 67).**

[0501] Compound **I-35** may be prepared according to Scheme 67:

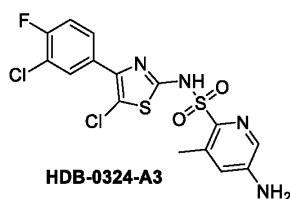


Scheme 67



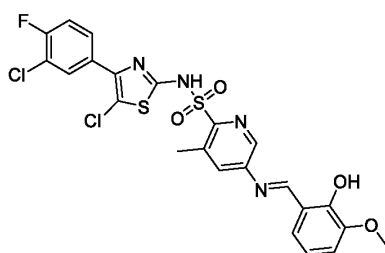
***N*-(6-(*N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

[0502] To a solution of **III-22** (2 g, 7.60 mmol, 1 *eq*; prepared via Scheme 28) in pyridine (20 mL) was added **II-2** (2.84 g, 11.40 mmol, 1.5 *eq*; prepared via Scheme 4). The mixture was stirred at 25 °C for 6 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient at 40 mL/min). *N*-(6-(*N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (2.7 g, 5.68 mmol, 75% yield) was obtained as a yellow solid.



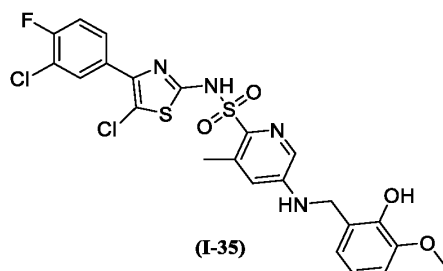
5-amino-*N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0503] To a solution of *N*-(6-(*N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (2.70 g, 5.68 mmol, 1 *eq*) in EtOH (10 mL) was added NaOH (1.14 g, 5.68 mmol, 10 mL, 20% solution, 1 *eq*). The mixture was stirred at 90 °C for 0.1 hr. The reaction mixture was quenched by addition H₂O (20 mL) at 25 °C and extracted with EA (50 mL × 3). The combined organic layers were Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. 5-amino-*N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (2.4 g, 5.54 mmol, 98% yield) was obtained as a yellow solid.



(*E*)-*N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0504] To a solution of 5-amino-*N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (1 g, 2.31 mmol, 1 *eq*) in Tol. (15 mL) was added 2-hydroxy-3-methoxybenzaldehyde (527 mg, 3.46 mmol, 1.5 *eq*). The mixture was stirred at 120 °C for 6 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. (*E*)-*N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (1.31 g, 2.31 mmol, 100% yield) was obtained as a white solid.



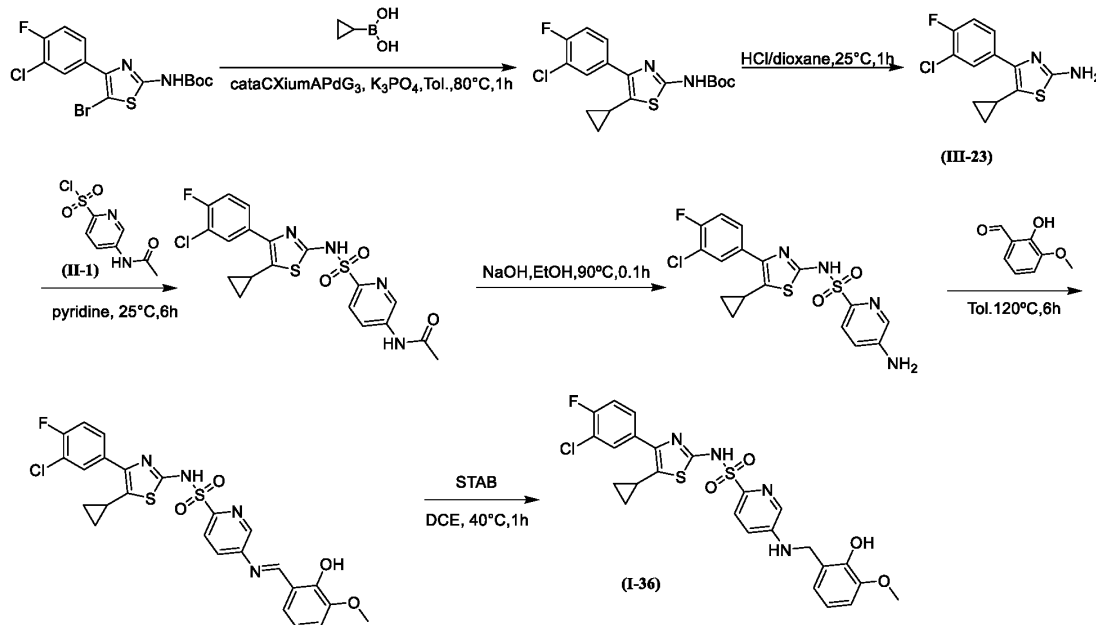
***N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0505] To a solution of (*E*)-*N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (1.31 g, 2.31 mmol, 1 *eq*) in DCE (13 mL) was added **STAB** (1.47 g, 6.93 mmol, 3 *eq*). The mixture was stirred at 40 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. Then the product was further purified by prep. HPLC (Column: Phenomenex luna 150 × 25mm × 10μm, Mobile Phase A: water (0.225%FA), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 52% B to 82%). The pure fractions were collected, and the volatiles were removed under vacuum. The residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give the product *N*-(5-chloro-4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-

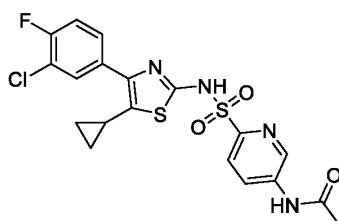
methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-35**, 418 mg, 701 μ mol, 30% yield) as a white solid.

[0506] Example 66: Synthesis of *N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)pyridine-2-sulfonamide (**I-36**, Scheme 68).

[0507] Compound **I-36** may be prepared according to Scheme 68:



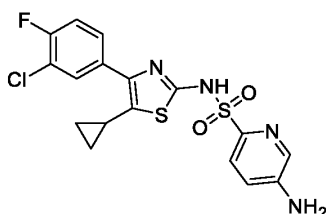
Scheme 68



N-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide

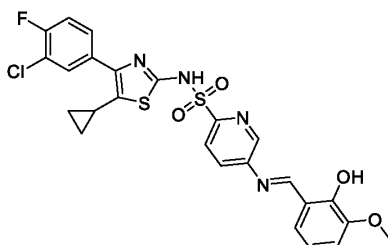
[0508] To a solution of **III-23** (700 mg, 2.60 mmol, 1 *eq*; prepared via Scheme 29) in pyridine (7 mL) was added 5-acetamidopyridine-2-sulfonyl chloride (**II-1**, 916.85 mg, 3.91 mmol, 1.5 *eq*; prepared via Scheme 3). The mixture was stirred at 25 °C for 6 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient at 30 mL/min). *N*-(6-(*N*-(4-(3-

chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (720 mg, 1.54 mmol, 59.20% yield) was obtained as a white solid.



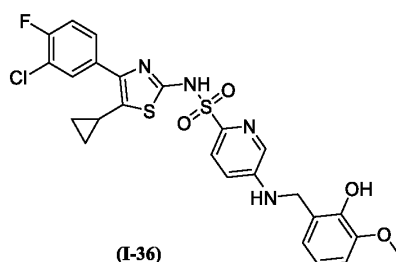
5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0509] To a solution of *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (720 mg, 1.54 mmol, 1 *eq*) in EtOH (4 mL) was added NaOH (308.37 mg, 1.54 mmol, 4 mL, 20% purity, 1 *eq*). The mixture was stirred at 90 °C for 0.1 hr. The reaction mixture was quenched by addition H₂O (20 mL) and extracted with EA (50 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-3-methylpyridine-2-sulfonamide (500 mg, 1.18 mmol, 76% yield) was obtained as a white solid.



(*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)pyridine-2-sulfonamide

[0510] To a solution of 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-3-methylpyridine-2-sulfonamide (500 mg, 1.18 mmol, 1 *eq*) in Tol. (5 mL) was added 2-hydroxy-3-methoxybenzaldehyde (269 mg, 1.77 mmol, 1.5 *eq*). The mixture was stirred at 120 °C for 6 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)pyridine-2-sulfonamide (650 mg, 1.16 mmol, 99% yield) was obtained as a white solid.

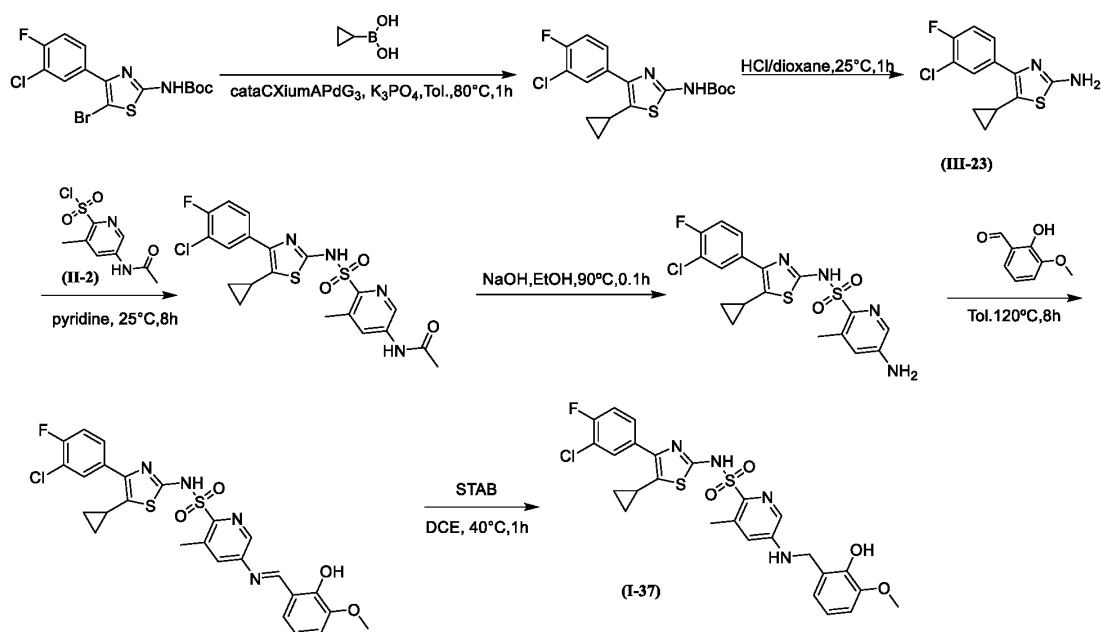


***N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)pyridine-2-sulfonamide**

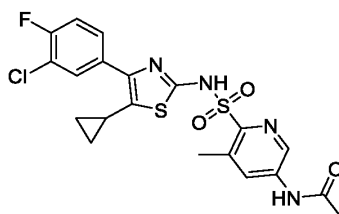
[0511] To a solution of (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)pyridine-2-sulfonamide (650 mg, 1.16 mmol, 1 *eq*) in DCE (6 mL) was added sodium triacetoxyborohydride (739 mg, 3.49 mmol, 3 *eq*). The mixture was stirred at 40 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. Then the product was further purified by prep. HPLC (Column: Phenomenex luna C18 150 × 25mm × 10μm, Mobile Phase A: water (0.225%FA), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 45% B to 75%). The pure fractions were collected, and the volatiles were removed under vacuum. The residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give the product *N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)pyridine-2-sulfonamide (**I-36**, 149 mg, 254 μmol, 22% yield) as a white solid.

[0512] Example 67: Synthesis of *N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-37**, Scheme 69).

[0513] Compound **I-37** may be prepared according to Scheme 69:

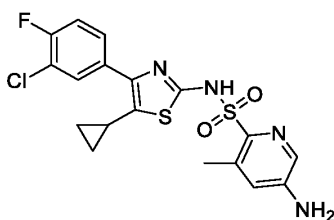


Scheme 69



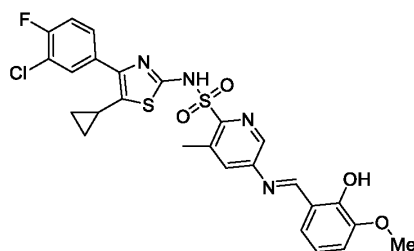
***N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

[0514] The mixture of **III-23** (300 mg, 1.12 mmol, 1 *eq*; prepared via Scheme 29) and **II-2** (416 mg, 1.67 mmol, 1.5 *eq*; prepared via Scheme 4) in pyridine (3 mL) was stirred at 25 °C for 8 hr. The reaction mixture was quenched by addition H₂O (100 mL) at 25 °C, and then extracted with EA (100 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient at 40 mL/min). *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (400 mg, 832 μmol, 75% yield) was obtained as a yellow solid.



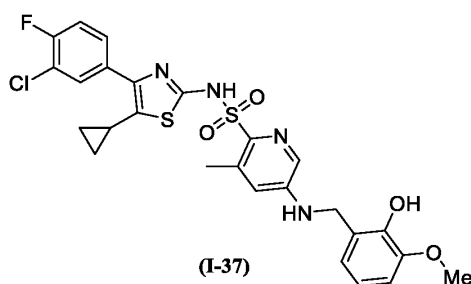
5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0515] To a solution of *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (400 mg, 832 μ mol, 1 *eq*) in EtOH (2 mL) was added NaOH (166 mg, 832 μ mol, 2 mL, 20% purity, 1 *eq*). The mixture was stirred at 90 °C for 0.1 hr. The reaction mixture was concentrated under reduced pressure to remove EtOH. The residue was diluted with H₂O (10 mL) and extracted with EA (20 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-3-methylpyridine-2-sulfonamide (330 mg, 752 μ mol, 90% yield) was obtained as a yellow solid.



(*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0516] To a solution of 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-3-methylpyridine-2-sulfonamide (330 mg, 752 μ mol, 1 *eq*) in Tol. (5 mL) was added 2-hydroxy-3-methoxybenzaldehyde (172 mg, 1.13 mmol, 1.5 *eq*). The mixture was stirred at 120 °C for 8 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (430 mg, 750 μ mol, 99.8% yield) was obtained as a yellow solid.

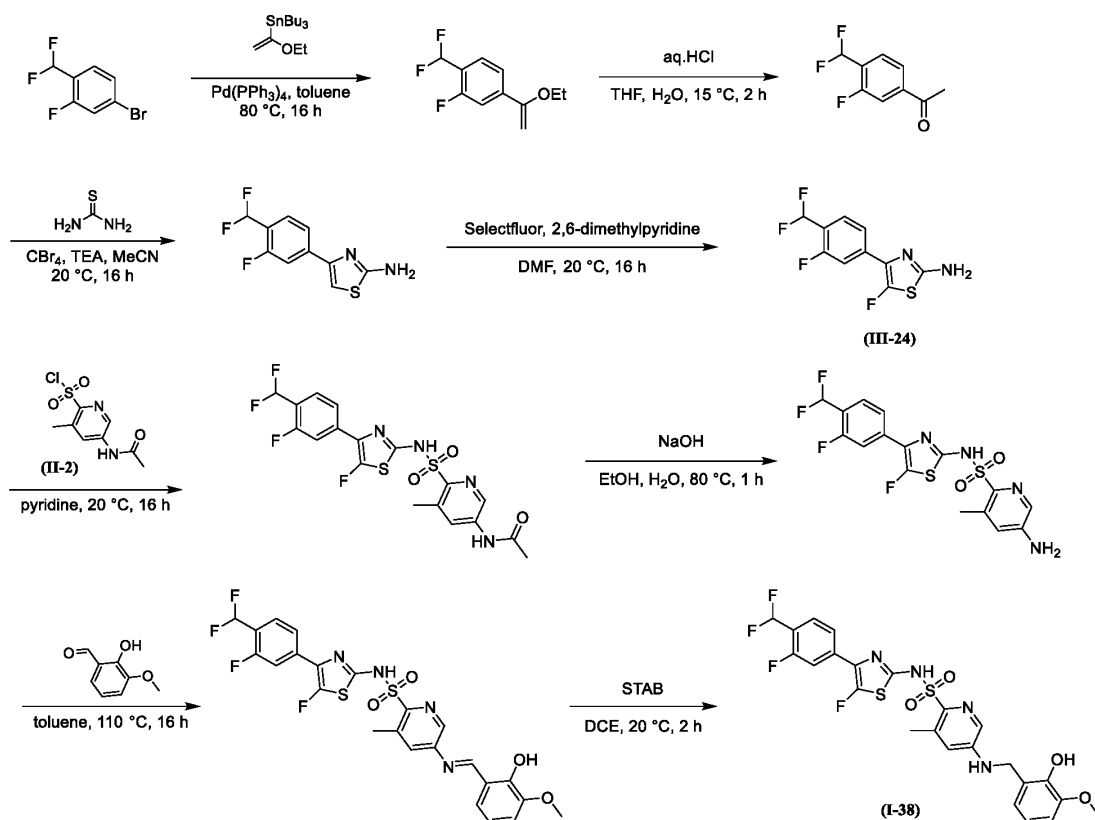


***N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

[0517] To a solution of (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (430 mg, 751 μ mol, 1 *eq*) in DCE (4 mL) was added **STAB** (477 mg, 2.25 mmol, 3 *eq*). The mixture was stirred at 40 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. Then the product was further purified by prep. HPLC (Column: Phenomenex Luna C18 150 $\times$ 25mm $\times$ 10 μ m, Mobile Phase A: water (0.225%FA), Mobile Phase B: acetonitrile, Flow rate: 25 mL/min, gradient condition from 46% B to 76%). The pure fractions were collected, and the volatiles were removed under vacuum. The residue was partitioned between acetonitrile (2 mL) and water (10 mL). The solution was lyophilized to dryness to give the product *N*-(4-(3-chloro-4-fluorophenyl)-5-cyclopropylthiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-37**, 29 mg, 50 μ mol, 7% yield) as a white solid.

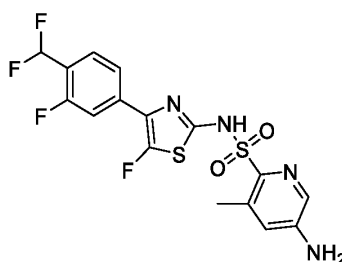
[0518] **Example 68:** Synthesis of *N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-38**, Scheme 70).

[0519] Compound **I-38** may be prepared according to Scheme 70:



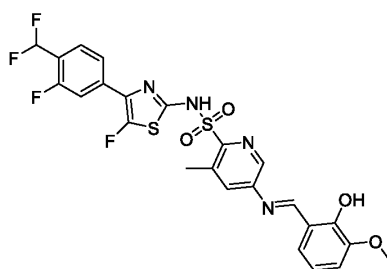
***N*-(6-(*N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

[0520] To a solution of **II-2** (313.91 mg, 1.26 mmol, 1 *eq*; prepared via Scheme 4) in pyridine (4 mL) was added **III-24** (331 mg, 1.26 mmol, 1.0 *eq*; prepared via Scheme 30). The mixture was stirred at 20 °C for 16 hr. To the reaction mixture was then added H₂O (30 mL) and extracted with EA (30 mL × 2). The combined organic layers were concentrated to give the crude product. The crude product was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 30/70) to give *N*-(6-(*N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (333 mg, 702 μmol, 56% yield) as a yellow solid.



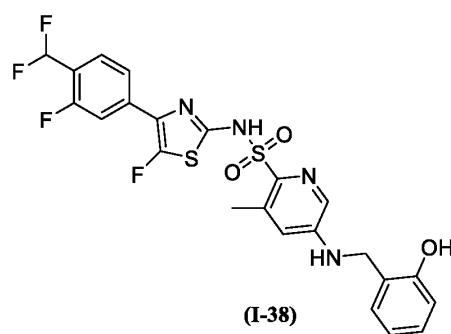
5-amino-*N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0521] To a solution of *N*-(6-(*N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (333 mg, 702 μmol , 1 *eq*) in EtOH (5 mL)/H₂O (0.5 mL) was added NaOH (500 mg, 12.50 mmol, 17.81 *eq*). The mixture was stirred at 80 °C for 1 hr then the reaction mixture was cooled to 25 °C and concentrated. The residue was re-dissolved in H₂O (30 mL) and extracted with EtOAc (30 mL $\times$ 2). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude product 5-amino-*N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)-3-methylpyridine-2-sulfonamide (222 mg, crude) as a red solid and used in the next step without further purification.



(*E*)-*N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0522] To a solution of 2-hydroxy-3-methoxybenzaldehyde (86 mg, 565 μmol , 1.1 *eq*) in toluene (5 mL) was added 5-amino-*N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)-3-methylpyridine-2-sulfonamide (222 mg, 513 μmol , 1.0 *eq*). The mixture was stirred at 110 °C for 16 hr then the reaction mixture was cooled to 20 °C and concentrated to remove the solvent. The crude product (*E*)-*N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (290 mg, crude) was obtained as a yellow solid and used in the next step without further purification.

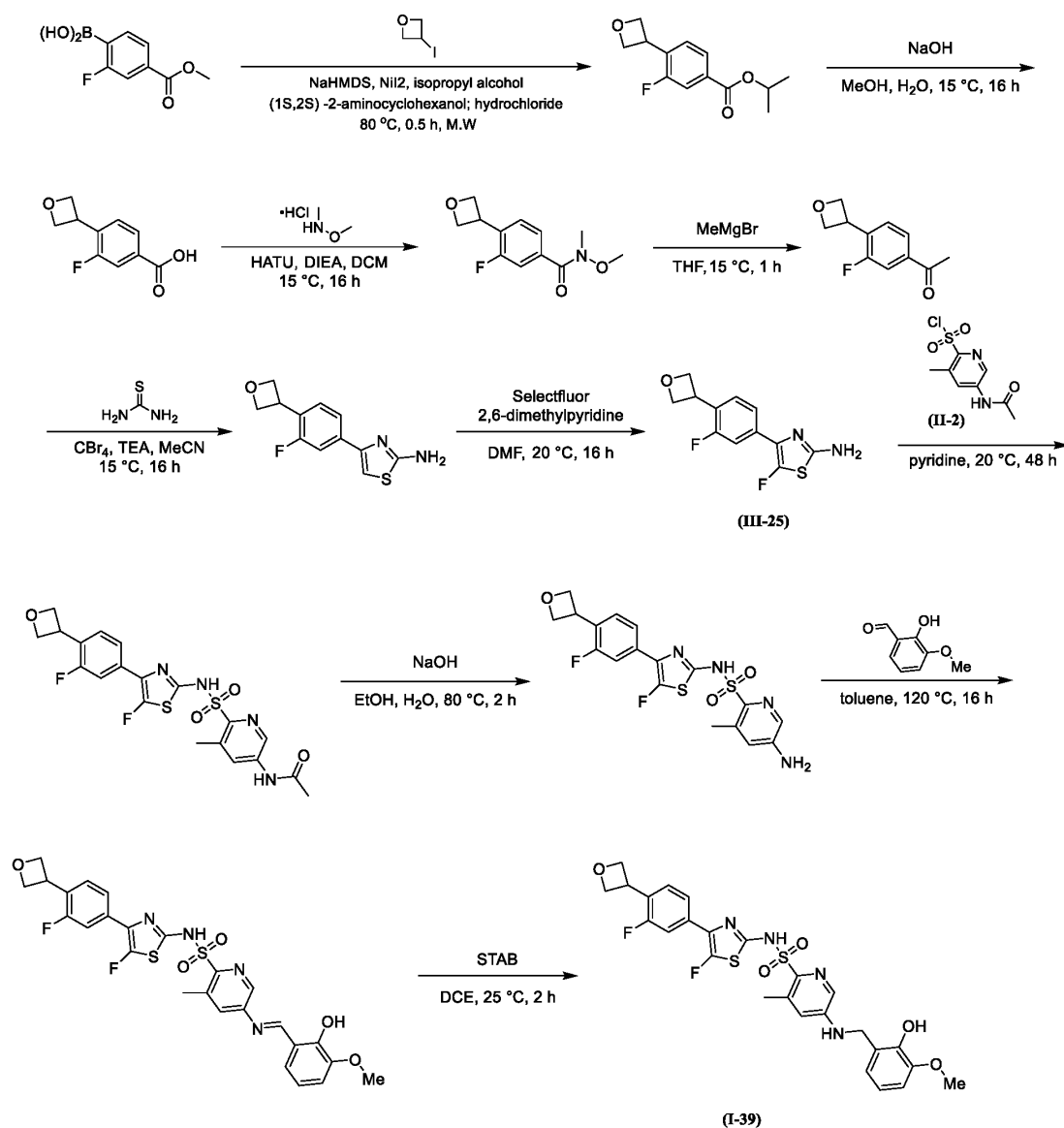


***N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

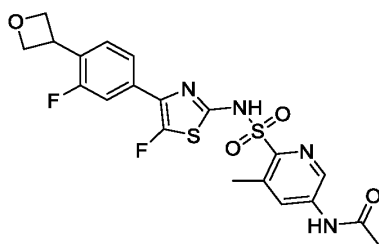
[0523] To a solution of (*E*)-*N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (290 mg, 512 μ mol, 1 *eq*) in DCE (5 mL) was added NaBH(OAc)₃ (325 mg, 1.54 mmol, 3.0 *eq*). The mixture was stirred at 20 °C for 2 hr then the reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (20 mL $\times$ 2). The combined organic layers were concentrated to give a residue which was purified by prep-HPLC to give *N*-(4-(4-(difluoromethyl)-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-38**, 145 mg, 255 μ mol, 50% yield) as a white solid.

[0524] Example 69: Synthesis of *N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-39**, Scheme 71).

[0525] Compound **I-39** may be prepared according to Scheme 71:

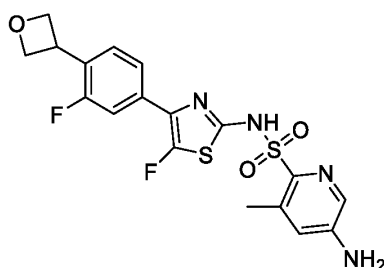


Scheme 71



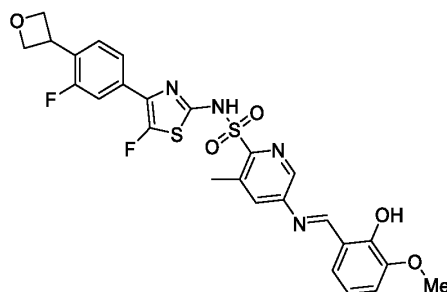
N-(6-(N-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide

[0526] To a solution of **II-2** (104 mg, 417 μmol , 1 *eq*; prepared via Scheme 4) in pyridine (1 mL) was added **III-25** (112 mg, 417 μmol , 1.0 *eq*; prepared via Scheme 31). The mixture was stirred at 20 °C for 48 hr under N_2 . LCMS most of **III-25** was consumed, and ~49% of desired product was observed. The reaction mixture was concentrated to remove the solvent. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=100/0 to 0/100). *N*-(6-(*N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (132 mg, 274 μmol , 66% yield) was obtained as a yellow solid.



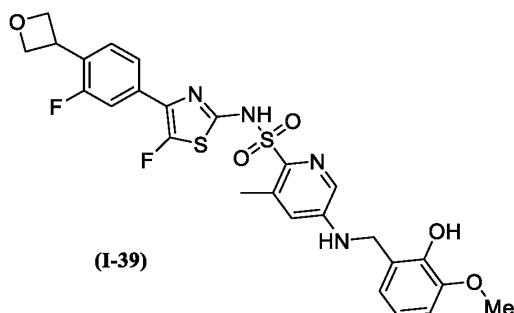
5-amino-*N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0527] To a solution of *N*-(6-(*N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (112 mg, 233 μmol , 1 *eq*) in EtOH (2 mL)/ H_2O (0.2 mL) was added NaOH (200 mg, 5.00 mmol, 21.45 *eq*). The mixture was stirred at 80 °C for 2 hr. LCMS showed *N*-(6-(*N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide was almost consumed, and ~92% of desired product was observed. The reaction mixture was concentrated to give a residue. The residue was added H_2O (15 mL) and extracted with EA (20 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated to give the crude product. The crude product 5-amino-*N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (101 mg, crude) was obtained as a red solid and used in the next step without further purification.



(*E*)-*N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0528] To a mixture of 5-amino-*N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (101 mg, 230.4 μ mol, 1 *eq*) and 2-hydroxy-3-methoxybenzaldehyde (35 mg, 230 μ mol, 1 *eq*) in toluene (2 mL) was heated to 120 °C and stirred for 16 hr. The reaction mixture was cooled to 20 °C and concentrated to remove the solvent. The crude product (*E*)-*N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (131 mg, crude) was obtained as a yellow solid and used in the next step without further purification.

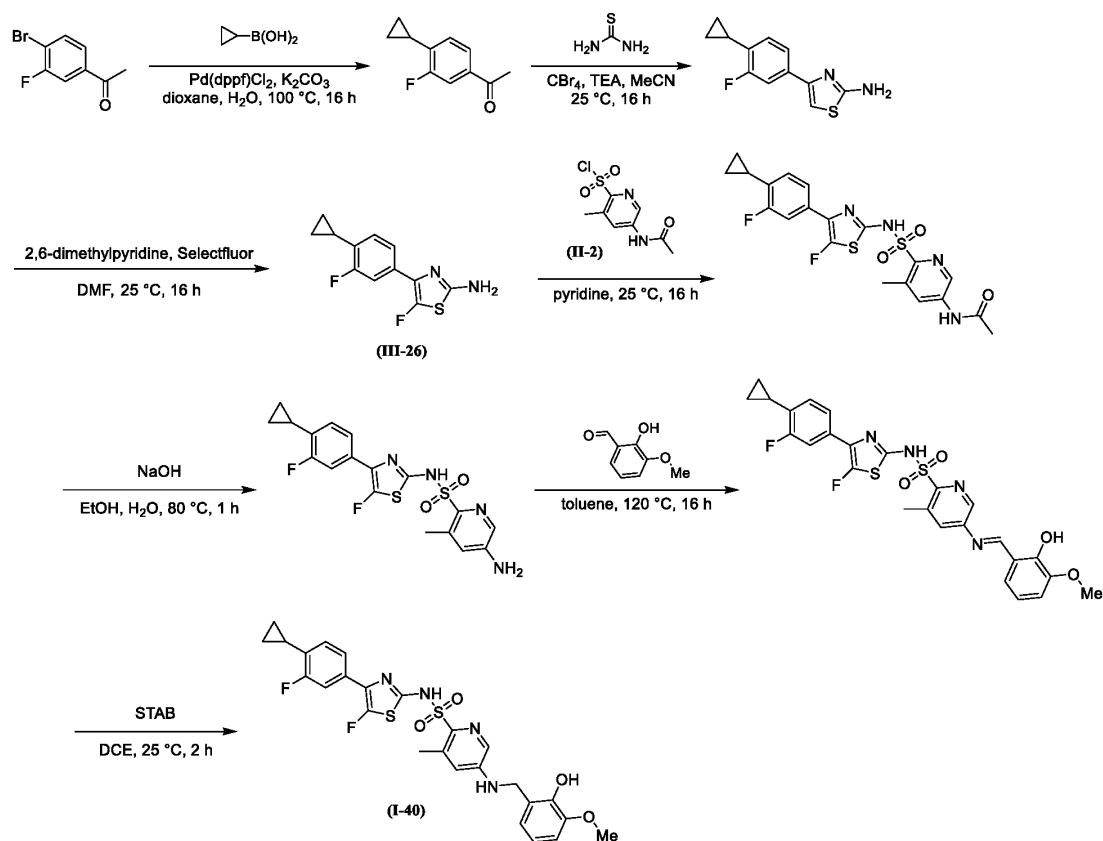


***N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

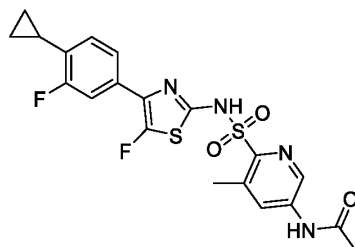
[0529] To a solution of (*E*)-*N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (131 mg, 229 μ mol, 1 *eq*) in DCE (2 mL) was added NaBH(OAc)₃ (145 mg, 686 μ mol, 3.0 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed the desired product was formed. The reaction mixture was added H₂O (20 mL) and extracted with EA (20 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give a residue. The residue was purified by prep-HPLC and *N*-(5-fluoro-4-(3-fluoro-4-(oxetan-3-yl)phenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-39**, 22 mg, 39 μ mol, 17% yield) was obtained as a white solid.

[0530] Example 70: Synthesis of *N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-40**, Scheme 72).

[0531] Compound **I-40** may be prepared according to Scheme 72:



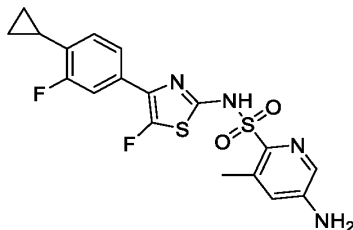
Scheme 72



***N*-(6-(*N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

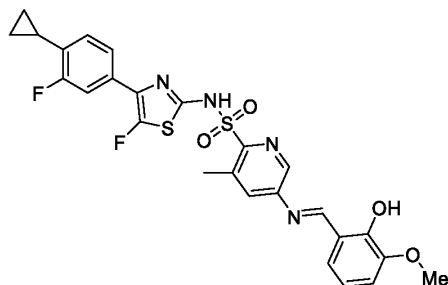
[0532] To a solution of **III-26** (590 mg, 2.34 mmol, 1 eq; prepared via Scheme 32) in pyridine (3 mL) was added **II-2** (640 mg, 2.57 mmol, 1.1 eq; prepared via Scheme 4). The mixture was stirred at 25°C for 16 hr then the reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL). The combined organic layers were washed with aqueous NaCl (50 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~56% Ethyl acetate/Petroleum

ether gradient at 25 mL/min) to give *N*-(6-(*N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (410 mg, 883 μ mol, 38% yield) as a black solid.



5-amino-*N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)-3-methylpyridine-2-sulfonamide

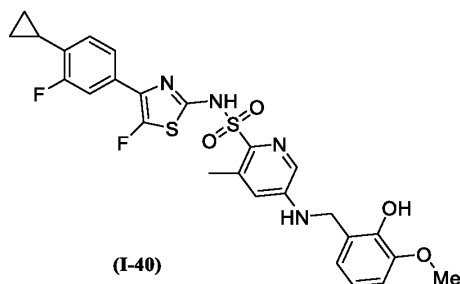
[0533] To a solution of *N*-(6-(*N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (410 mg, 882.65 μ mol, 1 *eq*) in EtOH (3 mL) and H₂O (1 mL) was added NaOH (353 mg, 8.83 mmol, 10 *eq*). The mixture was stirred at 80 °C for 1 hr then the reaction was diluted with H₂O (20 mL) and extracted with EtOAc (30 mL $\times$ 2). The combined organic layers were washed with aqueous NaCl (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The resulting solid was used without purification in the next step. 5-amino-*N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)-3-methylpyridine-2-sulfonamide (300 mg, 710.11 μ mol, 80% yield) was obtained as a red solid.



(*E*)-*N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0534] To a solution of 5-amino-*N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)-3-methylpyridine-2-sulfonamide (300 mg, 710 μ mol, 1 *eq*) in toluene (5 mL) was added 2-hydroxy-3-methoxybenzaldehyde (119 mg, 781 μ mol, 1.1 *eq*). The mixture was stirred at 120 °C for 16 hr then the reaction mixture was concentrated under reduced pressure to remove toluene (5 mL). The product was used crude in the next reaction. (*E*)-*N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-

methylpyridine-2-sulfonamide (395 mg, 710 μ mol, 100% yield) was obtained as a black solid.

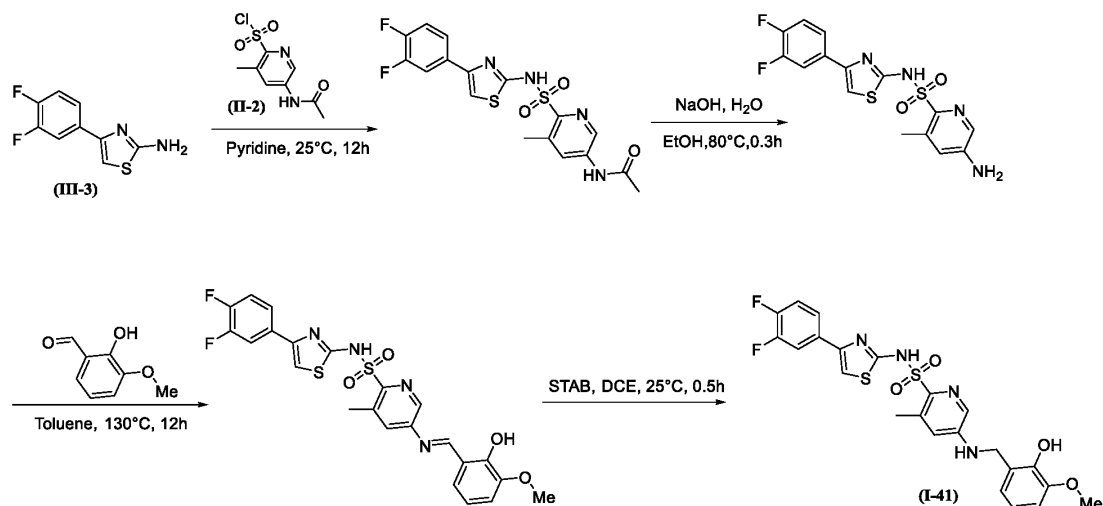


***N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

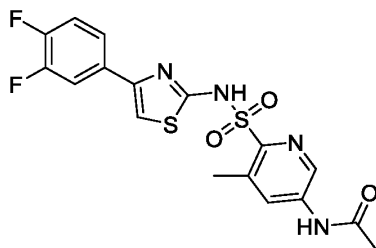
[0535] To a solution of (*E*)-*N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (395 mg, 709.6 μ mol, 1 *eq*) in DCE (5 mL) was added NaBH(OAc)₃ (451 mg, 2.13 mmol, 3 *eq*). The mixture was stirred at 25 °C for 2 hr then the reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL $\times$ 2). The combined organic layers were washed with aqueous NaCl (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The resulting residue was purified by prep-HPLC to give *N*-(4-(4-cyclopropyl-3-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-40**, 101 mg, 180.8 μ mol, 26% yield) as a yellow solid.

[0536] Example 71: Synthesis of *N*-(4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (I-41**, Scheme 73).**

[0537] Compound **I-41** may be prepared according to Scheme 73:

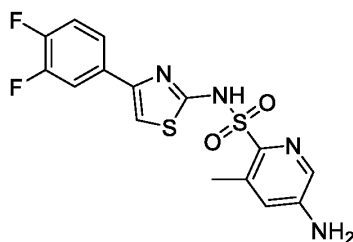


Scheme 73



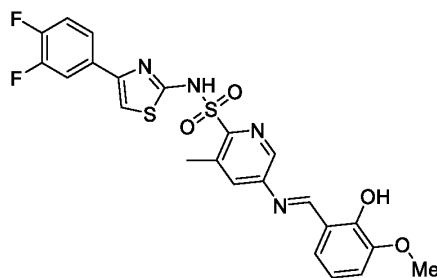
***N*-(6-(*N*-(4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

[0538] A mixture of **III-3** (3.56 g, 16.75 mmol, 1 *eq*; prepared via Scheme 9) in pyridine (60 mL) was degassed and purged with N₂ at 0 °C, and then added **II-2** (5 g, 20.11 mmol, 1.2 *eq* prepared via Scheme 4), the mixture was stirred at 25 °C for 12 hours under a N₂ atmosphere. The reaction mixture was extracted with ethyl acetate (60 mL × 3), washed with brine (40 mL × 2), dried over Na₂SO₄ and concentrated to dryness. The residue was purified by column chromatography (silica gel, 100-200 mesh, 60% ethyl acetate in petroleum ether) to afford compound *N*-(6-(*N*-(4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (6.68 g, 94% yield) as a brown solid.



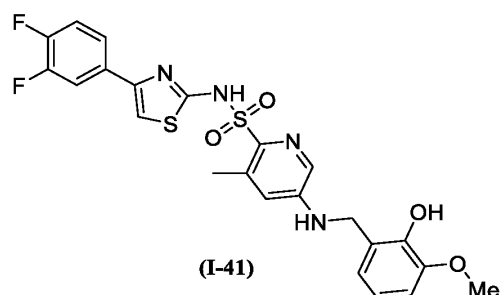
5-amino-*N*-(4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0539] To a solution of *N*-(6-(*N*-(4-(3,4-difluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (6.68 g, 15.74 mmol) in EtOH (30 mL) and H₂O (5 mL) was added NaOH (12.59 g, 62.97 mmol). The mixture was stirred at 80 °C for 0.3 hour. The reaction mixture was extracted with ethyl acetate (60 mL × 3), washed with brine (60 mL × 2), dried over Na₂SO₄ and concentrated to give the crude product 5-amino-*N*-(4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (4.7 g, crude) as a red solid, which was used in the next step directly.



(*E*)-*N*-(4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0540] To a solution of 2-hydroxy-3-methoxybenzaldehyde (167.10 mg, 1.10 mmol) in Toluene (5 mL) was added 5-amino-*N*-(4-(3,4-difluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (300 mg, crude). The mixture was stirred at 130 °C for 12 hours. The solvent was removed under pressure reduction to afford (*E*)-*N*-(4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (350 mg, crude) as a brown solid, which was used in the next step without further purification.

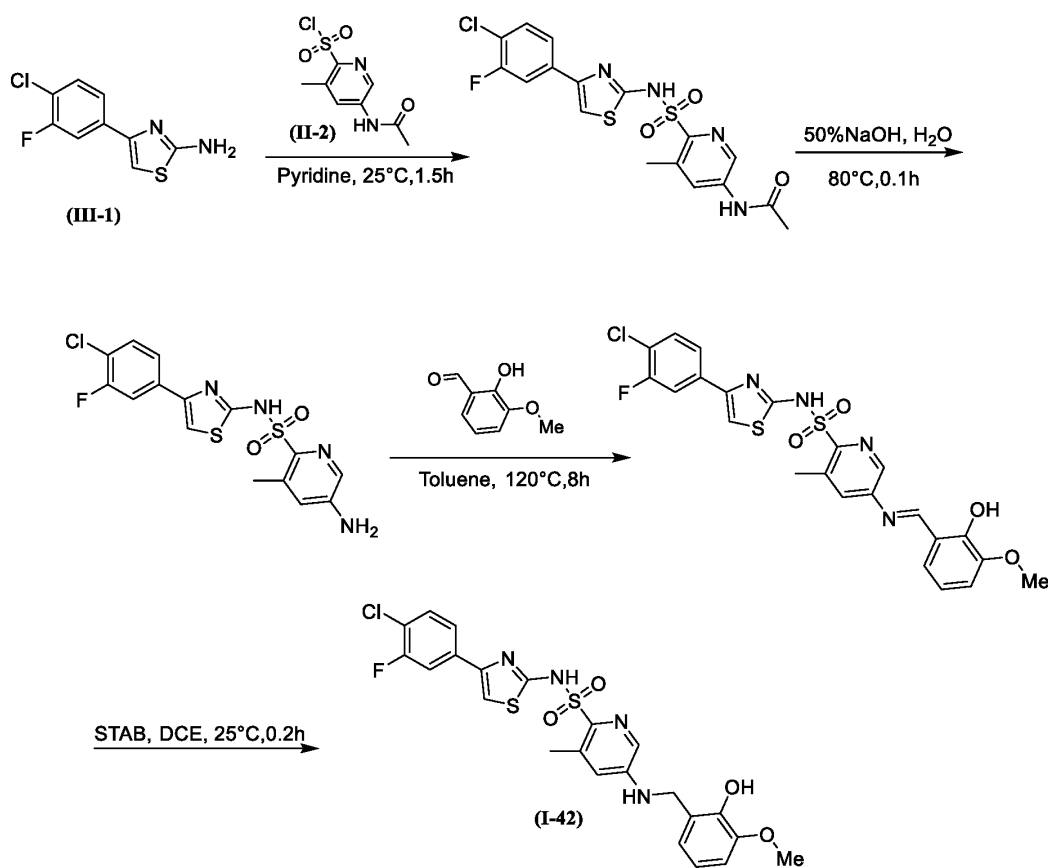


***N*-(4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

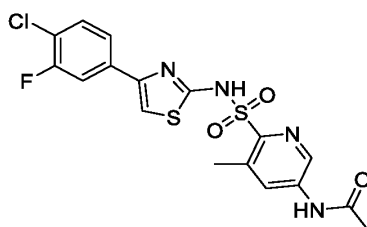
[0541] A mixture of (*E*)-*N*-(4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (350 mg, crude) was added into DCE (5 mL) and then added STAB (431 mg, 2.03 mmol), the mixture was stirred at 25 °C for 0.5 hour. The mixture was extracted with ethyl acetate (30 mL × 3), washed with brine (40 mL × 2), dried over Na₂SO₄ and concentrated to dryness. The residue was purified by column chromatography (silica gel, 100-200 mesh, 45% ethyl acetate in petroleum ether). The pure fractions were collected, and the volatiles were removed under vacuum. The residue was partitioned between acetonitrile (20 mL) and water (100 mL). The solution was lyophilized to dryness to give the product *N*-(4-(3,4-difluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-41**, 105 mg, 73% yield, 96%) as a white solid.

[0542] **Example 72:** Synthesis of *N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-42**, Scheme 74).

[0543] Compound **I-42** may be prepared according to Scheme 74:



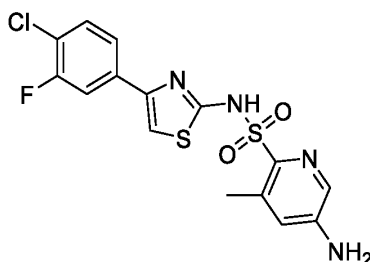
Scheme 74



***N*-(6-(*N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

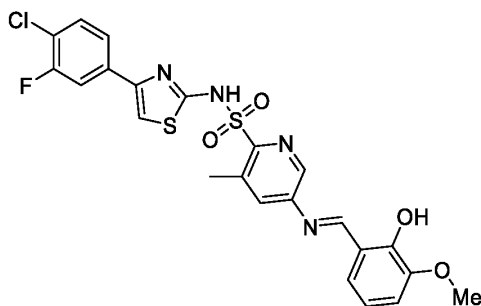
[0544] A mixture of **III-1** (4 g, 17.49 mmol; prepared via Scheme 7) in pyridine (60 mL) was degassed and purged with N₂ at 0 °C, and then added 5-acetamido-3-methylpyridine-2-sulfonyl chloride (**II-2**, 5.22 g, 20.99 mmol; prepared via Scheme 4), the mixture was stirred at 25 °C for 1.5 hours under N₂ atmosphere. The reaction mixture was extracted with ethyl acetate (100 mL × 3), washed with brine (120 mL × 2), dried over Na₂SO₄ and concentrated to dryness. The residue was purified by column chromatography (silica gel, 100-200 mesh,

60% ethyl acetate in petroleum ether) to afford *N*-(6-(*N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (7.0 g, 91% yield) as a brown solid.



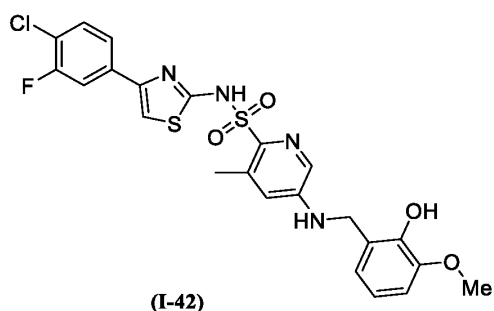
5-amino-*N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0545] To a solution of *N*-(6-(*N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (7.00 g, 15.88 mmol) in EtOH (8 mL) and H₂O (25 mL) was added NaOH (5.08 g, 127.0 mmol). The mixture was stirred at 80 °C for 0.1 hour. The reaction mixture was extracted with ethyl acetate (100 mL × 3), washed with brine (120 mL × 2), dried over Na₂SO₄ and concentrated to give the crude product 5-amino-*N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (6.68 g, crude) as a red solid, which was used directly in the next step.



(*E*)-*N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0546] To a solution of 2-hydroxy-3-methoxybenzaldehyde (267.0 mg, 1.75 mmol) in Toluene (15 mL) was added 5-amino-*N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (500 mg, crude). The mixture was stirred at 120 °C for 8 hours. The solvent was removed under pressure reduction to afford (*E*)-*N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (680 mg, crude) as a brown solid, which was used into the next step without further purification.

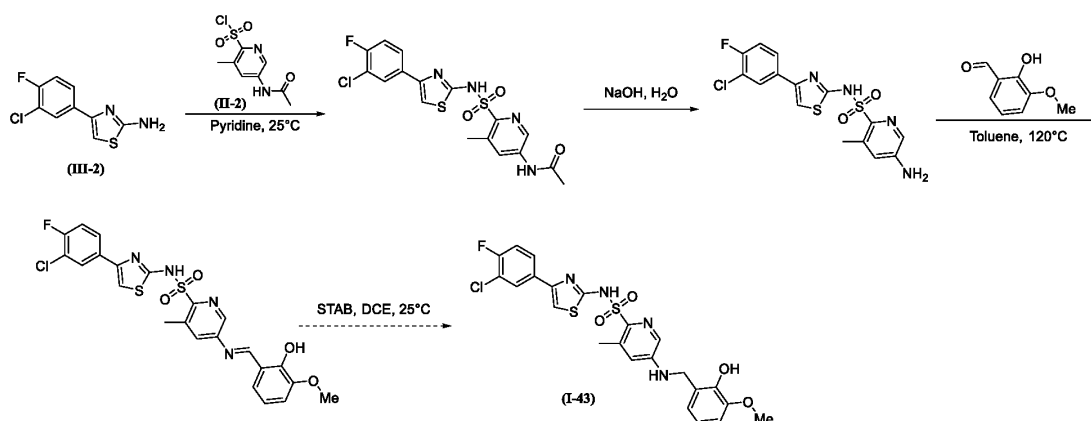


***N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

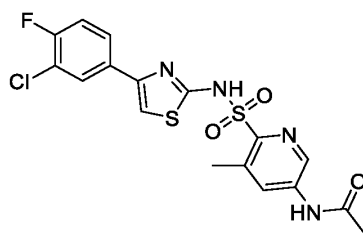
[0547] A mixture of (*E*)-*N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (680 mg, crude) was added into DCE (20 mL) and then added sodium triacetoxyborohydride (811 mg, 3.83 mmol), the mixture was stirred at 25 °C for 0.2 hour. The mixture was extracted with ethyl acetate (100 mL × 3), washed with brine (60 mL × 2), dried over Na₂SO₄ and concentrated to dryness. The crude was purified by *prep.*HPLC (column: Phenomenex luna C18 250 × 50mm × 15 μm; mobile phase: [water(FA)-ACN];gradient:26%-56% B over 25 min). The pure fractions were collected, and the volatiles were removed under vacuum. The residue was partitioned between acetonitrile (20 mL) and water (100 mL). The solution was lyophilized to dryness to give the product *N*-(4-(4-chloro-3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-42**, 304 mg, 44% yield) was obtained as a white solid.

[0548] Example 73: Synthesis of *N*-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (I-43**, Scheme 75).**

[0549] Compound **I-43** may be prepared according to Scheme 75:

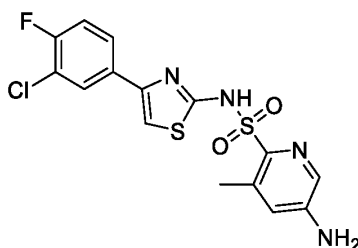


Scheme 75



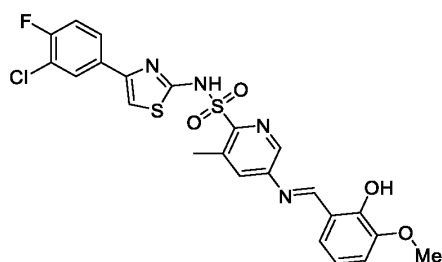
***N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide**

[0550] To a solution of **III-2** (3.83 g, 16.76 mmol, 1 *eq*; prepared via Scheme 8) in pyridine (80 mL) was added 5-acetamido-3-methyl-pyridine-2-sulfonyl chloride (**II-2**, 5 g, 20.11 mmol, 1.2 *eq*; prepared via Scheme 4). The mixture was stirred at 25 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H₂O (100 mL) and extracted with EA (100 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude was purified by FCC (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 20% Methanol : Dichloromethane ether gradient at 50 mL/min), Petroleum ether/Ethyl acetate=0: 1, R_f=0.5). *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (5.95 g, 13.50 mmol, 80% yield) was obtained as a brown solid.



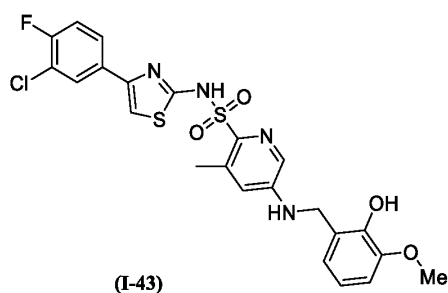
5-amino-*N*-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide

[0551] To a solution of *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)sulfamoyl)-5-methylpyridin-3-yl)acetamide (5.9 g, 13.38 mmol, 1 *eq*) in EtOH (25 mL) was added NaOH (535 mg, 13.38 mmol, 1 *eq*). The mixture was stirred at 80 °C for 1 hr. The residue was diluted with H₂O (200 mL) and extracted with EA (200 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (6.5 g, crude) was obtained as a brown solid.



(E)-N-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide

[0552] To a solution of 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-3-methylpyridine-2-sulfonamide (500 mg, 1.25 mmol, 1 *eq*) in toluene (5 mL) was added 2-hydroxy-3-methoxy-benzaldehyde (267.02 mg, 1.75 mmol, 1.4 *eq*). The mixture was stirred at 120 °C for 12 hr. The mixture was then concentrated to the crude product, (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (500 mg, crude) was obtained as a brown solid.

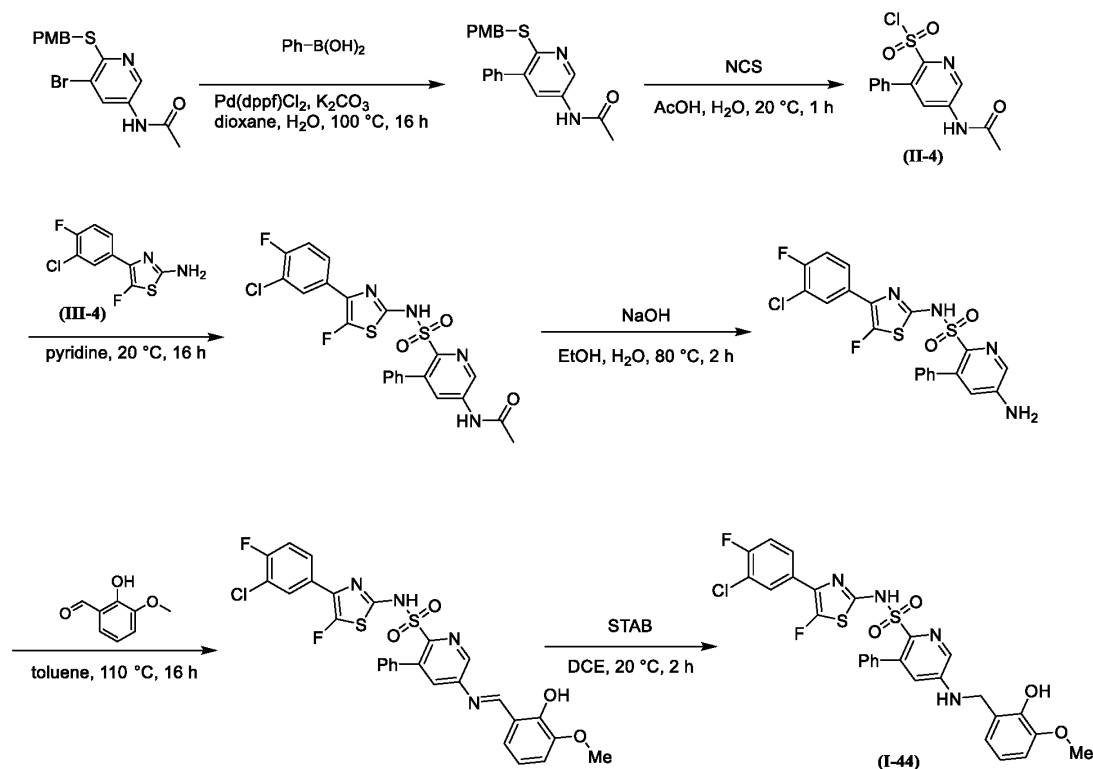


***N*-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide**

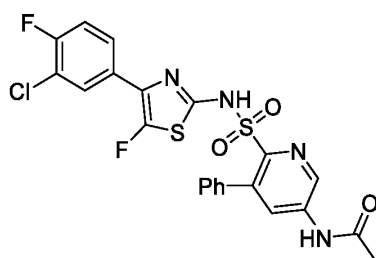
[0553] To a solution of (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-methylpyridine-2-sulfonamide (500 mg, crude) in DCE (8 mL) and MeOH (2 mL) was added sodium triacetoxyborohydride (597 mg, 2.81 mmol, 3 *eq*). The mixture was stirred at 25 °C for 1 hr. The residue was diluted with H₂O (20 mL) and extracted with EA (20 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude was purified by FCC (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 55% Ethyl acetate/Petroleum ether gradient at 18 mL/min), Petroleum ether/Ethyl acetate=1:1, R_f=0.4). *N*-(4-(3-chloro-4-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-43**, 178 mg, 320 μmol, 34% yield, 96% purity) was obtained as the white solid.

[0554] **Example 74:** Synthesis of *N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-phenylpyridine-2-sulfonamide (**I-44**, Scheme 76).

[0555] Compound **I-44** may be prepared according to Scheme 76:



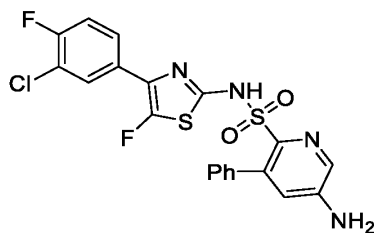
Scheme 76



N-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-phenylpyridin-3-yl)acetamide

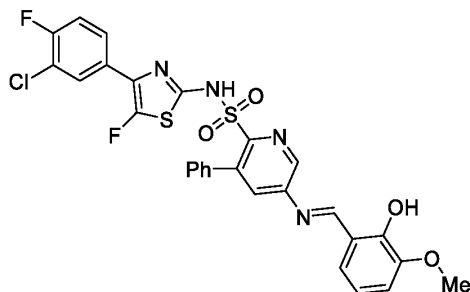
[0556] To a mixture of **III-4** (121 mg, 499 μ mol, 1 *eq*; prepared via Scheme 10) and **II-4** (260 mg, 837 μ mol, 1.68 *eq*; prepared via Scheme 6) in pyridine (4 mL) was stirred at 25 °C for 16 hr under N₂. The reaction mixture was adjusted to pH2 by 3M HCl and stirred at 25 °C for a further 1 hour. The mixture was then filtered to give the crude product. The crude product was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0

to 40/60) to give *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-phenylpyridin-3-yl)acetamide (103 mg, 198 μ mol, 40% yield) as a white solid.



5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-phenylpyridine-2-sulfonamide

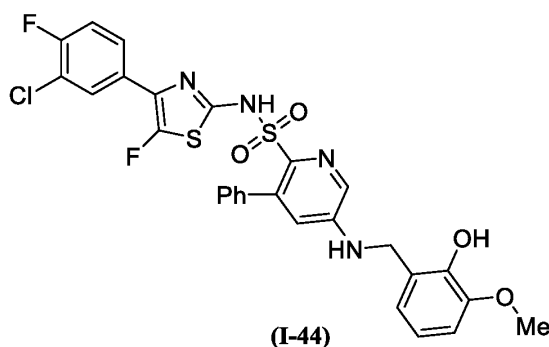
[0557] To a solution of *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-phenylpyridin-3-yl)acetamide (103 mg, 198 μ mol, 1 eq) in EtOH (1 mL)/H₂O (0.1 mL) was added NaOH (100 mg, 2.50 mmol, 12.65 eq) and stirred at 80 °C for 0.5 hr. The reaction mixture was then cooled to 25 °C and concentrated. The residue was diluted in H₂O (30 mL) and extracted with EA (30 mL $\times$ 2). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude product 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-phenylpyridine-2-sulfonamide (84 mg, crude) as a red solid and was used in the next step without further purification.



(*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-phenylpyridine-2-sulfonamide

[0558] To a solution of 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-phenylpyridine-2-sulfonamide (84 mg, 175 μ mol, 1.0 eq) in toluene (4 mL) was added 2-hydroxy-3-methoxybenzaldehyde (29. mg, 192.9 μ mol, 1.1 eq). The mixture was stirred at 120 °C for 16 hr under N₂. The reaction mixture was then cooled to 25 °C and concentrated to remove the solvent. The crude product (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-phenylpyridine-2-sulfonamide (107.5

mg, crude) was obtained as a yellow solid and used in the next step without further purification.

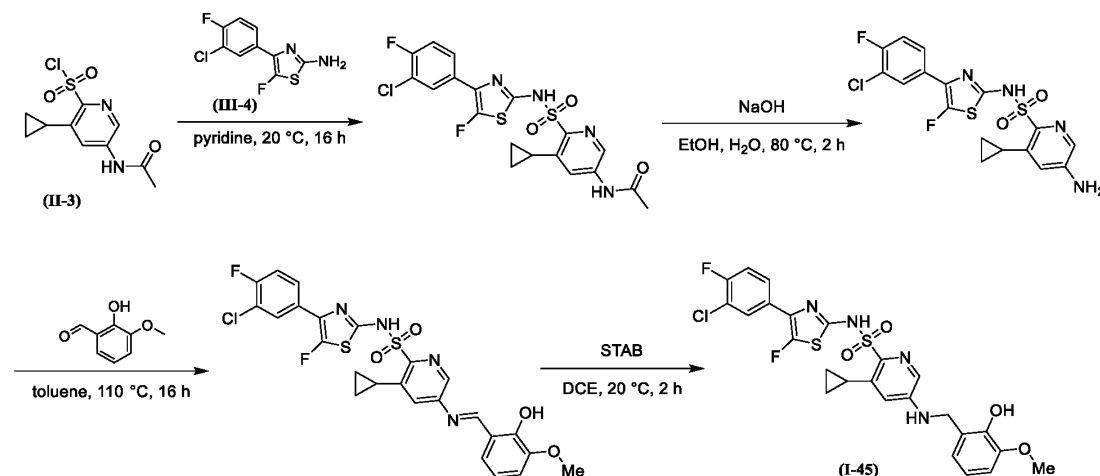


***N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-phenylpyridine-2-sulfonamide**

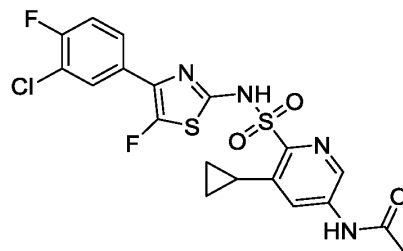
[0559] To a solution of (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzylidene)amino)-3-phenylpyridine-2-sulfonamide (107.5 mg, 175 μ mol, 1 *eq*) in DCE (1 mL) was added NaBH(OAc)₃ (111 mg, 526 μ mol, 3.0 *eq*). The mixture was stirred at 25 °C for 1 hr. then the reaction mixture was diluted with H₂O (20 mL) and extracted with EA (20 mL $\times$ 2). The combined organic layers were concentrated to give the crude product which was purified by prep-HPLC to give *N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-phenylpyridine-2-sulfonamide (**I-44**, 53.4 mg, 86.8 μ mol, 50% yield) as a white solid.

[0560] Example 75: Synthesis of *N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-cyclopropyl-5-((2-hydroxy-3-methoxybenzyl)amino)pyridine-2-sulfonamide (I-45**, Scheme 77).**

[0561] Compound **I-45** may be prepared according to Scheme 77:

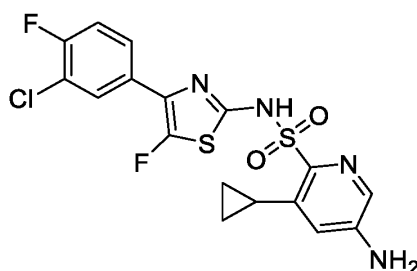


Scheme 77



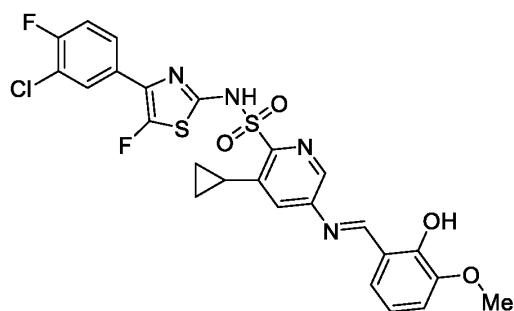
***N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-cyclopropylpyridin-3-yl)acetamide**

[0562] To a mixture of **III-4** (324 mg, 1.31 mmol, 1 *eq*; prepared via Scheme 11) and **II-3** (361 mg, 1.31 mmol, 1.0 *eq*; prepared via Scheme 6) in pyridine (4 mL) was stirred at 25 °C for 16 hr under N₂ then reaction mixture was adjusted to pH 2 by 3M HCl and stirred at 25 °C for an additional 1 hour. The mixture was then filtered to give the crude product which was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 40/60) to give *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-cyclopropylpyridin-3-yl)acetamide (260 mg, 536.16 μmol, 41% yield) as a white solid.



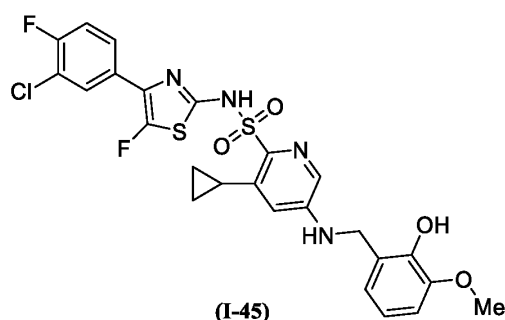
5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-cyclopropylpyridine-2-sulfonamide

[0563] To a solution of *N*-(6-(*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)sulfamoyl)-5-cyclopropylpyridin-3-yl)acetamide (260 mg, 536 μmol, 1 *eq*) in EtOH (2 mL)/H₂O (0.2 mL) was added NaOH (200 mg, 5.00 mmol, 9.33 *eq*) and stirred at 80 °C for 1 hr. The reaction mixture was then cooled to 25 °C and concentrated. The residue was re-dissolved in H₂O (30 mL) and extracted with EA (30 mL × 2). The combined organic layers were dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude product. The crude product 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-cyclopropylpyridine-2-sulfonamide (237 mg, 535.1 μmol, 100% yield) was obtained as a red solid and used in the next step without further purification.



(E)-N-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-cyclopropyl-5-((2-hydroxy-3-methoxybenzylidene)amino)pyridine-2-sulfonamide

[0564] To a solution of 5-amino-*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-cyclopropylpyridine-2-sulfonamide (237 mg, 535 μmol , 1.0 *eq*) in toluene (4 mL) was added 2-hydroxy-3-methoxybenzaldehyde (90 mg, 589 μmol , 1.1 *eq*). The mixture was stirred at 120 °C for 16 hr under N_2 . The reaction mixture was then cooled to 25 °C and concentrated to remove the solvent. The crude product (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-cyclopropyl-5-((2-hydroxy-3-methoxybenzylidene)amino)pyridine-2-sulfonamide (308 mg, crude) was obtained as a yellow solid and used in the next step without further purification.



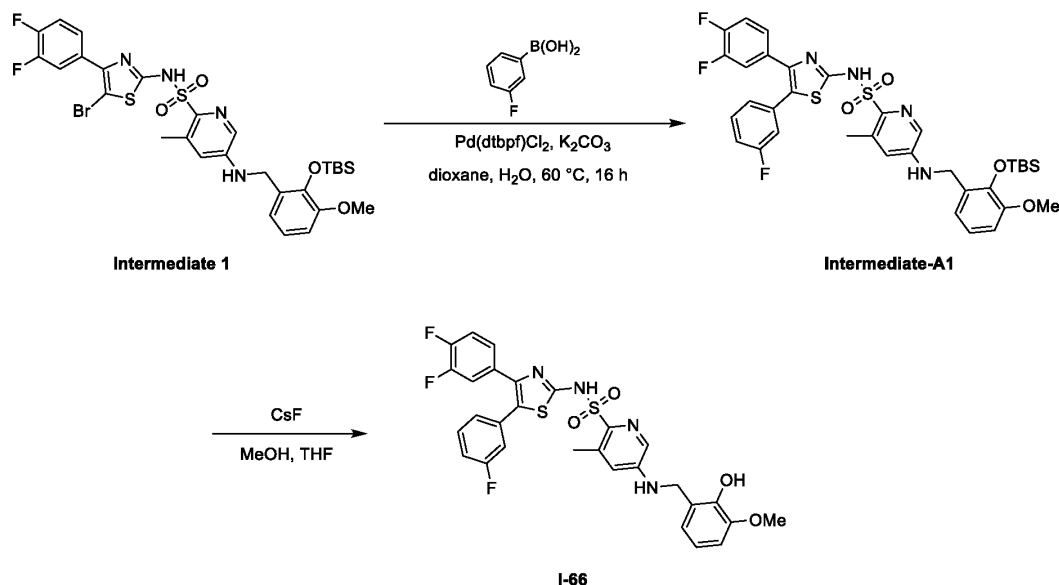
***N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-cyclopropyl-5-((2-hydroxy-3-methoxybenzyl)amino)pyridine-2-sulfonamide**

[0565] To a solution of (*E*)-*N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-cyclopropyl-5-((2-hydroxy-3-methoxybenzylidene)amino)pyridine-2-sulfonamide (308 mg, 534 μmol , 1 *eq*) in DCE (5 mL) was added $\text{NaBH}(\text{OAc})_3$ (339 mg, 1.60 mmol, 3.0 *eq*). The mixture was stirred at 25 °C for 2 hr. The reaction mixture was then diluted with H_2O (20 mL) and extracted with EA (20 mL $\times$ 2). The combined organic layers were concentrated to give the crude product. The residue was purified by prep-HPLC to give *N*-(4-(3-chloro-4-fluorophenyl)-5-fluorothiazol-2-yl)-3-cyclopropyl-5-((2-hydroxy-3-

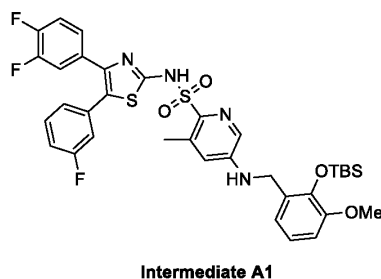
methoxybenzyl)amino)pyridine-2-sulfonamide (**I-45**, 117 mg, 202 μmol , 38% yield) was obtained as a white solid.

[0566] Example 76: Synthesis of *N*-(4-(3,4-difluorophenyl)-5-(3-fluorophenyl)thiazol-2-yl)-5-((2-hydroxy-3-methoxybenzyl)amino)-3-methylpyridine-2-sulfonamide (**I-66**, Scheme 78).

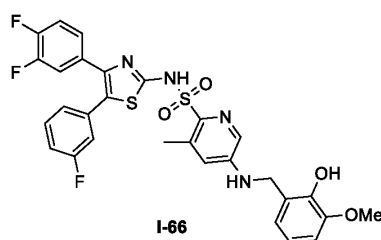
[0567] Compound **I-66** may be prepared according to Scheme 78:



Scheme 78



[0568] A mixture of (3-fluorophenyl)boronic acid (35.39 mg, 252.91 μmol , 3 eq), Intermediate 1 (60 mg, 84.30 μmol , 1 eq), Pd(dtbpf)Cl₂ (10.99 mg, 16.86 μmol , 0.2 eq), K₂CO₃ (34.95 mg, 252.91 μmol , 3 eq) in dioxane (2 mL) and H₂O (0.2 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 60 °C for 16 hr under N₂ atmosphere. LC-MS showed Intermediate 1 was consumed completely and desired mass was detected. The residue was diluted with H₂O (20 mL) and extracted with ethyl acetate (20 mL X 2). The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The product (Intermediate A1, 61 mg, 83.92 μmol , 99.54% yield) was used next step without purification.



[0569] To a solution of Intermediate A1 (61 mg, 83.92 μ mol, 1 eq) in THF (2 mL) and MeOH (1 mL) was added CsF (127.47 mg, 839.18 μ mol, 10 eq). The mixture was stirred at 25 °C for 16 hr. LC-MS showed starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove THF (2 mL) and MeOH (1 mL). The residue was purified by prep-HPLC (FA condition). Compound **I-66** (8.69 mg, 14.18 μ mol, 16.90% yield) was obtained as a solid.

[0570] LCMS: (M+H)⁺ = 613.1.

[0571] ¹H NMR (400 MHz, DMSO-d₆) δ = 8.77 (br s, 1H), 7.72 (s, 1H), 7.49 - 7.30 (m, 3H), 7.20 - 7.08 (m, 2H), 7.07 - 6.93 (m, 2H), 6.88 - 6.74 (m, 4H), 6.73 - 6.66 (m, 1H), 4.26 (br d, J = 5.7 Hz, 2H), 3.79 (s, 3H), 2.46 (s, 3H).

[0572] ¹⁹F NMR (376 MHz, DMSO-d₆) δ = -112.26, -136.48 - -140.40.

[0573] The following compounds of Formula (I) were prepared according to the methods described herein.

Table 1		
Cmpd. No.	Structure	NMR data
I-1		
I-2		¹ H NMR (400MHz, DMSO-d ₆) δ 12.83 (br s, 1H), 8.84 (s, 1H), 7.74 (d, J=2.3 Hz, 1H), 7.70 - 7.61 (m, 2H), 7.58 - 7.49 (m, 1H), 7.39 (br s, 1H), 6.95 - 6.84 (m, 2H), 6.82 - 6.76 (m, 2H), 6.74 - 6.69 (m, 1H), 5.76 (d, J=1.6 Hz, 1H), 4.26 (d, J=5.9 Hz, 2H), 3.80 (d, J=8.1 Hz, 6H), 2.45 (s, 3H)

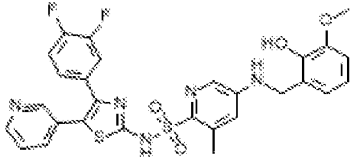
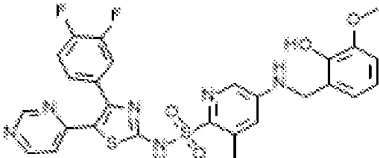
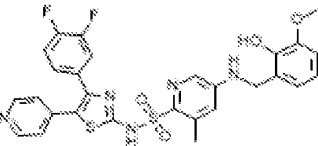
Table 1		
Cmpd. No.	Structure	NMR data
		¹⁹ F NMR (376MHz, DMSO-d6) δ -136.38 (br s, 1F), -137.67 (br s, 1F)
I-3		¹ H NMR (400MHz, DMSO-d6) δ 8.84 (s, 1H), 8.49 (d, J=3.6 Hz, 1H), 8.36 (d, J=1.8 Hz, 1H), 7.74 (d, J=2.4 Hz, 1H), 7.76 - 7.72 (m, 1H), 7.64 (td, J=1.9, 8.0 Hz, 1H), 7.53 - 7.40 (m, 2H), 7.38 (dd, J=4.8, 7.9 Hz, 1H), 7.19 - 7.13 (m, 1H), 6.93 (br t, J=5.8 Hz, 1H), 6.86 - 6.80 (m, 2H), 6.79 - 6.75 (m, 1H), 6.73 - 6.68 (m, 1H), 4.26 (d, J=5.8 Hz, 2H), 3.78 (s, 3H), 2.46 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d6) δ -136.90 (br s, 1F), -137.48 (br d, J=24.3 Hz, 1F)
I-4		¹ H NMR (400MHz, DMSO-d6) δ 9.07 (s, 1H), 8.84 (s, 1H), 8.52 (d, J=5.5 Hz, 1H), 7.80 (br t, J=8.8 Hz, 1H), 7.75 (d, J=2.4 Hz, 1H), 7.66 - 7.58 (m, 1H), 7.46 (br d, J=4.4 Hz, 1H), 6.96 (br t, J=5.7 Hz, 1H), 6.87 - 6.80 (m, 3H), 6.79 - 6.75 (m, 1H), 6.72 - 6.67 (m, 1H), 4.25 (br d, J=5.6 Hz, 2H), 3.78 (s, 3H), 2.44 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d6) δ -135.25 (br s, 1F), -136.74 (br s, 1F)
I-5		¹ H NMR (400MHz, DMSO-d6) δ 8.86 (s, 1H), 8.49 (br d, J=5.4 Hz, 2H), 7.75 (d, J=2.0 Hz, 1H), 7.63 - 7.56 (m, 1H), 7.55 - 7.47 (m, 1H), 7.25 (br s, 1H), 7.13 (d, J=5.7 Hz, 2H), 6.97 (br t, J=5.7 Hz, 1H), 6.88

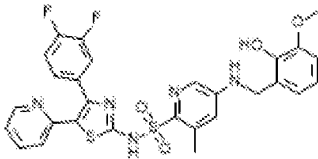
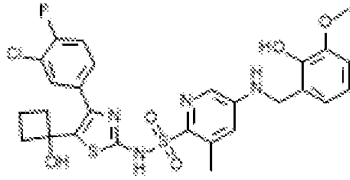
Table 1		
Cmpd. No.	Structure	NMR data
		- 6.81 (m, 2H), 6.80 - 6.75 (m, 1H), 6.74 - 6.68 (m, 1H), 4.27 (br d, J=5.7 Hz, 2H), 3.79 (s, 3H), 2.46 (s, 3H) ¹⁹F NMR (376MHz, DMSO-d6) δ -136.21 (br s, 1F), -137.27 (br s, 1F)
I-6		¹H NMR (400MHz, DMSO-d6) δ = 12.95 (br s, 1H), 8.85 (s, 1H), 8.52 (d, J=4.5 Hz, 1H), 7.77 - 7.67 (m, 2H), 7.63 - 7.53 (m, 2H), 7.40 (br s, 1H), 7.23 (dd, J=5.1, 7.2 Hz, 1H), 6.92 (br d, J=8.1 Hz, 2H), 6.87 - 6.83 (m, 1H), 6.82 - 6.76 (m, 2H), 6.73 - 6.68 (m, 1H), 4.26 (br d, J=5.9 Hz, 2H), 3.79 (s, 3H), 2.45 (s, 3H) ¹⁹F NMR (376MHz, DMSO-d6) δ = -135.83 (br s, 1F), -137.13 (br s, 1F)
I-7		¹H NMR (400MHz, DMSO-d6) δ = 7.99 (dd, J=2.1, 7.7 Hz, 1H), 7.79 (ddd, J=2.1, 5.0, 8.7 Hz, 1H), 7.64 (d, J=2.6 Hz, 1H), 7.31 (t, J=9.0 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.79 - 6.76 (m, 1H), 6.70 - 6.66 (m, 2H), 6.52 (br s, 1H), 5.73 (br s, 1H), 4.23 (br s, 2H), 3.78 (s, 3H), 2.43 (s, 3H), 2.18 - 2.11 (m, 4H), 1.73 - 1.66 (m, 1H), 1.36 (td, J=8.4, 10.7 Hz, 1H) ¹⁹F NMR (376MHz, DMSO-d6) δ = -119.73 - -119.92 (m, 1F)

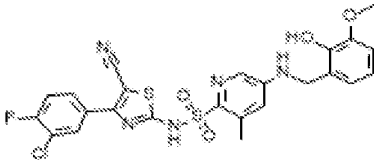
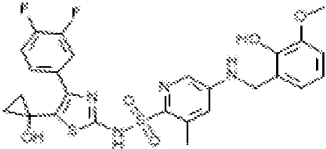
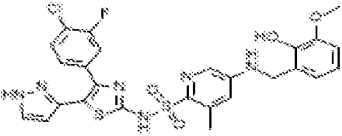
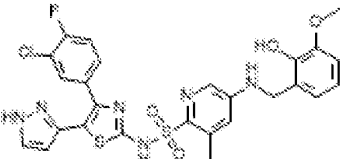
Table 1		
Cmpd. No.	Structure	NMR data
I-8		¹ H NMR (400MHz, DMSO-d ₆) δ 8.79 (s, 1H), 8.01 (dd, J=2.0, 7.2 Hz, 1H), 7.90 (br dd, J=2.3, 5.9 Hz, 1H), 7.67 (br s, 1H), 7.54 (t, J=9.0 Hz, 1H), 6.84 (br d, J=7.7 Hz, 1H), 6.79 - 6.66 (m, 4H), 4.24 (br d, J=4.2 Hz, 2H), 3.78 (s, 3H), 2.41 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ -112.44 - -117.07 (m, 1F)
I-9		
I-10		¹ H NMR (400MHz, DMSO-d ₆) δ 13.05 (br s, 1H), 8.81 (s, 1H), 7.77 - 7.54 (m, 4H), 7.36 (br d, J=7.6 Hz, 1H), 6.84 (br d, J=7.6 Hz, 2H), 6.77 (br d, J=7.7 Hz, 2H), 6.73 - 6.66 (m, 1H), 5.90 (br s, 1H), 4.25 (br d, J=5.7 Hz, 2H), 3.78 (s, 3H), 2.44 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ -70.03 - -76.91 (m, 1F)
I-11		¹ H NMR (400MHz, DMSO-d ₆) δ 13.05 (br s, 1H), 8.82 (s, 1H), 7.78 (br d, J=6.1 Hz, 1H), 7.73 (d, J=2.1 Hz, 1H), 7.67 (br s, 1H), 7.56 - 7.44 (m, 2H), 6.90 (br s, 1H), 6.84 (dd, J=1.1, 7.9 Hz, 1H), 6.81 - 6.75 (m, 2H), 6.73 - 6.67 (m, 1H), 5.80 (br s, 1H), 4.25 (br d, J=5.8 Hz, 2H), 3.78 (s, 3H), 2.44 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ -111.80 - -117.70 (m, 1F)

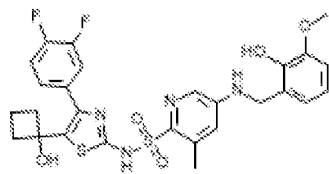
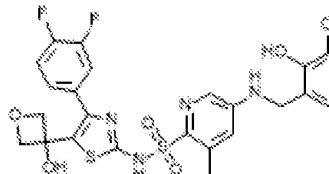
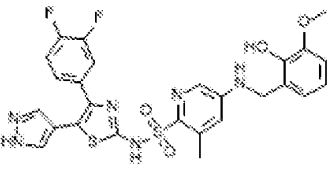
Table 1		
Cmpd. No.	Structure	NMR data
I-12		¹ H NMR (400 MHz, DMSO) δ 12.61 (br s, 1H), 8.85 (s, 1H), 7.68 (s, 1H), 7.42 (q, J=8.6 Hz, 1H), 7.23 - 7.17 (m, 1H), 6.95 (br s, 1H), 6.89 - 6.75 (m, 4H), 6.75 - 6.69 (m, 1H), 5.96 (br s, 1H), 4.26 (br d, J=5.4 Hz, 2H), 3.80 (s, 3H), 2.43 (s, 3H), 2.27 (br d, J=8.2 Hz, 2H), 2.15 - 2.01 (m, 3H), 1.68 - 1.59 (m, 1H) ¹⁹ F NMR (376MHz, DMSO-d6) δ -136.70 (br s, 1F), -138.50 (br s, 1F)
I-13		¹ H NMR (400MHz, DMSO-d6) δ 8.85 (s, 1H), 8.15 (s, 1H), 7.74 - 7.61 (m, 2H), 7.57 - 7.42 (m, 2H), 6.91 - 6.75 (m, 5H), 6.73 - 6.68 (m, 1H), 4.50 (br d, J=6.7 Hz, 2H), 4.39 (d, J=6.6 Hz, 2H), 4.25 (br d, J=5.7 Hz, 2H), 3.79 (s, 3H), 2.44 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d6) δ -136.40 (ddd, J=4.1, 9.5, 20.4 Hz, 1F), -138.22 (br dd, J=6.8, 20.4 Hz, 1F)
I-14		¹ H NMR (400MHz, DMSO-d6) δ 8.79 (br s, 1H), 8.23 (s, 1H), 7.66 (br d, J=2.1 Hz, 1H), 7.56 - 7.38 (m, 3H), 7.36 - 7.26 (m, 2H), 6.84 (br d, J=7.9 Hz, 1H), 6.79 - 6.75 (m, 1H), 6.75 - 6.68 (m, 2H), 6.66 (br d, J=13.1 Hz, 1H), 4.24 (br d, J=5.9 Hz, 2H), 3.79 (s, 3H), 2.44 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d6) δ -138.95 (br s, 1F)

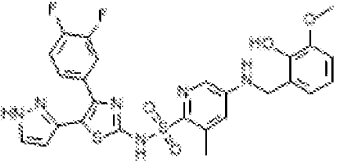
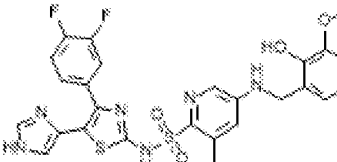
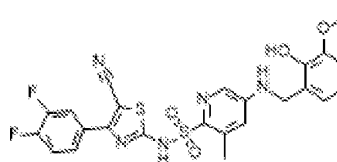
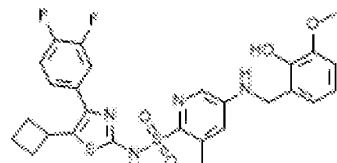
Table 1		
Cmpd. No.	Structure	NMR data
I-15		¹ H NMR (400MHz, DMSO-d ₆) δ 12.92 (br s, 2H), 8.86 (br s, 1H), 7.74 (s, 1H), 7.71 - 7.64 (m, 2H), 7.59 - 7.50 (m, 1H), 7.39 (br s, 1H), 6.93 - 6.58 (m, 5H), 5.81 (s, 1H), 4.26 (s, 2H), 3.78 (s, 3H), 2.45 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ -136.48 (br s, 1F), -137.66 (br s, 1F)
I-16		¹ H NMR (400MHz, DMSO-d ₆) δ 12.25 (br s, 1H), 8.82 (br s, 1H), 7.74 - 7.60 (m, 3H), 7.52 - 7.35 (m, 2H), 6.90 - 6.81 (m, 3H), 6.77 (br d, J=7.3 Hz, 2H), 6.72 - 6.67 (m, 1H), 4.24 (br d, J=5.6 Hz, 2H), 3.78 (s, 3H), 2.44 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ -138.02 (br s, 1F)
I-17		¹ H NMR (400MHz, DMSO-d ₆) δ 8.84 (br s, 1H), 8.13 (s, 1H), 7.89 - 7.78 (m, 1H), 7.71 (br d, J=2.0 Hz, 2H), 7.64 - 7.55 (m, 1H), 6.98 (br d, J=17.1 Hz, 1H), 6.87 - 6.80 (m, 2H), 6.78 - 6.74 (m, 1H), 6.73 - 6.66 (m, 1H), 4.25 (s, 2H), 3.78 (s, 3H), 2.43 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ -135.70 (br s, 1F), -137.32 (br s, 1F)
I-18		¹ H NMR (400 MHz, DMSO) δ 13.47 - 11.74 (m, 1H), 8.85 (br s, 1H), 7.71 (br s, 1H), 7.52 (quin, J=9.7 Hz, 2H), 7.24 (br d, J=8.1 Hz, 1H), 6.86 (br d, J=7.9 Hz, 2H), 6.78 (br d, J=8.6 Hz, 2H), 6.74 - 6.68 (m, 1H), 4.26 (br d, J=5.6 Hz, 2H), 3.79

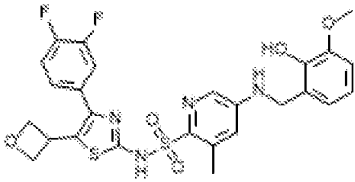
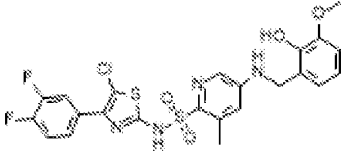
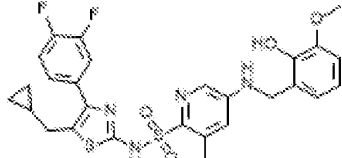
Table 1		
Cmpd. No.	Structure	NMR data
		(s, 3H), 3.60 (td, J=8.5, 17.1 Hz, 1H), 2.44 (s, 3H), 2.25 (br d, J=8.1 Hz, 2H), 1.99 (quin, J=9.2 Hz, 2H), 1.93 - 1.83 (m, 1H), 1.81 - 1.70 (m, 1H) ¹⁹ F NMR (376MHz, DMSO-d6) δ -137.85 (br s, 2F)
I-19		¹ H NMR (400MHz, DMSO-d6) δ = 8.79 (br s, 1H), 7.67 (br s, 1H), 7.49 - 7.31 (m, 2H), 7.15 (br s, 1H), 6.84 (br d, J=7.9 Hz, 1H), 6.80 - 6.75 (m, 1H), 6.75 - 6.61 (m, 3H), 4.82 (m, 1H), 4.50 - 4.39 (m, 3H), 4.24 (br d, J=5.3 Hz, 2H), 3.79 (s, 3H), 2.44 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d6) δ = -138.60 (br s, 1F), -140.46 (s, 1F)
I-20		¹ H NMR (400MHz, DMSO-d6) δ = 8.86 (s, 1H), 7.79 - 7.72 (m, 2H), 7.62 - 7.54 (m, 2H), 7.02 (br s, 1H), 6.88 - 6.82 (m, 2H), 6.80 - 6.75 (m, 1H), 6.74 - 6.68 (m, 1H), 4.27 (br d, J=4.3 Hz, 2H), 3.79 (s, 3H), 2.44 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d6) δ = -136.51 (br s, 1F), -137.11 - -137.61 (m, 1F)
I-21		¹ H NMR (400MHz, DMSO-d6) δ 8.91 (s, 1H), 7.69 (d, J=2.4 Hz, 1H), 7.61 - 7.48 (m, 2H), 7.34 - 7.27 (m, 1H), 7.35 - 7.27 (m, 1H), 6.91 (br t, J=5.9 Hz, 1H), 6.84 (dd, J=1.4, 7.9 Hz, 1H), 6.81 - 6.73 (m, 2H), 6.73 - 6.65 (m, 1H), 4.24 (br d, J=5.9 Hz, 2H), 3.77 (s, 3H), 2.48 (br s, 2H), 2.42 (s, 3H),

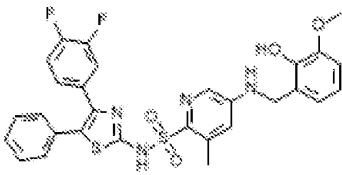
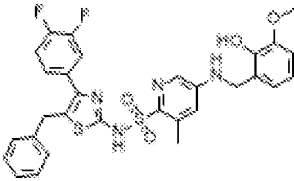
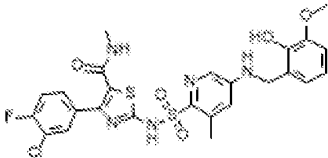
Table 1		
Cmpd. No.	Structure	NMR data
		0.95 - 0.80 (m, 1H), 0.53 - 0.42 (m, 2H), 0.21 - 0.10 (m, 2H) ¹⁹ F NMR (376MHz, DMSO-d6) δ -137.59 (br s, 1F)
I-22		¹ H NMR (400 MHz, DMSO-d6) δ = 13.11 - 12.84 (m, 1H), 8.79 (s, 1H), 7.74 (s, 1H), 7.52 - 7.38 (m, 2H), 7.37 - 7.27 (m, 3H), 7.26 - 7.11 (m, 3H), 6.95 - 6.83 (m, 2H), 6.82 - 6.75 (m, 2H), 6.74 - 6.65 (m, 1H), 4.26 (br d, J = 5.9 Hz, 2H), 3.79 (s, 3H), 2.46 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d6) δ = -136.88 (br s, 1F), -137.39 - -138.36 (m, 1F)
I-23		¹ H NMR (400MHz, DMSO-d6) δ 8.86 (br s, 1H), 7.66 (d, J=1.8 Hz, 1H), 7.64 - 7.57 (m, 1H), 7.56 - 7.49 (m, 1H), 7.36 (br d, J=8.4 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.25 - 7.21 (m, 1H), 7.16 (br d, J=7.3 Hz, 2H), 6.91 - 6.83 (m, 2H), 6.76 (br d, J=6.0 Hz, 2H), 6.73 - 6.68 (m, 1H), 4.24 (br d, J=5.7 Hz, 2H), 3.97 (s, 2H), 3.79 (s, 3H), 2.40 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d6) δ -137.69 (br s, 1F)
I-24		¹ H NMR (400MHz, DMSO-d6) δ d 8.80 (br s, 1H), 8.17 (s, 1H), 7.75 (br d, J=7.3 Hz, 1H), 7.66 - 7.53 (m, 3H), 7.33 (br t, J=9.0 Hz, 1H), 6.83 (br d, J=7.8 Hz, 1H), 6.79 - 6.74 (m, 1H), 6.72 - 6.61 (m, 3H), 4.23 (br d, J=5.5 Hz, 2H), 3.78 (s, 3H),

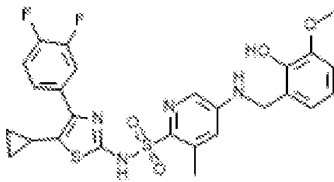
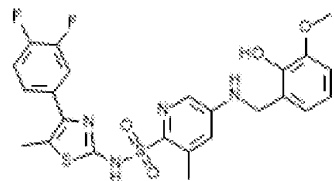
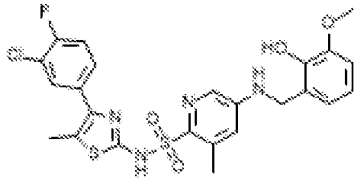
Table 1		
Cmpd. No.	Structure	NMR data
		2.57 (br d, J=3.7 Hz, 3H), 2.41 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d6) δ -118.49 (br s, 1F)
I-26		¹ H NMR (400MHz, DMSO-d6) δ 8.80 (br s, 1H), 8.17 (s, 1H), 7.75 (br d, J=7.3 Hz, 1H), 7.66 - 7.53 (m, 3H), 7.33 (br t, J=9.0 Hz, 1H), 6.83 (br d, J=7.8 Hz, 1H), 6.79 - 6.74 (m, 1H), 6.72 - 6.61 (m, 3H), 4.23 (br d, J=5.5 Hz, 2H), 3.78 (s, 3H), 2.57 (br d, J=3.7 Hz, 3H), 2.41 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d6) δ -118.49 (br s, 1F)
I-27		¹ H NMR (400 MHz, DMSO-d6) δ = 12.82 - 12.45 (m, 1H), 8.78 (s, 1H), 7.70 (s, 1H), 7.64 - 7.47 (m, 2H), 7.39 - 7.28 (m, 1H), 6.90 - 6.81 (m, 2H), 6.81 - 6.75 (m, 2H), 6.74 - 6.67 (m, 1H), 4.25 (br d, J = 5.6 Hz, 2H), 3.79 (s, 3H), 2.43 (s, 3H), 2.21 (s, 3H) ¹⁹ F NMR (377 MHz, DMSO-d6) δ = -137.79 (br s, 1F)
I-28		¹ H NMR (400 MHz, DMSO-d6) δ = 13.16 - 12.03 (m, 1H), 8.80 (s, 1H), 7.72 (br s, 2H), 7.56 - 7.42 (m, 2H), 6.90 - 6.82 (m, 2H), 6.79 (br d, J = 12.3 Hz, 2H), 6.74 - 6.67 (m, 1H), 4.26 (br d, J = 5.6 Hz, 2H), 3.79 (s, 3H), 2.44 (s, 3H), 2.20 (s, 3H) ¹⁹ F NMR (377 MHz, DMSO-d6) δ = -115.58 (br s, 1F)

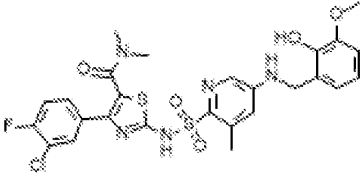
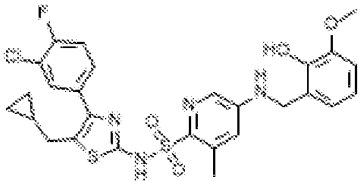
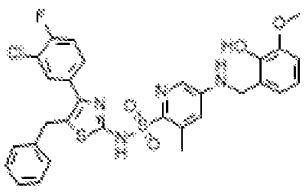
Table 1		
Cmpd. No.	Structure	NMR data
I-29		¹ H NMR (400MHz, DMSO-d ₆) δ 12.98 (br s, 1H), 8.82 (s, 1H), 7.75 - 7.65 (m, 2H), 7.52 - 7.45 (m, 1H), 7.43 (br d, J=2.7 Hz, 1H), 6.84 (br d, J=7.7 Hz, 2H), 6.77 (br d, J=7.2 Hz, 2H), 6.73 - 6.67 (m, 1H), 4.25 (br d, J=5.7 Hz, 2H), 3.78 (s, 3H), 2.76 (br s, 6H), 2.43 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ -73.47 (s, 1F)
I-30		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.04 - 12.18 (m, 1H), 8.80 (s, 1H), 7.84 - 7.67 (m, 2H), 7.61 - 7.42 (m, 2H), 6.85 (br d, J = 7.3 Hz, 2H), 6.82 - 6.75 (m, 2H), 6.75 - 6.67 (m, 1H), 4.26 (br d, J = 5.8 Hz, 2H), 3.79 (s, 3H), 2.44 (s, 3H), 1.05 - 0.78 (m, 1H), 0.61 - 0.37 (m, 2H), 0.29 - 0.04 (m, 2H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -115.47 (br s, 1F)
I-32		¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.87 - 12.52 (m, 1H), 8.81 (s, 1H), 7.80 - 7.71 (m, 1H), 7.68 (d, J = 2.3 Hz, 1H), 7.53 (d, J = 7.4 Hz, 2H), 7.36 - 7.28 (m, 2H), 7.27 - 7.21 (m, 1H), 7.17 (d, J = 7.0 Hz, 2H), 6.90 - 6.82 (m, 2H), 6.80 - 6.75 (m, 2H), 6.74 - 6.66 (m, 1H), 4.25 (d, J = 5.9 Hz, 2H), 3.96 (s, 2H), 3.79 (s, 3H), 2.41 (s, 3H) ¹⁹ F NMR (377 MHz, DMSO-d ₆) δ = -114.41 - -115.52 (m, 1F)

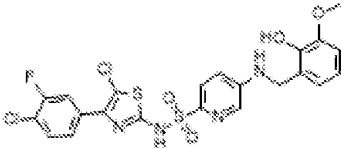
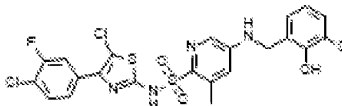
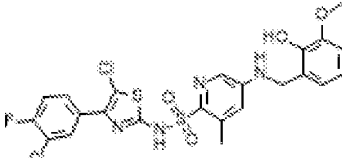
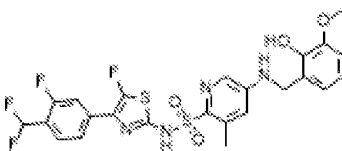
Table 1		
Cmpd. No.	Structure	NMR data
I-33		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.83 (s, 1H), 7.98 (d, J = 2.6 Hz, 1H), 7.76 - 7.69 (m, 2H), 7.66 (d, J = 8.8 Hz, 1H), 7.56 (br d, J = 7.6 Hz, 1H), 7.25 - 7.17 (m, 1H), 6.99 - 6.90 (m, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.79 - 6.74 (m, 1H), 6.74 - 6.68 (m, 1H), 4.27 (br d, J = 5.3 Hz, 2H), 3.79 (s, 3H) ¹⁹ F NMR (377 MHz, DMSO-d ₆) δ = -115.08 (br s, 1F)
I-34		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.82 (s, 1H), 7.77 - 7.69 (m, 3H), 7.58 (dd, J = 1.6, 8.6 Hz, 1H), 7.02 (br t, J = 5.6 Hz, 1H), 6.88 - 6.82 (m, 2H), 6.79 - 6.75 (m, 1H), 6.73 - 6.68 (m, 1H), 4.26 (br d, J = 5.4 Hz, 2H), 3.79 (s, 3H), 2.44 (s, 3H) ¹⁹ F NMR (377 MHz, DMSO-d ₆) δ = -115.18 (br s, 1F)
I-35		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.82 (s, 1H), 7.90 (dd, J = 2.2, 6.9 Hz, 1H), 7.80 - 7.68 (m, 2H), 7.63 - 7.52 (m, 1H), 7.06 - 6.96 (m, 1H), 6.89 - 6.82 (m, 2H), 6.80 - 6.76 (m, 1H), 6.75 - 6.69 (m, 1H), 4.27 (br d, J = 5.1 Hz, 2H), 3.80 (s, 3H), 2.45 (s, 3H) ¹⁹ F NMR (376 MHz, CDCl ₃) δ = -113.42 (br s, 1F)
I-38		¹ H NMR (400MHz, DMSO-d ₆) δ = 8.85 (br s, 1H), 7.78 - 7.71 (m, 2H), 7.67 - 7.57 (m, 2H), 7.39 - 7.05 (m, 2H), 6.85 (br s, 2H), 6.80 - 6.75 (m, 1H), 6.74 - 6.68 (m, 1H), 4.27 (br d,

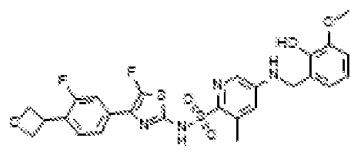
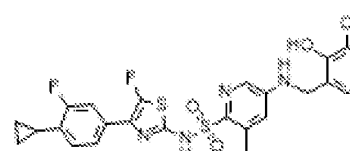
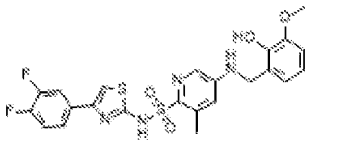
Table 1		
Cmpd. No.	Structure	NMR data
		J=2.9 Hz, 2H), 3.79 (s, 3H), 2.46 (s, 3H) ¹⁹F NMR (376MHz, DMSO-d6) δ = -113.36 (br s, 1F), -113.51 (br s, 1F), -117.33 (br s, 1F), -148.93 (br s, 1F)
I-39		¹H NMR (400 MHz, DMSO) δ 8.87 (s, 1H), 7.74 (s, 1H), 7.67 - 7.62 (m, 1H), 7.53 (br d, J=7.9 Hz, 1H), 7.44 (br d, J=11.6 Hz, 1H), 7.03 (br s, 1H), 6.89 - 6.79 (m, 2H), 6.79 - 6.75 (m, 1H), 6.73 - 6.68 (m, 1H), 4.93 (dd, J=6.4, 7.9 Hz, 2H), 4.71 (t, J=6.5 Hz, 2H), 4.50 (quin, J=7.7 Hz, 1H), 4.26 (br d, J=5.5 Hz, 2H), 3.79 (s, 3H), 2.45 (s, 3H) ¹⁹F NMR (376MHz, DMSO-d6) δ -117.09 (br s, 1F), -150.74 - -152.75 (m, 1F).
I-40		¹H NMR (400MHz, DMSO-d6) δ 8.84 (s, 1H), 7.73 (s, 1H), 7.38 (br d, J=9.9 Hz, 2H), 7.08 (t, J=8.1 Hz, 1H), 7.00 (br s, 1H), 6.87 - 6.80 (m, 2H), 6.79 - 6.74 (m, 1H), 6.74 - 6.67 (m, 1H), 4.26 (br d, J=5.5 Hz, 2H), 3.78 (s, 3H), 2.44 (s, 3H), 2.09 - 2.05 (m, 1H), 1.04 - 0.96 (m, 2H), 0.79 - 0.72 (m, 2H) ¹⁹F NMR (376MHz, DMSO-d6) δ -119.70 (br s, 1F), -152.29 (br s, 1F)
I-41		¹H NMR (400 MHz, DMSO-d6) δ = 8.80 (s, 1H), 7.89 - 7.78 (m, 1H), 7.70 (br s, 1H), 7.59 (br s, 1H), 7.56 - 7.44 (m, 1H), 7.23 (br s, 1H), 6.92 - 6.65 (m,

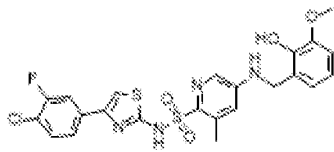
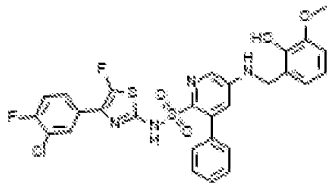
Table 1		
Cmpd. No.	Structure	NMR data
		5H), 4.25 (br d, J = 5.4 Hz, 2H), 3.78 (s, 3H), 2.44 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d6) δ = -134.52 - -142.20 (m, 2F)
I-42		¹ H NMR (400 MHz, DMSO-d6) δ = 8.80 (s, 1H), 7.81 (dd, J = 1.6, 10.8 Hz, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.69 - 7.59 (m, 2H), 7.37 (br s, 1H), 6.91 (br d, J = 5.1 Hz, 1H), 6.85 (dd, J = 1.3, 7.8 Hz, 1H), 6.80 (d, J = 2.3 Hz, 1H), 6.78 - 6.74 (m, 1H), 6.73 - 6.68 (m, 1H), 4.25 (d, J = 5.9 Hz, 2H), 3.78 (s, 3H), 2.45 (s, 3H) ¹⁹ F NMR (377 MHz, DMSO-d6) δ = -115.49 (br s, 1F)
I-43		¹ H NMR (400 MHz, DMSO-d6) δ = 8.81 (s, 1H), 8.03 - 7.95 (m, 1H), 7.83 - 7.67 (m, 2H), 7.49 (br t, J = 9.0 Hz, 1H), 7.35 - 7.23 (m, 1H), 6.97 - 6.63 (m, 5H), 4.25 (br d, J = 5.6 Hz, 2H), 3.78 (s, 3H), 2.45 (s, 3H) ¹⁹ F NMR (377 MHz, DMSO-d6) δ = -111.91 - -119.99 (m, 1F)
I-44		¹ H NMR (400MHz, DMSO-d6) δ = 13.12 - 11.92 (m, 1H), 8.82 (s, 1H), 7.92 (br s, 1H), 7.82 (br d, J=7.1 Hz, 1H), 7.68 - 7.64 (m, 1H), 7.55 (br t, J=9.0 Hz, 1H), 7.34 (s, 5H), 7.15 (br s, 1H), 6.86 (br d, J=7.6 Hz, 1H), 6.80 - 6.77 (m, 1H), 6.75 - 6.68 (m, 2H), 4.29 (br d, J=5.3 Hz, 2H), 3.78 (s, 3H)

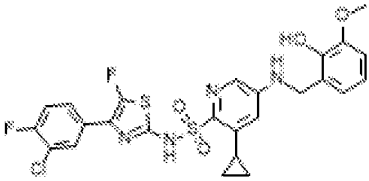
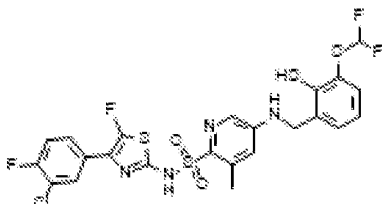
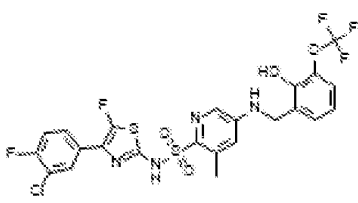
Table 1		
Cmpd. No.	Structure	NMR data
		¹⁹ F NMR (376MHz, DMSO-d6) δ = -113.36 - -116.18 (m, 1F), -152.51 (br d, J=65.4 Hz, 1F)
I-45		¹ H NMR (400MHz, DMSO-d6) δ = 8.86 (s, 1H), 7.83 (br d, J=7.0 Hz, 1H), 7.70 - 7.62 (m, 2H), 7.60 - 7.51 (m, 1H), 6.98 (br s, 1H), 6.85 (br d, J=7.9 Hz, 1H), 6.78 - 6.74 (m, 1H), 6.73 - 6.66 (m, 1H), 6.43 (s, 1H), 4.24 (br d, J=5.0 Hz, 2H), 3.79 (s, 3H), 2.64 - 2.59 (m, 1H), 0.99 (br d, J=8.2 Hz, 2H), 0.66 (br d, J=4.9 Hz, 2H) ¹⁹ F NMR (376MHz, DMSO-d6) δ = -115.20 (br d, J=139.0 Hz, 1F), -151.93 (br s, 1F)
I-46		¹ H NMR (400 MHz, DMSO-d6) δ = 9.50 (s, 1H), 7.86 - 7.72 (m, 2H), 7.69 - 7.61 (m, 1H), 7.58 - 7.49 (m, 1H), 7.27 - 6.71 (m, 6H), 4.31 (br d, J = 5.1 Hz, 2H), 2.46 (s, 3H) ¹⁹ F NMR (377 MHz, DMSO-d6) δ = -81.35 (s, 1F), -115.43 (br dd, J = 12.7, 21.2 Hz, 1F), -151.96 - -152.20 (m, 1F)
I-47		¹ H NMR (400 MHz, DMSO-d6) δ = 9.94 (s, 1H), 7.85 - 7.73 (m, 2H), 7.58 - 7.49 (m, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.13 - 7.03 (m, 1H), 6.89 - 6.76 (m, 2H), 4.33 (d, J = 5.9 Hz, 2H), 2.46 (s, 3H) ¹⁹ F NMR (377 MHz, DMSO-d6) δ = -56.92 (s, 1F)

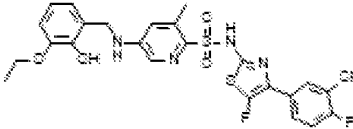
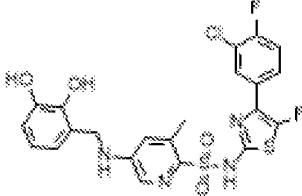
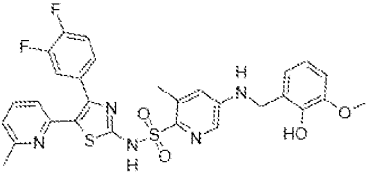
Table 1		
Cmpd. No.	Structure	NMR data
I-48		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.61 (br s, 1H), 7.85 - 7.73 (m, 2H), 7.70 - 7.61 (m, 1H), 7.58 - 7.47 (m, 1H), 7.09 - 6.99 (m, 1H), 6.90 - 6.80 (m, 2H), 6.76 (br d, J = 7.4 Hz, 1H), 6.72 - 6.63 (m, 1H), 4.27 (br s, 2H), 4.08 - 3.98 (m, 2H), 2.45 (s, 3H), 2.07 (d, J = 3.5 Hz, 1H), 1.37 - 1.30 (m, 3H) ¹⁹ F NMR (377 MHz, DMSO-d ₆) δ = -115.52 (br s, 1F), -151.95 (br s, 1F)
I-49		¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.55 - 9.19 (m, 1H), 8.71 - 8.36 (m, 1H), 7.82 (dd, J = 2.1, 7.1 Hz, 1H), 7.76 (d, J = 2.3 Hz, 1H), 7.69 - 7.62 (m, 1H), 7.55 (t, J = 8.9 Hz, 1H), 6.84 (d, J = 2.0 Hz, 1H), 6.68 (dd, J = 1.4, 7.6 Hz, 1H), 6.65 - 6.59 (m, 1H), 6.59 - 6.52 (m, 1H), 4.24 (s, 2H), 2.45 (s, 3H) ¹⁹ F NMR (377 MHz, DMSO-d ₆) δ = -115.19 - -115.60 (m, 1F), -151.79 - -152.21 (m, 1F)
I-50		¹ H NMR (400MHz, DMSO-d ₆) δ 8.85 (s, 1H), 7.76 - 7.67 (m, 2H), 7.61 - 7.53 (m, 1H), 7.49 (t, J=7.8 Hz, 1H), 7.39(br s, 1H), 7.10 (d, J=7.7 Hz, 1H), 6.97 - 6.89 (m, 1H), 6.87 - 6.74 (m, 3H), 6.74 - 6.66 (m, 2H), 4.25 (d, J=5.9 Hz, 2H), 3.78 (s, 3H), 2.45 (s, 6H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ-135.25 (br s, 1F), -136.74 (br s, 1F)

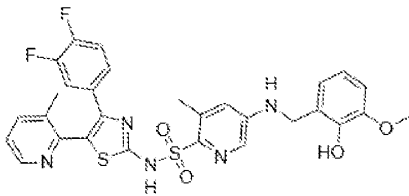
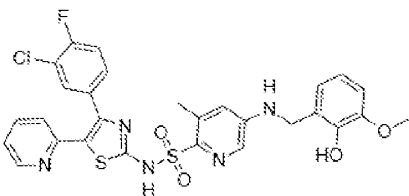
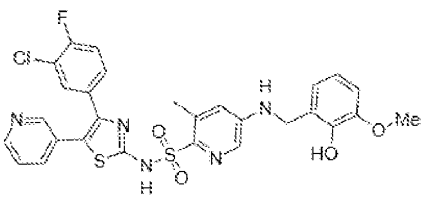
Table 1		
Cmpd. No.	Structure	NMR data
I-51		¹ H NMR (400MHz, DMSO-d ₆) δ 9.15 - 8.62 (m, 1H), 8.52 (br d, J=4.6 Hz, 1H), 7.76 (d, J=2.4 Hz, 1H), 7.73 -7.68 (m, 1H), 7.47 - 7.29 (m, 3H), 6.97 (br dd, J=1.8, 6.7 Hz, 1H), 6.88 - 6.82 (m, 2H), 6.81 - 6.76 (m, 1H), 6.74- 6.68 (m, 1H), 4.27 (s, 2H), 3.79 (s, 3H), 3.62 (br s, 58H), 2.47 (s, 3H), 1.84 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ-74.03 -75.75 (m, 1F)
I-52		¹ H NMR (400MHz, DMSO-d ₆) δ 8.87 (s, 1H), 8.52 (d, J=4.4 Hz, 1H), 7.85 (br d, J=7.1 Hz, 1H), 7.74 (d, J=2.4Hz, 1H), 7.62 (dt, J=1.7, 7.8 Hz, 1H), 7.55 (d, J=7.2 Hz, 2H), 7.24 (dd, J=5.2, 7.0 Hz, 1H), 6.98 - 6.88 (m, 2H), 6.85 (dd, J=1.4, 7.9 Hz, 1H), 6.82 - 6.75 (m, 2H), 6.74 - 6.67 (m, 1H), 4.26 (br d, J=5.9 Hz, 2H), 3.78 (s, 3H), 2.45 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ-113.71 (br s, 1F)
I-53		¹ H NMR (400MHz, DMSO-d ₆) δ 8.88 (s, 1H), 8.49 (br d, J=4.2 Hz, 1H), 8.34 (s, 1H), 7.72 (d, J=1.6 Hz, 1H), 7.63 (br t, J=7.8 Hz, 2H), 7.43 - 7.35 (m, 2H), 7.33 - 7.26 (m, 1H), 6.99 - 6.90 (m, 1H), 6.85 - 6.80 (m, 2H), 6.78 - 6.74 (m, 1H), 6.72 - 6.66 (m, 1H), 4.25 (br d, J=5.6 Hz, 2H), 3.77 (s, 3H), 2.45 (s, 3H)

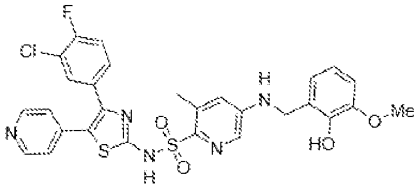
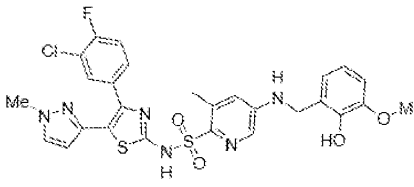
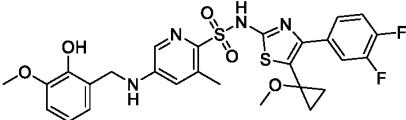
Table 1		
Cmpd. No.	Structure	NMR data
I-54		¹ H NMR (400MHz, DMSO-d ₆) δ8.85 (s, 1H), 8.48 (br d, J=5.1 Hz, 2H), 7.76 - 7.70 (m, 2H), 7.51 - 7.44 (m, 1H), 7.42 - 7.35 (m, 1H), 7.13 (br d, J=5.6 Hz, 2H), 6.96 (br s, 1H), 6.88 - 6.80 (m, 2H), 6.79 - 6.74 (m, 1H), 6.73 - 6.67 (m, 1H), 4.26 (br d, J=5.4 Hz, 2H), 3.78 (s, 3H), 2.45 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ-112.60 -115.09 (m, 1F)
I-55		¹ H NMR (400MHz, DMSO-d ₆) δ8.83 (s, 1H), 7.77 (br d, J=6.4 Hz, 1H), 7.72 (d, J=2.2 Hz, 1H), 7.61 (d, J=2.1 Hz, 1H), 7.56 - 7.40 (m, 2H), 6.89 - 6.76 (m, 4H), 6.74 - 6.68 (m, 1H), 5.77 (d, J=2.0 Hz, 1H), 4.26 (br d, J=5.9 Hz, 2H), 3.80 (d, J=6.6 Hz, 6H), 2.44 (s, 3H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ-73.46 (s, 1F)
I-56		¹ H NMR (400MHz, DMSO-d ₆) δ = 13.63 - 12.01 (m, 1H), 8.82 (s, 1H), 7.80 - 7.72 (m, 2H), 7.63 - 7.52 (m, 2H), 6.92 (br s, 1H), 6.86 (br d, J=7.9 Hz, 1H), 6.82 (br s, 1H), 6.79 - 6.75 (m, 1H), 6.74 - 6.68 (m, 1H), 4.27 (br d, J=5.5 Hz, 2H), 3.79 (s, 3H), 3.26 (s, 3H), 2.45 (s, 3H), 1.07 (m, 2H), 0.65 (m, 2H) ¹⁹ F NMR (376MHz, DMSO-d ₆) δ = -137.05 (br s, 1F), -138.03 (br s, 1F)

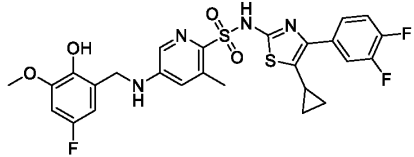
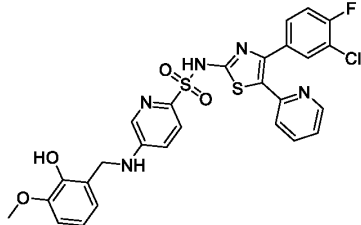
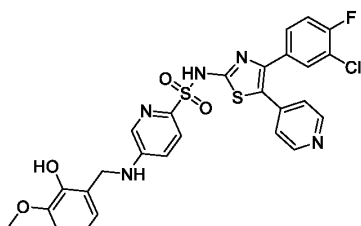
Table 1		
Cmpd. No.	Structure	NMR data
I-57		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.26 - 12.14 (m, 1H), 8.80 (s, 1H), 7.81 - 7.64 (m, 2H), 7.60 - 7.47 (m, 2H), 6.91 (br t, J = 5.7 Hz, 1H), 6.83 - 6.75 (m, 2H), 6.57 (dd, J = 2.9, 9.4 Hz, 1H), 4.27 (d, J = 6.1 Hz, 2H), 3.81 (s, 3H), 2.44 (s, 3H), 2.04 - 1.96 (m, 1H), 0.97 - 0.91 (m, 2H), 0.55 - 0.49 (m, 2H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = 0.88 (s, 1F), -122.72 (s, 1F)
I-58		¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.05 - 8.61 (m, 1H), 8.47 (br d, J = 4.1 Hz, 1H), 8.19 (br s, 1H), 7.93 (br d, J = 1.8 Hz, 1H), 7.74 - 7.52 (m, 3H), 7.49 - 7.37 (m, 2H), 7.24 - 7.07 (m, 1H), 6.99 - 6.82 (m, 4H), 6.80 - 6.66 (m, 2H), 4.26 (br d, J = 5.5 Hz, 2H), 3.79 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -113.11 - -121.28 (m, 1F)
I-59		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.82 (s, 1H), 8.44 (br d, J = 5.5 Hz, 2H), 7.94 (d, J = 2.5 Hz, 1H), 7.66 - 7.60 (m, 2H), 7.46 - 7.38 (m, 1H), 7.37 - 7.31 (m, 1H), 7.11 (d, J = 5.8 Hz, 2H), 7.02 - 6.96 (m, 1H), 6.93 - 6.83 (m, 2H), 6.79 - 6.75 (m, 1H), 6.73 - 6.67 (m, 1H), 4.26 (br d, J = 5.8 Hz, 2H), 3.79 (s, 3H). ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -134.42 - -145.10 (m, 1F)

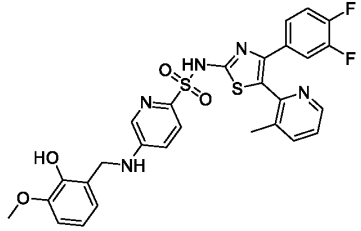
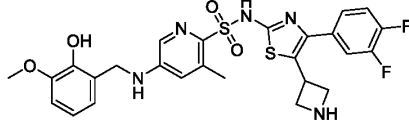
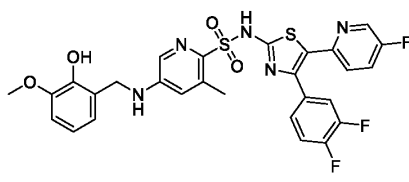
Table 1		
Cmpd. No.	Structure	NMR data
I-60		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.39 - 12.76 (m, 1H), 8.84 (s, 1H), 8.50 (d, J = 3.8 Hz, 1H), 7.99 (d, J = 2.5 Hz, 1H), 7.66 (br d, J = 8.8 Hz, 2H), 7.45 - 7.28 (m, 3H), 7.18 - 7.09 (m, 1H), 7.00 - 6.90 (m, 2H), 6.85 (dd, J = 1.3, 7.9 Hz, 1H), 6.79 - 6.74 (m, 1H), 6.73 - 6.67 (m, 1H), 4.27 (d, J = 5.7 Hz, 2H), 3.78 (s, 3H), 2.08 - 2.05 (m, 1H), 1.83 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -136.60 (br d, J = 31.2 Hz, 1F), -137.23 (br d, J = 20.8 Hz, 1F)
I-61		¹ H NMR (DMSO-d ₆ , 400 MHz) δ 7.67 (br s, 1H), 7.35 (m, 2H), 7.0-7.3 (m, 1H), 6.83 (m, 1H, J=7.4 Hz), 6.6-6.8 (m, 3H), 4.24 (m, 5H), 3.90 (m, 2H), 3.7-3.8 (s, 3H), 2.51 (br s, 3H) ¹⁹ F NMR (DMSO-d ₆ , 376 MHz) δ -138.48, -140.05
I-62		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.36 - 12.47 (m, 1H), 8.84 (s, 1H), 8.56 (d, J = 2.6 Hz, 1H), 7.77 - 7.69 (m, 1H), 7.62 - 7.54 (m, 2H), 7.39 (br dd, J = 3.5, 7.9 Hz, 1H), 6.99 - 6.90 (m, 2H), 6.85 (br d, J = 7.7 Hz, 1H), 6.82 - 6.76 (m, 2H), 6.74 - 6.69 (m, 1H), 4.26 (br d, J = 6.1 Hz, 2H), 3.79 (s, 3H), 2.45 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -127.25, -127.91, -137.06

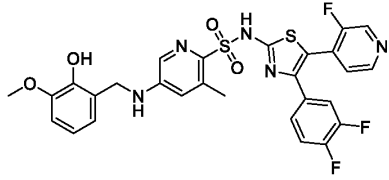
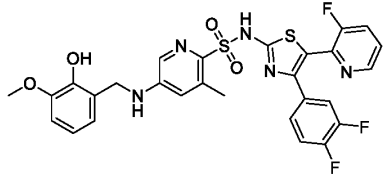
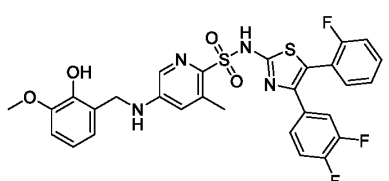
Table 1		
Cmpd. No.	Structure	NMR data
I-63		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.82 (s, 1H), 8.57 (s, 1H), 8.36 (d, J = 5.0 Hz, 1H), 7.73 (d, J = 1.8 Hz, 1H), 7.56 - 7.38(m, 2H), 7.29 (br t, J = 5.8 Hz, 1H), 7.16 (br dd, J = 1.8, 6.5 Hz, 1H), 7.00 - 6.88 (m, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.83 - 6.75 (m, 2H), 6.74 - 6.67 (m, 1H), 4.26 (br d, J = 5.8 Hz, 2H), 3.79 (s, 3H), 2.46 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -73.43, -127.16
I-64		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.16 (br s, 1H), 8.82 (s, 1H), 8.47 (br d, J = 4.5 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.54 (br dd, J = 8.5, 10.0 Hz, 1H), 7.50 - 7.42 (m, 2H), 7.19 (td, J = 2.2, 8.3 Hz, 1H), 6.95 (br s, 1H), 6.87 - 6.84 (m, 1H), 6.82 (d, J = 2.3 Hz, 1H), 6.80 - 6.77 (m, 1H), 6.74 - 6.69 (m, 1H), 4.27 (d, J = 5.8 Hz, 2H), 3.79 (s, 3H), 2.47 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -117.13, -136.43 - -137.06, -137.68 - -138.48
I-65		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.70 (br s, 1H), 7.67 (br s, 1H), 7.39 - 7.21 (m, 4H), 7.20 - 7.11 (m, 2H), 7.02 (br d, J = 7.9Hz, 1H), 6.84 - 6.67 (m, 4H), 6.67 - 6.60 (m, 1H), 4.20 (br d, J = 5.7 Hz, 2H), 3.72 (s, 3H), 2.40 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -112.52, -135.87

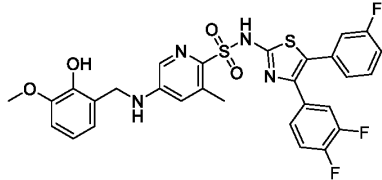
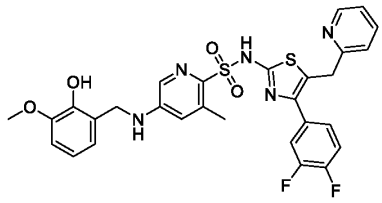
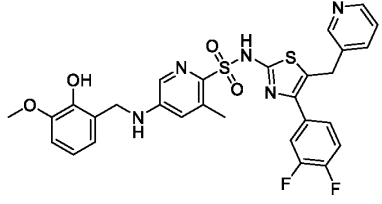
Table 1		
Cmpd. No.	Structure	NMR data
I-66		¹ H NMR (DMSO-d ₆ , 400 MHz) δ 12.5-13.6 (m, 1H), 8.88 (s, 1H), 7.8-7.8 (m, 1H), 7.4-7.6 (m, 3H), 7.2-7.3 (m, 2H), 7.09 (br d, 2H, J=8.1 Hz), 7.0-7.0 (m, 1H), 6.8-6.9 (m, 2H), 6.82 (br d, 1H, J=7.3 Hz), 6.7-6.8 (m, 1H), 4.31 (br d, 2H, J=5.1Hz), 3.83 (s, 3H), 2.51 (s, 3H) ¹⁹ F NMR (DMSO-d ₆ , 376 MHz) δ -111.94, -112.0--111.7, -137.0--136.5, -137.49, -137.55, -137.9-137.4
I-67		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.01 - 12.37 (m, 1H), 8.82 (s, 1H), 8.54 (d, J = 4.1 Hz, 1H), 7.81 - 7.74 (m, 2H), 7.68 (d, J = 2.4 Hz, 1H), 7.58 - 7.48 (m, 2H), 7.34 - 7.27 (m, 2H), 6.86 (br d, J = 6.6 Hz, 2H), 6.78 (br d, J = 7.4 Hz, 2H), 6.74 - 6.69 (m, 1H), 4.25 (br d, J = 6.0 Hz, 2H), 4.08 (s, 2H), 3.80 (s, 3H), 2.42 (s, 3H)
I-68		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.12 - 12.44 (m, 1H), 8.82 (s, 1H), 8.44 (br d, J = 4.1 Hz, 1H), 8.39 (s, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.64 - 7.49 (m, 1H), 7.39 - 7.35 (m, 1H), 7.32 (dd, J = 4.6, 7.7 Hz, 1H), 6.86 (dd, J = 1.5, 7.9 Hz, 1H), 6.84 - 6.74 (m, 2H), 6.73 - 6.69 (m, 1H), 4.25 (d, J = 6.0 Hz, 2H), 4.02 (s, 2H), 3.80 (s, 3H), 2.41 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -137.88

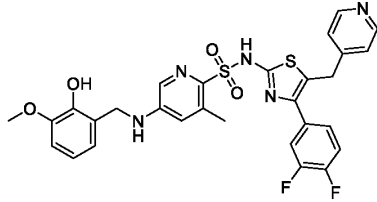
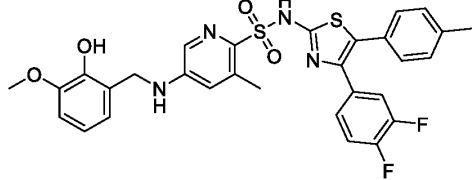
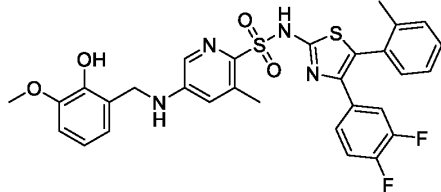
Table 1		
Cmpd. No.	Structure	NMR data
I-69		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.79 (br s, 1H), 8.46 (d, J = 5.8 Hz, 2H), 7.66 (d, J = 2.4 Hz, 1H), 7.59 - 7.52 (m, 1H), 7.51 - 7.41 (m, 1H), 7.33 - 7.28 (m, 1H), 7.16 (d, J = 5.8 Hz, 2H), 6.85 (dd, J = 1.3, 7.9 Hz, 1H), 6.81 - 6.73 (m, 3H), 6.72 - 6.68 (m, 1H), 4.24 (d, J = 5.8 Hz, 2H), 4.01 (s, 2H), 3.79 (s, 3H), 2.41 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -137.59 - -138.18, -138.32 - -139.10
I-70		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.41 - 12.49 (m, 1H), 8.83 (s, 1H), 7.74 (d, J = 1.7 Hz, 1H), 7.45 (td, J = 8.8, 17.9 Hz, 2H), 7.19 - 7.13 (m, 3H), 7.12 - 7.07 (m, 2H), 6.92 (br s, 1H), 6.88 - 6.84 (m, 1H), 6.83 - 6.75 (m, 2H), 6.74 - 6.68 (m, 1H), 4.27 (br d, J = 5.8 Hz, 2H), 3.79 (s, 3H), 2.46 (s, 3H), 2.29 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -137.79
I-71		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.59 - 12.33 (m, 1H), 8.84 (s, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.41 - 7.23 (m, 6H), 7.01 (td, J = 2.5, 8.6 Hz, 1H), 6.94 (br s, 1H), 6.86 (dd, J = 1.4, 8.0 Hz, 1H), 6.82 (d, J = 2.3 Hz, 1H), 6.80 - 6.76 (m, 1H), 6.75 - 6.68 (m, 1H), 4.27 (d, J = 5.8 Hz, 2H), 3.80 (s, 3H), 2.47 (s, 3H), 2.02 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -137.69

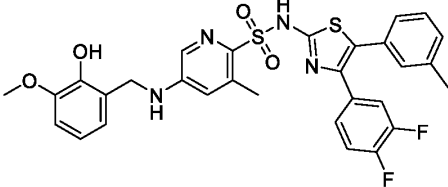
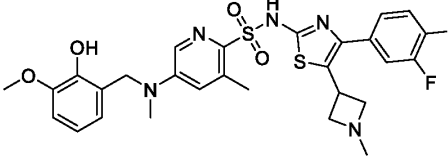
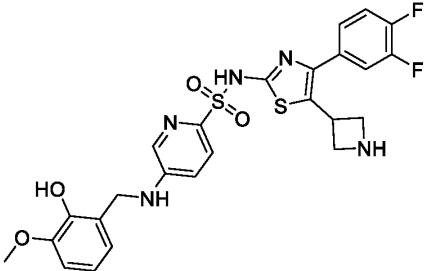
Table 1		
Cmpd. No.	Structure	NMR data
I-72		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.59 - 12.43 (m, 1H), 8.83 (s, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.52 - 7.39 (m, 2H), 7.25 - 7.19 (m, 1H), 7.19 - 7.13 (m, 2H), 7.08 (s, 1H), 6.99 - 6.88 (m, 2H), 6.86 (dd, J = 1.4, 7.9 Hz, 1H), 6.83 - 6.76 (m, 2H), 6.74 - 6.68 (m, 1H), 4.27 (d, J = 6.0 Hz, 2H), 3.79 (s, 3H), 2.46 (s, 3H), 2.26 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -132.38 - -143.51
I-73		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.13 - 12.59 (m, 1H), 8.96 - 8.72 (m, 1H), 7.73 - 7.70 (m, 1H), 7.62 - 7.55 (m, 2H), 7.34 - 7.28 (m, 1H), 6.88 - 6.83 (m, 2H), 6.80 - 6.77 (m, 1H), 6.74 - 6.70 (m, 1H), 4.58 - 4.43 (m, 1H), 4.42 - 4.25 (m, 6H), 3.80 (s, 3H), 3.21 (s, 3H), 3.16 - 3.09 (m, 3H), 2.46 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -138.10 - -138.61, -139.16
I-74		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.77 (br s, 1H), 8.20 (br s, 1H), 7.87 (d, J = 2.6 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.42 - 7.35 (m, 2H), 7.21 - 7.16 (m, 1H), 6.85 - 6.81 (m, 2H), 6.78 - 6.75 (m, 1H), 6.72 - 6.67 (m, 2H), 4.24 (br d, J = 5.8 Hz, 3H), 4.18 - 4.12 (m, 2H), 3.88 - 3.83 (m, 2H), 3.78 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -138.70 - -138.87, -140.65

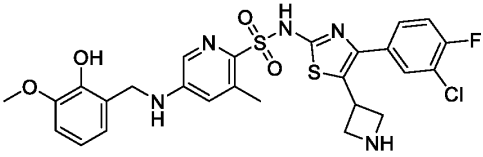
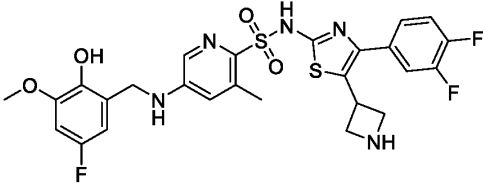
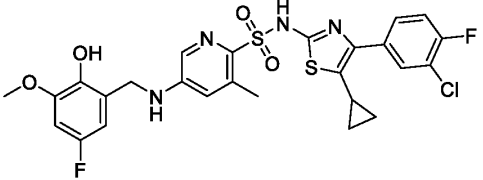
Table 1		
Cmpd. No.	Structure	NMR data
I-75		¹ H NMR (DMSO-d ₆ , 400 MHz) δ 8.79 (br s, 1H), 8.25 (br s, 1H), 7.64 (s, 1H), 7.5-7.6 (m, 1H), 7.3-7.4 (m, 1H), 7.22 (br d, 1H, J=8.6 Hz), 6.84 (d, 1H, J=8.0 Hz), 6.8-6.8 (m, 1H), 6.7-6.7 (m, 2H), 6.5-6.6 (m, 1H), 4.2-4.3 (m, 3H), 4.14 (br t, 2H, J=8.3 Hz), 3.8-3.9 (m, 5H), 2.44 (s, 5H) ¹⁹ F NMR (DMSO-d ₆ , 376 MHz) δ -116.53
I-76		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.68 (br s, 1H), 8.24 (s, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.42 - 7.33 (m, 2H), 7.20 - 7.14 (m, 1H), 6.78 - 6.72 (m, 2H), 6.61 (br t, J = 5.9 Hz, 1H), 6.58 - 6.54 (m, 1H), 4.28 - 4.14 (m, 5H), 3.85 (br t, J = 8.9 Hz, 2H), 3.80 (s, 3H), 2.45 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -122.70 - -122.80, -138.71 -138.86, -140.62
I-77		¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.70 (br s, 1H), 8.81 (s, 1H), 7.84 (dd, J = 1.8, 7.0 Hz, 1H), 7.75 - 7.69 (m, 1H), 7.69 - 7.61 (m, 1H), 7.59 - 7.49 (m, 1H), 6.94 (br s, 1H), 6.85 - 6.74 (m, 2H), 6.57 (dd, J = 2.6, 9.4 Hz, 1H), 4.27 (br d, J = 5.8 Hz, 1H), 3.81 (s, 3H), 2.48 - 2.41 (m, 3H), 2.05 - 1.93 (m, 1H), 0.93 (br d, J = 6.8 Hz, 2H), 0.64 - 0.40 (m, 2H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -122.70

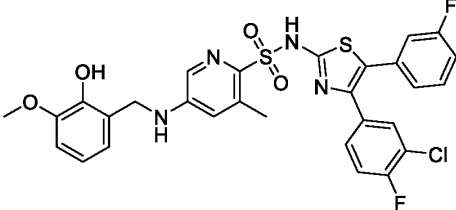
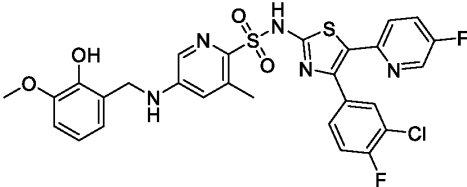
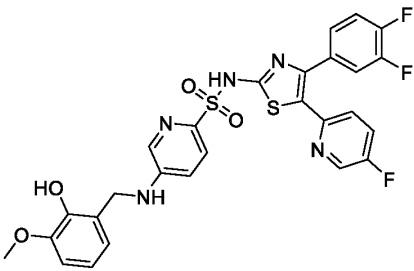
Table 1		
Cmpd. No.	Structure	NMR data
I-78		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.08 (br s, 1H), 8.82 (s, 1H), 7.79 - 7.73 (m, 1H), 7.65 (br d, J = 5.6 Hz, 1H), 7.46 - 7.36 (m, 2H), 7.35 - 7.29 (m, 1H), 7.21 - 7.15 (m, 1H), 7.05 (br d, J = 8.3 Hz, 2H), 6.99 - 6.90 (m, 1H), 6.87 - 6.81 (m, 2H), 6.80 - 6.75 (m, 1H), 6.74 - 6.67 (m, 1H), 4.27 (br s, 2H), 3.79 (s, 3H), 2.47 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -111.79 - -111.99, -114.53
I-79		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.82 (s, 1H), 8.55 (d, J = 2.4 Hz, 1H), 7.90 - 7.78 (m, 1H), 7.74 (d, J = 1.9 Hz, 1H), 7.62 - 7.50 (m, 3H), 6.98 (dd, J = 4.2, 8.8 Hz, 1H), 6.94 - 6.88 (m, 1H), 6.85 (br d, J = 7.3 Hz, 1H), 6.82 - 6.77 (m, 2H), 6.73 - 6.69 (m, 1H), 4.26 (br d, J = 5.8 Hz, 2H), 3.79 (s, 3H), 2.45 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -113.75, -127.59 - -128.27
I-80		¹ H NMR (DMSO-d ₆ , 400 MHz) δ 8.81 (s, 1H), 8.50 (br s, 1H), 7.93 (s, 1H), 7.62 (d, 1H, J=8.6 Hz), 7.4-7.6 (m, 3H), 7.28 (td, 1H, J=2.0, 3.5 Hz), 6.99 (dd, 1H, J=4.3, 8.8 Hz), 6.8-7.0 (m, 3H), 6.8-6.8 (m, 1H), 6.7-6.7 (m, 1H), 4.26 (br d, 2H, J=6.0 Hz), 3.79 (s, 3H) ¹⁹ F NMR (DMSO-d ₆ , 376 MHz)

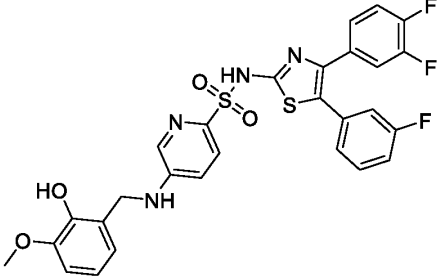
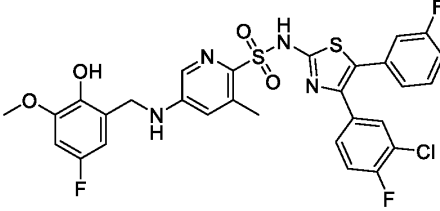
Table 1		
Cmpd. No.	Structure	NMR data
I-81		¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.57 - 12.56 (m, 1H), 8.83 (s, 1H), 7.98 (d, J = 2.5 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.53 - 7.37 (m, 3H), 7.22 - 7.15 (m, 2H), 7.12 (br t, J = 5.8 Hz, 1H), 7.06 (br d, J = 9.1 Hz, 2H), 6.96 - 6.91 (m, 1H), 6.88 - 6.83 (m, 1H), 6.79 - 6.75 (m, 1H), 6.74 - 6.68 (m, 1H), 4.28 (br d, J = 5.6 Hz, 2H), 3.79 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -111.65 - -112.09, -136.66, -137.28 - -137.72
I-82		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.81 (s, 1H), 7.75 (s, 1H), 7.68 - 7.55 (m, 1H), 7.48 - 7.37 (m, 2H), 7.34 - 7.15 (m, 2H), 7.06 (br d, J = 7.5 Hz, 2H), 6.97 (br s, 1H), 6.85 - 6.76 (m, 2H), 6.57 (dd, J = 2.5, 9.3 Hz, 1H), 4.27 (br d, J = 5.8 Hz, 2H), 3.80 (s, 3H), 2.47 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -111.93, -111.97, -122.69

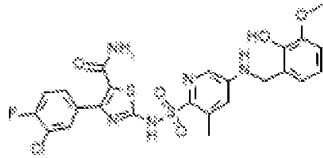
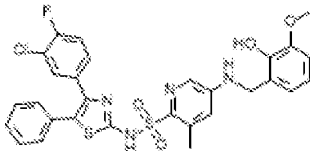
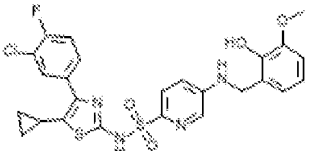
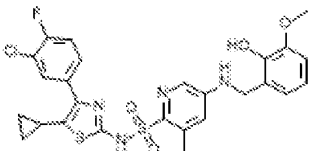
Table 1A		
Cmpd. No.	Structure	NMR data
I-25		¹ H NMR (400MHz, DMSO-d ₆) δ 8.92 (s, 1H), 7.88 (br d, J=7.0 Hz, 1H), 7.83 (s, 1H), 7.63 (br d, J=3.2 Hz, 1H), 7.62 - 7.56 (m, 1H), 7.45 (br s, 2H), 7.08 (br s, 1H), 6.95 (br d, J=7.3 Hz, 1H), 6.91 (br s, 1H), 6.89 - 6.85 (m, 1H), 6.83 - 6.78 (m, 1H), 4.35 (br d, J=4.0 Hz, 2H), 3.88 (s, 3H), 2.53 (s, 3H)

Table 1A		
Cmpd. No.	Structure	NMR data
		¹⁹ F NMR (376MHz, DMSO-d ₆) δ = 72.40 - -75.27 (m, 1F)
I-31		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.80 (s, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.62 (br d, J = 6.5 Hz, 1H), 7.44 - 7.37 (m, 1H), 7.37 - 7.26 (m, 4H), 7.25 - 7.17 (m, 2H), 6.90 (br s, 1H), 6.85 (br d, J = 7.8 Hz, 1H), 6.83 - 6.75 (m, 2H), 6.74 - 6.65 (m, 1H), 4.26 (br d, J = 5.9 Hz, 2H), 3.79 (s, 3H), 2.46 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) δ = -114.41 - -115.30 (m, 1F)
I-36		¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.90 - 12.47 (m, 1H), 8.82 (s, 1H), 7.95 (d, J = 2.5 Hz, 1H), 7.82 (dd, J = 2.1, 7.1 Hz, 1H), 7.69 - 7.58 (m, 2H), 7.57 - 7.46 (m, 1H), 7.12 - 7.01 (m, 1H), 6.91 (dd, J = 2.6, 8.8 Hz, 1H), 6.88 - 6.83 (m, 1H), 6.79 - 6.74 (m, 1H), 6.74 - 6.67 (m, 1H), 4.27 (br d, J = 5.8 Hz, 2H), 3.79 (s, 3H), 2.04 - 1.94 (m, 1H), 1.02 - 0.88 (m, 2H), 0.60 - 0.47 (m, 2H) ¹⁹ F NMR (377 MHz, DMSO-d ₆) δ = -113.12 - -118.37 (m, 1F)
I-37		¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.80 (s, 1H), 8.13 (s, 1H), 7.87 - 7.79 (m, 1H), 7.73 - 7.69 (m, 1H), 7.68 - 7.62 (m, 1H), 7.56 - 7.45 (m, 1H), 6.88 - 6.81 (m, 2H), 6.77 (br d, J = 7.3 Hz, 2H), 6.74 - 6.67 (m, 1H), 4.25 (br d, J = 5.8 Hz, 2H), 3.79 (s, 3H), 2.43 (s, 3H), 2.03 - 1.91 (m, 1H), 0.99 - 0.84 (m, 2H), 0.59 - 0.40 (m, 2H) ¹⁹ F NMR (377 MHz, DMSO-d ₆) δ = -114.33 - -118.78 (m, 1F)

[0574] **Example 77.** Evaluating the Biological Activity of Compounds Disclosed Herein

[0575] The compounds were evaluated for inhibition of 12-LOX, as well as selectivity by measuring inhibition against 15-LOX for some compounds, using a UV-Vis assay.

Arachidonic acid (AA) was used as a substrate for 12-LOX and 15-LOX. ML355 was used as the control inhibitor for 12-LOX. ML351 (5-(Methylamino)-2-(1-naphthalenyl)-4-oxazolecarbonitrile) was used as the control inhibitor for 15-LOX.

[0576] Reaction buffers used for the lipoxygenase assay were as follows: 25 mM HEPES (pH 7.5), with 0.01 % Triton X-100. 1 mM 12-HPETE or 1 mM 15-HPETE stock solution was prepared in 25 mM HEPES with 0.01% Triton X-100.

[0577] The standard curve of 12-HPETE was made by serial dilution of 0, 6.25, 12.5, 25, 50, 75 and 100 μ M, and the final reaction volume in 96 Well Clear Flat Bottom UV-Transparent Microplate is 100 μ L. The absorbance of the 12-HPETE at each concentration was measured at 234 nm.

[0578] The standard curve of 15-HPETE was made by serial dilution of 0, 3.125, 6.25, 12.5, 25, 50 and 100 μ M, and the final reaction volume in 96 Well Clear Flat Bottom UV-Transparent Microplate is 100 μ L. The absorbance of the 12-HPETE at each concentration was measured at 234 nm.

[0579] IC_{50} values were obtained by determining the % inhibition at various inhibitor concentrations. The final concentrations of the control inhibitors and test compounds in the IC_{50} determination assay are 0, 0.03, 0.1, 0.3, 1, 3, 10 and 20 μ M. The final concentration of DMSO in the assay is 0.05%.

[0580] 12-LOX IC_{50} determination. The 12-LOX enzyme and AA were diluted in the HEPES buffer to 120 nM and 200 μ M, respectively. Pre-incubation 50 μ L of indicated test compounds and 25 μ L 120 nM enzyme at room temperature for 5 min. The reaction is started by adding 25 μ L 200 μ M AA. After a short spin (1000 rpm, 15 s), incubate the reaction system for 5 min. The blank control was set by adding 25 μ L HEPES to 50 μ L of control inhibitor compound (ML355) and 25 μ L 200 μ M AA. The final concentrations of 12-LOX enzyme and AA were 30 nM and 50 μ M, respectively. The absorbance of the 12-HPETE at 234 nm was measured.

[0581] 15-LOX IC_{50} determination. The 15-LOX enzyme and AA were diluted in the HEPES buffer to 480 nM and 200 μ M, respectively. Pre-incubation 50 μ L of indicated test compounds and 25 μ L 480 nM enzyme at room temperature for 5 min. The reaction is started by adding 25 μ L 200 μ M AA. After a short spin (1000 rpm, 15 s), incubate the reaction system for 3 min. The blank control was set by adding 25 μ L HEPES to 50 μ L of control inhibitor compound (ML355) and 25 μ L 200 μ M AA. The final concentrations of 15-

LOX enzyme and AA were 120 nM and 50 μ M, respectively. The absorbance of the 15-HPETE at 234 nm was measured. The assay was performed in duplicate.

[0582] The IC₅₀ value was calculated by using GraphPad Prism 8.0.2.

[0583] The IC₅₀ values are calculated with remaining activity (%) and logarithm of inhibitor concentrations. Remaining Activity (%) = OD value inhibitor / OD value vehicle $\times$ 100

[0584] The IC₅₀ values for the compounds are in Table 2 below:

TABLE 2

Compound No.:	IC ₅₀ 12-LOX (μ M)	Selectivity over 15-LOX
I-1	ND	ND
I-2	ND	ND
I-3	+++	>50-fold
I-4	ND	ND
I-5	+++	>50-fold
I-6	+++	>50-fold
I-7	ND	ND
I-8	++	>20-fold
I-9	ND	ND
I-10	+++	>50-fold
I-11	+++	>50-fold
I-12	+++	>50-fold
I-13	+	<20-fold
I-14	++	>30-fold
I-15	+++	>50-fold
I-16	ND	ND
I-17	+++	>50-fold
I-18	++	>50-fold
I-19	++	>50-fold
I-20	+++	>50-fold
I-21	++	>20-fold
I-22	+++	>50-fold
I-23	++	>50-fold
I-24	++	>50-fold
I-25	++	>50-fold
I-26	+++	>50-fold
I-27	+++	>50-fold
I-28	++	>50-fold
I-29	++	>50-fold
I-30	+++	>50-fold
I-31	+++	>50-fold
I-32	+++	>50-fold
I-33	++	<30-fold

Compound No.:	IC ₅₀ 12-LOX (μM)	Selectivity over 15-LOX
I-34	+++	>50-fold
I-35	++	>50-fold
I-36	++	<10-fold
I-37	+++	>40-fold
I-38	+++	>50-fold
I-39	++	>50-fold
I-40	+++	>50-fold
I-41	+++	>50-fold
I-42	+++	>50-fold
I-43	+++	>50-fold
I-44	+++	>50-fold
I-45	+	<10-fold
I-46	++	<20-fold
I-47	+	<10-fold
I-48	+	<10-fold
I-49	++	<20-fold
I-50	++	>20-fold
I-51	+++	>20-fold
I-52	+++	9.5-fold
I-53	+++	>20-fold
I-54	+++	11.4-fold
I-55	+++	>20-fold
I-56	+++	>20-fold
I-57	+++	17.7-fold
I-58	+++	13.8-fold
I-59	+++	8.38-fold
I-60	+++	>20-fold
I-61	+++	>20-fold
I-62	+++	15.1-fold
I-63	+++	>20-fold
I-64	+++	15.2-fold
I-65	+++	11.1-fold
I-66	+++	10.5-fold
I-67	+++	>20-fold
I-68	+++	>20-fold
I-69	+++	>20-fold
I-70	+++	>20-fold
I-71	+++	>20-fold
I-72	+++	>20-fold
I-73	+++	>20-fold
I-74	+	>20-fold
I-75	+++	>20-fold
I-76	++	>20-fold

Compound No.:	IC ₅₀ 12-LOX (μM)	Selectivity over 15-LOX
I-77	++	>20-fold
I-78	+++	5.29-fold
I-79	+++	9.74-fold
I-80	+++	>20-fold
I-81	+++	>20-fold
I-82	+++	10.8-fold

+++ = <250 nM

++ = 250 nM-1000 nM

+ = > 1000 nM

[0585] Example 78: Evaluation of Microsomal Stability of Disclosed Compounds

[0586] Microsomal stability of disclosed compounds is evaluated with cofactors (NADPH and UDPGA) and without cofactors.

[0587] Protocol with cofactors: 25 μL of 10 mM NADPH and 25 μL of 20 mM UDPGA are added to an aqueous stock solution containing 100 mM phosphate buffer, 5 mM MgCl₂, 0.025 mg/mL of alamethacin, and 0.5 mg/mL of microsomes. The final concentration of microsomes, NADPH and UDPGA is 0.5 mg/mL, 1 mM and 2 mM, respectively.

[0588] Protocol without cofactors: 50 μL of H₂O is added to an aqueous stock solution containing 100 mM phosphate buffer, 5 mM MgCl₂, 0.025 mg/mL of alamethacin, and 0.5 mg/mL of microsomes. The final concentration of microsomes is 0.5 mg/mL. The mixture is pre-warmed at 37°C for 10 minutes.

[0589] Procedure:

[0590] The reaction is started with the addition of 2.5 μL of 100 μM control compound or test compound solutions. Verapamil and Raloxifene are used as positive controls in this study. The final concentration of test compound or control compound is 1 μM. The incubation solution is incubated at 37°C.

[0591] Aliquots of 25 μL are taken from the reaction solution at 0.5, 5, 15, 30 and 60 minutes. The reaction is stopped by the addition of 5 volumes of cold acetonitrile with IS (100 nM alprazolam, 200 nM caffeine and 100 nM tolbutamide). Samples are centrifuged at 3,220 g for 40 minutes. An aliquot of 100 μL of the supernatant is mixed with 100 μL of ultra-pure H₂O and then used for LC-MS/MS analysis.

[0592] Calculations:

[0593] Peak areas are determined from extracted ion chromatograms obtained on a Shimadzu Triple QuadTM 4500 LC-MS/MS instrument with ESI interface (Waters XSelect[®] HSS T3 2.5

μm column; column temp = 40 °C; 8 μL injection volume 0.5 mL/min elution rate; mobile phase: 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B)). The slope value, k , is determined by linear regression of the natural logarithm of the remaining percentage of the parent drug vs. incubation time curve. In vitro half-life ($t_{1/2}$) is determined and used to calculate in vitro intrinsic clearance (in vitro CL_{int} , in $\mu\text{L}/\text{min}/\text{mg}$ protein). Scale-up CL_{int} (mL/min/kg), Predicted Hepatic CL_{H} (mL/min/kg) and Hepatic Extraction Ratio (ER) are also calculated. Scaling factors for intrinsic clearance prediction in human, monkey, dog, rat, and mouse liver microsomes are provided in the table below.

Species	Microsomal Protein	Liver Weight per Kilogram of Body Weight	Scaling Factor ^a	Hepatic Blood Flow (mL/min/kg)
	per Gram of Liver			
Human	40	25.7	1028	21
Monkey	40	30	1200	44
Dog	55	32	1760	31
Rat	61	40	2440	68
Mouse	47	88	4136	90

^a Scaling Factor = (microsomal protein per gram of liver) $\times$ (liver weight per kilogram of body weight)

[0594] **Example 79:** Evaluation of Pharmacokinetics of Disclosed Compounds

[0595] Male C57BL/6 mice are administered with a single oral dose of the disclosed compound at 30 mg/kg (formulation: 0.5% methyl cellulose (400 cp) in water). The concentration of the oral dosing solution is 3 mg/mL. Blood samples of the mice are obtained at about 5 min, 15min, 0.5h, 1h, 2h, 4h, 8h, and 24h post dose.

[0596] Plasma Sample Preparation:

[0597] The desired serial concentrations of working solutions are achieved by diluting stock solution of analyte with 50% acetonitrile in water solution. 5 μL of working solutions (2, 4, 10, 20, 100, 200, 1000, 2000, 4000 ng/mL) are added to 10 μL of the blank C57BL/6 Mice plasma to achieve calibration standards of 1~2000 ng/mL (0.5, 1, 2, 5, 10, 50, 100, 500, 1000, 2000 ng/mL) in a total volume of 15 μL . Six quality control samples at 1 ng/mL, 2ng/mL, 5 ng/mL, 50 ng/mL, 800 ng/mL and 1600 ng/mL for plasma are prepared independently of those used for the calibration curves. These QC samples are prepared on the day of analysis in the same way as calibration standards.

[0598] 15 μL standards, 15 μL QC samples and 15 μL unknown samples (10 μL plasma with 5 μL blank solution) are added to 200 μL of acetonitrile containing IS mixture for precipitating protein, respectively. Then the samples are vortexed for 30 seconds. After centrifugation at 4 degrees Celsius, 3900 rpm for 15 min, the supernatant is diluted 3 times

with water. 15 μ L of diluted supernatant is injected into the LC/MS/MS system for quantitative analysis.

[0599] Instrument: Shimadzu with Raptor Biphenyl 2.7 μ m column.

[0600] HPLC Conditions:

[0601] Injection Volume: 15 μ L

[0602] Mobile Phase: Solution A- 95% water (0.1% formic acid); Solution B – 95% acetonitrile (0.1% formic acid)

[0603] Flow rate: 0.6 mL/min

Time (min)	A (%)	B (%)
0.01	90.0	10.0
0.30	90.0	10.0
2.00	0.00	100
2.20	0.00	100
2.21	90.0	10.0
2.50	90.0	10.0

[0604] The foregoing merely summarizes certain aspects of this disclosure and is not intended, nor should it be construed, as limiting the disclosure in any way.

INCORPORATION BY REFERENCE

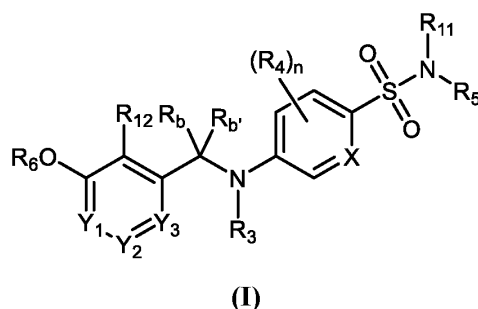
[0605] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0606] The present disclosure may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. The scope of the disclosure is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein

X is N or CR₄;

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R_b and R_{b'} are each independently H, F, or CH₃, or R_b and R_{b'} taken together with the carbon atom to which they are attached form a cyclopropyl;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, or R₃ and Y₃ taken together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl;

R₄ is each independently hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is each independently hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

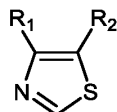
R₁₀ is hydrogen or halogen;

R₁₁ is C₆-C₁₂ aryl or 5- to 14-membered heteroaryl, each of which is substituted with one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, aryl, -(C₁-C₃ alkylene)-aryl, C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl), 3- to 14-membered heterocyclyl, and -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl);

R₁₂ is halogen, -OH, or -OR₆; and

n is 1 or 2,

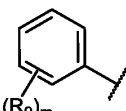
with the proviso that when X is CR₄, at least one R₄ is not H.



2. The compound of claim 1, wherein R_{11} is , wherein:

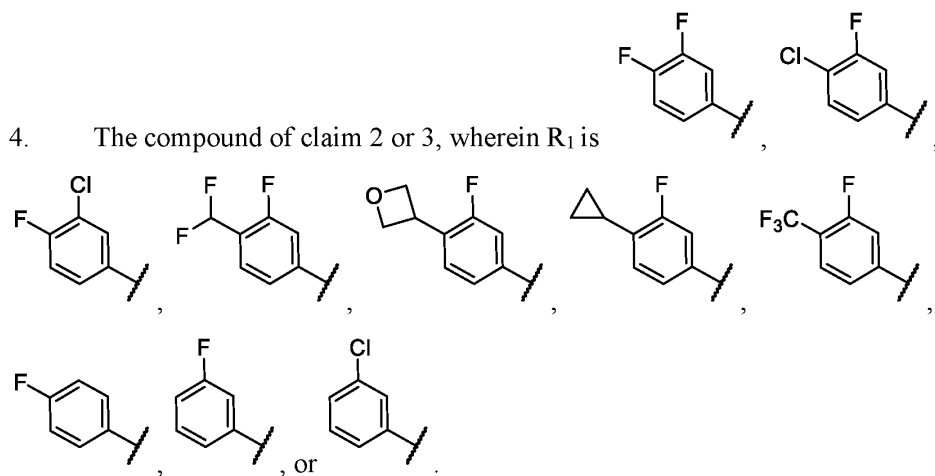
R_1 is C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, or C₁-C₃-alkylene-C₆-C₁₄-aryl, each of which is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₃-C₈ cycloalkyl, and 3- to 14-membered heterocyclic ring; and

R_2 is a substituted or unsubstituted group selected from the group consisting of 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 14-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl), C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), phenyl, and -(C₁-C₃ alkylene)-phenyl.



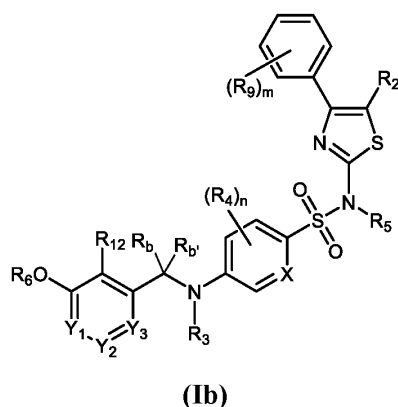
3. The compound of 2, wherein R_1 is , wherein R_9 is each independently halogen, C₁₋₄ haloalkyl, or C₃₋₆ cycloalkyl, or 4- to 6-membered heterocyclyl; and m is 1 or 2.

4. The compound of claim 2 or 3, wherein R_1 is



5. The compound of any one of claims 1-4, wherein with the proviso that at least one of R_{10} is not H or at least one of Y_1 , Y_2 , and Y_3 is N.

6. A compound of Formula (Ib):



or a pharmaceutically acceptable salt thereof,

wherein

X is N or CR₄;

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R_b and R_{b'} are each independently H, F, or CH₃, or R_b and R_{b'} taken together with the carbon atom to which they are attached form a cyclopropyl;

R₂ is a halogen or a substituted or unsubstituted group selected from the group consisting of 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl), C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), phenyl, and -(C₁-C₃ alkylene)-phenyl;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl, or R₃ and Y₃ taken together with the atoms to which they are attached form a 4- to 6-membered heterocyclyl;

R₄ is each independently hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₉ is each independently halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy or 3- to 14-membered heterocyclic ring;

R₁₀ is hydrogen or halogen;

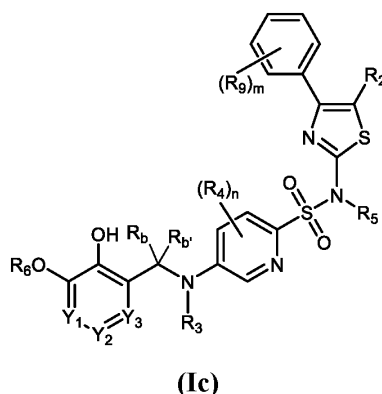
R₁₂ is halogen, -OH, or -OR₆;

m is 0, 1, 2, or 3; and

n is 1 or 2,

with the proviso that when X is CR₄, at least one R₄ is not H.

7. The compound of any one of claims 1-6, wherein R₁₂ is halogen or -OH.
8. The compound of any one of claims 1-7, wherein R₁₂ is -OH.
9. The compound of any one of claims 1-8, wherein X is N.
10. The compound of any one of claims 1-9, wherein the compound is not a compound disclosed in Table A.
11. A compound of Formula (Ic):



or a pharmaceutically acceptable salt thereof,

wherein

Y₁, Y₂, and Y₃ are each independently N or CR₁₀, wherein no more than two of Y₁, Y₂, and Y₃ are N;

R_b and R_{b'} are each independently H, F, or CH₃, or R_b and R_{b'} taken together with the carbon atom to which they are attached form a cyclopropyl;

R₂ is a substituted or unsubstituted group selected from the group consisting of 3- to 14-membered heterocyclyl, 5- to 14-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), -(C₁-C₃ alkylene)-(3- to 14-membered heterocyclyl), C₃-C₈ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₈ cycloalkyl), phenyl, and -(C₁-C₃ alkylene)-phenyl;

R₃ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

R₄ is each independently hydrogen, CD₃, substituted or unsubstituted phenyl, C₃-C₈ cycloalkyl, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, or halogen;

R₅ is hydrogen, C₁-C₃ alkyl, or C₁-C₃ haloalkyl;

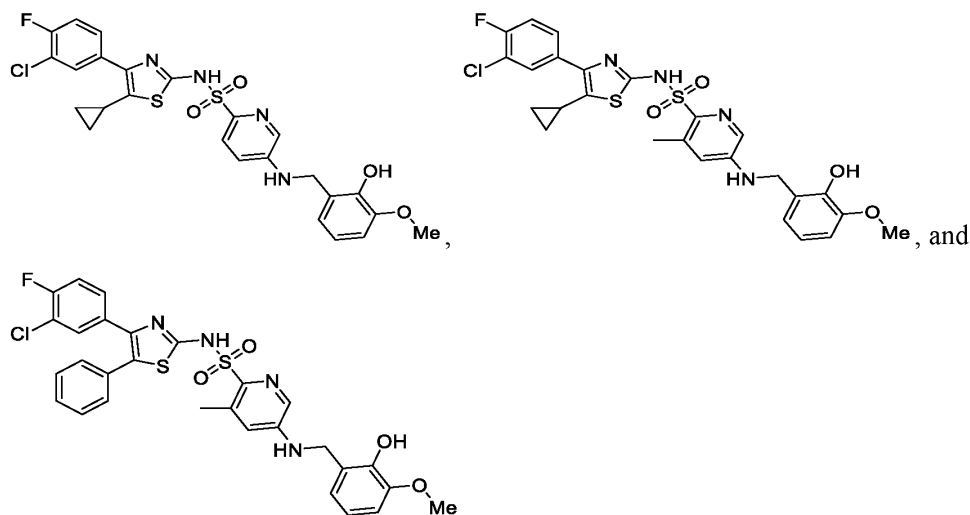
R₆ is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₈ cycloalkyl, or C₃-C₈ halocycloalkyl;

R₉ is each independently halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy or 3- to 14-membered heterocyclic ring;

R₁₀ is hydrogen or halogen; and

m is 0, 1, 2, or 3,

provided that the compound is not:



12. The compound of any one of claims 1-11, wherein R_b and R_{b'} are each independently H or Me.

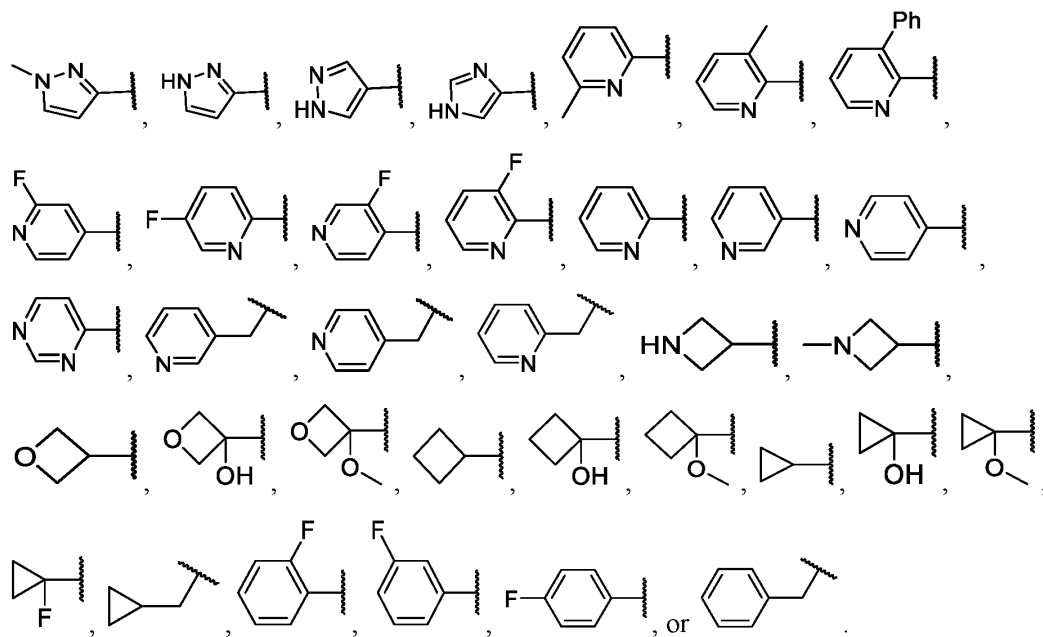
13. The compound of any one of claims 1-12, wherein R_b and R_{b'} are H.

14. The compound of any one of claims 2-13, wherein R₂ is a substituted or unsubstituted group selected from the group consisting of 4- to 6-membered heterocyclyl, -(C₁-C₃ alkylene)-(4- to 6-membered heterocyclyl), 5- or 6-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), C₃-C₆ cycloalkyl, -(C₁-C₃ alkylene)-(C₃-C₆ cycloalkyl), phenyl, and -(C₁-C₃ alkylene)-phenyl.

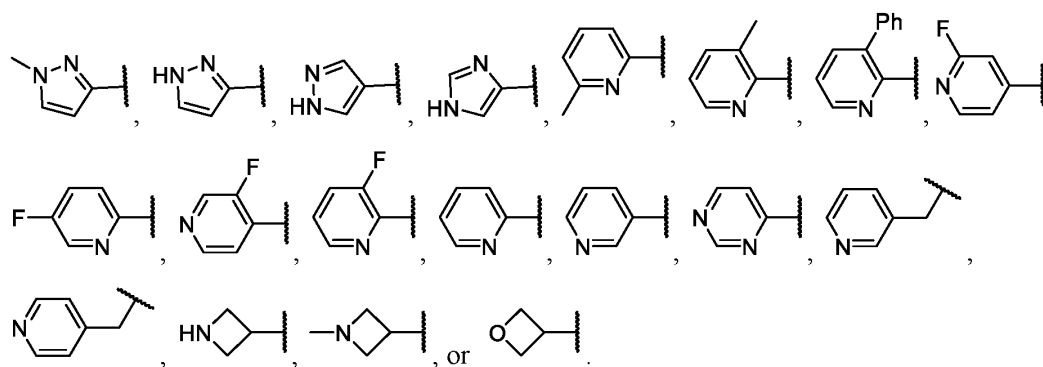
15. The compound of any one of claims 2-14, wherein R₂ is a substituted or unsubstituted group selected from the group consisting of 4- to 6-membered heterocyclyl, 5- or 6-membered heteroaryl, -(C₁-C₃ alkylene)-(5- to 6-membered heteroaryl), and -(C₁-C₃ alkylene)-(4- to 6-membered heterocyclyl).

16. The compound of any one of claims 2-15, wherein R₂ is a 5- to 6-membered heteroaryl or 4- to 6-membered heterocyclyl, each of which is optionally substituted.

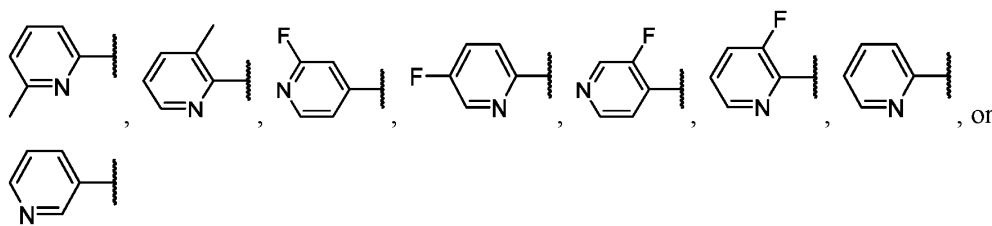
17. The compound of any one of claims 2-16, wherein R₂ is a 5- to 6-membered heteroaryl and the 5- to 6-membered heteroaryl is a 5- to 6-membered N-heteroaryl.
18. The compound of any one of claims 2-11, wherein R₂ is a 4- to 6-membered heterocyclyl and the 4- to 6-membered heterocyclyl is an azetidiny, a pyrrolidinyl, a piperidinyl, an oxetanyl, a pyranal, or a morpholinyl, each of which is optionally substituted.
19. The compound of any one of claims 2-13, wherein R₂ is:



20. The compound of any one of claims 2-13, wherein R₂ is:

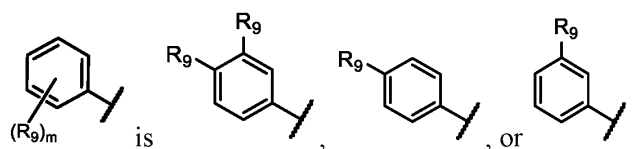


21. The compound of any one of claims 2-20, wherein R₂ is:

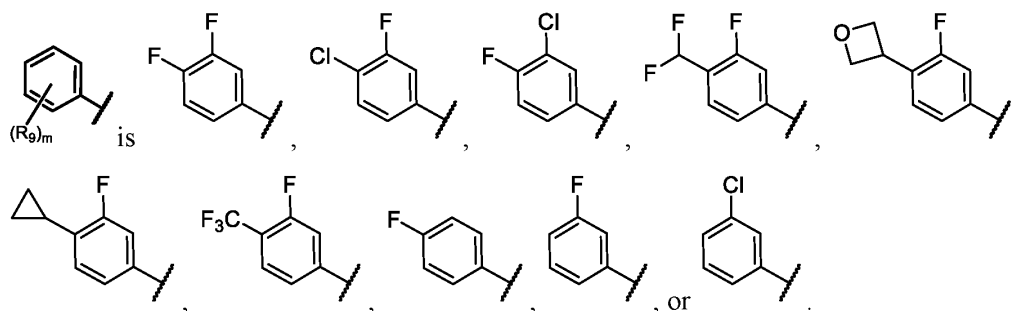


22. The compound of any one of claims 2-18, wherein R_2 is substituted with:
- a halogen, C_{1-5} alkyl, C_{1-5} haloalkyl, C_{1-5} alkoxy, C_{1-5} haloalkoxy, -CN, -OH, C_{3-6} cycloalkyl, phenyl, or a combination thereof; or
 - one or more halogens, C_{1-5} alkyl, or a combination thereof; or
 - one or more halogens; or
 - F, Cl, Me, Et, *i*Pr, *t*Bu, CF_3 , CF_2H , CFH_2 , CH_2CF_3 , CF_2CH_3 , -OMe, -OEt, O-*i*Pr, O-*t*Bu, -OCF₃, -OCF₂H, -OCFH₂, -OCH₂CF₃, -OCF₂CH₃, -CN, -OH, cyclopropyl, phenyl, or a combination thereof; or
 - F, Cl, Me, Et, *i*Pr, *t*Bu, or a combination thereof; or
 - F, Me, or a combination thereof.
23. The compound of any one of claims 1-22, wherein R_3 is H.
24. The compound of any one of claims 1-22, wherein R_3 and Y_3 taken together with the atoms to which they are attached form a 5- or 6-membered heterocycl.
25. The compound of any one of claims 1-24, wherein R_4 is H, halogen, C_{1-4} alkyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, or phenyl
26. The compound of any one of claims 1-25, wherein R_4 is H, F, Cl, Me, cyclopropyl, CF_3 , CD_3 , or phenyl.
27. The compound of any one of claims 1-26, wherein R_4 is H or Me.
28. The compound of any one of claims 1-27, wherein R_5 is H.
29. The compound of any one of claims 1-28, wherein R_6 is H, C_{1-4} alkyl, CD_3 , CF_3 , CHF_2 , CH_2F , or C_{3-6} cycloalkyl.
30. The compound of any one of claims 1-29, wherein R_6 is H, Me, Et, CD_3 , CF_3 , CHF_2 , CH_2F , or cyclopropyl.
31. The compound of any one of claims 1-30, wherein R_6 is Me.

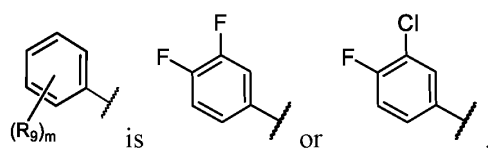
32. The compound of any one of claims 6-31, wherein



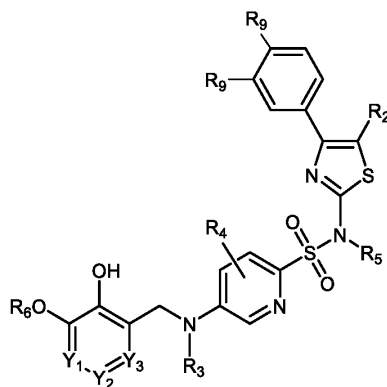
33. The compound of any one of claims 6-32, wherein



34. The compound of any one of claims 6-33, wherein



35. The compound of any one of claims 1-34, having the structure of Formula (Id):



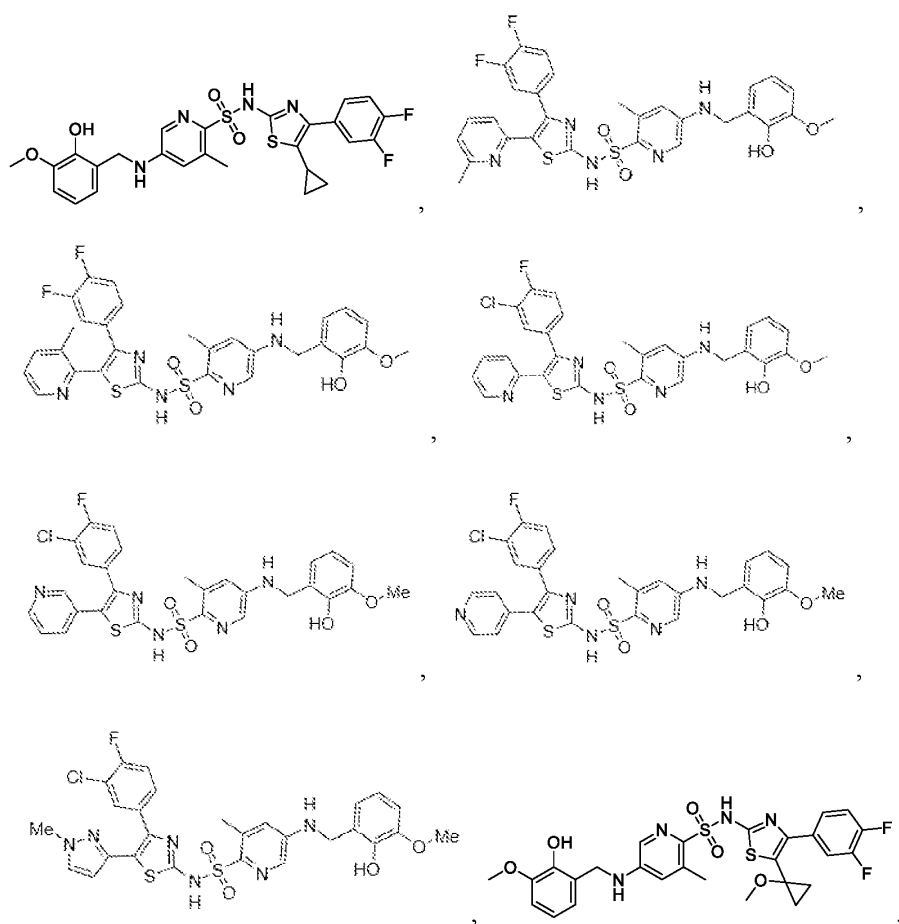
(Id)

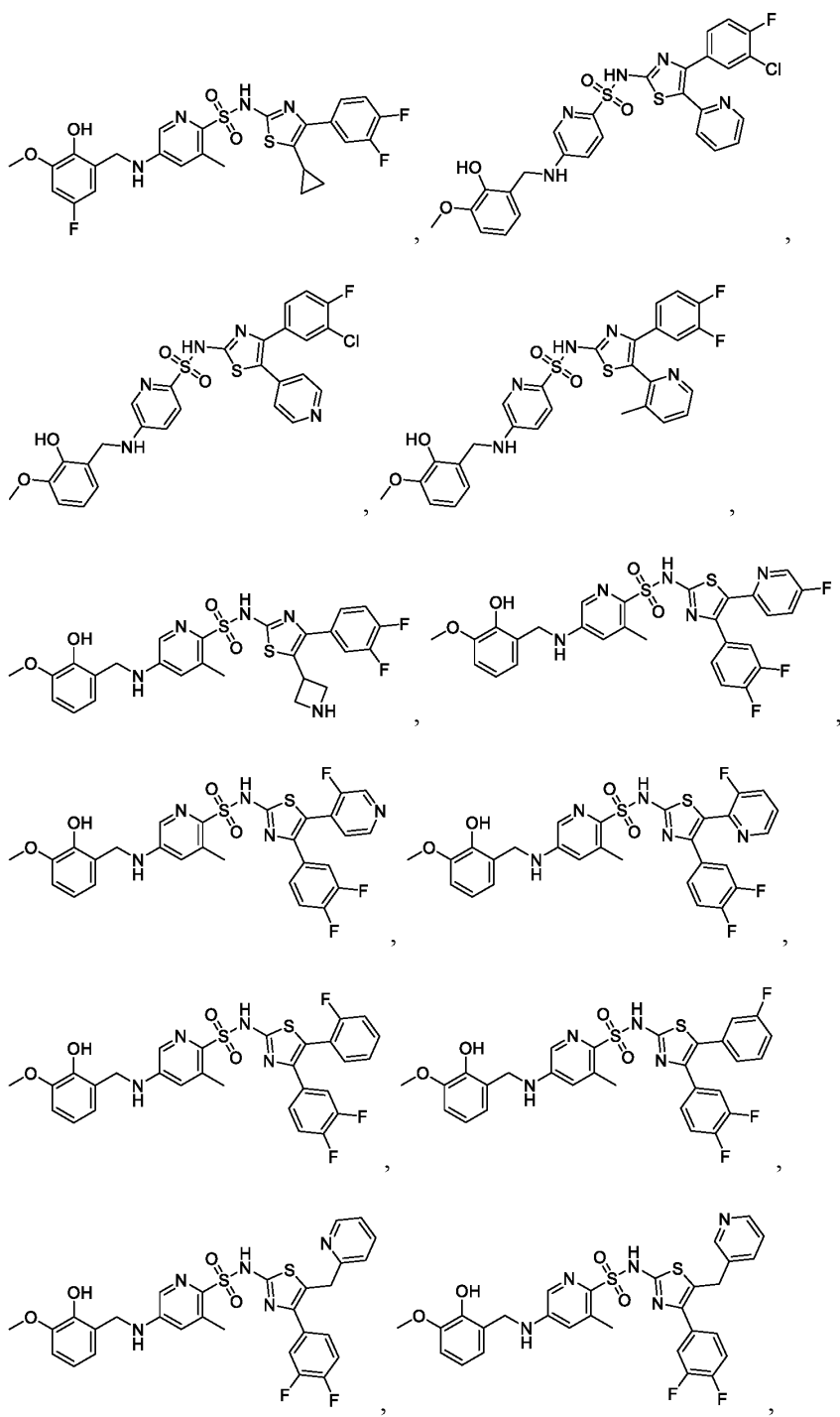
or a pharmaceutically acceptable salt thereof.

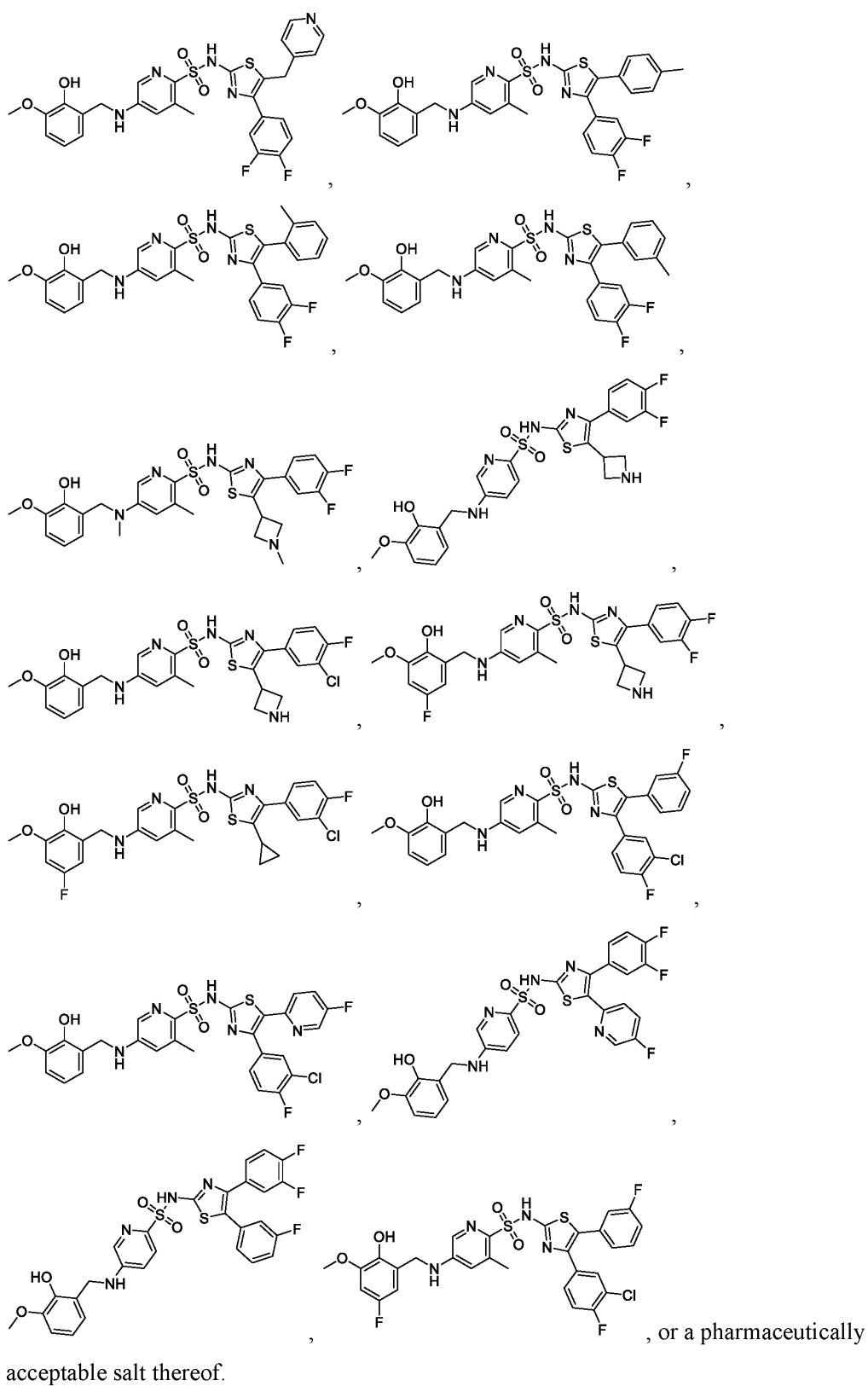
36. The compound of any one of claims 1-35, wherein Y_1 is CH and Y_2 is CH.

37. The compound of any one of claims 1-36, wherein Y_3 is CH.

38. The compound of any one of claims 1-36, wherein Y_3 is C-F or N.
39. The compound of any one of claims 1-35, wherein Y_1 is CH and Y_3 is CH.
40. The compound of any one of claims 1-35 and 39, wherein Y_2 is CH.
41. The compound of any one of claims 1-35 and 39, wherein Y_2 is C-F or N.
42. The compound of any one of claims 1-35, wherein Y_2 is CH and Y_3 is CH.
43. The compound of any one of claims 1-35 and 42, wherein Y_3 is CH.
44. The compound of any one of claims 1-35 and 42, wherein Y_1 is C-F or N.
45. The compound of any one of claims 1-44, wherein the compound has the structure:







46. A pharmaceutical composition comprising (a) a compound of any one of claims 1-45; and (b) one or more pharmaceutically acceptable carriers or excipients.
47. A method of treating a disease or condition mediated by 12-lipoxygenase (12-lox), comprising administering to a subject in need thereof an effective amount of a compound or pharmaceutically acceptable salt of any one of claims 1-45 of the composition of claim 46.
48. The method of claim 47, wherein the disease is selected from the group consisting of thrombosis, heparin-induced thrombocytopenia; anti-phospholipid syndrome; and thrombosis associated with therapeutic or diagnostic monoclonal antibodies.
49. The method of claim 47, wherein the disease is heparin-induced thrombocytopenia.
50. The method of claim 47, wherein the disease is type 1 diabetes or type 2 diabetes.
51. The method of claim 47, wherein the disease is diabetic kidney disease or diabetic neuropathy.
52. The method of claim 47, wherein the disease is lupus.
53. The method according to claim 52, wherein the lupus is systemic lupus erythematosus.
54. The method according to claim 53, wherein the treatment comprises amelioration of one or more symptoms of systemic lupus erythematosus.
55. The method according to claim 54, wherein the one or symptoms includes lupus nephritis.
56. The method of claim 47, wherein the disease is a cardiovascular disease.
57. The method of claims 56, wherein the cardiovascular disease is selected from the group consisting of congestive heart failure, myocardial infarction and stroke.